CHAPTER 8

Bioactive Compounds from Marine Sponges and Their Symbiotic Microbes: A Potential Source of Nutraceuticals

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Contents

Abstract

Sponges are considered as the chemical factory in marine environment because of its immense production of chemically diverse compounds. Other than the chemical diversity, these compounds possess remarkable bioactivities. This great potential has aroused applications of sponge-derived compounds as therapeutics and at present, a number of promising compounds are in clinical and preclinical trials. Recently, nutraceuticals have received considerable interest among the health conscious community because of its multiple therapeutic effects. Natural health-promoting substances

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gain continuous popularity as nutraceuticals due to its reduced risk of side effects. This overview discusses the potentials of marine sponge-derived bioactivities as natural health-promoting compounds.

I. INTRODUCTION

Marine sponges are one the most prolific and important source of new bioactive compounds. Hundreds of interesting new compounds have been discovered from sponges. Hence, marine sponges have been considered as a gold mine to scientists (Baby and Sujatha, 2010). Chemical and physical conditions in the marine environment and intensive pressure from competitors, predators, and pathogens have resulted in producing wide array of chemically diverse secondary metabolites. There have been several reviews which discuss different classes of secondary metabolites of marine sponges and their bioactivities (John *et al*., 2010; Keyzers and Coleman, 2005; Taylor *et al*., 2007; Webster and Taylor, 2011). Medicinal applications of sponges go back to ancient times, and sponges saturated with solutions had been used for various diseases such as heartaches, detoxifications of bites of poisonous animals, and wound healing (Sipkema *et al*., 2005a). Discovery of an unusual nucleoside and development of commercially important anticancer drug Ara-C (Fig. 8.1) and

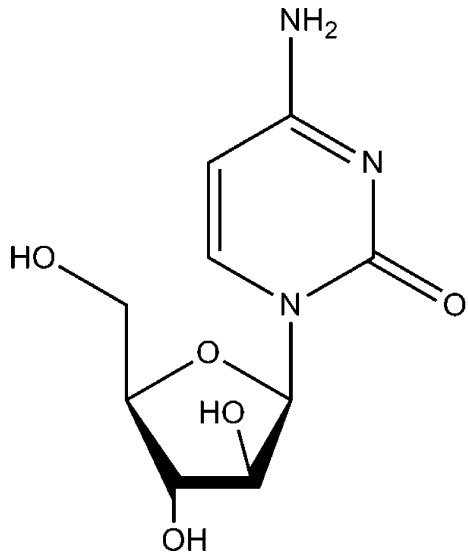

FIGURE 8.1 Ara-C (cytarabine).

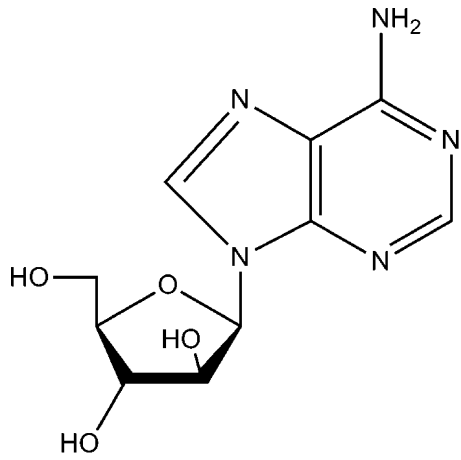

FIGURE 8.2 Ara-A (spongothymidine).

antiviral drug Ara-A (Fig. 8.2) aroused pharmaceutical interest of marine sponge (Proksch *et al*., 2002). A number of secondary metabolites that have been isolated from sponges are in clinical trials for use as drugs. Further, health-promoting abilities of many more compounds have been proved (David and Gordon, 2004).

There have been continuous search for new substances that can improve biological functions and possibility of applying these compounds to promote well-being of human. This has resulted in development of products such as vitamins, dietary supplements, functional foods, nutraceuticals, phytochemicals, bio-chemopreventatives, and designer foods (Zeisel, 1999). Nutraceuticals, accounted for an estimated 5% market growth annually, are the fastest growing segment. The popularity has gained through the belief that nutraceuticals prevent chronic diseases, promote human health, and delay the onset of aging (Le and Pathak, 2011). The term nutraceutical is a hybrid of two terms ''nutrition'' and ''pharmaceutical.'' A number of definitions have been given based on countries' regulations. Barrow and Shahidi (2008) define marine nutraceuticals as marine-derived substances that can be used as dietary supplements or food ingredients that provide medicinal or health benefits beyond nutrition. Among the commercially available nutraceuticals, products derived from marine sources are considered as a rich source of health-promoting substances (Shahidi, 2009). Long-chain ω-3 fatty acids and glucosamine are well-established marine-derived nutraceuticals. However, other than common health benefits of nutraceuticals, innovative developments are required to combat with emerging ''lifestyle diseases'' (Dharti *et al*., 2010).

Thousands of bioactive compounds that have fascinating potentials to develop as nutraceuticals have been identified from marine sources. This chapter investigates the possibility of developing nutraceuticals from bioactive compounds, identified from marine sponges and symbiotic microorganisms.

II. MARINE SPONGES AND THEIR SYMBIOTIC MICROBES

Sponges, sessile metazoans consist of a gelatinous material—mesophyl, are the simplest form of multicellular animals. The hollow pitcher-like body is reinforced by spicules (a needle-like silica or calcium structure) and spongia (collagen fibers) (Uriz *et al*., 2003). This efficient filter feeder obtained microbes and microparticles in the water as nutrients through the unique water circulation system (Lafi *et al*., 2005). Basically, marine sponges consist of three sublineages such as Hexactinellida, Calcarea, and Demospongiae. True sponging is found in the class of demospongiae and is considered as the most economically important group of sponges. Wide range of chemically diverse compounds, alkaloids, terpenoids, polyketides, macrolides, polyphenolic compounds, peptides, and sterols, exhibit the potential of marine sponge (Thoms and Schupp, 2007).

Association of sponges and microbes has been highlighted in several reviews (Hentschel *et al*., 2006; Taylor *et al*., 2007; Thomas *et al*., 2010; Webster and Taylor, 2011). Mesophyl matrix is a good shelter of extracellular heterotrophic and autotrophic microbes while the outer layer is occupied by photosynthetic microbes. Novel molecular biological techniques such as 16S rRNA gene library, fluorescence *in situ* hybridization, denaturing gradient gel electrophoresis, and lipid biomarkers enable identification of microbial community associated with marine sponges (Hentschel *et al*., 2006). Interestingly, microbial density in some marine sponges may account up to 60% of sponge biomass. Microbial association of sponge spans a wide range of microbial groups starting from prokaryotic archaea to filamentous fungi. The symbiotic microbial community contributes to a number of physiological processes such as photosynthesis, nitrogen and carbon cycles, and dehalogenation. Bright colors of sponges are usually a result of symbiotic cyanobacteria. Despite the fact that sponge harbors large number of microorganism, it has been proved that symbiotic microbes are responsible for production of biologically important chemical compounds (Table 8.1). This has given a hope of producing active metabolites in large scale to address the so-called supply problem (Taylor *et al*., 2007).

TABLE 8.1 Secondary metabolites of marine sponges associated microorganisms.

Group of organisms	Compound class	Bioactivity	Reference
Fungi	Polyketides, cyclohexane, terpenes, amino acid derivatives	Cytotoxic, antioxidant, antimicrobial, kinase inhibitors	Li *et al.* (2011); Bugni and Ireland (2004)
Bacteria	Proteins, peptides, propionic acid, indole, PAFA	Antimicrobial	Boobathy *et al.* (2009); Taylor *et al.* (2007); Devi *et al.* (2010); Patnayak and Sree (2005)
Cyanobacteria	Ether, chlorinated metabolites, pigments		Hentschel *et al.* (2006)
Actinobacteria	Amino acid, polyketides, glycosides, methyl esters	Anti-inflammation, antimicrobial, antioxidant, hypocholesterolemic	Schneemann *et al.* (2010)
Actinomycetes	Carotenoids	Antioxidant	Dharmaraj *et al.* (2009a)
Yeast	Indole derivatives	Radical scavengers	Sugiyama *et al.* (2009)

III. BIOACTIVE COMPOUNDS

A. Anti-inflammatory compounds

Classically, inflammation is a protective reaction of the body in response to some physical, chemical, or microbial injury and insult of the cells. Acute inflammation, rapid onset and shorter duration, is considered as a healthy response. However, when inflammation continues for prolonged period of time, it becomes detrimental and may raise the first step of a chronic disease (Medzhitov, 2008). Arachidonic acid/COX and nuclear factor-κB (NF-κB) are well known inflammatory pathways which induce production of inflammatory mediators such as prostaglandins, thromboxanes, leukotrienes, and cytokines. Most commonly accepted mechanism of anti-inflammation is inhibition of cyclooxygenase (COX) activity. There are two kinds of cyclooxygenases: COX-1 is natural protective enzyme of intestinal mucosa while COX-2 is induced by tissue damage as an inflammatory mediator (Maroon *et al.*, 2006). NF-κB is a recently identified

complex inflammatory pathway which produces inflammatory cytokines and proinflammatory enzymes. Curcumin, γ-linolenic acid, epigallocatechin gallate, eugenol, [6]-gingerol, and many more flavanoids are well known natural anti-inflammatory agents (Aggarwal *et al.*, 2009). However, commonly used non-steroidal anti-inflammatory drugs (NSAIDs) have been creating some complications like gastrointestinal hemorrhage, myocardial infarction, and stroke due to lack of selectivity (Maroon *et al.*, 2006). Thus, natural and selective inhibitors of the inflammatory cascade have gained much attention.

Sponge-derived sesterterpenoids are potent anti-inflammatory metabolites which inhibit phospholipase A_2 (Sipkema *et al.*, 2005a). In arachidonic acid pathway of inflammatory response (Fig. 8.3), phospholipase A_2 catalyzes the release of membrane-bound phospholipids to produce inflammatory mediators once stimulated by tissue injury. Manoalide (Fig. 8.4) is a best known sponge-derived anti-inflammatory sesterterpenoid. Dysidotronic acid (Fig. 8.5), non-complex manoalide analogue, has been identified as an anti-inflammatory metabolite of the sponge *Dysidea* sp. The mechanism by which dysidotronic acid inhibit inflammation is much more selective and potent than manoalide. This sesquiterpenoid

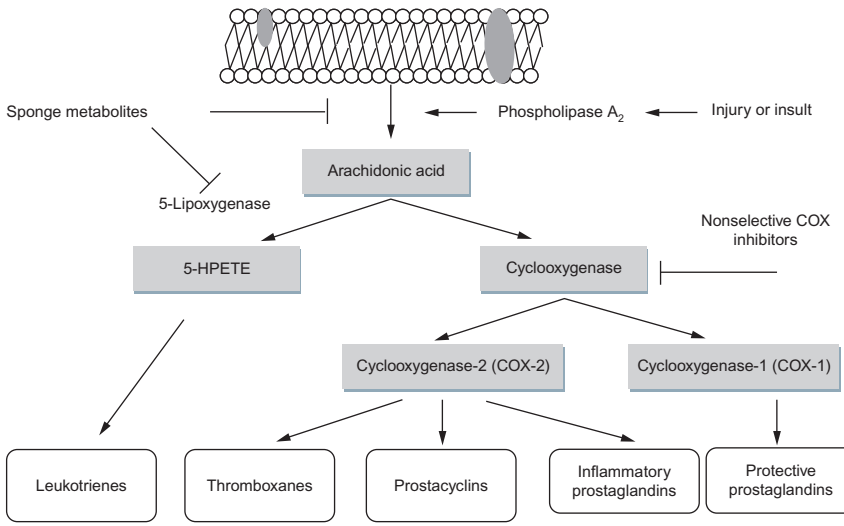

FIGURE 8.3 Schematic diagram of arachidonic acid pathway of inflammatory response. In tissue damage or insult, inflammatory mediators leukotrienes, thromboxanes, and prostaglandins are produced as a result of releasing membrane-bound arachidonic acid by phospholipase A_2. 5-Lipoxygenase and cyclooxygenase-2 (COX-2) mediate the conversion of free arachidonic acid into inflammatory mediates. Sponge metabolites inhibit phospholipase A_2 and 5-lipoxygenase followed by inhibition of production of inflammatory mediators.

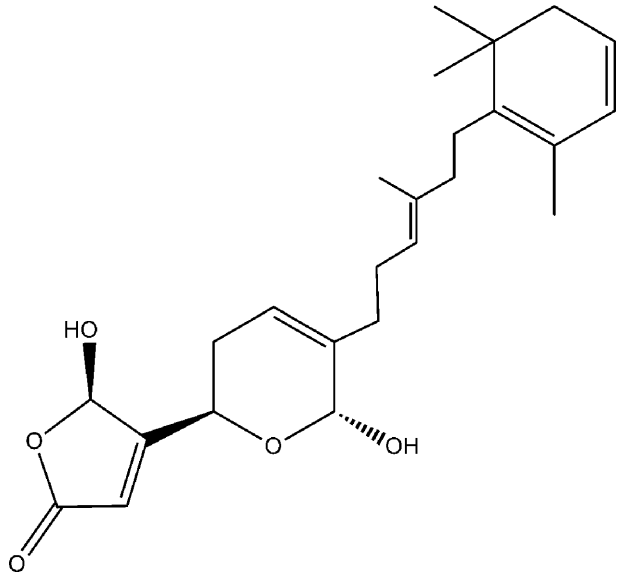

FIGURE 8.4 Manoalide.

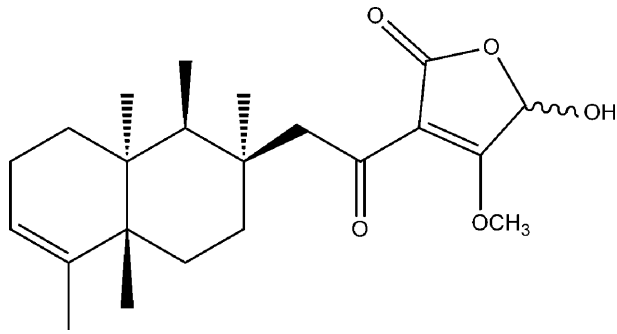

FIGURE 8.5 Dysidotronic acid.

inhibits cytokine production, consequently decreasing the production of inducible nitric oxide synthase and prostaglandin E_2 (Posadas *et al.*, 2001). Carroll *et al.* (2001) revealed that bioactive metabolites of *Jaspis splendens* and *Suberea* sp. inhibit lipoxygenase, a group of enzymes that oxygenate polyenoic fatty acids followed by production of inflammatory mediators leukotrienes, lipoxins, and hepoxilins. In contrast to the NSAIDs, sponge-derived anti-inflammatory metabolites are selective inhibitors of enzymes. Therefore, these metabolites have a clear potential of overcoming complication associated with non-selective inhibitors.

B. Novel antioxidants

Environmental as well as lifestyle changes are responsible for increasing reactive oxygen species in the body. Overproduction of oxidative free radicals, when cell's natural controlling mechanism (superoxide dismutase and catalase) is not effective or enough, creates an oxidative stress due to imbalance of pro-oxidants and antioxidants (Kelsey *et al*., 2010). The chronic oxidative stress leads to various kinds of degenerative diseases and aging process. In this scenario, antioxidant-rich sources and supplements are under spotlight to offer extra protection. Although many chemical substances have been proved for their antioxidant activity, there has been continuous search for new antioxidants due to poor bioavailability, cumulative effects inside the body, and adverse side effects of synthetic antioxidants (Jorge *et al*., 2011). Among novel antioxidants, marine sponges are highly ranked source. A number of metabolites derived from marine sponges, indole derivatives, aromatic alkaloids, aromatic polyketides, and phenolic compounds have exhibited strong antioxidant effect compared to vitamin E, ascorbic acid, and butylated hydroxyanisole (Longeon *et al*., 2011; Utkina, 2009; Utkina *et al*., 2004). Aromatic polyketides isolated from marine sponge-derived fungus *Aspergillus versicolor* have shown significantly higher antioxidant capacity than that of butylated hydroxytoluene (Li *et al*., 2011). Sugiyama *et al*. (2009) reported that marine-derived yeasts are capable of producing antioxidative indole derivatives. These findings were very attractive since these microbes are culturable, and there is a possibility of reproducing the compound in large scale.

C. Hypocholesterolemic compounds

Cholesterol, an essential steroid which is produced by human body, acts as a cell membrane modulator and facilitator of absorption in the intestine. In addition, it serves as a substrate for hormones, bile acid, and vitamin D (Chen *et al*., 2008). Water-insoluble cholesterol is transported throughout the body by four lipoproteins in the blood. Among them, cholesterol carrier lipoprotein, low-density lipoprotein (LDL), and high-density lipoprotein are strictly regulated to maintain cholesterol hemostasis in blood (Deng, 2009). High total serum cholesterol level has been recognized as a highly ranked risk factor of world biggest killer, cardiovascular disease (Roth *et al*., 2011). Inhibition of cholesterol biosynthesis to control serum cholesterol is a widely accepted hypothesis, and various natural and synthetic products have been employed at different steps of the biosynthesis pathway. Cholesterol biosynthesis enzyme HMG-CoA reductase is the target of most of the hypocholesterolemic drugs since it is the rate-limiting enzyme. However, myositis, gastrointestinal symptoms,

pharyngitis, and pain are commonly associated side effects with these types of drugs. In this regard, recent studies have focused on identifying more specific inhibitors, especially later stage of the biosynthesis pathway (Korosec *et al.*, 2008).

Marine sponge *Spirastrella abata*-derived Lyso-PAF analogues and lysophosphatidylcholines have been reported as successful inhibitors of cholesterol biosynthesis (Fig. 8.6). An *in vitro* study shows that active compounds specifically blocked the conversion of lanosterol into cholesterol in the liver cells with more specific inhibition (Shin *et al.*, 1999). Zhao *et al.* (2003) have reported that marine sponges are a source of novel lysophosphatidylcholines and thereby aroused an interest of hypocholesterolemic compounds from marine sponge due to short lifespan of conventional lysophosphatidylcholines *in vivo*. Another interesting target of hypocholesterolemia is increasing bile acid biosynthesis in liver, as bile acids are the major metabolites of cholesterol (Chen *et al.*, 2008). Farnesoid X-activated receptor (FXR) antagonists from a marine sponge *Spongia* sp. have been discovered as an interesting molecular target of hypocholesterolemia. The FXR suppresses the production of cholesterol 7a-hydroxylase (CYP7A1), which is the rate-limiting enzyme of the bile acid biosynthetic pathway. This novel compound increases the biosynthesis of bile acid and

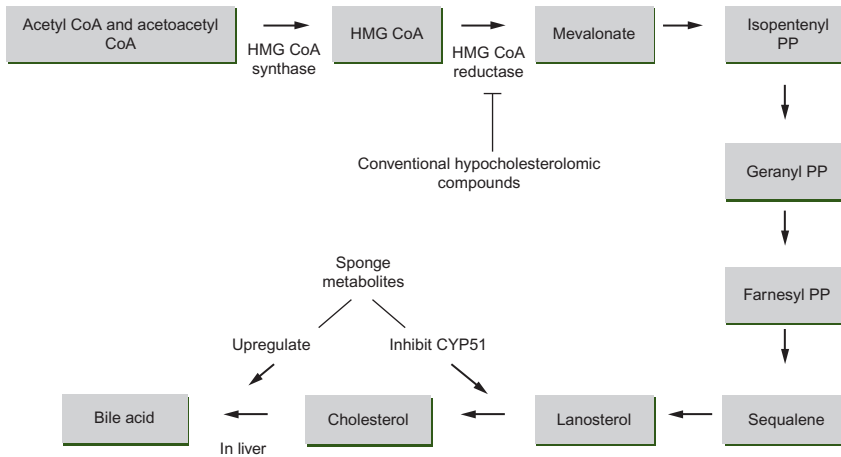

FIGURE 8.6 Cholesterol biosynthesis pathway. 3-Hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase is considered as the rate-limiting step of the pathway. Even though HMG-CoA is the main target of common hypocholesterolemic drugs, more specific inhibitors which act on later stages of the pathway claim lesser number of adverse side effects. Lyso-PAF analogues isolated from marine sponge inhibit lanosterol 14α-demethylase (CYP51) followed by inhibiting conversion of lanosterol into cholesterol. Farnesoid X-activated receptor (FXR) antagonists upregulate the cholesterol metabolism in the liver and lower the serum cholesterol.

lower the hepatic cholesterol followed by removal of cholesterol from the circulation and decreases LDL level in the blood (Nam *et al*., 2006).

D. Sponge collagen

Collagen is the most abundant structural protein in animals, accounts up to 25–35% of total protein content. Unique triple-strand helical polypeptide chains are rich in proline and glycine. This natural polymer is widely used in pharmaceutics and cosmetics because of its biodegradability, biocompatibility, low toxicity, and immunogenicity. Biomaterials as a coating or a carrier of drugs, moisturizers, and health supplements are known applications of collagen (Olsen *et al*., 2003; Swatschek *et al*., 2002). Even though animal-derived collagen is the main source of collagen, transmissible diseases (bovine spongiform encephalopathy), antigenic response and its variations, and issues related to food laws limit its applicability and create a demand for alternative sources (Pallela *et al*., 2011).

Biochemical similarity of amino acid composition and structural similarities to bovine collagen fibrils observed under TEM, SEM, X-ray diffraction, and atomic force microscopy have proved the possibility of substituting conventional collagen for sponge collagen (Heinemann *et al*., 2007). Overcoming the difficulties associated with isolation and purification of marine sponge collagen, Swatschek *et al*. (2002) suggested a modified method yielding 30% of collagen. Among natural polymers which have been approved for drug coatings for sustained delivery of a dosage, sponge collagen shows distinguish characteristics owing to its stability against pepsin, trypsin, collagenases, and acid media. Nicklas *et al*. (2009) used these properties and developed delayed-release enteric coating from marine sponge *Chondrosia reniformis* Nardo (Demospongiae: Hadromerida: Chondrosiidae) with good mechanical properties and storage stability. In addition, collagen possesses a promising ability of delivering drugs into specific target sites overcoming undesirable interactions (Ruszczak and Friess, 2003). Improved ability of sponge microparticles can be used to deliver anti-inflammatory compounds as they have a tendency of accumulation on inflamed tissues. Moreover, sponge collagen is the best solution for susceptibility of degradation of calf collagen by intestinal pepsin (Berthold *et al*., 1998; Swatschek *et al*., 2002).

E. Natural pigments

Appearance, particularly color, is an important characteristic of a food or a supplement because the first impression is made on that. Thus, natural or synthetic colorants play a vital role in food and pharmaceutical industries. Certain legal aspects related to biological effects, purity of synthetic

colorants, and poor stability of natural colorants under processing conditions demand alternatives (Mortensen, 2006).

Pigments from marine sponges have long been an interesting topic because of their brilliant color range. Sponge colors are either their own synthesis in pigment granules or a product of symbiotic microbes (Bandaranayake, 2005). Drumm *et al.* (1945) have isolated and characterized carotenoid pigments of marine sponge *Hymeniacidon sanguineum*. Carotenoid pigments are responsible for most bright color sponges, and more than 20 characteristic aryl carotenoids have been identified in sponges (Maoka, 2011). By contrast, carotenoid pigments are strong radical scavengers, are inhibitors of lipid peroxidation, and offer health benefits and higher stability for food and pharmaceuticals than other colorants (Hix *et al.*, 2004). In recent years, the interest of carotenoid production by microbial fermentation has increased instead of extracting from plant tissues or chemical synthesis. Marine sponge-derived actinomycetes sp. (Dharmaraj *et al.*, 2009a), *Streptomyces* sp. (Dharmaraj *et al.*, 2009b), and fungus *Paecilomyces lilacinus* (Elbandy *et al.*, 2009) have been proved for the production of carotenoid pigments and showed the potential as sources of natural colorants. In addition, mytiloxanthin derivatives, red color pigments of bright orange sponge *Phakellia stellidem*, have been identified as bioactive pigments (Higa *et al.*, 1994).

IV. SUSTAINABLE PRODUCTION OF SPONGE METABOLITE

Despite the chemical diversity and biological activities of marine sponge metabolites, large-scale commercial supply of these compounds remains as a challenge. This seems to be a reason why only a few sponge metabolites, out of thousands of novel compounds, are in clinical trials. Wild harvest of sponges for bioactive compounds is not feasible as it threatens the marine environment. Likewise, chemical synthesis of compounds is much more difficult since they are structurally complex (Thakur and Müller, 2004). Therefore, production of bioactive compounds in a sustainable manner became an interesting focus of sponge's research. Several attempts including sponge cell culture, culturing of symbiotic microorganism, or metagenomic approaches in which large gene fragments responsible for production of the bioactive compounds are identified and transferred into a suitable host and sponge aquaculture have been performed to overcome this problem.

Discovery of medicinally important metabolites from marine sponges renewed the interest of sponge aquaculture which has been studied early in the twentieth century for commercial supply of sponge metabolites. Sponge mariculture is considered to be the most cost-effective method (Duckworth and Battershill, 2003). Several drawbacks associated with the

mariculture turn the way of sponge culturing into *ex situ* cultivation with controlled conditions. Optimal conditions for growth as well as metabolite production and continuous growth could be achieved with *ex situ* cultivation (Sipkema *et al*., 2005b). This is an economically feasible option for the production of sponge metabolites, and optimal conditions close to *in situ* double the production of metabolites (Kloppel *et al*., 2008). Sponge-associated microbes are a promising hope to obtain bioactive metabolites. In addition to culturing of symbiotic microbes, metagenomic approach offers biotechnological solution for unculturable microbial species. Sponge cell culture for production of bioactives was started a decade ago. Muller *et al*. (2000) revealed that proliferative cells of *Dysidea avara* can be used to produce avarol *in vitro*, and cell assemblies termed primmorphs are more capable of producing metabolites than single cells. With these interesting findings, several studies were carried out to optimize the condition of sponge cell culture (Caralt *et al*., 2007; Schippers *et al*., 2011; Zhao *et al*., 2005). In recent future, sponge metabolites for therapeutic applications would be produced *in vitro* instead of wild harvesting.

REFERENCES

Aggarwal, B. B., Kuiken, M. E. V., Iyer, L. H., Harikumar, K. B., and Sung, B. (2009). Molecular targets of nutraceuticals derived from dietary spices: Potential role in suppression of inflammation and tumorigenesis. *Exp. Biol. Med.* **243**, 825–849.

Baby, J. and Sujatha, S. (2010). Pharmacologically important natural products from marine sponges. *J. Nat. Prod.* **4**, 5–12.

Bandaranayake, W. M. (2005). The nature and role of pigments of marine invertebrates. *Nat. Prod. Rep.* **23**, 223–255.

Barrow, C. and Shahidi, F. (2008). Marine Nutraceuticals and Functional Foods. CRC Press Publishing, New York.

Berthold, A., Cremer, K., and Kreuter, J. (1998). Collagen microparticles: Carriers for glucocorticosteroids. *Eur. J. Pharm. Biopharm.* **45**, 23–29.

Boobathy, S., Kumar, T. T. A., and Kathiresann, K. (2009). Isolation of symbiotic bacteria and bio active proteins from marine sponge, Callyspongia diffusa. *Indian J. Biotechnol.* **8**, 272–275.

Bugni, T. S. and Ireland, C. M. (2004). Marine derived fungi: A chemically and biologically diverse group of microorganism. *Nat. Prod. Rep.* **21**, 143–163.

Caralt, S. D., Uriz, M. J., and Wijffels, R. H. (2007). Cell culture from sponges: Pluripotency and immortality. *Trends Biotechnol.* **25**, 467–471.

Carroll, J., Jonsson, E. N., Ebel, R., Hartman, M. S., Holman, T. R., and Crews, P. (2001). Probing sponge-derived terpenoids for human 15-lipoxygenase inhibitors. *J. Org. Chem.* **66**, 6847–6851.

Chen, Z., Jiao, R., and Ma, K. Y. (2008). Cholesterol-lowering nutraceuticals and functional foods. *J. Agric. Food Chem.* **56**, 8761–8773.

David, J. N. and Gordon, M. C. (2004). Marine natural products and related compounds in clinical and advanced preclinical trials. *J. Nat. Prod.* **67**, 1216–1238.

Deng, R. (2009). Food and food supplements with hypocholesterolemic effects. *Recent Pat. Food. Nutr. Agric.* **1**, 15–24.

Devi, P., Wahidullah, S., Rodrigues, C., and Souza, L. D. (2010). The Sponge-associated bacterium bacillus licheniformis SAB1: A source of antimicrobial compounds. *Mar. Drugs* **8**, 1203–1212.

Dharmaraj, S., Ashokkumar, B., and Dhevendaran, K. (2009a). Fermentative production of carotenoids from marine actinomycetes. *Iran. J. Microbiol.* **1**, 36–41.

Dharmaraj, S., Ashokkumar, B., and Dhevendaran, K. (2009b). Food-grade pigments from Streptomyces sp. isolated from the marine sponge Callyspongia diffusa. *Food Res. Int.* **42**, 487–492.

Dharti, T. S., Gandhi, S., and Shah, M. (2010). Nutraceuticals—Portmanteau of science and nature. *Int. J. Pharm. Sci. Rev. Res.* **5**, 33–38.

Drumm, P. J., O'connor, W. F., and Renouf, L. P. (1945). The pigments of sponges. *Biochem. J.* **39**(2), 208–210.

Duckworth, A. and Battershill, C. (2003). Sponge aquaculture for the production of biologically active metabolites: The influence of farming protocols and environment. *Aquaculture* **221**, 311–329.

Elbandy, M., Shinde, P. B., Hong, J., Bae, K. S., Kim, M. A., Lee, S. M., and Jung, J. H. (2009). α-pyrones and yellow pigments from the sponge-derived fungus paecilomyces lilacinus. *Bull. Korean chem. Soc.* **30**, 188–192.

Heinemann, S., Ehrlich, H., Douglas, T., Heinemann, C., Worch, H., Schatton, W., and Hanke, T. (2007). Ultrastructural studies on the collagen of the marine sponge Chondrosia reniformis Nardo. *Biomacromolecules* **8**, 3452–3457.

Hentschel, U., Usher, K. M., and Taylor, M. W. (2006). Marine sponges as microbial fermenters. *FEMS Microbiol. Ecol.* **55**, 167–177.

Higa, T., Tanaka, J., Kitamura, A., Koyama, T., Takahashi, M., and Uchida, T. (1994). Bioactive compounds from marine sponges. *Pure Appl. Chem.* **66**, 2227–2230.

Hix, L. M., Lockwood, S. F., and Bertram, J. S. (2004). Bioactive carotenoids: Potent antioxidants and regulators of gene expression. *Redox Rep.* **9**, 181–191.

John, W. B., Brent, R. C., Murray, H. G. M., Peter, T. N., and Michele, R. P. (2010). Marine natural products. *Nat. Prod. Rep.* **27**, 165–237.

Jorge, A. T. S., Arroteia, K. F., Lago, J. C., Sa´-Rocha, V. M. D., Gesztesi, J., and Moreira, P. L. (2011). A new potent natural antioxidant mixture provides global protection against oxidative skin cell damage. *Int. J. Cosmet. Sci.* **33**, 113–119.

Kelsey, N. A., Wilkins, H. M., and Linseman, D. A. (2010). Nutraceutical antioxidants as novel neuroprotective agents. *Molecules* **15**, 7792–7814.

Keyzers, R. A. and Coleman, M. T. D. (2005). Anti-inflammatory metabolites from marine sponges. *Chem. Soc. Rev.* **34**, 355–365.

Kloppel, A., Pfannkuchen, M., Putz, A., Proksch, P., and Brummer, F. (2008). Ex situ cultivation of Aplysina aerophoba close to in situ conditions: Ecological, biochemical and histological aspects. *Mar. Ecol.* **29**, 259–272.

Korosec, T., Acimovic, J., Seliskar, M., Kocjan, D., Tacer, K. F., Rozman, D., and Urleb, U. (2008). Novel cholesterol biosynthesis inhibitors targeting human lanosterol 14a-demethylase (CYP51). *Bioorg. Med. Chem.* **16**, 209–221.

Lafi, F. F., Garson, M. J., and Fuerst, J. A. (2005). Culturable bacterial symbionts isolated from two distinct sponge species (Pseudoceratina clavata and Rhabdastrella globostellata) from the great barrier reef display similar phylogenetic diversity. *Microb. Ecol.* **50**, 213–220.

Le, U. and Pathak, Y. (2011). Nutraceuticals—Advancing in a right direction. *In* ''Hand Book of Nutraceuticals'', (Y. Pathak, Ed.), Vol. 2, pp. 1–14.

Li, J. L., Lee, Y. M., Hong, J., Bae, K. S., Choi, J. S., and Jung, J. H. (2011). A new antioxidant from the marine sponge-derived fungus *Aspergillus versicolor*. *Nat. Prod. Sci.* **17**(1), 14–18.

Longeon, A., Copp, B. R., Quévrain, E., Roué, M., Kientz, B., Cresteil, T., Petek, S., Debitus, C., and Kondracki, M. L. B. (2011). Bioactive indole derivatives from the south pacific marine sponges. *Mar. Drugs* **9**, 879–888.

Maoka, T. (2011). Carotenoids in marine animals. *Mar. Drugs* **9**, 278–293.

Maroon, J. C., Bost, J. W., Borden, M. K., Lorenz, K. M., and Ross, N. A. (2006). Natural anti-inflammatory agents for pain relief in athletes. *Neurosurg. Focus* **21**, 1–13.

Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature* **454**, 428–435.

Mortensen, A. (2006). Carotenoids and other pigments as natural colorants. *Pure Appl. Chem.* **78**, 1477–1491.

Muller, W. E. G., Bohm, M., Batel, R., Rosa, S. D., Tommonaro, G., Muller, I. M., and Schroder, H. C. (2000). Application of cell culture for the production of bioactive compounds from sponges: Synthesis of avarol by primmorphs from Dysidea avara. *J. Nat. Prod.* **63**, 1077–1081.

Nam, S. J., Ko, H., Shin, M., Ham, J., Chin, J., Kim, Y., Kim, H., Shin, K., Choi, H., and Kang, H. (2006). Farnesoid X-activated receptor antagonists from a marine sponge Spongia sp. *Bioorg. Med. Chem. Lett.* **16**, 5398–5402.

Nicklas, M., Schatton, W., Heinemann, S., Hanke, T., and Kreuter, J. (2009). Enteric coating derived from marine sponge collagen. *Drug Dev. Ind. Pharm.* **35**, 1384–1388.

Olsen, D., Yang, C., Bodo, M., Chang, R., Leigh, S., Baez, J., Carmichael, D., Perala, M., Hamalainen, E. R., Jarvinen, M., and Polarek, J. (2003).*Adv. Drug Deliv. Rev.* **55**, 1547–1567.

Pallela, R., Bojja, S., and Janapala, V. R. (2011). Biochemical and biophysical characterization of collagens of marine sponge, Ircinia fusca (Porifera: Demospongiae: Irciniidae). *Int. J. Biol. Macromol.* **49**, 85–92.

Patnayak, S. and Sree, A. (2005). Screening of bacterial associates of marine sponges for single cell oil and PUFA. *Lett. Appl. Microbiol.* **40**, 358–363.

Posadas, I., Terencio, M. C., Giannini, C., D'Auria, M. V., and Paya, M. (2001). Dysidotronic acid, a new sesquiterpenoid, inhibits cytokine production and the expression of nitric oxide synthase. *Eur. J. Pharmacol.* **415**, 285–292.

Proksch, P., Edrada, R. A., and Ebel, R. (2002). Drugs from the seas—Current status and microbiological implications. *Appl. Microbiol. Biotechnol.* **59**, 125–134.

Roth, G. A., Fihn, S. D., Mokdad, A. H., Aekplakorn, W., Hasegawa, T., and Lim, S. S. (2011). High total serum cholesterol, medication coverage and therapeutic control: An analysis of national health examination survey data from eight countries. *Bull. World Health Organ.* **89**, 92–101.

Ruszczak, Z. and Friess, W. (2003). Collagen as a carrier for on-site delivery of antibacterial drugs. *Adv. Drug Deliv. Rev.* **55**, 1679–1698.

Schippers, K. J., Martens, D. E., Pomponi, S. A., and Wijffels, R. H. (2011). Cell cycle analysis of primary sponge cell cultures. *In Vitro Cell. Dev. Biol. Anim.* **47**, 302–311.

Schneemann, I., Nagel, K., Kajahn, I., Labes, A., Wiese, J., and Imhof, J. F. (2010). Comprehensive investigation of marine actinobacteria associated with the sponge Halichondria panacea. *Appl. Environ. Microbiol.* **76**, 3702–3714.

Shahidi, F. (2009). Nutraceuticals and functional foods: Whole versus processed foods. *Trends Food Sci. Technol.* **20**, 376–387.

Shin, B. A., Kim, Y. R., Lee, I. S., Sung, C. K., Hong, J., Sim, C. J., Im, K. S., and Jung, J. S. (1999). Lyso-PAF analogues and lysophosphatidylcholines from the marine sponge *Spirastrella abata* as inhibitors of cholesterol biosynthesis. *J. Nat. Prod.* **62**, 1554–1557.

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

Sipkema, D., Osinga, R., Schatton, W., Mendola, D., Tramper, J., and Wijffels, R. H. (2005b). Large-scale production of pharmaceuticals by marine sponges: Sea, cell, or synthesis? *Biotechnol. Bioeng.* **90**, 202–222.

Sugiyama, Y., Ito, Y., Suzuki, M., and Hirota, A. (2009). Indole Derivatives from a marine sponge-derived yeast as DPPH radical scavengers. *J. Nat. Prod.* **72**, 2069–2071.

Swatschek, D., Schatton, W., Muller, W. E. G., and Kreuter, J. (2002). Microparticles derived from marine sponge collagen (SCMPs): Preparation, characterization and suitability for dermal delivery of all-trans retinol. *Eur. J. Pharm. Biopharm.* **54**, 125–133.

Taylor, M. W., Radax, R., Steger, D., and Wagner, M. (2007). Sponge-associated microorganisms: Evolution, ecology, and biotechnological potential. *Microbiol. Mol. Biol. Rev.* **71**, 295–347.

Thakur, N. L. and Müller, W. E. G. (2004). Biotechnological potential of marine sponges. *Curr. Sci.* **86**, 1506–1512.

Thomas, T. R. A., Kavlekar, D. P., and LokaBharathi, P. A. (2010). Marine drugs from sponge-microbe association—A review. *Mar. Drugs* **8**, 1417–1468.

Thoms, C. and Schupp, P. J. (2007). Chemical defense strategies in sponges: A review. *In* ''Porifera Research: Biodiversity, Innovation and Sustainability'', (M. R. Custódio, G. L. Hajdu, E. Hajdu, and G. Muricy, Eds), pp. 627–637. IMOS, Brazil.

Uriz, M., Turon, X., Becerro, M. A., and Agell, G. (2003). Siliceous spicules and skeleton frameworks in sponges: Origin, diversity, ultrastructural patterns, and biological functions. *Microsc. Res. Tech.* **62**, 279–299.

Utkina, N. K. (2009). Antioxidant activity of aromatic alkaloids from marine sponges Aaptos aaptos and Hyrtios sp. *Chem. Nat. Compd.* **6**, 849–853.

Utkina, N. K., Makarchenko, A. E., Shchelokova, O. V., and Virovaya, M. V. (2004). Antioxidant activity of phenolic metabolites from marine sponges. *Chem. Nat. Compd.* **40**, 373–377.

Webster, N. S. and Taylor, M. W. (2011). Marine sponges and their microbial symbionts: Love and other relationships. *Environ. Microbiol.* doi: 10.1111/j.1462-2920.2011.02460.x.

Zeisel, S. H. (1999). Regulation of nutraceuticals. *Science* **285**, 1835–1855.

Zhao, Q., Mansoor, T. A., Hong, J., Lee, C. O., Im, K. S., Lee, D. S., and Jung, J. H. (2003). New lysophosphatidylcholines and monoglycerides from the marine sponge Stelletta sp. *J. Nat. Prod.* **66**, 725–728.

Zhao, Q., Zhang, W., Jin, M., Yu, X., and Deng, M. (2005). Formulation of a basal medium for primary cell culture of the marine sponge Hymeniacidon perleve. *Biotechnol. Prog.* **21**, 1009–1012.