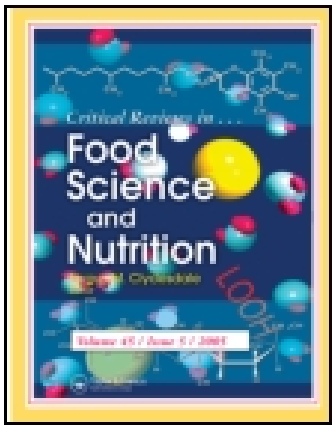

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Bioactive Substances from Marine Fishes, Shrimps, and Algae and Their Functions: Present and Future

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Bioactive Substances from Marine Fishes, Shrimps, and Algae and Their Functions: Present and Future

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Marine fishes, shrimps, and algae have many important bioactive substances, such as peptides, unsaturated fatty acids, polysaccharides, trace elements, and natural pigments. The introduction of these substances contributes to a significant improvement in developing them in final processed products. In fact, the knowledge of these bioactive substances has experienced a rapid increase in the past 20 years and prompted the relevant technological revolution with a decisive contribution to the final application. The purpose of this review was to introduce critically and comprehensively the present knowledge of these bioactive substances and pointed out their future developmental situation.

Keywords Bioactive substances, fishes, shrimps and algae, functions, present and future

INTRODUCTION

The annual total output of aquatic products has already exceeded one hundred millions of tons in the world, 10% and 30% of which are discarded because of the deterioration and processed to be the animal's forage, respectively (Wang, 2003; Li et al., 2009; Gao et al., 2011). In China, the total output of low-value fishes, shrimps, and algae has increased steadily in the past 20 years (Wu, 2007; Li et al., 2009; Wang and Lu, 2010). With the improvement of the people's living standard, the possibility of eating them directly is much lower than ever. Therefore, there is an increasing potential to convert and utilize low-value aquatic products to be valuable products. Most of marine fishes, shrimps, and algae and their processed byproducts are employed presently to prepare fish oil, fishmeal, fertilizer, and pet food (We et al., 2000; Choudhury and Gogoi, 1995; Choudhury and Bublitz, 1996). However, these products possess a relatively low economic value. A number of bioactive substances from marine fishes, shrimps, and algae and their processed byproducts have been isolated and identified so far. In general, a far better profitability can be achieved by producing human consumables and the highest profitability is currently expected from bioactive substances. These bioactive substances can be extracted and purified with technologies varying from simple to complex and they may include the isolation and preparation of peptides, unsaturated fatty acids, polysaccharides, trace elements, and natural pigments for applications in fields of foods, chemical engineering, agricultures, pharmaceuticals, and medicines. Moreover, some of these bioactive substances have been demonstrated to possess highly nutritional potentials which can promote the health of human body (Defelice, 1995). The development and application of new technologies in search for novel bioactive substances from marine fishes, shrimps, and algae and their processed byproducts will bring unique challenges and opportunities for the aquatic industry. Thus, the purpose of this review is to introduce critically the present knowledge of these bioactive substances and pointed out their future developmental situation.

PEPTIDES

Peptides are some important bioactive substances which are abundant in marine organisms. In the past 20 years, scientists have found that peptides from fishes, shrimps, and algae play an important role in the immunoregulation, resisting hypertension, antiblood fat, and inhibiting the growth of tumor cells (Zhao et al., 2000). Antimicrobial peptides are some peptide-like antibiotic molecules encoded by particular genes in organisms. They distribute widely in nature and are key factors of the congenital immunity system of vertebrates, invertebrates, and plants (Hancock, 1997; Hancock and Scott, 2000).

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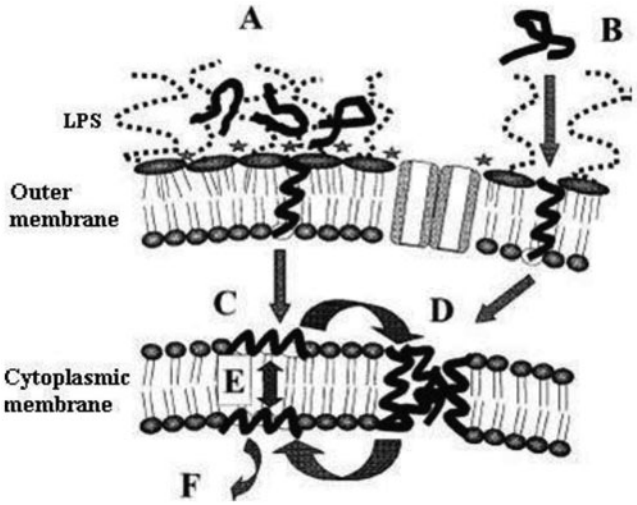

Figure 1 The interactive mode of antimicrobial peptide cations in membrane system. The interactive mechanism of cationic antimicrobial peptides with the cell envelope of bacteria.

Antimicrobial peptides belong to a larger group of naturally occurring short polypeptides, sharing similar amphipathic α-helical structures, which can interact strongly with and permeate phospholipid membranes (Segrest et al., 1990; Saberwal and Nagaraj, 1994; Zasloff, 2002). Two structural models have been proposed to explain the mechanism of the action of antimicrobial peptides so far. A structural model is that the action of these peptides is from the outside and over the pathogen's membrane either by increasing their permeability or by destabilizing membranes by changing the net charge of the composed system (Matzusaki, 1999). The interaction of these peptides with cell envelope membranes of bacteria is given in Fig. 1. Most of antimicrobial peptides from marine organisms have no disulfide bridges, and so have random structures in water and it is only when they bind to a membrane or are in other hydrophobic environment, or self-aggregate, these peptides form a structure. It is known that the dual cationic and hydrophobic nature of these peptides is important for the initial interaction between the peptide and the bacterial membrane. The cationcity promotes the interaction with bacterial outer and cytoplasmic membranes. Also, the hydrophobicity is important, e.g., increasing the hydrophobic moment of magainin analogues, and causes an increased binding of the peptide to the membrane due to increased hydrophobic interactions between lipid acryl chains and the hydrophobic helix core (Wieprecht et al. 1997). Another structural model is the Shai–Matsuzaki–Huang (SMH) model (Fig. 2) (Matsuzaki, 1999; Shai, 1999; Yang et al. 2000). This model proposes the interaction of antimicrobial peptides with cell envelope membranes of bacteria, followed by the displacement of lipids, the alteration of membrane structure, and in certain cases entry of peptides into the interior of target cells. The presence of cholesterol in the target membrane in general reduces the activity of antimicrobial peptides, due to either the stabilization of the lipid bilayer or interactions between the cholesterol and the peptide. Similarly, it is believed that increasing ionic strength, which in general reduces the activity of most antimicrobial peptides, does so in part by weakening the electrostatic charge interactions required for the initial interaction. In addition, many hypotheses have been proposed for explaining how do antimicrobial peptides actually kill microbes, which include: fatal depolarization of the normally energized bacterial membrane (Westerhoff et al., 1989); the creation of physical holes that cause cellular contents to leak out (Yang et al., 2000); the activation of dead processes such as the induction of hydrolases that degrade the cell wall (Bierbaum and Sahl, 1985); the scrambling of the usual distribution of lipids between the leaflets of the bilayer, resulting in the disturbance of membrane functions (Matsuzaki, 1999); and the damage of critical intracellular targets after the internalization of the peptide.

Studies with regard to antimicrobial peptides focused on higher animals and some insects 10 years ago (Tincu and Tailor, 2004). There has been a gradual increasing trend in the research of them from marine organisms in recent 10 years (Zhao et al., 2000). Fish antimicrobial peptides are some important components of the natural immune system in its body, whose structures are complicate (Ourth and Chung, 2004; Jorge and Fernandes, 2004). The antimicrobial peptide can be produced rapidly to prevent from the invasion of pathogenic microorganisms when fishes are injured or attacked (Boman, 1991). Most of the studies on the function of antimicrobial peptides from fishes are carried out in vitro (Ravichandran et al., 2010). Israeli scholars Orenz and Shaiy (1996) isolated an antimicrobial peptide

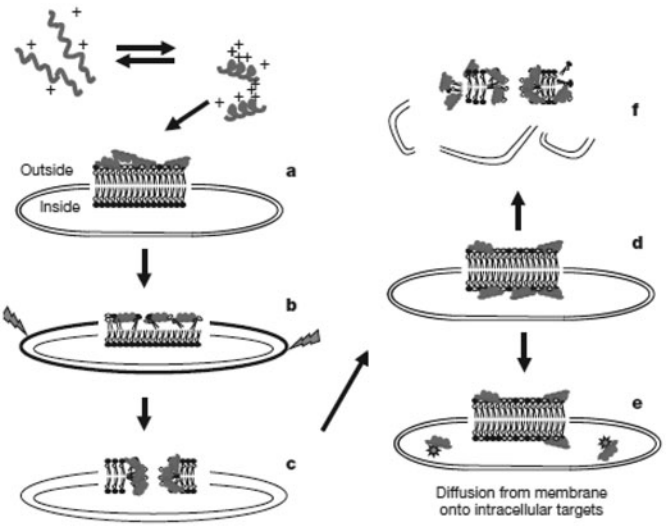

Figure 2 The Shai–Matsuzaki–Huang model of the mechanism of the action of an antimicrobial peptide. An α-helical peptide is depicted. **a**, Carpeting of the outer leaflet with peptides. **b**, Integration of the peptide into the membrane and thinning of the outer leaflet. The surface area of the outer leaflet expands relatively to the inner leaflet, resulting in strain within the bilayer (jagged arrows). **c**, Phase transition and "wormhole" formation. Transient pores form at stage. **d**, Transport of lipids and peptides into the inner leaflet. **e**, Diffusion of peptides onto intracellular targets (in some cases). **f**, Collapse of the membrane into fragments and the physical disruption of the target cell's membrane. Lipids with yellow headgroups are acidic, or negatively charged. Lipids with black headgroups have no net charge.

Table 1 Antimicrobial peptides isolated from fishes

Peptides	Fishes	Approximate MW and number of amino acids	Location	References
HFIAP	Hagfish intestinal atlantic	3.5–4.6 kDa (30–37AAs)	Intestine	Shinnar et al. (1996)
Pardaxins	Red sea moses sole	3.3 kDa (33AAs)	Skin (Mucus glands)	Oren and Shai (1996)
Pleurocidins	Winter flounder	2.7 kDa (25AAs)	Skin intestine	Cole et al. (1997) Douglas et al. (2001)
Piscindis	Hybrid striped bass	2.5 kDa (22AAs)	Skin, gill	Silphaduang and Noga (2001), Lauth et al. (2002)
Misgurin	Loach	2.5 kDa (21AAs)	Whole fish	Park et al. (1997)
Hepcidins	White bass in other tissues	2.3 kDa (21AAs)	Liver, low expression	Shike et al. (2002)
LCRP	Sea lamprey	2.2 kDa (19AAs)	Skin	Colon and Sower (1996)
Parasin-I	Asian catfish	2.0 kDa (19AAs)	Skin	Park et al. (1998) Cho et al. (2002)
HSDF	Coho salmon	NR (26AAs)	Mucus, blood	Patrzykat et al. (2001)
Cathelicidins	Atlantic hagfish	5.7 kDa (53AAs)	Liver	Uzzell et al. (2003)
Cathelicidins	Rainbow trout	6.4 kDa (66AAs)	Liver	Chang et al. (2005)
Hepicidin	Red sea bream	2.4 kDa (22AAs)	Spleen	Chen et al. (2005)

NR: not reported, AA: amino acids.

composed of 33 amino acid residues from *Pardachirus marmoratus*. They found that this peptide had a strong antimicrobial activity and could decrease the hemolytic activity of red cells more obviously than bee toxin and other natural ones. Coieam and Diamond (1997) purified a linear antimicrobial peptide from the skin mucus of *Pleuronectes americanus*. It is composed of 25 amino acid residues and has a similar α-helix structure with many other linear antimicrobial peptides. Jorge et al. (2002) isolated a new ribose peptide with an antimicrobial activity from the skin of rainbow salmon, whose molecular weight was 6676.6 Da. This peptide is very similar to a 40S ribosome protein. Jorge and Fernandesa (2004) purified a new antimicrobial peptide oncorhyncin II from the skin of rainbow salmon and found that the first 17 amino acid residues of this peptide were the same as the ones (138–154) of the histone H1 from rainbow salmon. The molecular weight of this peptide is 7195.3 Da. Furthermore, they also found an active peptide with an antimicrobial activity from blood cells of rainbow salmon, but it was sensitive for heat and could be digested easily by the protease.

It should be emphasized that there is an increasing attention to fish peptides or their hydrolysates with activities of the antihypertension and the growth inhibition of tumor cells. The antihypertensive peptide can inhibit the activity of angiotensin I transformation enzyme to lower blood pressure. A lot of enzymatically hydrolyzed products from albumen contain ACE- inhibiting peptides. Hu and Zhang (2010) reported that hydrolytic products from sardine and hairtail contained ACE-inhibiting peptides. Molecular weights of them are within a range of 1000 to 2000 Da. Matsui et al. (1993) used an alkaline protease to hydrolyze sardine to obtain 11 ACE-inhibiting peptides. The peptide having the strongest ACE-inhibiting activity is Lys-Tyr. Hee-Guk (2001) hydrolyzed the skin of Alaska cod to obtain some peptide segments whose molecular weights are within a range of 900 to 1900 Da. Various fish albumens were studied in Japan, such as the sardine's peptides with a blood pressure-lowering activity. They were prepared from the sardine's muscle and had molecular weights within a range of 1000 to 2000 Da (Wu, 1998). There is a peptide in the shark's cartilage which can inhibit the growth of tumor cells by inhibiting the capillary growth around them, such as lung cancer, liver cancer, breast cancer, alimentary canal tumor, cervix cancer, and bone cancer. (Moore et al., 1993). Chen and Jiao (2000) used hydrochloric acid guanidine, in combination with the super filtration and the molecular sieve column chromatography, to hydrolyze and purify the shark's cartilage albumen and obtained a new blood vessel inhibiting factor Sp8. It can inhibit the replication of endothelial cells and the growth of the mouse transplant sarcomas S_{180}. The peptide from the muscle of the seal has also an inhibitory effect on tumor cells. Gourin et al. (1971) and Frater et al. (1984) reported that the protamine could decrease obviously the density of the blood vessel in tumor cells and reduce the aggregation of the blood vessel in the chicken chorioallantoic membrane by in vitro experiment. When injected to transplant tumor cells, it can obviously inhibit the growth of them.

There are about 15 to 22% unique proteins in the muscle of eel, cod, and sardine. Fishes also contain an abundant GSH, which is quite important for keeping the balance of the oxidative potential of the blood circulation system (Qi and Cheng, 2002). It also plays an important role in many biological processes (Yuan and Zheng, 1999; Cai, 2000). There is an abundant taurine in fishes. It is an important sulf-amino acid and an important substance which can protect the eyesight and develop the neonate's brain (Cao, 1994). It has been shown that the human's body cannot synthesize endogenous taurine and must be supplied from the exogenous meal, and thus fishes become a good source. Other important antimicrobial peptides from fishes are listed in Table 1. Some of the antimicrobial peptides have a high sequence homology to known proteins with other functions, suggesting a derivation from cleavage products of larger proteins, such as histones (Park et al., 1998; Patrzykat et al., 2001; Birkemo et al., 2003; Fernandes et al., 2003, 2004;) and ribosomal proteins (Fernandes and Smith, 2002). Peptides considered to be dedicated to an innate immunity have been isolated or cloned from fishes and their expression has been analyzed. However, sequences have been reported from only a minimal number of fish species (Douglas et al., 2003a, 2003b), the largest vertebrate group containing over 23,000 species.

There are a little fewer researches on antimicrobial peptides from shrimps than from fishes. To date, only two families of antimicrobial peptides have been purified from them: penaeidins and crustins. Penaeidins are first characterized from *Litopenaeus vannamei* using a biochemical approach and molecular cloning techniques. Three peptides (initially named penaeidins 1, 2, and 3) were isolated in their active and mature forms (5.48–6.62 kDa) from hemocytes of shrimps (Bachere et al., 2000). However, the subsequent phylogenetic analysis indicates that penaeidins 1 and 2 can be classified in the same class (Cuthbertson et al., 2002, 2004). Penaeidin sequences were determined from eight shrimp species: *L. vannamei* (Pacific White Shrimp or White leg Shrimp), *L. setiferus* (Atlantic White Shrimp or Northern White Shrimp), *L. stylirostris* (Blue Shrimp), *Farfantepenaeus paulensis* (Sao Paulo Shrimp), *L. schmitti* (Southern white shrimp), *Penaeus semisulcatus* (Green tiger Prawn), *Fenneropenaeus chinensis* (Fleshy Prawn), and *P. monodon* (Giant or Black tiger prawn). The biosynthesis of penaeidins-2 and -3 from mRNA to mature peptides from *L. vannamei* is presented in Fig. 3 (Destoumieux et al., 2000). The sequence analysis shows that penaeidins are composed of an N-terminal proline-rich domain, followed by a C-terminal domain containing six cysteine residues organized in two doublets. This overall structure is quite unique among AMP families (Destoumieux et al., 1997; Destoumieux-Garzon et al., 2001). The antimicrobial activity spectra of penaeidins-2 and -3 from *L. vannamei* have been established through the production and analysis of recombinant peptides (Destoumieux et al., 2000; Hu et al., 2006). A new subgroup of penaeidins, named penaeidin-4, has been identified in *L. vannamei* using a genomic approach (Cuthbertson et al., 2002), and a synthetic chemical peptide (penaeidin-4) was produced to investigate and characterize functional properties and the spectrum of its activity (Cuthbertson et al., 2004). Penaeidin-4 sequence has a feature consistent with a diverse family of the penaeidin antimicrobial peptide, including a highly conserved leader sequence, the presence of a PRD (proline-rich domain), and a cysteine-rich domain with a conserved cysteine array (Bachere et al., 2000; Cuthbertson et al., 2002). An extended proline-rich region that includes a Pro-Arg-Pro motif is identical between penaeidin classes 2 and 3 in *L. vannamei*, but is divergent in the penaeidin-4 sequences (Bachere et al., 2000). Penaeidins possess an antibacterial activity predominantly directed against Gram-positive bacteria and an antifungal activity against filamentous fungi. Structures of the recombinant penaeidin-3 from *L. vannamei* and of a synthetic penaeidin-4 from *L. setiferus* have been determined, revealing an overall organization of two domains and an arrangement of disulfide bonds (Yang et al., 2003; Cuthbertson et al., 2005). Destoumieux et al. (1997) purified several antimicrobial peptides from blood cells and the plasma of *P. vannamei*, three of which can inhibit the growth of fungi and bacteria, especially the gram-positive bacteria. They also studied the synthesizing and depositing places of these peptides in *P. vannamei* by immune methods, and found that the density of them increased

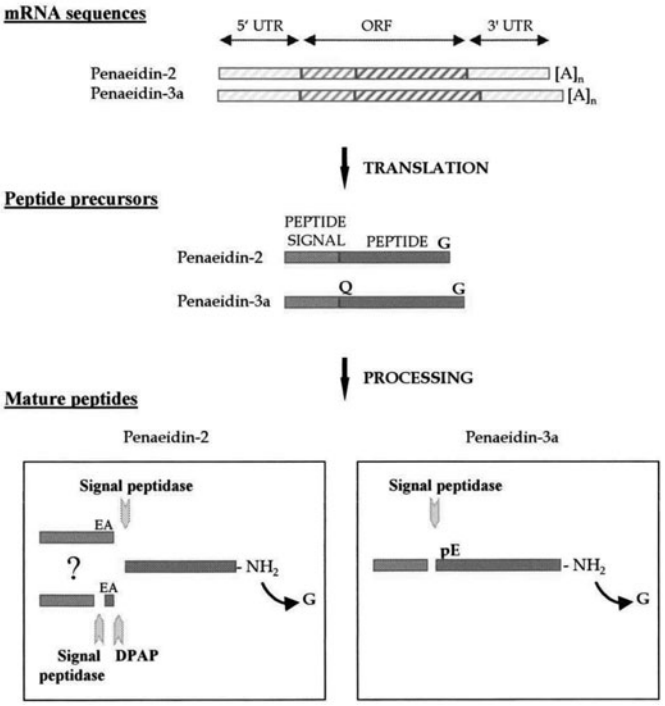

Figure 3 Penaeidins-2 and -3 biosynthesis from mRNA to mature peptides in *P. vannamei* hemocytes. After transcription and translation, two molecules undergo posttranslational modifications including elimination of the signal peptide, and COOH-terminal amidation by elimination of a glycine residue. In Pen-3, an additional step involving formation of a pyroglutamic acid by cyclization of a glutamine residue occurs. Two different processing pathways leading to the removal of the 21 first amino acids of Pen-2 precursor are represented with (i) elimination of a 21-residue signal peptide, or (ii) a two-step process including elimination of a 19-residue signal peptide and subsequent removal of a Glu-Ala dipeptide by a dipeptidyl aminopeptidase.

in the plasma. The immune response of antimicrobial peptides presents in the cuticle of the plasma.

Crustins are also a widely distributed family and many full-length cDNAs or ESTs have been described in a wide range of decapods, including *Panulirus argus* (Stoss et al., 2003), *L. vannamei* (Gross et al., 2001; Bartlett et al., 2002; Vargas-Albores et al., 2004), *L. setiferus*

(Gross et al., 2001; Bartlett et al., 2002), *P. monodon* (Supungul et al., 2004), *Marsupenaeus japonicus* (Rattanachai et al., 2004), and *Homarus gammarus* (Hauton et al., 2006). Crustins have been proved to be important antimicrobial proteins in the plasma and hemocyte granules of crustaceans and described as a component of an innate immune system (Vargas-Albores et al., 2004). They have a characteristic four-disulfide core-containing whey acidic protein (WAP) domain and a more-restricted activity spectrum, affecting mainly marine Gram-positive bacteria (Relf et al., 1999; Zhang et al., 2007; Zhu et al., 2008). Crustins were first identified in granular hemocytes of the shore crab *Carcinus maenas* and referred to as a 11.5-kDa peptide (Relf et al., 1999) and later as a carcinin (Brockton et al., 2007). Bartlett et al. (2002) screened an antimicrobial peptide (crustins) from *L. vannamei*. The amino acid sequence of this peptide is

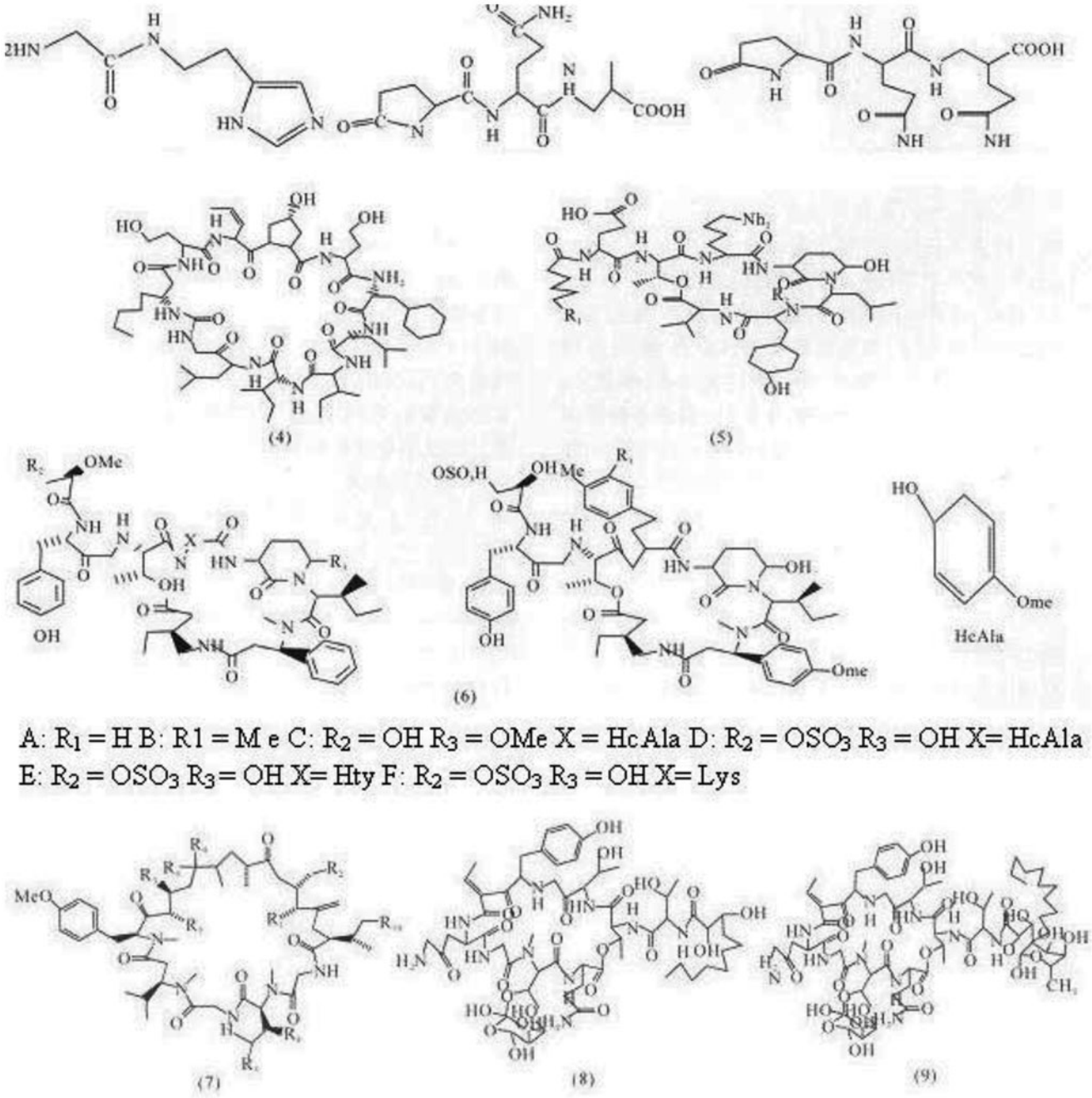

Figure 4 Chemical structures of some peptides from marine algae. (1) Carnosine, (2) eisenine, (3) fastigiata, (4) hormothamnin A, (5) majusculamide C, (6) micropeptins A–F, (7) blue algae lipopeptide, (8) hassallidin A, (9) hassallidin B.

very similar to that from the bank crab. In 2004, Chen et al. cloned its cDNA sequence and compared its amino acid homology with those from *L. vannamei* and *L. setiferus*. They pointed out that the repeated amino acid sequences of crustins from *P. monodon* were higher, and also illustrated its significance. Supungul et al. (2004) prepared two cDNA libraries from hemocytes of normal and *Vibrio harveyi* challenged black tiger shrimps *P. monodon* and sequenced unidirectionally a total of 1062 expressed sequence tag clones. Based on them, they discovered some antimicrobial peptides belonging to the penaeidin- and crustin-family. They predominate among immune-related genes, representing 29.2% and 64.0% of the normal and challenged libraries, respectively. Only one major type of the penaeidin (pen*Pm*3) was found in *P. monodon*. Crustin homologues (crus*Pm*s1 to 4) and a newly identified glycine-rich antimicrobial peptide (GAMP*Pm*1) were also isolated and characterized. In addition, recent studies utilizing a genomic approach led to the characterization of other antimicrobial effectors in shrimp,

i.e. anti-LPS factor (ALF) (Gross et al., 2001; Supungul et al., 2002).

Marine algae are rich in peptides. There has been a gradual increasing attention to them due to their significantly physiological activities and pharmaceutical functions in recent several years (Chen et al., 2001). Furthermore, studies on amino acid sequences of antimicrobial peptides from marine algae and their functions have also made an important progress (Su, 1992). Peptides found in marine algae are over 50 species. They mainly include dipeptides, circular peptides, and lipopeptides. Chemical structures of some dipeptides and circular peptides from marine algae are listed in Fig. 4. The carnosine was isolated from *Acanthophora spicifera* of red algae, and is a good natural antioxidant with an obvious inhibition to free radicals and the lipid perioxidation caused by metal ions (Fu et al., 2009). The eisenine from *Eisenia bicyclis* has an antiviral function and is often added to the forage for combating the viral infection of fishes and poultries (Sugiura et al., 2009). Nara et al. (2005) reported the mechanism of the inhibition of the fastigiata from *Pelvetia fastigiata* and *fucito* to Hela cells. The fastigiata functions to stimulate the intestinal and stomach wriggling and enhances the secretion of the alimentary gland. Judged from its molecular structure, the fastigiata also has quite strong ion-exchanging and absorption abilities. The hormothamnin A is a circular peptide from blue algae and toxic to nerve cells. This mechanism was studied in detailed by Noh et al. (2006) and is that the hormothamnin A can affect a Ca^{2+} channel and enhance the release of Ca^{2+} to promote the increase in the secretion of hormones in brain, and then exert its toxicity to nerve cells. The majusculamide C from blue-green algae has strong blocking and inhibiting functions to myeloma cells. Micropeptins A–F are strong inhibitors of the elastase and the trypsin (Itou et al., 1999). Lipopeptides are interesting and biochemically active, having cytotoxic, anticancer, antibiotic, enzymatic inhibitor, antiviral, and antifungal activities (Burja et al., 2001). They have a good affinity for liposomes and cell membranes and an ability to pass through blood tissue and blood–brain barrier leading to direct application as a drug delivery system because of their low molecular weight (Burja et al., 2001). Three lipopeptides that have a definite chemical structure have been isolated from marine algae. They are a blue-alga lipopeptide with an obvious antiviral activity and hassallidins A and B with an antifungal activity (Neuhof et al., 2006; 2006). The difference between hassallidin A and B is that B has a more glycoside bond than A. In addition, some peptide extracts from marine algae were also found to have obvious bioactivities. In 2004, Suetsuna et al. reported that water-extracting peptides from *Undaria pinnatifida* could lower the hypertension, and determined their amino acid composition: Tyr-His, Lys-Trp, Lys-Tyr, Lys-Phe, Phe-Tyr, Val-Trp, Val-Phe, Ile-Tyr, Ile-Trp, and Val-Tyr. Yang et al. (2009) found that some shorter peptides from *Plumbago zeylanica L* could inhibit obviously the growth of human umbilical vein endothelial cells by inducing their apoptosis. Also, they have an inhibitory rate of up to 68.6% to melanoma cells of the mouse B16 in vivo. Crude extracts from *Sargassum* have a good promotion for rat adrenal pheochromocytoma cells PC12 to differentiate into nerve cells, and it is dose-dependent (Yang et al. 2009). Heo et al. (2005) obtained from brown algae some peptides that could scavenge free radicals effectively, and so show a strong antioxidative activity.

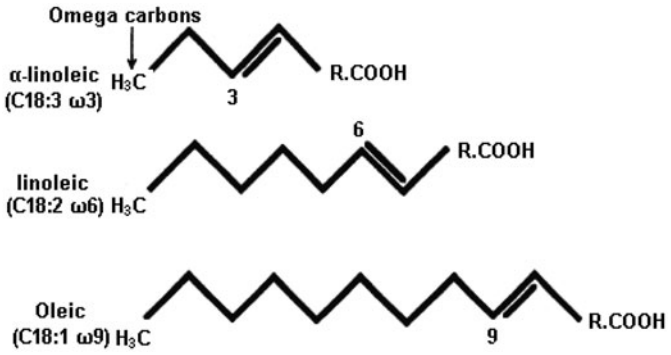

Figure 5 Structural formulas for $\omega 3$ (α-linoleic), $\omega 6$ (linoleic), and $\omega 9$ (oleic) fatty acids. The first number (before the colon) gives the number of carbon atoms in the molecule and the second gives the number of double bonds. $\omega 3$, $\omega 6$, and $\omega 9$ indicate position of the first double bond in a given fatty acid molecule.

Amino acids found in nature have exceeded 100 species so far. Different combinations and modifications of them make the number of bioactive peptides very large. Scientists predict that new pharmaceuticals for the therapy of difficult diseases may be from marine bioactive peptides, especial ones from fishes, shrimps, and algae. But at present, studies on them are still at the preliminary stage. Structures and functions of some peptides are somewhat unclear. With the development of the molecular biology and the proteome, new peptides will be isolated and identified gradually from fishes, shrimps, and algae, and the relationship of their structure and function will also be further confirmed. These will become an important research field in future.

UNSATURATED FATTY ACIDS

Unsaturated fatty acids are some important structural components of fishes and algae and play an important role in promoting the health of human body. They consist of monounsaturates and polysaturates. There are two classes of polyunsaturated fatty acids (PUFAs): $\omega 3$ and $\omega 6$. The distinction between $\omega 3$ and $\omega 6$ fatty acids is based on the location of the first double bond, counting from the methyl end of the fatty acid molecule (Fig. 5). Monounsaturates are represented by oleic acid, which can be synthesized by all mammals including humans. Its double bond is between the 9th and 10th carbon atoms (Fig. 5). $\omega 3$ and $\omega 6$ fatty acids are also known as essential fatty acids because humans, like all mammals, cannot synthesize them and must obtain them from their diet. $\omega 6$ Fatty acids are represented by linoleic acid (LA) and $\omega 3$ fatty acids by α-linolenic acid (LNA). LA is plentiful in nature and is found in seeds of

most plants except for coconut, cocoa, and palm. LNA on the other hand is found in the chloroplast of green leafy vegetables. Both essential fatty acids are metabolized to longer-chain fatty acids of 20 and 22 carbon atoms. LA is metabolized to the arachidonic acid (AA) and LNA, to EPA and DHA, increasing the chain length and the degree of unsaturation by adding extra double bonds to the carboxyl group (Fig. 6). ω-3-Fatty acids are essential for the normal growth and development and play an important role in the prevention and treatment of the coronary artery disease, cancer, hypertension, arthritis, other inflammatory, and autoimmune disorders. A number of important conferences about PUFAs had been held before 1985, such as the Reading conference held in 1984, but the expansion of this impressive growth can almost be dated from the 1985 conference Health Effects of Polyunsaturated Fatty Acid in Seafood, held on June 24 to 25, 1985 in Washington, DC (Simopoulos et al., 1986). The 1985 conference is the first major international conference to establish the fact that ω-3-fatty acids of marine origins, EPA and DHA, play an important role in the prostaglandin metabolism, thrombosis and atherosclerosis, immunology and inflammation, and membrane function. The 1985 conference participants recommended (1) the support research on the role of ω-3-fatty acids in growth and development, in health and disease, and on the mechanism involved, and (2) the establishment of a test-materials program to specifically define nutritional requirements throughout the life cycle, and dose and type of ω-3- fatty acids in invention studies and in clinical trials.

There are some Unsaturated fatty acids in fishes essential for the human body's health, especial ω-3-unsaturated fatty acids. The content of ω-3-fatty acids and other fat components in selected fishes are listed in Table 2. EPA and DHA are found in the oils of fish, particularly fatty fish (Table 2). Diep et al. (2000) reported that DHA and EPA could affect the structure of the coronary artery thrombosis, and so has a function of lowering blood pressure. An increasing in the understanding of the pathophysiology of the coronary artery thrombosis has led to a hypothesis that preventing the platelet activation and aggregation are some essential steps in the prevention of coronary artery thrombotic complications. ω-3-fatty acid ingestion may also be able to prevent the increase in cellular components and interfere at many steps in the development of the atherogenic process.

Birch (2002) reported that the vision of babies supplementing DHA in foods was better than that of the other babies. Many studies also point out that supplementing EPA and DHA in

Table 2 The contents of ω3 fatty acids and other fat contents in selected fishes*

			Fatty acids					
Fish	Total fat	Total saturated	Total monosaturated	Total polysaturated g/100g	18:3	20:5	22:6	Cholesterol mg/100g
Anchovy European	4.8	1.3	1.2	1.6	—	0.5	0.9	—
Bass, stripped	2.3	0.5	0.7	0.8	Tr	0.2	0.6	80
Bluefish	6.5	1.4	2.9	1.6	—	0.4	0.8	59
Carp	5.6	1.1	2.3	1.4	0.3	0.2	0.1	67
Catfish, brown bullhead	2.7	0.6	1.0	0.8	0.1	0.2	0.2	75
Catfish, Channel	4.3	1.0	1.0	1.0	Tr	0.1	0.2	58
Cod, Atlantic	0.7	0.1	0.1	0.3	Tr	0.1	0.2	43
Croaker, Atlantic	3.2	1.1	1.2	0.5	Tr	0.1	0.1	63
Flounder, unspecific	0.1	0.2	0.3	0.3	Tr	0.1	0.1	46
Grouper, Red	0.8	0.2	0.1	0.2	—	Tr	0.2	—
Haddock	0.7	0.1	0.1	0.2	Tr	0.1	0.1	63
Halibut, Greenland	13.8	2.4	8.4	1.4	Tr	0.5	0.4	46
Halibut, Pacific	2.3	0.3	0.8	0.7	0.1	0.1	0.3	32
Herring, Pacific	13.9	6.3	6.9	2.4	0.1	1.0	0.7	77
Herring, round	4.4	1.3	0.8	1.5	0.1	0.4	0.8	28
Mackerel, king	13.0	2.5	5.9	3.2	—	1.0	1.2	53
Mullet, Striped	3.7	1.2	1.1	1.1	0.1	0.3	0.2	49
Ocean Perch	1.6	0.3	0.6	0.5	Tr	0.1	0.1	42
Plaice, European	1.5	0.3	0.5	0.4	Tr	0.1	0.1	70
Pollock	1.0	0.1	0.1	0.5	—	0.1	0.4	71
Pompano, Florida	9.5	3.5	2.6	1.1	—	0.2	0.4	50
Salmon, Chinook	10.4	2.5	4.5	2.1	0.1	0.8	0.6	—
Salmon, pink	3.4	0.6	0.9	1.4	Tr	0.4	0.6	—
Snapper, red	1.2	0.2	0.2	0.4	Tr	Tr	0.2	—
Sole, European	1.2	0.3	0.4	0.2	Tr	Tr	0.1	50
Swordfish	2.1	0.6	0.8	0.2	—	0.1	0.1	39
Trout, rainbow	3.4	0.6	1.0	1.2	0.1	0.1	0.4	57
Tuna, albacore	4.9	1.2	1.2	1.8	0.2	0.3	1.0	54
Tuna, unspecified	2.5	0.9	0.6	0.5	—	0.1	0.4	—

*Per 100 g editable portion, raw. Dashes denote lack of reliable data for nutrients known to be present; Tr, trace (<0.05 g/100g food).

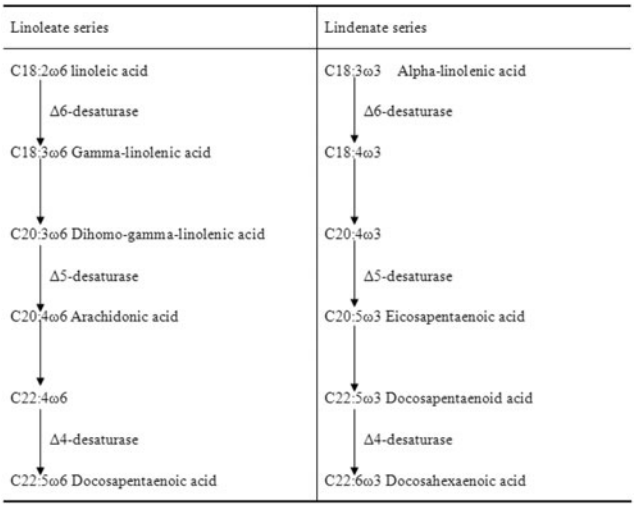

Figure 6 Essential fatty acid metabolism. Desaturation and elongation of $\omega 3$ and $\omega 6$ fatty acids.

foods has certain functions of lowering cholesterol content and preventing blood from coagulation (Bronte-Sewart et al., 1956; Keys et al., 1957; Ahrens et al., 1959). However, it should be emphasized that there is little EPA and DHA in dietary fat under the natural state, and so supplementing EPA and DHA for human body's health is sometimes essential. There are a large amount of highly unsaturated fatty acids in sea urchin and mussel (Cook et al., 2000). Contents of the oil and squalene in the shark's liver are up to 60% and 40%, respectively (Catchpole et al., 1997; Catchpole and von Kamp, 1997). The squalene and squalene-2, 3-diol have a remarkable anticancer activity, and have not a negative effect if taken up in succession (Wang and Luo, 1999).

Beginning from 1980s, scientists from America, Japan, and Israeli have devoted to developing unsaturated fatty acids from marine algae, especially polyunsaturated fatty acids (PUFAs) with more than 4 to 5 double bonds. Obviously, contents of PUFAs in algae are higher than those in other organisms, and up to 5 to 6% of their cell dry weight. Some microalgal strains, such as *Diatom*, *Ptricornutum*, *Porphyridiumcruentum*, *Nannochloropisissalina*, and *Isochrysisgalbana,* have been demonstrated to be promising industrialized strains for producing PUFAs (Renaud and Parry, 1996). Fatty acid compositions of some species of marine microalgae are listed in Table 3 (Li et al., 1998). In microalgae, EPA is found in the classes of *Bacillariophceae (diatoms), Chlorophyceae, Chrysophyceae, Cryptophyceae, Eustigmatophyceae*, and *Prasinophyceae.* Cohen and Heimer (1992) reported that EPA yields were up to 1.0 mg/L·d in summer and 0.5 mg/L·d in winter in the outdoor-cultured *Porphyridium cruentum*. Barelay et al. (1992) predicted that the highest theoretical yield of PUFAs in the outdoor-cultured photolithotrophic algae was 16.7 mg/L·day based on the reports of Vonshak and Richmond (1988) and Phol and Zurheide (1979). Dai and Wu (2000) investigated the possibility of producing DHA and EPA using microalgal strain *Isochrysisgalbana*. Furthermore, they made more detailed studies on the key factors that affected the growth and biochemical composition of algae and the yields of PUFAs. These factors include the dilution rate, the light intensity, the light quality, the photoperiodicity, the temperature, the pH, the salty degree, concentrations of nitrogen and phosphate sources, NaCl concentrations, trace elements, vitamins, and CO_2. Based on these studies, they obtained optimal culture conditions of some microalgae for the effective production of PUFAs. Although these enhance the microalgal biomass and the yields of PUFAs, many adverse factors during the outdoor culture of algae cannot nevertheless be overcome basically. Thereafter, the photobioreactor was designed to solve above problems, and the continuous culture of marine microalgae was realized using it (Grima et al., 2003).

With the rapid development of the genetic and metabolic engineering in recent 10 years, the biosynthetic pathway of some PUFAs in algae has been elucidated (Fig. 7) (Wen et al., 2000), and applied to enhance their yields. The biosynthesis of unsaturated fatty acids occurs in two steps. In the first step, the de novo synthesis of oleic acid from acetate takes place followed by conversion of oleic acid to linoleic acid and α-linolenic acid. After a number of subsequent steps of desaturation and elongation, it forms PUFAs including EPA. Biosynthesis starts with the carboxylation of acetyl CoA to form acetate or pyruvate by the action of glycolytic enzyme and then the acetyl CoA is converted to malonyl CoA, which is used to derive a condensation reaction to extend the acetyl group to stearic acid and desaturate to oleic acid. Many genes encoding enzymes in the biosynthetic pathway of PUFAs were cloned gradually and over-expressed in algae (Qin and Ceng, 1996). However, compared to other microorganisms, methods for the genetic transformation of algae still need to be improved. Some algae, such as *Ceratophyllaceae*, *Microcystis novacekii*, or *M. pseudofilamentosa*, are quite difficult to establish their genetic transformation pattern because it is somewhat unclear that they are prokaryotic or eukaryotic until now.

Although the production of unsaturated fatty acids using algae is still at laboratory stage, they have much more significant advantages compared to fishes: (1) higher content and more species of PUFAs, (2) shorter culture cycle, (3) more simple extraction process, (4) no fishy taste, (5) no cholesterol, (6) easy large-scale culture, and (7) no contamination of pesticides and heavy metal ions (Belarbi et al., 2000). Therefore, it is predictable that marine algae will become a better choice for the production of PUFAs in future.

POLYSACCHARIDES

Polysaccharides are some important substances synthesized in organisms. At present, studies on the polysaccharides focused on shrimps and algae and very little on fishes. Chitin is a major structural component of shells of shrimps and has been studied in detailed in the past 20 years. The positive charged chitin can absorb the superfluous Cl^-, and so be applied in the field of biomedical engineering (Wang and Wang, 2002). Besides this, it

Table 3 Composition of fatty acids in some algae strains

	Rhodophyceae		Phaeophyceae		Chlorophyceae		
Fatty acid	*Corallina granifera*	*Phyllophora nervosa*	*Cystoseira barbata*	*Ultra riqida*	*Cladophora* sp	*Bryopsis hypnoides*	*Chara* sp
14:0	4.5	2.2	5.4	6	9.3	6	8
14:1 (n-7)							1
4,8,12-trimethyl-13:0	0.5					2	
meso 14:0	0.5	0.8			1	1	
15:0	0.8	0.3			1		1
16:0	38.6	26.2	15.3	4.9	17.2	15.0	9.7
16:1 (n-9)	0.3	0.1		0.4	0.8	0.8	0.1
16:1 (n-7)	3.0	19	2.7	2.3	8.6	1.4	5.0
16:1 (n-5)	0.4	0.4					0.1
16:2 (n-6)	0.1	0.2			0.6	0.6	1.5
16:2 (n-4)	0.2		0.1	0.6	0.6	0.1	0.4
16:3 (n-3)	0.5	0.3	0.1	11.1		14.7	8.5
16:4 (n-3)	0.6			1.7	9.2		
meso 16:0		0.1			1.1	1.5	
10-methyl 16:0		0.1	0.1				
17:0		0.7				0.1	0.1
17:1 (n-8)	0.1	0.3					
18:0	0.6	1.1		0.3	0.1	0.5	0.5
18:1 (n-9)	6.8	7.0	20.8	1.4	10.6	2.6	2.2
18:1 (n-7)	2.5	2.1	0.3	3.0	3.6	6.9	0.6
18:2 (n-8)	0.1				0.5		
18:2 (n-6)	1.2	0.9	6.1	7.5	6.3	6.2	10.2
18:3 (n-6)	0.2	0.3	0.8	1.7			1.7
18:3 (n-3)	0.9	2.1	15.2	42.6	17.3	34.9	29.3
18:4 (n-3)	1.0	1.4	8.4	10.5	0.8	2.1	1.2
19:1 (n-8)	0.1						
20:1n-11	0.1					0.2	
20:1 (n-9)	0.2						
20:2 (n-6)			0.1				1.6
20:3 (n-9)	0.4		0.4				
20:3 (n-6)		0.3	1.5	0.4			2.3
20:3 (n-3)	4.2		0.1	2.2			1.2
20:4 (n-6)	0.3	44.3	15.5		0.8	3.0	9.9
20:4 (n-3)	30.3		0.8		0.5	0.5	1.5
20:5 (n-3)		56	5.6	3.3	6.2	3.9	9.6
20:5 (n-3)				1.4	1.3	0.1	
20:6 (n-3)					0.3	0.3	

has many other bioactivities, including enhancing the immunity, reducing the content of cholesterol, controlling the transfer of cancer cells, and inhibiting the growth of bacteria and epiphytes (Li et al., 1999). Also, it is quite suitable for being developed to be a functional ingredient of various healthcare foods, the operation suture and the artificial skin. Among its degradable products, chitooligosaccharides (CHOS) have important applications in fields of the medicine, pharmaceutical, environmental protection, and chemical engineering. In 2008, we prepared them that have a high bioactivity by the chitin degradation with the recombinant endochitinase expressed in *Escherichia coli* BL21 (Yu and Li, 2008). The prepared CHOS are composed of —four to eight units of *N*-acetyl-β-D-glucosamine and have a quite strong antitumor activity (Yu et al., 2009). They have also an obvious antifungal activity. This seems to be caused by its interaction with lipids in the plasma membrane, leading to morphological changes and the cell-surface disruption (Park et al., 2008; Palma-Guerrero et al., 2009). The composition of the fungal plasma-membrane seems to be important for the sensitivity against it, and a higher content of polyunsaturated fatty acids makes the fungi more sensitive (Palma-Guerrero et al., 2010). From literature studies, it is clear that the CHOS indeed have a considerable potential in above areas (Tao et al., 2006; Harish Prashanth and Tharanathan, 2007; Aranaz et al., 2009; Jayakumar et al., 2010). This is a good reason for giving the application of the CHOS to combat the fungal infection in humans, more research attention than it has received so far. In addition, the mineralization process and bone strength are dependent on Ca^{2+}, which helps to support the structure. There is evidence that the CHOS increase the calcium deposition in bone (Kim et al., 2005; Jung et al., 2006; Ratanavaraporn et al., 2009). Jung et al. (2006) found that the CHOS could inhibit efficiently the formation of insoluble calcium-phosphate salts and consequently increase the Ca^{2+} bioavailability and the bone strength. They also found that the CHOS (<5 kDa) gave an increase in the calcium retention and decreased the bone turnover in a rat osteoporosis model. This indicates that the CHOS may have beneficial effects as a calcium fortifier in the condition

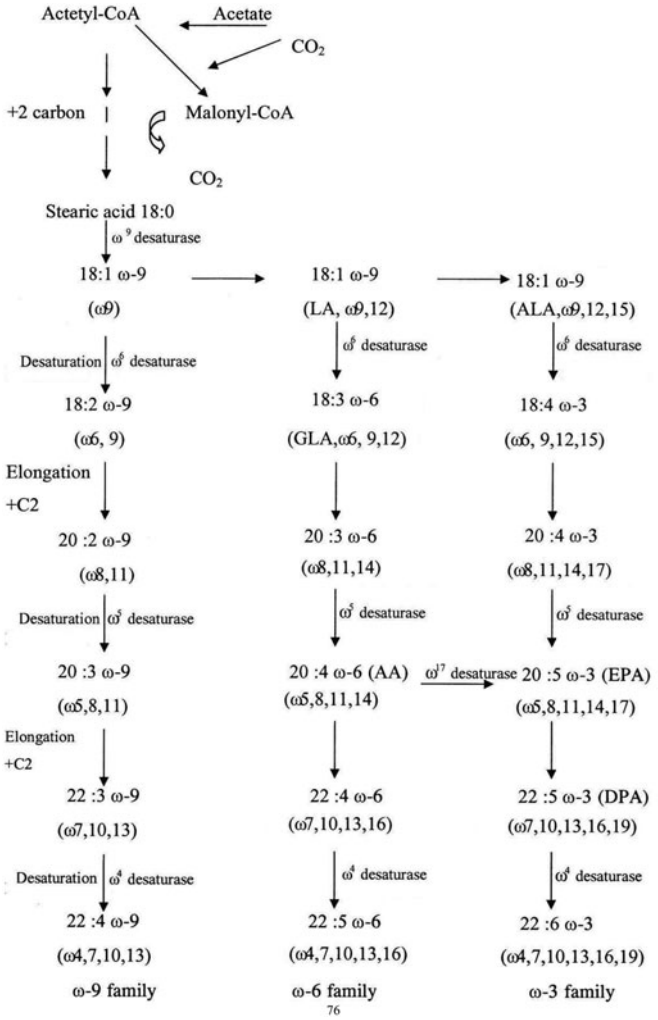

Figure 7 Biosynthesis of three families of polyunsaturated fatty acids by microalgae.

of Ca^{2+} deficiency, such as in the osteoporosis. The CHOS have also been used successfully as a vector for the delivery of genes (gene therapy) since the first paper was reported about 15 years ago (Mumper et al., 1995; Jayakumar at al., 2010). They form a stable complex with the plasmid DNA and can be used as a vector for the administration of genes to mucosal tissues, such as lungs (Köping-Hoggard et al., 2001) and the intestinal epithelium (MacLaughlin et al., 1998; Roy et al., 1999). There are, however, a certain drawbacks connected to the use of high molecular weight chitosans because of the low solubility at the physiological pH, the high viscosity, and the fact that CHOS complexes often tend to form aggregates. Köping-Höggård et al. (2003) showed that fully deacetylated CHOS formed stable complexes with the plasmid DNA, and in vitro and in vivo experiments proved that these CHOS complexes were effective vectors for the delivery of genes. It has been speculated that a delicate balance between the stability of the CHOS-DNA- complexes at lower pH values (around pH 6) and their instability at higher pH values (above pH 7) could be the reason for their efficiency (Sharon and Ofek, 2000; Strand et al., 2010). This has recently been confirmed in detailed studies of how the CHOS chemistry can be used to create an optimal balance between the stability of the complexes and their unpacking (Strand et al., 2010).

Glycosaminoglycans (GAGs) are long unbranched polysaccharides which consist of a repeating unit of disaccharide. The repeating unit consists of a hexose or a hexuronic acid linked to a hexosamine (six-carbon sugar containing nitrogen). Glycosaminoglycans form an important component of connective tissues. Their chains may be covalently linked to a protein to form proteoglycans. The density of sugar molecules and the net negative charges can attract cations, such as Na^{+} and Ca^{2+}, etc. After they bind to glycosaminoglycans, water molecules can be further attracted by these cations. Some examples of glycosaminoglycan applications include heparin as an anticoagulant, hyaluronan as a component in the synovial fluid lubricant in body joints and chondroitins which can be found in connective tissues, cartilage, and tendons (Hirsh, 1991). The GAG from shrimps has physiological functions of resisting blood coagulation, lowering the content of fat in blood and enhancing the immunity (Zhang and Wen, 1995). Brito et al. (2008) found that glycosaminoglycans from *L. vannamei* could reduce significantly the influx of inflammatory cells to injury site in a model of acute inflammation and the metalloproteinase activity in the peritoneal lavage of inflamed animals. Moreover, they can also reduce almost 90% of the MMP-9 activity. Negligible anticoagulant activities and a poor bleeding potential make them better alternatives than mammalian heparin as possible antiinflammatory drugs. The chondroitin sulfate is an acidic polysaccharide whose molecular weights are 20 to 50 kDa. Because it can lower the content of fat in blood, it may resist the blood coagulation obviously, and is used widely to prevent the cardiovascular disease (Yan and He, 2004). When its molecular weights are 2 to 10 kDa, it has a better effect on preventing the scleratheroma, the rheumatism inflammation, and the wound concrescence (Yan and He, 2004). The chondroitin sulfate D that derives from the fin and the vertebra of shark can resist the inflammation and the schistosoma and reduce the content of the blood fat (Nadanaka et al., 1998). The chondroitin sulfate from whale cartilage and its decomposed products can inhibit obviously the absorption of glucose in human intestine, and so act as a functional substance to alleviate adiposities and diabetes (Sugahara et al., 1991).

Besides proteins and nucleic acids, polysaccharides are the third biomacromolecules in marine algae. They exist mainly in the form of glycoprotein, glycolipid, and proteoglycan. The difference in physiological activities of polysaccharides from different algae is quite big (Chen et al., 2009). Many reports pointed out that microalgal polysaccharides had different physiological activities, including enhancing the immunity, antivirus, resisting the malignant tumor, antiinflammation, etc. (Sogawa et al., 1998; Sun et al., 1998; Huleihel at al., 2001; Sun and Wang, 2003; Tannin et al., 2005). Main polysaccharides from marine algae are *Spirulina* polysaccharides, green-algae polysaccharides, selenium-polysaccharides, *Dunaliella salina* polysaccharides,

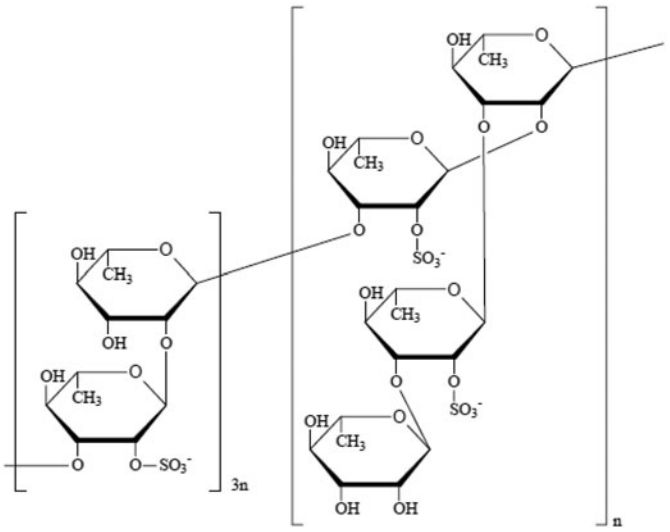

Figure 8 The proposed structure of rhamnan sulfate from *Monostroma nitidum*.

Porphyridium cruentum polysaccharides, sulfated polysaccharides, and sulfated polymannuroguluronates (Chen et al., 2009). *Spirulina* polysaccharides are complicate polysaccharides that are composed of different monosaccharides which are linked by β-glycosidic bonds. Liu et al. (2007) reported that polysaccharides from *S. platensis* had an antiaging function and an obvious inhibition to cancer cells. They can enhance the nonspecific immunity of animal cells, promote the specific immunity, and improve the SOD activity of the blood vessel of the aged mice. Guzman et al. (2003) found that green-algae polysaccharides had immunomodulation activities in vitro and in vivo and an antiinflammatory activity. Umemura et al. (2003) isolated a galactogen GA3P and a sulfated dextran from *Dinoflagellate gymnodinium*, and found that they could inhibit the growth of tumor cells by enhancing the human body's immunity. Suzuki et al. (2001) purified a new polysaccharide from *Chlorella pyrenoidosa* which was composed of arabinose and galactose. They also demonstrated that it had an immunity-stimulating function and a herpesvirus-inhibiting activity in vitro. The selenium-polysaccharide was isolated mainly from algae cultured in the sodium selenite-enriched media. It not only acts as an organic selenium-supplementing agent, but also has an immune-modulating activity of the polysaccharide. The selenium-polysaccharide from *S. platensis* can enhance mouse's indexes of thymus and spleen obviously, promote the proliferation of lymph cells, and improve the activity of NK cells. The effect of it is stronger than that of *S. platensis* polysaccharide containing no selenium. Fabregas et al. (1999) reported that the water-extracting sulfated polysaccharides from *D. salina* had an obvious inhibitory effect on the replication of the septicemia virus and the African swine fever virus. Ding et al. (2000) found that polysaccharide complexes from *D. salina* had an over 80% inhibitory rate to tumor cells S_{180}. Polysaccharides from *Porphyridium cruentum* are mainly composed of xylose, galactose, and glucose. As an adhesive and emulsifier, they are used widely in the fields of foods, cosmetics, and pharmaceuticals. The sulfated polysaccharide is composed of 10 monosaccharides, among which xylose, galactose, and glucose are main ingredients. Besides these, it also contains the uronic acid and the sulfate, and so is a polyanion polymer. The sulfated polysaccharide has not only a strong resistance to the hemorrhagic disease and the African swine fever virus, but also a strong inhibition to the proliferation of I and II-type herpesvirus and varicella virus. The sulfated polysaccharide from *Impudicum* can protect the growth and proliferation of algal cells under the extreme environment, such as drought, strong light, and sediment environment. This mechanism is that it has a strong antioxidative ability, and so may scavenge free radicals and transport them into outside of the cells. The sulfated polysaccharide from red alga is a cell-wall polysaccharide. It can change the replication cycle of the virus and has an obvious inhibition to many viruses, such as I- and II-type herpes simplex virus and varicella-zoster virus (Huleihel et al., 2001; Erukhimovitch et al., 2003). Jounge et al. (2004, 2005) was the first time to report that the sulfated polysaccharide P-KG03 from *Impudicum* had a quite strong inhibitory effect on the encephalomyocarditis virus and a good immunoregulatory function to the human body. The rhamnan sulfate was found in *Monostromaceae*, which is taxonomically related to *Ulvaceae* and *Enteromorpha ceae*. This polysaccharide is known to be a good source of naturally occurring heparinoids. The structure of the rhamnan sulfate has been determined (Harada and Maeda, 1998). It consists of α-1, 3-linked-rhamnose residues, some of which are substituted with sulfate groups, mainly at position O-2. Minor amounts of the internal 1, 2-linked rhamnose and branched rhamnose are also detected (Fig. 8). Some rhamnan sulfate possess biological functions such as the antitumor and anti-HIV activities (Hayashi et al., 1996). The fucoidan is a complex sulfated polysaccharide, derived from marine brown algae (Percival and McDowell, 1967; Painter, 1983; Nishino et al., 1991), the jelly coat from sea urchin eggs (SeGall and Lennarz, 1979; 1981; Glabe et al., 1982), and the sea cucumber body wall (Mourao and Bastos, 1987; Vieira and Mourao, 1988; Mulloy et al., 1994). Most investigations with regard to its biological activity have involved fucoidans from brown algae such as *Fucus vesiculosus*. The fucoidan from it mediates a variety of significant biological effects on mammalian cells. *Fucus* fucoidan has an anticoagulant activity (Bernardi and Springer, 1962; Colliec et al., 1991; Nishino et al., 1991; Nishino and Nagumo, 1992; Sinniger et al., 1993) and is a potential activator of both antithrombin III and heparin cofactor II (Sinniger et al., 1993). The fucoidan inhibits both the initial binding of sperm and subsequent recognition (Mahony et al., 1991). It also prevents the infection of human cell lines by several enveloped viruses (Baba et al., 1988; 1988) and blocks cell–cell binding mediated by P- or L-selectin but not E-selectin (Foxall et al., 1992). Furthermore, it may bind differentially to interleukins l α and β, 2, and 6 (Ramsden and Rider, 1992) and the hepatocyte growth factor (Kobayashi et al., 1994). Since this polysaccharide causes no toxicity or irritation, it may be useful as an anticoagulant, antiviral, antiinflammatory, and contraceptive agent (Arfors and Ley,

1993; Mahony et al., 1991; Oehninger et al., 1991). The proposed structure of *Fucus* fucoidan consists mainly of 4-sulfated and 2-linked α-fucopyranosyl units (Percival and McDowell, 1967) and has recently been revised so that α-fucopyranosyl units are now 1 to 3 linked (Fig. 9) (Patankar et al., 1993). This structure resembles that determined for a fucoidan from *Ecklonia kurome*, another brown seaweed (Nishino et al., 1991; Nishino and Nagumo, 1992). According to most authors, sulfate groups are linked mainly to the 4-position of a fucose residue (Nishino et al., 1991). The fucoidan proved effective in healing and preventing of gastric ulcers in experimental animal models in the oral administration (Shibata et al., 1998). Notably, the fucoidan from *Cladosiphon okamuranus* (Okinawa Mozuku) is more effective in healing ulcers than that from *F. vesiculosus*. Furthermore, this fucoidan blocks both led- and sulfatide-mediated adhesion of *Helicobacter pylori* to gastric cells (Shibata et al., 1999). *Helicobacter pylori* are a specific human pathogen. They colonize human gastric epithelium and are linked to serious diseases in the upper gastrointestinal tract, such as gastric and duodenal ulceration and gastric carcinoma (Lambert et al., 1995). *Cladosiphon* fucoidan has a sulfate group for every 2 mol of fructose and has a glucuronic acid residue for every 6 mol of fructose as a branched chain (Fig. 10) (Nagaoka et al., 1999). The change in the symptoms of nonulcer dyspepsia induced by oral administration of *Cladosiphon* fucoidan had also been examined. The two-way crossover test was carried out by the administration of fucoidan and placebo each for two weeks. The fucoidan (1.5–4.5 mg/kg·day) relieves symptoms of the nonulcer dyspepsia as determined from a structured interview. No serious adverse effects caused by fucoidan were observed during this study (Yamamoto et al., 2000). This result suggests that daily intake of the fucoidan has a useful effect on the nonulcer dyspepsia.

Polysaccharides from marine shrimps and algae are an exceptionally potential research field. We consider that it should be further strengthened in future and put forward the following suggestions: (1) Changing the molecular conformation of polysaccharides. Bioactivities of polysaccharides are closely related to their primary and higher structures. We may obtain new derivatives of polysaccharides by selecting suitable methods to modify their molecules. This may not only reduce their toxicity, but also enhance their bioactivities. (2) Improvement and screening of microalgal strains and the optimization of their culture conditions. The high polysaccharide-producing strain can be obtained by the genetic and metabolic engineering, in combination with traditional methods. The effect of culture conditions on the yield of the polysaccharide may be studied in detailed for maximizing its yield. (3) Applying polysaccharides for biomaterials, including thermal-insulation and heat-proof materials, medical materials, and artificial-organ materials, etc. (4) Applying polysaccharides for the biofertilizer in agricultural fields. The effect of polysaccharides on the physicochemical properties of the soil may be studied to improve its quality. (5) The treatment of wastes by polysaccharides. Developing polysaccharides to be a biomembrane or an effective bioabsorbent pertinent to the treatment of the industrial waste water or the desalinization of seawater. (6) Applying polysaccharides for an effective ingredient of pharmaceuticals, healthcare foods, and cosmetics. Polysaccharides have a wide immunoregulation function for the body, and so may be developed to be new humectants. In addition, they can combine with proteins in skin to form retentive gels. Also, they can form a protective membrane to prevent water in skin from evaporation, and so may be developed to be an effective ingredient of cosmetics. In conclusion, studies of polysaccharides from shrimps and algae will be quite prospective in future.

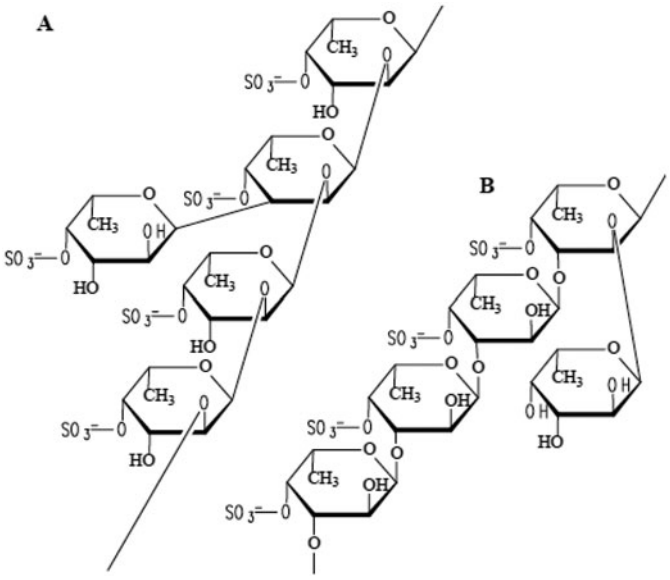

Figure 9 Fucoidan structures proposed by Percival (A) and by Patankar et al. (B).

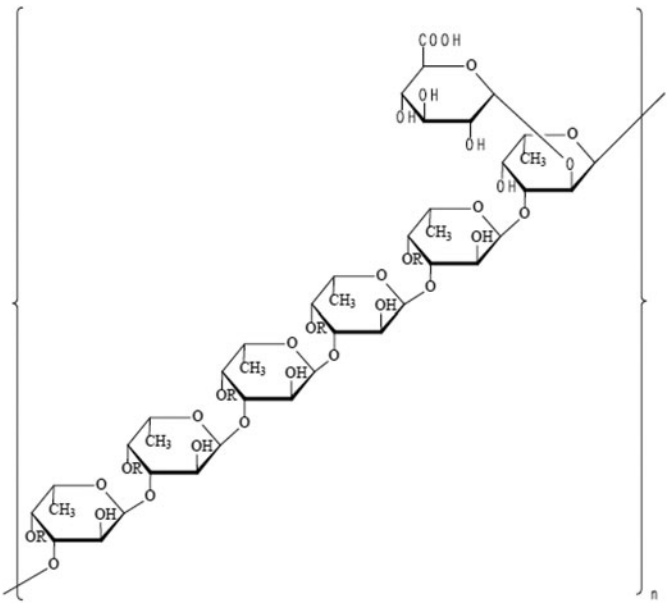

Figure 10 The structure of fucoidan from *Cladosiphon okamuranus*.

TRACE ELEMENTS

Studies on trace elements from marine algae focus on their enrichment capacity, but the mechanism of this process is somewhat unclear due to its complication till now (Chen et al., 1999). Selenium is a rare element and has been regarded as an essential trace element for the human body until 1970 year. It can destroy the aflatoxin to prevent cancer diseases. It can also scavenge too many free radicals in the body, and so has a strong antioxidative capacity (Huang, 1996). Furthermore, supplementing selenium in the diet has an important role in preventing tumors and the cardiovascular disease and keeping the balance of the blood pressure. Thus, it is an important trace element that was studied most early on its enrichment by algae. In China, the study of selenium is still the hot topic because of the outbreak of the Keshan disease due to the lack of it in Xinjiang district. Huang et al. (2002) obtained optimal selenium-enriching conditions of *S. platensis*: selenium concentration 300 mg/L and sodium carbonate 16.8 g/L. Under these conditions, the total content of selenium is up to 460 μg/g, 80% of which is organic selenium. Li et al. (2001a,b) cultured *S. platensis* in a selenium-enriching medium, and studied in detailed the effect of the selenium concentration and sulfite on its growth and the effect of the selenium enrichment on molecular functional groups of *S. platensis* cells. They found that selenium could prompt the growth of *S. platensis* and enhanced its biomass when the concentration of selenium was 0.02 to 40.00 mg/mL. Furthermore, the enriching ability of *S. platensis* to selenium increases when the concentration of the selenium increases. The enrichment process does not damage molecular functional groups of *S. platensis* cells. Wang et al. (1997) investigated the effect of the selenium on the growth of *D. salina* and the selenium distribution in cells. They pointed out that the growth of *D. salina* was closely related to the concentration of selenium and culture times. When the concentration of selenium in the culture broth is lower than 100 mg/mL, the growth of *D. salina* is not affected at the former stage, but is to some extent inhibited at the later stage. When the concentration of the selenium is over 100 mg/mL, its growth is inhibited significantly at the later stage, but it is not toxic to the cells of *D. salina*. Zhou et al. (1997) studied the effect of different selenium concentrations on the growth of *S. maxima*. They found that selenium could promote its growth at less than 40 mg/mL and the optimal concentration of it was 12 mg/mL. The growth inhibition presents when its concentration is over 60 mg/mL and algal cells die at more than 400 mg/mL of selenium.

Zinc is another trace element with an important physiological function and a less toxicity. It participates in many metabolic processes, such as metabolisms of carbohydrates, lipids, proteins, and nucleic acids. It also keeps the completeness of the structure of cell membranes. In addition, it is an important ingredient or an activator of many metal enzymes and also essential for keeping activities of DNA or RNA polymerase. Chen et al. (1998) reported the content of zinc in two algal strains *S. platensis* and *Pavlova viridis*. They pointed out that when *S. platensis* and *P. viridis* were subject to the enrichment of zinc, the contents of zinc in two strains were up to 371.2 μg/g and 110.3 μg/g, respectively. However, the growth rate of them and the activity of the nitrite reductase are slightly lower compared to those of the control strains (not adding zinc). Zhang et al. (2006) studied the effect of the zinc concentration on the proliferation of *Microcystis aeruginosa* and *Fragilaria*. The result showed that the proliferation of *Microcystis aeruginosa* was quick when the concentration of zinc was within the range of 0.02 to 1.00 μg/mL, but inhibited significantly when its concentration was over 100 μg/mL. The proliferation of *Fragilaria* is quick at 0.02 μg/mL of zinc, but is to some extent inhibited when its concentration is over 10 μg/mL. *Pavlova viridis* has a high tolerance to zinc, and can grow quickly at a higher concentration (40 mg/L). However, the superfine structure of cells in the zinc-enriching algal strain (*P. viridis*) varies, and so do the physiological and biochemical characters, including activities of some reductases and the biomass, etc. The highest zinc-enriching content of the enriched algae is 11.03×10^4 mg/kg, and it is 1107-fold higher than that of the primitive one (Chen et al., 1998).

Chromium (Cr^{3+}) is an essential trace element for human body and plays an exceptionally important role in the glycometabolism and lipid metabolism. It can also lower the content of cholesterol and triglycerides to prevent cardiovascular diseases, and is also a stabilizer of DNA or RNA for preventing some genes from mutagenesis. It should point out that Cr^{3+} is beneficial to the human body's health, whereas Cr^{6+} is toxic. Zhang et al. (2003) determined the effect of the Cr^{3+} concentration on the biomass, the content of protein, the content of β-carotene, and the content of the soluble sugar of *D. salina*. They found that the addition of Cr^{3+} at a low or middle concentration during microalgal culture might enhance their contents, and hence improved the nutritional quality of *D. salina*. The contents of proteins, carotenes and soluble sugars in *D. salina* are 3.6%, 3.93%, and 2.38% higher than those in the control strain, respectively. *Spirulina* has a strong absorption and enrichment ability to Cr^{3+}. The inorganic Cr^{3+} can be transformed into the organic one that can combine with proteins in cells. This is a quite complicate biochemical process that is affected by the enrichment time, the Cr^{3+} source and concentration, the density of *Spirulina*, pH, temperature, light, etc. The bioenrichment process of Cr^{3+} by *Chlorella vulgaris* and its mechanism were studied in detailed (Chen et al., 2003). It has the strongest bioenrichment ability for Cr^{3+} at 72 hours of the culture and pH 4.5–5.0. This process includes the surface absorption and the active passport. The surface absorption is predominant at inhibition and death stages of *C. vulgaris*, and the active passport is predominant at logarithm and steady stages. Li et al. (2003) made a study on factors that affected Cu^{2+} absorption by *Dicrateria zhanjiangensi*. They found that this process had a positive correlation with Cu^{2+} concentration and the absorption capacity increased with the increase in the density of algal cells. Wu et al. (2001) studied absorption processes of Cu^{2+} by *Chlorella pyrenoidosa*, *Scenedesmus obliquus*, and *Closterium lunula* and

Table 4 Carotenoids in marine organisms

Carotenoids	Marine organisms
α-Carotenoid	*Rhizosolenia*
β-Carotenoid	Green algae, *Phaeophyta*
Echinenone	Sea urchin
Astaxanthin	Crustacean, *Echinoderm*
Astacim	Crustacean
Fucoxanthin	*Phaeophyta*
Xanthophyll	Red algae
Neoxanthin	*Rhizosolenia*
Ioroxanthin	*Cladophora oligoclona*
Myxoxanthin	Blue algae

found that these processes were a dynamic balance. Cao and Hu (1996) studied the Ca^{2+}-fortified process by *Spirulina*. Chen et al. (1993) studied the effect of Fe^{3+} on the growth of marine *Diatom*.

NATURAL PIGMENTS

With the rapid development of food industry, edible natural pigments are no longer satisfied with its requirement. Furthermore, synthetic ones are toxic for human health if taken up for a long time (Mekkawy et al., 1998). Therefore, it is quite enormously prospective to develop edible natural pigments from marine organisms. Main natural pigments from marine organisms are carotenoids, chlorophyll, and phycocyanobilin. Carotenoids are distributed in nature and more than 400 species of them have a definite chemical structure. Chemical structures of some carotenoids are listed in Fig. 11 (Urich, 1994). They are a precursor of vitamin A and can be transformed to be it in human body (Parajo et al, 1998b). Carotenoids which are abundant in marine organisms are listed in Table 4. In addition, carotenoids whose end groups are 1, 2, 5- or 1, 2, 3-trimethylphenyl group are also found in marine algae.

In recent 20 years, astaxanthin has been one of the important carotenoids that are studied most widely (Higuera-Ciapara et al., 2006). Its chemical name is 3, 3′-dihydroxyl-4, 4′-diketone-β-carotenoid, and the molecular formula is $C_{40}H_{52}O_4$. Given that each molecule has two chiral centers in C-3 and C-3′, astaxanthin may present three configurational isomers: two enantiomers (3R, 3′R and 3S, 3′S) and a meso form (3R, 3′S) (Fig. 12) (Osterlie et al., 1999; Turujman et al., 1997). Among all these isomers, the 3S, 3′S is the most abundant in nature (Parajo et al., 1996). The synthetic astaxanthin consists of a racemic mixture of the two enantiomers and the meso form (Turujman et al., 1997). Astaxanthin was separated firstly from shells of shrimps in 1930, and has been subject to extensive researches since 1980s owning to its obvious biological functions: enhancing the immunity, protecting the retina from radiation, antioxidization, antiinflammation, and preventing the blood LDL-cholesterol from oxidization (Wei and Yan, 2001). It has also been reported that the astaxanthin attenuates the liver metastasis induced by stress in mice thus promoting the immune response through the inhibition of lipid peroxidation (Kurihara et al., 2002). Kang et al. (2001) also reported that the synthetic astaxanthin protected the rat liver from damage induced by CCl_4 through the inhibition of lipid peroxidation and the stimulation of the cell antioxidant system. In addition, the effect of the astaxanthin and other carotenoids on the proliferation of human breast cancerous cells has also been studied in detailed. This study showed that β-carotene and lycopene were more effective than astaxanthin in inhibiting the proliferation of MCF-7 cell lines in vitro (Li et al., 2002). Gradelet et al. (1998) evaluated the antioxidative ability of the astaxanthin, and found that it had a function of notably reducing the accumulation of peroxide. Iwamoto et al. (2000) performed in vivo and ex vivo studies and their results suggest that the astaxanthin inhibits the oxidation of LDL which presumably contributes to the arteriosclerosis prevention. Miki et al. (1998) proposed the manufacture of a drink containing the astaxanthin whose antioxidant action on LDL would be useful for the prevention of arteriosclerosis, ischemic heart disease, or ischemic encephalopathy. While it is feasible that the oxidation of LDL may be decreased by the antioxidant consumption, more researches are needed to establish the true effect on the coronary heart disease (Jialal and Fuller, 1995). The ability of the astaxanthin extracted from algae to protect against DNA damage by UV radiation has been shown in studies with cultured rat kidney fibroblasts (Lorenz and Cysewsky, 2000; O'Connor and O'Brien, 1998) and human skin cells (Lyons and O'Brien, 2002). Various astaxanthin supplements consisting of injectable solutions, capsules, or topical creams have been manufactured for sunburn prevention from UV exposure (Lorenz, 2002). The use of astaxanthin and/or canthaxantin as pigmenting agents in aquaculture species has been well documented through many scientific publications for more than two decades (Meyers and Chen, 1982; Torrisen, 1989; Torrisen et al., 1981; Yamada et al., 1990; No and Storebakken, 1991; Putnam, 1991; Smith et al., 1992; Storebakken and No, 1992; Choubert and Heinrich, 1993; Coral et al., 1998; Bowen et al., 2002; Gouveia et al., 2002).

Chlorophyll exists widely in marine algae, especially in green algae. It is an important light-harvesting pigment in algae cells. All chlorophyll molecules are a porphyrin ring comprising four tetrapyrrole rings, inside which is a Mg^{2+} (Fig. 13) (Hosikian et al., 2010). Genetic analysis of the biosynthetic pathway of the chlorophyll *a* in algae was initiated in the mid-1940s by Granick, who isolated chlorophyll-deficient strains of *Chlorella* (Granick, 1948a, 1948b, 1950, 1953, 1961). These studies were complemented by the characterization of additional *Chlorella* mutants by Ellsworth and Aronoff in the late 1960s (Ellsworth and Aronoff, 1968a, 1968b, 1969; Falbel and Staehlin, 1994). Work with the green alga, *Chlamydomonas reinhardtii*, began in 1955 (Sager, 1955), and it has become the model organism for genetic analysis of chlorophyll *a* biosynthesis in algae. One of the first detailed studies of a chlorophyll biosynthesis mutant of *C. reinhardtii* was performed by Ruth Sager, who used the mutant *y–l* to help define the nuclear inheritance patterns of this organism (Sager, 1955, 1959). *y–l* mutants exhibit a "yellow in

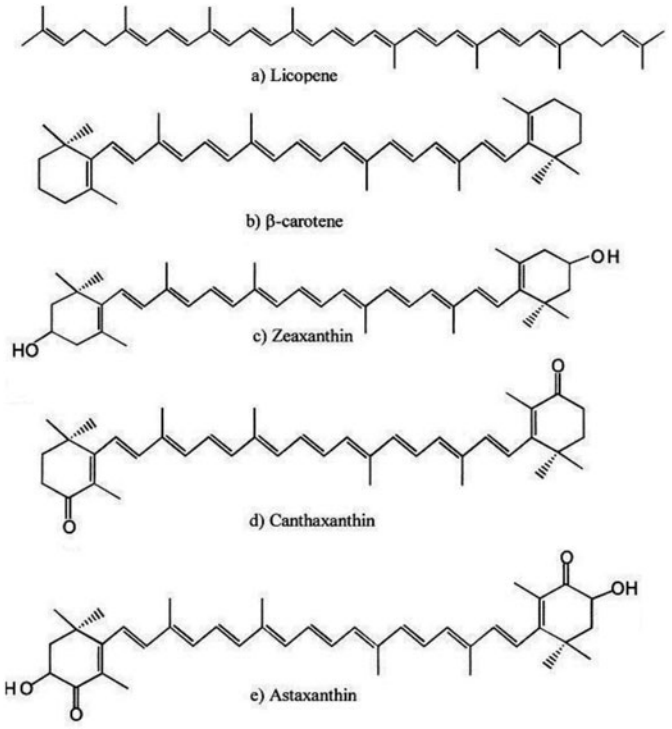

Figure 11 Chemical structures of some carotenoids.

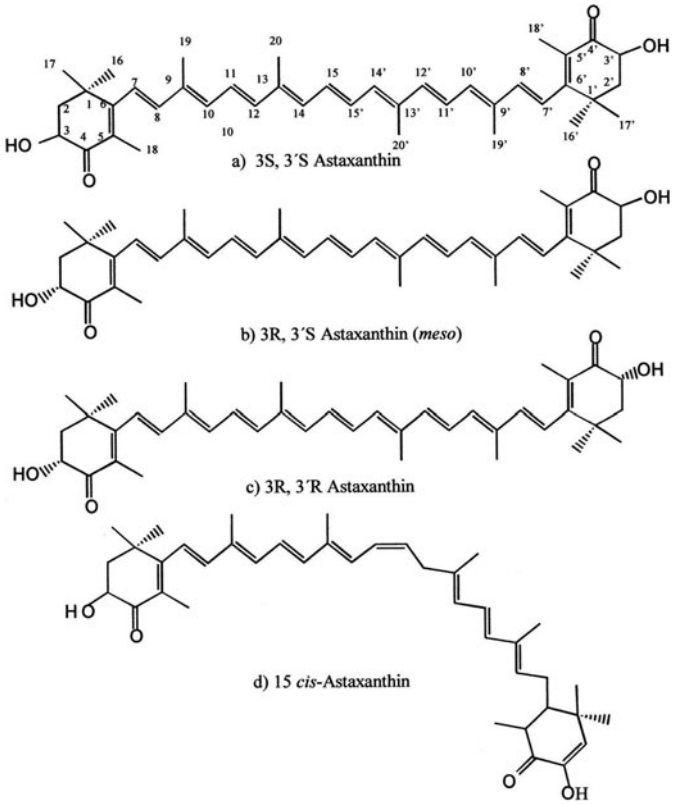

Figure 12 Astaxanthin configurational isomers (a–c) and a geometric *cis* isomer (d).

the dark" phenotype as a result of dark accumulation of protochlorophyllide, although these cells are still capable of synthesizing chlorophyll in the light. Despite many attempts over the years, no additional loci with a similar phenotype were identified, until Ford and Wang described a series of temperature-sensitive mutants that were generated by UV mutagenesis (Ford and Wang, 1980a, 1980b; Ford et al., 1981). Their work led to the identification of six more nuclear loci with similar "yellow in the dark" phenotypes, as described for *y–l*. A set of brown mutants (*br*), also isolated by Wang et al. (1974), accumulate protoporphyrin IX that presumably contains a defect in

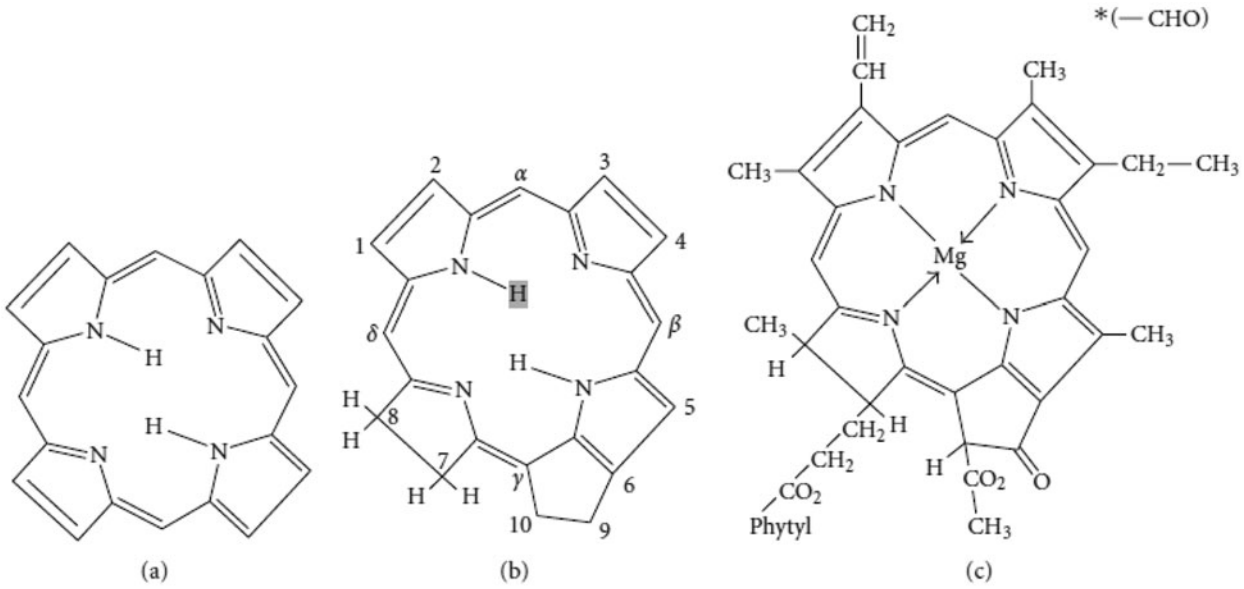

Figure 13 Chemical structures of chlorophyll and its constituents. (a) Porphyrin macrocycle. (b) Phorbin. (c) Chlorophyll *a*. Chlorophyll *b* is a variant with the methyl group in position 3 being replaced by a formal group.

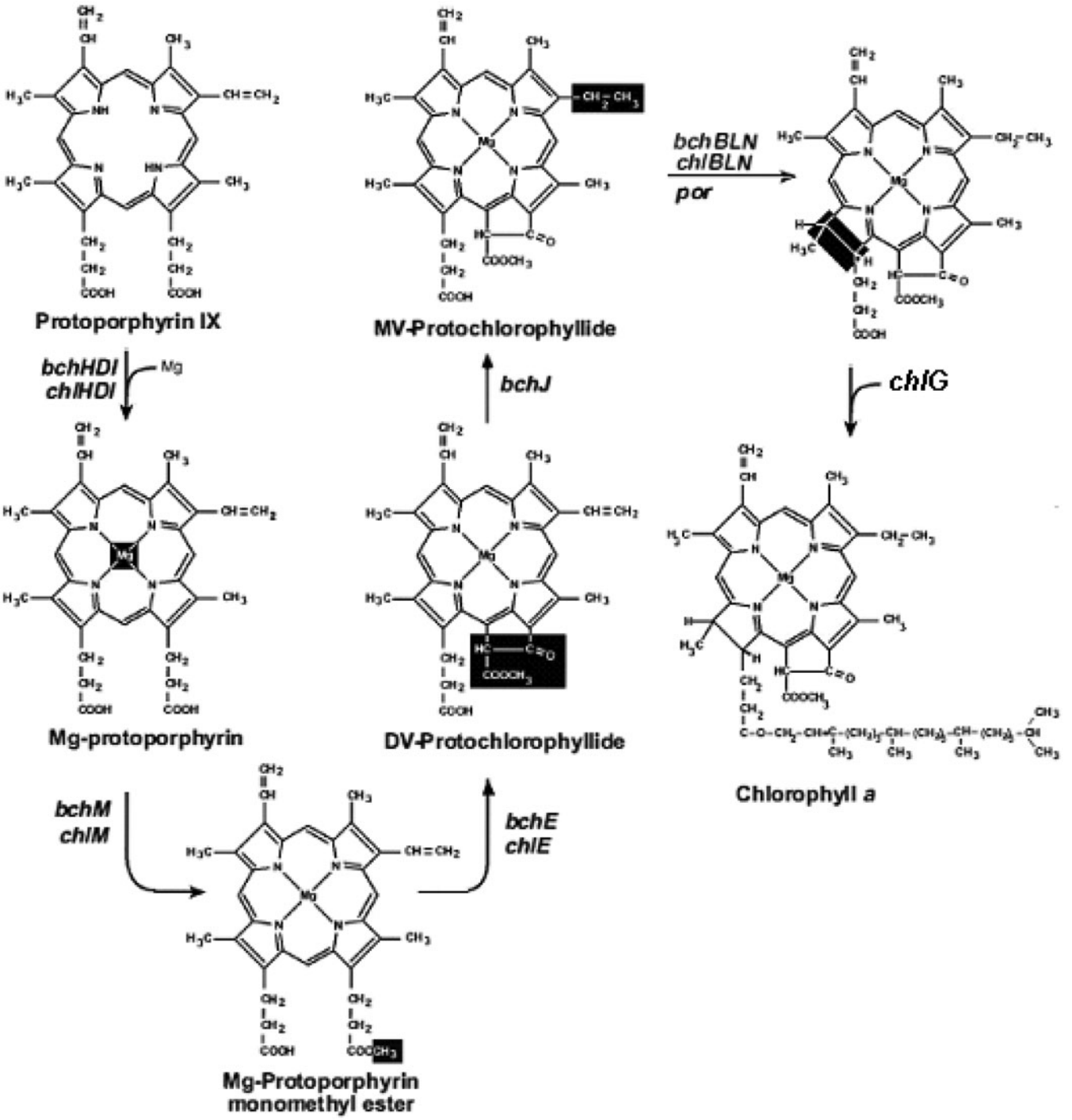

Figure 14 The Mg-branch of the chlorophyll *a* biosynthetic pathways. Modifications of the tetrapyrrole ring at various stages of the pathway are highlighted with a black box. Genetic loci that affect individual steps of the pathway are also indicated above the arrows.

Mg-chelatase. The development of mutagenesis techniques that allow the creation of nuclear insertion mutations in *C. reinhardtii* should facilitate the cloning of some of these nuclear-encoded *y* and *br* loci in the future. The utility of such an approach is highlighted by the cloning of nuclear genes from *C. reinhardtii* that are involved in the flagellar biosynthesis (Tam and Lefebvre, 1993). The biosynthetic pathway of the chlorophyll *a* in algae is presented in Fig. 14. In China, the chlorophyll is prepared mainly from marine algae, such as *S. platensis*. When it is used to produce the edible pigment, Mg^{2+} is replaced by Cu^{2+}. The resultant chlorophyll-Cu^{2+} reacts with Na^{+} to form the final chlorophyll–Cu–Na salt.

Phycocyanobilin is a brilliant blue pigment and prepared from marine blue algae. It often exists in the form of the

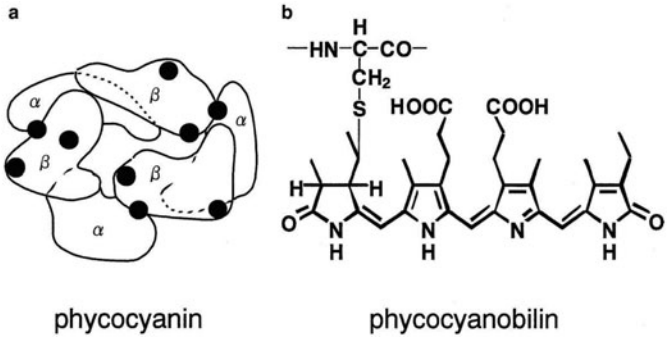

Figure 15 Structures of phycocyanin and phycocyanobilin. Phycocyanin is a tightly associated $\alpha\beta$ heterodimer in which each subunit carries bilin(s) thioether linked to particular cysteinyl residues.

conjugated protein (phycobiliprotein) in nature (Fig. 15). With the development of single cell protein (SCP) from algae, phycocyanobilin has also been used widely in fields of the medicine, pharmaceutical, chemical industry, and medicinal diagnose (Liu et al. 2000). Ceng et al. (1986, 1992) found that it had a strong inhibitory function to cancer cells and a good therapy effect to diabetes. Owning to its strong florescence and easy combination with the isotope and biotin, phycocyanobilin can be developed to be the florescence probe that has deserved more attention in china in recent 10 years. We carried out a series of researches about the molecular recombination of phycocyanin from *S. maxima* in *E. coli* into which five genes from its biosynthetic pathway were transformed. Properties of the expressed phycocyanin are the same as those of the natural one, but the content of it in *E. coli* is 5.7-fold higher than that in *S. maxima*. It was found that the expressed phycocyanin had a strong induction of apoptosis of human carcinoma COLO 205 cells. The apoptotic process is associated with the Bax/Bcl-2 ratio upregulation, cytochrome *c* release, mitochondrial membrane depolarization, and caspase-9 activation (Lu et al. 2009; Yu et al., 2009; Lu et al., 2011). These lay a good foundation for the potential application of it as a novel anticancer pharmaceutical in future.

CONCLUSIONS

The purpose of this review is to introduce critically and comprehensively present future situations of bioactive substances from marine fishes, shrimps, and algae and their function. It will provide the elaborate information for researchers and other persons pertinent to final products containing these bioactive substances. With the improvement of research approaches, studies on these bioactive substances will become deeper. We believe that these will become a trend in future.

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