CHAPTER 9

Medicinal Benefits of Marine Invertebrates: Sources for Discovering Natural Drug Candidates

Mahanama De Zoysa[1]

Contents

Abstract

Marine invertebrates are one of the major groups of organisms, which could be diversified under the major taxonomic groups of Porifera, Cnidaria, Mollusca, Arthropoda, Echinodermata, and many other minor phyla. To date, range of medicinal benefits and a significant number of marine natural products (MNPs) have been discovered from marine invertebrates. Seafood diet from edible marine invertebrates such as mollusks and crustaceans has been linked with various medicinal benefits to improve human health. Among marine invertebrates, spongers from phylum Porifera is the most dominant group responsible for discovering large number of

College of Veterinary Medicine, Chungnam National University, Yuseong-gu, Daejeon, Republic of Korea
[1] Corresponding author: Mahanama De Zoysa, *E-mail address:* mahanama@cnu.ac.kr

Advances in Food and Nutrition Research, Volume 65
ISSN 1043-4526, DOI: 10.1016/B978-0-12-416003-3.00009-3

MNPs, which have been used as template to develop therapeutic drugs. MNPs isolated from invertebrates have shown wide range of therapeutic properties including antimicrobial, antioxidant, antihypertensive, anticoagulant, anticancer, anti-inflammatory, wound healing and immune modulator, and other medicinal effects. Therefore, marine invertebrates are rich sources of chemical diversity and health benefits for developing drug candidates, cosmetics, nutritional supplements, and molecular probes that can be supported to increase the healthy life span of human.

I. INTRODUCTION

Marine ecosystem has a higher diversity of living organisms compared to the land that provides numerous resources to human societies (Hill and Fenical, 2010). Marine invertebrates are a diverse group having habitats in all ocean ecosystems, ranging from intertidal zone to the deep sea environments. Animals belong to marine invertebrates are composed of different taxonomic groups, which can be classified into several major phyla, namely, Porifera (sponges), cnidaria (corals, sea anemones, hydrozoans, jellyfish), annelida (Polychaetes, marine worms), bryozoa (moss animals or sea mats), mollusca (oysters, abalones, clams, mussels, squids, cuttlefish, octopuses), arthropoda (horseshoe, lobsters, crabs, shrimps, prawns, crayfish), and echinodermata (sea stars, sea cucumbers, sea urchin) (Thorpe *et al*., 2000). Historically, the dietary and medicinal uses of marine invertebrates were recorded in various literatures of different countries and communities (Gopal *et al*., 2008; Lev, 2003; Yesilada, 2005). The most notably the ''father of modern medicine,'' Hippocrates has described the use of various marine invertebrates, their ingredients, and therapeutic effects on human health (Grammaticos and Diamantis, 2008; Voultsiadou, 2010; Voultsiadou and Vafidis, 2007). Marine invertebrates account nearly 40% of the world fishery trade, and sea foods obtained from them are highly recognized for health benefits and wellbeing that have been attributed to higher amounts of polyunsaturated fatty acids, various peptides, minerals (selenium and iodine), and other bioactive compounds such as carotenoids and taurine (Borresen, 2009; Caddy, 1989; Erwin *et al*., 2010; Harris *et al*., 2009; Larsen *et al*., 2011; Voultsiadou, 2010).

In 1951, the pioneering work related to nucleosides spongouridine and spongothymidine from the Caribbean sponge *Tethya crypta* (formerly *Cryptotethya crypta*) has introduced new era on drug discovery from marine invertebrates (Bergmann and Feeney, 1951). Thereafter, marine invertebrates are increasingly being selected for screening of bioactive marine natural products (MNPs) to develop new therapeutic agents (Hill and Fenical, 2010; Pawlik, 1993). A recent study conducted by Hu *et al*. (2011)

described that nearly 20,000 MNPs have been isolated from all marine organisms to date and around 75% of that are from marine invertebrates. The most common chemical classes of natural products are belonging to terpenoids, steroids, alkaloids, ethers, phenols, strigolactones, and peptides which all are greatly isolated from marine invertebrates compared to marine plants and microorganisms (Hu *et al.*, 2011). Compounds or extracts obtained from marine invertebrates have shown antiviral, antibacterial, antifungal, antiprotozoal, anthelmintic, anti-inflammatory, antihypertension, anticancer, antituberculosis, and immune modulatory properties, and these candidate molecules lead to enter research pipelines that targeted to develop novel therapeutic agents (Blunt *et al.*, 2004, 2007; Erwin *et al.*, 2010; Folmer *et al.*, 2008; Jha and Zi-rong, 2004; Mayer *et al.*, 2009; Newman and Cragg, 2004; Riguera, 1997; Rinehart *et al.*, 1981; Smith *et al.*, 2010). More importantly, MNPs isolated from marine invertebrates are being evaluating different levels of clinical trials at present and few of them may enter into commercial scale as marine-derived drugs. It is further reported that among the 13 clinically testing MNPs, 12 of them are new drug candidates from marine invertebrates (Thomas *et al.*, 2010). Also, recent trends in MNPs research have reached to set another important stage by developing MNPs database which contains over 12,000 novel compounds isolated from marine organisms (http:momdc.sysu.edu.cn). Additionally, present status of marine-derived compounds that are either been approved by Food Drug Administration (FDA) or are in different phases of clinical pipelines is available at http://marinepharmacology.midwestern.edu/clinPipeline.htm.

Sample collection is the first and one of the most important steps to be considered during natural product drug discovery programs. It is hypothesized that taxonomic diversity correlates to chemical diversity of natural products (Williams, 2008). Therefore, marine ecosystem offers unlimited sources of marine invertebrates to isolate new bioactive compounds under diversified chemical spectrum, which are potent templates for drug discovery. However, researchers need to have a sound understanding about the most potential marine invertebrates for developing health foods or therapeutic agents. Even though there have been a number of recent reviews illustrating MNPs related to their chemical structure, biological function, and applications (Bugni *et al.*, 2008; Erwin *et al.*, 2010; Hill and Fenical, 2010; Hu *et al.*, 2011; Mayer *et al.*, 2009; Voultsiadou, 2010), it is important to update the species of marine invertebrates, which are potential sources for medicinal foods and MNPs for selecting drug candidate species more systematically. However, the research effort on marine drug discovery has not been equally distributed among taxonomic groups. Moreover, discussing on medicinal benefits of these animals will be aimed to introduce new types of invertebrates, which can consume or otherwise use for commercial applications in future. This chapter aims to focus the medicinal benefits, bioactive MNPs, and therapeutic properties

of some of the marine invertebrates' phyla such as Porifera, cnidaria, bryozoa, mollusca, arthropoda, and echinodermata. It is also discussing on marine invertebrates as potential sources for discovering natural drug candidates. This approach allows researchers to culture the most promising and demanded groups of marine invertebrates for the production of MNPs.

II. PHYLUM PORIFERA

Spongers from phylum Porifera are the most primitive, evolutionarily ancient metazoan animals. Although spongers are not using as human food, particular sponge species such as *Spongia officinalis* are roasted to produce syrups for homeopathic treatments (Sipkema *et al.*, 2005). Sponges are the major contributing species among invertebrates for discovering MNPs, as they are one of the richest animals with natural secondary metabolites (Belarbi *et al.*, 2003; Blunt *et al.*, 2007; Hu *et al.*, 2011). Hence, they have been regarded as a gold mine and future miracles of sea during the past 50 years (Sipkema *et al.*, 2005). Sponges are simple multicellular animals attached to a substrate and distributed mainly in tropical and temperate waters (Hentschel *et al.*, 2002). Nearly 15,000 sponges have been identified and majority of them belong to be in marine water. Sponges are grouped in three major classes, namely, Calcarea, Demospongiae, and Hexactinellida (Fieseler *et al.*, 2004). They are filter feeders and have unique feeding system, which contains numerous tiny pores on body surface. It facilitates higher chances to intake, and circulates the water with various ions, microorganisms that support for producing secondary metabolites in their body. However, they play an important role in the food chains at intermediate level, as sponges are eaten by other marine animals like chitons, snails, crustaceans, and fish (Meylan, 1990).

Since ancient time, spongers have been used for enhancing of blood coagulation, treating wounds, bone fractures, dropsy, stomach disorders, and other infectious diseases showing that they have being continuously applying in human medicine (Gopal *et al.*, 2008; Sipkema *et al.*, 2005). Large-scale screening of marine spongers for MNPs has been conducted massively. As few examples, it was reported that 37 unidentified sponge species from total of 71 species have antimicrobial properties, in which samples were isolated from west coast of Baja California and Gulf of California (Rinehart *et al.*, 1981). It was revealed that 28% of the sponge samples (from total 302 species) collected from New Zealand, Antarctica, and Western Samoa has shown antimicrobial activity (Munro *et al.*, 1989). The most reported therapeutic properties of MNPs from sponge include antiviral (Cutignano *et al.*, 2000; Martinez *et al.*, 2008), antibacterial (Amade *et al.*, 1987; Andersson *et al.*, 1983; Linington *et al.*, 2006; Lippert

et al., 2003; Tadesse *et al*., 2008; Volk and Kock, 2004), antifungal (Phillipson and Rinehart, 1983), antiparasitic (Capon *et al*., 2005), antitumor (Schwartsmann *et al*., 2001), and anti-inflammatory (Fakhr *et al*., 2006). Cytarabine drug used for treating leukemia and lymphoma patients was developed based on C-nucleosides isolated from Caribbean sponge *C. crypta* (Schwartsmann *et al*., 2001). Sipkema *et al*. (2005) have summarized bioactive compounds and products from the marine spongers with relation to their various therapeutic properties which show the remarkable potency of sponge-derived medicinal drugs.

The important question is which factors associated with availability of higher MNPs particularly in sponges. Mainly, it is believed that sponges have been emerged for 700–800 million years ago, and early appearance has supported them to develop diversified, complex, and advance defense system against their pathogens and predators through these MNPs (Belarbi *et al*., 2003; Sipkema *et al*., 2005). Another important fact is that sponges maintain numerous symbiotic relationships between other marine organisms including bacteria, fungi, and microalgae, which associations are involved in the biosynthesis of range of MNPs (Lee *et al*., 2001; Thomas *et al*., 2010). Sponge-bacteria or fungal associations have yielded large number of biologically active compounds such as acetic acid-butyl-ester (antimicrobial), chloriolin B (antitumor), oleic acids (anti-inflammatory), sorbicillactone A (anti-HIV), and roridin A (antileukemic) (Thomas *et al*., 2010). These finding are very promising, as identifying specific sponge species and related symbiosis relationships can enhance the production of these compounds through mariculture. Antiviral compounds Ara-A and anticancer Ara-C (cytarabine) are two marine sponge (*C. crypta*)-derived compounds currently using as commercial drugs (Newman and Cragg, 2007). As a summary, results discussed in large number of studies greatly proved that marine sponges are promising source for the discovery of therapeutic drugs and large number of sponge species have not been screened for their potential yet.

III. PHYLUM CNIDARIA

Invertebrate animals such as corals, jellyfish, and sea anemones are belonging to phylum Cnidaria. Corals are used as an ingredient in traditional medicine for treating various diseases such as pulmonary tuberculosis, asthma, chronic bronchitis, urinary diseases, and cancer (Gopal *et al*., 2008). Corals contain mostly Ca and minor amounts of Mg, Fe, and P. Calcined corals or calcium extracted from marine corals have shown effective as therapeutic agent for controlling cancer, diabetes, and many other deadly diseases. Corals with high species diversity in the tropical oceans are often rich in bioactive molecules and preferential

targets in drug discovery (Sammarco and Coll, 1992). In 1969, natural source of prostaglandins was first discovered in coral *Plexaura homomalla* (Weinheimer and Spraggins, 1969). The discovery of prostaglandins has greatly contributed to realize the potential and importance of corals as rich source of MNPs. Antimicrobial activities have been reported from different species of corals such as *Xenia macrospiculata* (Kelman *et al*., 2006), *Alcyonium digitatum* (Andersson *et al*., 1983, 2005; Tadesse *et al*., 2008), and *Alcyonium paessleri* (Slattery *et al*., 1995). Fluorescent proteins of seven Caribbean hard coral species have shown significantly higher H_2O_2 scavenging activity indicating their antioxidant potential to reduce the oxidative stress caused by reactive oxygen species (Palmer *et al*., 2009). Corals of genus *Montipora* contains high levels of acetylenic compounds and proved to process antimicrobial and cytotoxic properties. More than 10 diacetylene compounds have been isolated from the stony coral *Montipora* spp. which are cytotoxic against human lung, ovarian, skin, and colon cancer cells (Alam *et al*., 2002). Based on various other Cnidarians, derived MNPs indicate that they have open wide area to conduct further research for extracting new bioactive materials.

Jellyfish has been consuming as a food for more than 1000 years in the world. The processed jellyfish (dried) was first introduced by China for human consumption and recognized as one of Asia's top food with unique taste (Hsieh *et al*., 2001). Analysis of chemical composition of jellyfish has shown that it contains low levels of protein and calories, with less than 0.35mg/100g of cholesterol (Hsieh *et al*., 2001). Also, fresh jellyfish believed to be rich in minerals such as Na, Ca, K, and Mg (Hsieh *et al*., 1996). Based on the nutritional facts of jellyfish, it is considered as low-fat and cholesterol-free marine food. Collagen is the main protein ingredient in jellyfish, which acts as a major connective and building component of tissues, cartilages, and bones. Moreover, jellyfish has been effectively used for obtaining medicinal benefits against various types of diseases such as arthritis, hypertension, ulcers and improving digestion, and skin condition. Also, powder of jellyfish has strong curing power of burning damage (Hsieh and Rudloe, 1994). However, the exact bioactive molecules associated with jellyfish medicinal effects are largely unknown, yet suggesting that further investigating of medicinal values and MNPs can have higher chances to discover natural drug candidates for these diseases.

IV. PHYLUM BRYOZOA

More than 5700 bryozoans species have been recorded and most of them are marine sessile species (Montoya-Cadavid *et al*., 2007). Lesser number of MNPs have been identified from phylum Bryozoa compared to other

main invertebrates (Jha and Zi-rong, 2004). Two novel nematocidal compounds, (brominated alkaloids) named as convolutindol A and convolutamine H, have been isolated from marine bryozoan *Amathia convoluta* extracts (Narkowicz *et al*., 2002). Most of the MNPs isolated from bryozoans are belonging to group of alkaloid chemicals (Blunt *et al*., 2004). Bryozoan *Bugula neritina* grows in upright and branching tufts up to 15 m, which is a rich source of anticancer compounds named as bryostatins (Davidson and Haygood, 1999). However later, it was reported that symbiosis bacteria such as *Candidatus Endobugula sertula* could be the main source of bryostatins. It was explained by growing *B. neritina* colonies in the laboratory conditions with antibiotic treatments (to reduce the symbiosis bacteria population) that finally resulted in the reduction of bryostatin production (Davidson *et al*., 2001). Until today, 20 different bryostatins have been synthesized and some of them are under clinical trials for the treatments against cancer and Alzheimer's disease (Hale and Manaviazar, 2010). Moreover, in animal models, it has been acted as a memory enhancing agent (Kuzirian *et al*., 2006). If these clinical trials are successful, bryostatin originated from Bryozoans will become a commercial drug for treating different diseases.

V. PHYLUM MOLLUSKA

Mollusks are the second largest animal phylum on earth, and approximately 50,000 living marine species with estimated animals of 100,000–200,000 have been reported (Bouchet, 2006; Pechenic, 2000). They are belonged to eight taxonomic classes including Aplacophora, Monoplacophora, Polyplachophora (chitons), Scaphopoda (tusk shells and tooth shells), Gastropoda (abalones, sea slugs, sea snails, and sea hares), Bivalves (scallops, mussels, oysters, and clams), and Cephalopoda (squids, octopuses, cuttlefish, and nautiluses). It is estimated that about 90% of molluscan species are belonged to one class, the Gastropoda next followed by Bivalves (Ponder and Lindberg, 2008). Among them, gastropods, Bivalves, and cephalopods play important role as food source. Shelled mollusk species are widely used in traditional medicine compared with other groups of mollusks (Benkendorff, 2010). Whole-body or ground shell powders of mollusks with different combinations of other natural sources are common approach in traditional medicine.

Several reports have described the application of oyster shells for treating wound and healing urinary diseases (Gopal *et al*., 2008; Voultsiadou, 2010), osteoporosis (Fujita *et al*., 1990), headache, dizziness, and uterine bleeding (Yeung, 1983). Also, dietary supplement containing natural taurine has developed from Pacific oyster *Crassostrea gigas* powder for treating liver disorders, arthritis, and skin problems

(Aroma New Zealand Ltd., 2007). Lipid extracts of oyster *C. gigas* have shown anticancer properties (Kim *et al*., 2010). Antioxidant peptide purified from gastrointestinal digests of oyster *C. gigas* has shown protective effect of free radical-induced DNA damage (Qian *et al*., 2008). Experiments conducted using other animal models also have shown health benefits of oyster-derived products. Prevention of gastric ulcers and liver damage has been reported in rat by treating with oyster shell materials (Nie *et al*., 1994) and water extracts (Kimura *et al*., 1998), respectively.

Abalone is another important marine gastropod mollusk with high medicinal effects, therefore recommended to physically weak or sick patients. There are number of evidences for beneficial effects or bioactivities of abalone extracts that include antioxidant (Kim *et al*., 2006), anticancer (Lee *et al*., 2010; Uchida *et al*., 1987), antihypertensive (Kim *et al*., 2006), and anticoagulant (Kim *et al*., 2006). Immunomodulatory effects have been reported from abalone glycoprotein fraction separated from water extract (Uchida *et al*., 1987). Marine bivalve clam species are good source of anticoagulants. Sulfated polysaccharides with anticoagulant activities have been isolated from several clam species *Callista chione* (Luppi *et al*., 2005), *Anomalocardia brasiliana* and *Tivela mactroides* (Pejler *et al*., 1987), *Mercenaria mercenaria* (Jordan and Marcum, 1986), and *Tapes philippinarum* (Cesaretti *et al*., 2004). Also, two epidioxysterols isolated from hard clam *Meretrix lusoria* can induce the apoptosis in HL-60 cells and showed its potential for treating liver disease and hepatitis (Pan *et al*., 2007). Low-molecular-weight (620 Da) peptide with antioxidant activity was discovered from the sauce of fermented blue mussel *Mytilus edulis* (Jung *et al*., 2005). Marine invertebrates like oysters and mussels are fermented to make varieties of food sources, which contain considerably higher nutritional value and biological activities (Jung *et al*., 2005). It indicates that fermentation of marine invertebrates can further enhanced the potential of developing health foods and different bioactive molecules. Moreover, mollusks have different feeding habits such as predatory, herbivorous, and scavenging and filter feeding. Most of the mollusks consume large amount of micro- and macroalgae (seaweed) such as *Ecklonia*, *Laminaria*, and *Undaria*. These algae are also rich sources for various MNPs such as polysaccharides, glycoproteins which exhibit potent antimicrobial, anticancer, and antioxidant like therapeutic properties. Therefore, a visceral extract of the mollusks may contain algae-derived bioactive products, thus producing these marine foods with added health benefits.

Corn shell is carnivorous snail belongs to the world's largest genus of marine invertebrates (Conus) under the phylum of mollusks (Bingham *et al*., 2010). Corn shell species are able to secrete venom, which contains corn shell toxins (conotoxins) of bioactive peptides called as conopeptides (Layer and McIntosh, 2006). Different structural classes of

conopeptides belong to six super-families (A, M, O, P, S, and T) that have been identified from various conus species such as *Conus amadis*, *C. geographus*, *C. imperialis*, and *C. magus*, in which data were summarized in a recent review by Bingham *et al*. (2010). Conopeptides are being widely used in clinical as well as in biomedical research for developing analgesic, antinoceptive, anticancer, and cardio- and neuroprotective drugs (Han *et al*., 2008; Layer and McIntosh, 2006; Twede *et al*., 2009). Conopeptide isolated from mollusk *C. geographus* has been used to develop drug called Ziconotide/Prialt® which represent the first corn shell drug from marine invertebrate snail (Olivera *et al*., 1984). It is now in the list of FDA-approved drugs in the United States as well as in European Union for treating chronic pain. Moreover, there are few conotoxins candidates like conantokin-G, conantokin-T, and contulakin-G which are being under clinical phase of drug discovery (Bingham *et al*., 2010; Skov *et al*., 2007).

The sea hares are another potential mollusk group with reported pharmacologic substances (Kamiya *et al*., 2006). The sea hare species Aplysia and Dolabella have been shown to produce antibacterial molecules and cytotoxins (Yamazaki, 1993). Mainly, these bioactive molecules are reported from purple gland or immune response tissues which are involved in the host defense of these invertebrates (Melo *et al*., 1998; Rajaganapathi *et al*., 2002). The 60-kDa protein named as bursatellanin-P purified from purple fluid of sea hare *Bursatella leachii* has shown anti-HIV activity (Rajaganapathi *et al*., 2002). Dolastatins are cytotoxic peptides isolated from mollusk sea hare, *Dolabella auricularia*, which entered into phase II clinical trials as anticancer agents (Schwartsmann *et al*., 2001). Even though large number of bioactive products has been isolated from mollusks, there are only few approved drugs derived from MNPs isolated from marine mollusks.

As in all invertebrates, mollusks only have an innate immunity and do not develop adaptive immune reactions against pathogens. With higher pathogenic exposure from the environment, marine mollusks require to have efficient defense system through various immune components like antimicrobial peptides (AMPs). These AMPs are cationic and amphipathic peptides with low molecular mass that generally expressed constitutively and induced upon stress and pathogenic challenge to maintain efficient innate immune responses (Smith *et al*., 2008). Purified proteins or gene encoding for AMPs are being reported at significant phase due to rapid development of genomics in marine organisms. Researchers are continuously searching different AMPs, and their mechanisms of action using native proteins or purifying recombinant proteins since AMPs are alternatives to antibiotics. AMPs like defensins have been identified from various mollusks species including Pacific oyster, *C. gigas* defensins (Gonzales *et al*., 2007), American oyster *Crassostrea virginica* (Seo *et al*.,

2005), abalone *Haliotis discus discus* (De Zoysa *et al*., 2010), and Mediterranean mussel *Mytilus galloprovincialis* (Hubert *et al*., 1996). Several types of AMPs that are identified from various marine invertebrates including mollusk are summarized by Sperstad *et al*. (2011). Even though mollusk AMPs have shown strong activities against serious pathogens, development of mollusk AMPs for using clinical purposes needs further research. With the growing interest on MNPs and rapid development of biotechnology, various species of mollusks have become sources for isolating bioactive products and studying their medicinal values. However, many mollusk species have not been screened for their medicinal benefits to date, and with utilization of these new species of Phylum, mollusk can have unlimited potential for discovering novel drug candidates.

VI. PHYLUM ARTHROPODA

Arthropoda is the largest phylum of all living organisms and having members with characteristic exoskeleton and segmented bodies. Class Crustacea is the largest and the most economically important group of marine arthropods. Among them, crabs, shrimps, and prawns are some of the most attracted species and giving attention in relation to their use as health foods and various types of MNPs (Smith *et al*., 2008). New sources of marine crustacean such as krill species have been suggested for human consumption and to develop value added health food products due to presence of higher nutritional value (Tou *et al*., 2007). Higher fat consumption mainly with saturated fatty acids is linked with risk of cardiovascular diseases. But omega 3 polyunsaturated fatty acids, particularly eicosapentaenoic acids (EPA) and decosahexaenoic acids (DHA), are associated with reducing cardiovascular diseases. Analysis of nutrient composition has shown that marine crustaceans like shrimps and krills contain lower total lipids and higher protein, vitamin A, EPA, DHA than some selected fish (Tou *et al*., 2007).

Chitin is a polysaccharide primarily found in the exoskeleton of crustaceans. It is the main raw material of chitosan, which both have wide range of applications including dietary supplements, functional foods, drugs, cosmetics, antioxidants, and immune stimulants. Harish Prashanth and Tharanathan (2007) have reviewed the use of chitin and chitosan and their potential for medicinal benefits such as hemostasis, drug release, antitumor, anticoagulant, wound healing, antiulcer, antimicrobial, and immune modulatory agents. Biomedical and therapeutic importance of chitin and chitosan highlights the marine crustaceans as an important source of raw materials.

Crabs, lobsters, and shrimps are important sources for natural carotenoids, which are a group of fat soluble pigments such as astaxanthin,

canthaxanthin, cryptoxanthin and lutein. Presence of astaxanthin as a major carotenoid and higher levels of unsaturated fatty acids have been found in different crab species (Sachindra *et al*., 2005). Carotenoids have shown antioxidant properties, and therefore, edible crustaceans are candidates for developing functional food ingredients. It was reported that astaxanthin is potential antiaging compound, while canthaxanthin could be used for treating cancer, stroke, high cholesterol, and Parkinson's disease (Miyashita and Hosokawa, 2008).

Numerous types of AMPs from crustaceans are also isolated and evaluated for their ability to control pathogenic microorganisms. The first crustacean AMP of proline-rich cationic peptide was purified from the hemocytes of shore crab *Carcinus maenas* with activity against both Gram-negative and -positive bacteria (Schnapp *et al*., 1996). As an example, over 50 different sequences of crustin type AMPs have been reported from crabs, crayfish, and white shrimp. These crustins have shown to inhibit the growth of pathogenic bacteria such as *Staphylococcus aureus*, *Streptococcus iniae*, and *Bacillus* spp. (Smith *et al*., 2008). Hovingh and Linker (1982) have reported the presence of glucuronic acid-containing heparan sulfate in a species of Crustacea (lobsters) *Homarus americanus*. Numerous reports of marine crustaceans indicate their potential in health benefits and medical applications.

VII. LIMITATIONS OF MARINE INVERTEBRATES AS SOURCE FOR HEALTH FOODS AND DRUG CANDIDATES

There are several problems associated with medicinal foods and discovery of natural drug candidates from marine invertebrates. Even though large numbers of potential marine invertebrates are available as health foods, there is a high risk of biotoxins and environmental intoxicants on public health. Different toxic levels have been reported by consuming marine invertebrates including species of sea anemone, sea urchins, clam, mussels, oysters, abalone, squid, octopus, crab, and lobsters (Bagnis *et al*., 1970). Therefore, proper quality assurance is necessary for introducing marine invertebrates as health foods for human. However, those toxic marine organisms are potential sources of new pharmaceutical products. Also, drug discovery from marine invertebrates has been slowed due to lack of sufficient amounts of biological materials (Folmer *et al*., 2008). The sample collection from marine environment may be more difficult than terrestrial sources, although some animals are easily accessible (spongers) which can be collected by hand. The most commonly reported technical problem is the presence of large quantities of inorganic salts in the invertebrate extracts. Additionally, wide variation of chemical diversity within one type of source can exhibit different or opposite activities and

presence of major active compounds can mask the activity of minor molecules in the crude extracts. So that could be affected with low detection of bioactive molecules from crude extract of marine invertebrates during drug discovery screening programs (Bugni *et al.*, 2008). Another limitation is that it required very sensitive analytical tools, as the recovery of bioactive material is significantly low. Most of the invertebrates are maintaining symbiotic relationship with other organisms such as fungi, bacteria, and microalgae that could cause difficulties to find out exact origin of the bioactive material (Riguera, 1997). There were some controversial suspicions that MNP isolated from invertebrates may be produced by symbiotic microorganisms. In general, several limiting factors are associated and make it more complicated in the search of natural drug screening programs from marine invertebrates. In many occasions, MNPs isolated from invertebrates have shown excellent activities as therapeutic compound but unable to use as medicinal drug due to high toxicity or other side effects.

VIII. CONCLUSION

As summary, marine invertebrates have a wide range of biological activities with unique chemical structures. Also, focus of medicinal foods and drug discovery from marine invertebrates mainly have touched the tropical and temperate environments whereas large extents of polar area are unexploded yet. Therefore, it is necessary to identify potential species with specific parts or organs of the animal, where the bioactive molecules are abundant. Based on the present status, we can assume that these marine invertebrates will become sources of MNPs than any other terrestrial animal group to provide health benefits for developing drug candidates, cosmetics, nutritional supplements, and molecular probes that can be supported to increase the healthy life span of human.

REFERENCES

Alam, N., Hong, J., Lee, C. O., Choi, J. S., Im, K. S., and Jung, J. H. (2002). Additional cytotoxic diacetylenes from the stony coral *Montipora* sp. *Chem. Pharm. Bull. (Tokoyo)* **50**, 661–662.

Amade, P., Charroin, C., Baby, C., and Vacelet, J. (1987). Antimicrobial activities of marine sponges from the Mediterranean Sea. *Mar. Biol.* **94**, 271–275.

Andersson, L., Lidgren, G., Bohlin, L., Magni, L., Ogren, S., and Afzelius, L. (1983). Studies of Swedish marine organisms I: Screening of biological activity. *Acta Pharm. Suec.* **20**, 401–414.

Aroma New Zealand Ltd (2007). Company Profile and Product Specification. www.aromanz.com.

Bagnis, R., Berglund, F., Elias, P. S., Van Esch, G. J., Halstead, B. W., and Kojima, K. (1970). Problems of toxicants in marine food products. *Bull. World Health Organ.* **42**, 69–88.

Belarbi, E. H., Gomez, A. C., Chisti, Y., Camacho, F. G., and Grima, E. M. (2003). Producing drugs from marine sponges. *Biotechnol. Adv.* **21**, 585–598.

Benkendorff, K. (2010). Molluscan biological and chemical diversity: Secondary metabolites and medicinal resources produced by marine mollusks. *Biol. Rev.* **85**, 757–775.

Bergmann, W. and Feeney, R. J. (1951). Contributions to the study of marine products XXXII. The nucleosides of sponges. *J. Org. Chem.* **16**, 981–987.

Bingham, J. P., Mitsunaga, E., and Bergeron, Z. L. (2010). Drugs from slugs-past, present and future perspectives of ώ-conotoxin research. *Chem. Biol. Interact.* **183**, 1–18.

Blunt, J. W., Copp, B. R., Munro, M. H. G., Northcote, P. T., and Prinsep, M. R. (2004). Marine natural products. *Nat. Prod. Rep.* **21**, 1–49.

Blunt, J. W., Copp, B. R., Hu, W. P., Munro, M. H. G., Northcote, P. T., and Prinsep, M. R. (2007). Marine natural products. *Nat. Prod. Rep.* **24**, 31–86.

Borresen, T. (2009). Seafood for improved health and wellbeing. *Food Technol.* **63**, 88.

Bouchet, P. (2006). The magnitude of marine biodiversity. *In* ''The Exploration of Marine Biodiversity, Scientific and Technological Challenges'', (C. M. Duarte, Ed.), pp. 33–64. Foundation BBVA, Francewww.fbbva.es.

Bugni, T. S., Harper, M. K., McCulloch, M. W. B., Reppart, J., and Ireland, C. M. (2008). Fractionated marine invertebrate extract libraries for drug discovery. *Molecules* **13**, 1372–1383.

Caddy, J. F. (1989). Marine Invertebrate Fisheries: Their Assessment and Management. John Wiley and Sons, New York, p. 752.

Capon, R. J., Vuong, D., Lacey, E., and Gill, J. H. (2005). Echinobetaine A: Isolation, structure elucidation, synthesis, and preliminary SAR studies on a new nematocidal betaine from a southern Australian marine sponge, *Echinodictyum* sp.. *J. Nat. Prod.* **68**, 179–182.

Cesaretti, M., Luppi, E., Maccari, M., and Volpi, N. (2004). Isolation and characterization of a heparin with high anticoagulant activity from the clam *Tapes philippinarum*. Evidence for the presence of a high content of antithrombin III-binding site. *Glycobiology* **14**, 1275–1284.

Cutignano, A., Bifulco, G., Bruno, I., Casapullo, A., Gomez-Paloma, L., and Riccio, R. (2000). Dragmacidin F: A new antiviral bromoindole alkaloid from the Mediterranean sponge *Halicortex* spp. *Tetrahedron* **56**, 3743–3748.

Davidson, S. K. and Haygood, M. G. (1999). Identification of sibling species of the Bryozoan *Bugula neritina* that produce different anticancer bryostatins and harbor distinct strains of the bacterial symbiont ''*Candidatus Endobugula sertula*''. *Biol. Bull.* **196**, 273–280.

Davidson, S. K., Allen, S. W., Lim, G. E., Anderson, C. M., and Haygood, M. G. (2001). Evidence for the biosynthesis of bryostatins by the bacterial symbiont ''*Candidatus* Endobugula sertula'' of the Bryozoan *Bugula neritina*. *Appl. Environ. Microbiol.* **67**, 4531–4537.

De Zoysa, M., Whang, I., Lee, Y., Lee, S., Lee, J. S., and Lee, J. (2010). Defensin from disk abalone *Haliotis discus discus*: Molecular cloning, sequence characterization and immune response against bacterial infection. *Fish Shellfish Immunol.* **28**, 261–266.

Erwin, P. M., Lopez-Legentil, S., and Schuhmann, P. W. (2010). The pharmaceutical value of marine biodiversity for anti-cancer drug discovery. *Ecol. Econ.* **70**, 445–451.

Fakhr, I., Hamdy, N., Radwan, M., El-Batran, S., and El Shabrawy, O. (2006). Studies on the anti-inflammatory and analgesic effects of extracts from marine sponges. *Nat. Prod. Sci.* **12**, 74–78.

Fieseler, L., Horn, M., Wagner, M., and Hentschel, U. (2004). Discovery of the novel candidate Phylum ''*Poribacteria*'' in marine sponges. *Appl. Environ. Microbiol.* **70**, 3724–3732.

Folmer, F., Jaspars, M., Dicato, M., and Diederich, M. (2008). Marine natural products as targeted modulators of the transcription factor NF-κB. *Biochem. Pharmacol.* **75**, 603–617.

Fujita, T., Fukase, M., Miyamoto, H., Matasumoto, T., and Ohue, T. (1990). Increase of bone mineral density by calcium supplement with oyster shell electrolysate. *Bone Miner.* **11**, 85–91.

Gonzales, M., Gueguen, Y., Desserre, G., de Lorgeril, J., Romestand, B., and Bachere, E. (2007). Molecular characterization of two isoforms of defensin from hemocytes of the oyster *Crassostrea gigas*. *Dev. Comp. Immunol.* **31**, 332–339.

Gopal, R., Vijayakumaran, M., Venkatesan, R., and Kathiroli, S. (2008). Marine organisms in Indian medicine and their future prospects. *Nat. Prod. Rad.* **7**, 139–145.

Grammaticos, P. C. and Diamantis, A. (2008). Useful known and unknown views of the father of modern medicine Hippocrates and his teacher Democritus. *Hell. J. Nucl. Med.* **11**, 2–4.

Hale, K. J. and Manaviazar, S. (2010). New approaches to the total synthesis of bryostatin antitumor macrolides. *Chem. Asian J.* **5**, 704–754.

Han, T. S., Teichert, R. W., Olivera, B. M., and Bulaj, G. (2008). Conus venoms-a rich source of peptide-based therapeutics. *Curr. Pharm. Des.* **14**, 2462–2479.

Harish Prashanth, K. V. and Tharanathan, R. N. (2007). Chitin/chitosan: Modifications and their unlimited application potential. *Trends Food Sci. Technol.* **18**, 117–131.

Harris, M., Bruhn, C., Schor, D., Kapsak, W. R., and Blakistone, B. (2009). Communicating the net benefits of seafood consumption. *Food Technol.* **63**, 38–44.

Hentschel, U., Hopke, J., Horn, M., Friedrich, A. B., Wagner, M., Hacker, J., and Moore, B. S. (2002). Molecular evidence for a uniform microbial community in sponges from different oceans. *Appl. Environ. Microbiol.* **68**, 4431–4440.

Hill, R. T. and Fenical, W. (2010). Pharmaceuticals from marine natural products: Surge or ebb? *Curr. Opin. Biotechnol.* **21**, 777–779.

Hovingh, P. and Linker, A. (1982). An unusual heparin sulfate isolated from lobsters (Homarus americanus). *J. Biol. Chem.* **16**, 9840–9844.

Hsieh, Y. H. P. and Rudloe, J. (1994). Potential of utilizing jellyfish as food in Western countries. *Trends Food Sci. Technol.* **5**, 225–229.

Hsieh, Y. H. P., Leong, F. M., and Barnes, K. W. (1996). Inorganic constituent in fresh and processed cannonball jellyfish (*Stomolophus meleagris*). *J. Agric. Food Chem.* **44**, 3117–3119.

Hsieh, Y. H. P., Leong, F. M., and Rudloe, J. (2001). Jellyfish as food. *Hydrobiologia* **451**, 11–17.

Hu, G. P., Yuan, J., Sun, L., She, Z. G., Wu, J. H., Lan, X. J., Zhu, X., Lin, Y. C., and Chen, S. P. (2011). Statistical research on marine natural products based on data obtained between 1985 and 2008. *Mar. Drugs* **9**, 514–525.

Hubert, F., Noel, T., and Roch, P. (1996). A member of the arthropod defensin family from edible Mediterranean mussels (*Mytilus galloprovincialis*). *Eur. J. Biochem.* **240**, 302–306.

Jha, R. K. and Zi-rong, X. (2004). Biomedical compounds from marine organisms. *Mar. Drugs* **2**, 123–146.

Jordan, R. E. and Marcum, J. A. (1986). Anticoagulant active heparin from clam (*Mercenaria mercenaria*). *Arch. Biochem. Biophys.* **248**, 690–695.

Jung, W. K., Rajapakse, N., and Kim, S. K. (2005). Antioxidative activity of a low molecular weight peptide derived from the sauce of fermented blue mussel, *Mytilus edulis*. *Eur. Food Res. Technol.* **220**, 535–539.

Kamiya, H., Sakai, R., and Jimbo, M. (2006). Bioactive molecules from sea hares. *Prog. Mol. Subcell. Biol.* **43**, 215–239.

Kelman, D., Kashman, Y., Rosenberg, E., Kushmaro, A., and Loya, Y. (2006). Antimicrobial activity of red sea corals. *Mar. Biol.* **149**, 357–363.

Kim, H. L., Kang, S. G., Kim, I. C., Kim, S. J., Kim, D. W., Ma, S. J., Gao, T., Li, H., Kim, M. U., and Lee, T. H. (2006). In vitro Anti-hypertensive, antioxidant and anticoagulant activities of extracts from *Haliotis discus hannai*. *J. Korean Soc. Food Sci. Nutr.* **35**, 835–840.

Kim, E. K., Kim, Y. S., Lee, S. J., Jeon, Y. J., Lee, J. D., Son, T. I., Ahn, C. B., Kim, Y. T., Moon, S. H., and Jeon, B. T. (2010). Anticancer effect of lipids partially purified from Pacific oyster, *Crassostrea gigas* on PC3 cells. *Food Sci. Biotechnol.* **19**, 213–217.

Kimura, Y., Ohminami, H., and Okuda, H. (1998). Effects of extract of oyster on lipid metabolism in rats. *J. Ethnopharmacol.* **59**, 117–123.

Kuzirian, A. M., Epstein, H. T., Gagliardi, C. J., Nelson, T. J., Sakakibara, M., Taylor, C., Scioletti, A. B., and Alkon, D. L. (2006). Bryostatin enhancement of memory in Hermissenda. *Biol. Bull.* **210**, 201–214.

Larsen, R., Eilertsen, K. E., and Elvevoll, E. O. (2011). Health benefits of marine foods and ingredients. *Biotechnol. Adv.* **29**, 508–518.

Layer, R. T. and McIntosh, J. M. (2006). Conotoxins: Therapeutic potential and application. *Mar. Drugs* **4**, 119–142.

Lee, Y. K., Lee, J. H., and Lee, H. K. (2001). Microbial symbiosis in marine sponges. *J. Microbiol.* **39**, 254–264.

Lee, C. G., Kwon, H. K., Ryu, J. H., Kang, S. J., Im, C. R., Kim, J. I., and Im, S. H. (2010). Abalone visceral extract inhibit tumor growth and metastasis by modulating Cox-2 levels and CD8+ T cell activity. *BMC Complement. Altern. Med.* **10**, 60.

Lev, E. (2003). Traditional healing with animals (Zootherapy): Medieval to present day Levantine practice. *J. Ethnopharmacol.* **86**, 107–118.

Linington, R. G., Robertson, M., Gauthier, A., Finlay, B. B., MacMillan, J. B., Molinski, T. F., van Soest, R., and Andersen, R. J. (2006). Caminosides B–D, antimicrobial glycolipids isolated from the marine sponge *Caminus sphaeroconia*. *J. Nat. Prod.* **69**, 173–177.

Lippert, H., Brinkmeyer, R., and Iken, K. (2003). Antimicrobial activity in sub-Arctic marine invertebrates. *Polar Biol.* **26**, 591–600.

Luppi, E., Cesaretti, M., and Volpi, N. (2005). Purification and characterization of heparin from the Italian clam *Callista chione*. *Biomacromolecules* **6**, 1672–1678.

Martinez, M. J. A., Olmo, L. M. B. D., and Benito, P. B. (2008). Natural marine antiviral products. *Bioact. Nat. Prod.* **35**, 101–134.

Mayer, A. M. S., Rodriguez, A. D., Berlinck, R. G. S., and Hamann, M. T. (2009). Marine pharmacology in 2005–6: Marine compounds with anthelmintic, antibacterial, anticoagulant, antifungal, antiinflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems, and other miscellaneous mechanisms of action. *Biochim. Biophys. Acta* **5**, 283–308.

Melo, V. M. M., Fonseca, A. M., Vasconcelos, I. M., and Carvalho, A. F. (1998). Purification of a novel antibacterial and haemagglutinating protein from the purple gland of the sea hare, *Aplysia dactylomela* Rang, 1828. *Toxicon* **38**, 1415–1427.

Meylan, A. (1990). Nutritional characteristics of the sponges in the diet of the hawksbill turtle *Eretmochelys imbricata*. *In* ''New Perspectives in Sponge Biology'', (K. Rutzler, Ed.), pp. 472–477. Smithsonian, Institution Press, Washington, DC.

Miyashita, K. and Hosokawa, M. (2008). Beneficial health effects of seaweed carotenoid, fucoxanthin. *In* ''Marine Nutraceuticals and Functional Foods'', (C. Barrow and F. Shahidi, Eds), pp. 297–320. CRC Press, Boca Raton, USA.

Montoya-Cadavid, E., Romero, P. F., and Winston, J. E. (2007). Check list of the marine Bryozoa of the Colombian Caribben. *Biota Colombiana* **8**, 159–184.

Munro, M. H. G., Blunt, J. W., Barns, G., Battershill, C. N., Lake, R. J., and Perry, N. B. (1989). Biological activity in New Zealand marine organisms. *Pure Appl. Chem.* **61**, 529–534.

Narkowicz, C. K., Blackman, A. J., Lacey, E., Gill, J. H., and Heiland, K. (2002). Convolutindole A and convolutamine H, new nematocidal brominated alkaloids from the marine bryozoan *Amathia convoluta*. *J. Nat. Prod.* **65**, 938–941.

Newman, D. and Cragg, G. M. (2004). Marine natural products and related compounds in clinical and advanced preclinical trials. *J. Nat. Prod.* **67**, 1216–1238.

Newman, D. and Cragg, G. M. (2007). Natural products as sources of new drugs over the last 25 years. *J. Nat. Prod.* **70**, 461–477.

Nie, S. Q., Li, T. L., Jiang, A. H., and Li, G. Q. (1994). A comparative study on anti-ulcer action of unprepared and calcined oyster shell. *Zhongguo Zhong Yao Za Zhi* **19**, 405–407.

Olivera, B. M., McIntosh, J. M., Lourdes, J. C., Luque, F. A., and Gray, W. R. (1984). Purification and sequence of a presynaptic peptide toxin from *Conus geographus* venom. *Biochemistry* **23**, 5087–5090.

Palmer, C. V., Modi, C. K., and Mydlarz, L. D. (2009). Coral fluorescent proteins as antioxidants. *PLoS One* **4**, e7298.

Pan, H. M., Huang, Y. T., Chang, C. I., Ho, C. T., and Pan, B. S. (2007). Apoptotic-inducing epidioxysterols identified in hard clam (*Meretrix lusoria*). *Food Chem.* **102**, 788–795.

Pawlik, J. R. (1993). Marine invertebrate chemical defenses. *Chem. Rev.* **93**, 1911–1922.

Pechenic, J. A. (2000). Biology of Invertebrates. 4th edn. McGraw Hill, New York.

Pejler, G., Danielsson, A., Bjork, I., and Lindahl, U. (1987). Structure and antithrombin-binding properties of heparin isolated from the clams *Anomalocardia brasiliana* and *Tivela mactroides*. *J. Biol. Chem.* **262**, 11413–11421.

Phillipson, D. W. and Rinehart, K. L., Jr. (1983). Antifungal peroxide-containing acids from two Caribbean sponges. *J. Am. Chem. Soc.* **105**, 7735–7736.

Ponder, W. F. and Lindberg, D. R. (2008). Phylogeny and Evolution of Mollusca. University of California Press, Berkley, p. 469.

Qian, Z. J., Jung, W. K., Byun, H. G., and Kim, S. K. (2008). Protective effect of an antioxidative peptide purified from gastrointestinal digests of oyster, *Crassostrea gigas* against free radical induced DNA damage. *Bioresour. Technol.* **99**, 3365–3371.

Rajaganapathi, J., Kathiresan, K., and Singh, T. P. (2002). Purification of Anti-HIV Protein from Purple fluid of the sea hare *Bursatella leachii* de Blainville. *Mar. Biotechnol.* **4**, 447–453.

Riguera, R. (1997). Isolating bioactive compounds from marine organisms. *J. Mar. Biotechnol.* **5**, 187–193.

Rinehart, K. L., Shaw, P. D., Shield, L. S., Gloer, J. B., Harbour, G. C., Koker, M. E. S., Samain, D., Schwartz, R. E., Tymiak, A. A., Weller, D. L., Carter, G. T., Munro, M. H. G., *et al*. (1981). Marine natural products as sources of antiviral, antimicrobial, and antineoplastic agents. *Pure Appl. Chem.* **59**, 795–817.

Sachindra, N. M., Bhaskar, N., and Mahendrakar, N. S. (2005). Carotenoids in crabs from marine and fresh waters of India. *Food Sci. Technol.* **38**, 221–225.

Sammarco, P. W. and Coll, J. C. (1992). Chemical adaptations in the Octocorallia: Evolutionary considerations. *Mar. Ecol. Prog. Ser.* **88**, 93–104.

Schnapp, D., Schnapp, D., Kemp, G. D., and Smith, V. J. (1996). Purification and characterization of a proline-rich antibacterial peptide, with sequence similarity to bactenecin 7, from the haemocytes of the shore crab, *Carcinus maenas*. *Eur. J. Biochem.* **240**, 532–539.

Schwartsmann, G., da Rocha, A. B., Berlinck, R. G., and Jimeno, J. (2001). Marine organisms as a source of new anticancer agents. *Lancet Oncol.* **2**, 221–225.

Seo, J. K., Crawford, J. M., Stone, K. L., and Noga, E. J. (2005). Purification of a novel arthropod defenisn from the American oyster, *Crassostrea virginica*. *Biochem. Biophys. Res. Commun.* **338**, 1998–2004.

Sipkema, D., Franssen, M. C. R., Osinga, R., Tramper, J., and Wijffels, R. H. (2005). Marine sponges as pharmacy. *Mar. Biotechnol.* **7**, 142–162.

Skov, M. J., Beck, J. C., de Kater, A. W., and Shopp, G. M. (2007). Nonclinical safety of ziconotide: An intrathecal analgesic of a new pharmaceutical class. *Int. J. Toxicol.* **26**, 411–421.

Slattery, M., McClintock, J. B., and Heine, J. N. (1995). Chemical defense in Antarctic soft corals: Evidence for antifouling compounds. *J. Exp. Mar. Biol. Ecol.* **190**, 61–71.

Smith, V. J., Fernandes, J. M. O., Kemp, G. D., and Hauston, C. (2008). Crustins: Enigmatic WAP domain-containing antibacterial proteins from crustaceans. *Dev. Comp. Immunol.* **32**, 758–772.

Smith, V. J., Desbois, A. P., and Dyrynda, E. A. (2010). Conventional and unconventional antimicrobials from fish, marine invertebrates and micro-algae. *Mar. Drugs* **8**, 1213–1262.

Sperstad, S. V., Haug, T., Blencke, H. M., Styrvol, O. B., Li, C., and Stensvag, K. (2011). Antimicrobial peptides from marine invertebrates: Challengers and perspectives in marine antimicrobial peptide discovery. *Biotechnol. Adv.* **29**, 519–530.

Tadesse, M., Gulliksen, B., Strøm, M. B., Styrvold, O. B., and Haug, T. (2008). Screening for antibacterial and antifungal activities in marine benthic invertebrates from northern Norway. *J. Invertebr. Pathol.* **99**, 286–293.

Thomas, T. R. A., Kavlekar, D. P., and LokaBharathi, P. A. (2010). Marine drugs from sponge-microbe association. *Mar. Drugs* **8**, 1417–1468.
Thorpe, J. P., Sole-Cava, A. M., and Watts, P. C. (2000). Exploited marine invertebrates: Genetics and fisheries. *Hydrobiologia* **420**, 165–184.
Tou, J. C., Jaczynski, J., and Chen, Y. C. (2007). Krill for human consumption: Nutritional value and potential health benefits. *Nutr. Rev.* **65**, 63–77.
Twede, V. D., Miljanich, G., Olivera, B. M., and Bulaj, G. (2009). Neuroprotective and cardioprotective conopeptides: An emerging class of drug leads. *Curr. Opin. Drug Discov. Devel.* **12**, 231–239.
Uchida, H., Sasaki, T., Uchida, N. A., Takasuka, N., Endo, Y., and Kamiya, H. (1987). Oncostatic and immunomodulatory effects of a glycoprotein fraction from water extract of abalone, *Haliotis discus hannai*. *Cancer Immunol. Immunother.* **24**, 207–212.
Volk, C. A. and Kock, M. (2004). Viscoline: New 3-alkyl pyridinium from the Arctic sponge *Haliclona viscose*. *Org. Biomol. Chem.* **2**, 1827–1830.
Voultsiadou, E. (2010). Therapeutic properties and uses of marine invertebrates in the ancient Greek world and early Byzantum. *J. Ethnopharmacol.* **130**, 237–247.
Voultsiadou, E. and Vafidis, D. (2007). Marine invertebrates diversity in Aristotle's zoology. *Contrib. Zool.* **76**, 103–120.
Weinheimer, A. J. and Spraggins, R. L. (1969). The occurrence of two new prostaglandin derivatives (15-epi-PGA2 and its acetate, methyl ester) in the gorgonian Plexaura homomalla, Chemistry of coelenterates. *Tetrahedron Lett.* 5185–5188.
Williams, P. G. (2008). Panning for chemical gold: Marine bacteria as a source of new therapeutics. *Trends Biotechnol.* **27**, 45–52.
Yamazaki, M. (1993). Antitumor and antimicrobial glycoproteins from sea hare. *Comp. Biochem. Physiol. C* **105**, 141–146.
Yesilada, E. (2005). Past and future contributions to traditional medicine in the health care system of the Middle-East. *J. Ethnopharmacol.* **100**, 135–137.
Yeung, H. C. (1983). Handbook of Chinese Herbal Formulas. Institute of Chinese Medicine, Rosemead, LA, USA.