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Review Article

Chemical Constituents and Biological Activities of South East Asia Marine Sponges: A Review

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ABSTRACT

The ocean has an exceptional resource with various groups of natural products that are potentially useful for biomedical and other applications. Marine sponges have prominent characteristic natural products with high diversity. They produce many vital therapeutic metabolites with prominent biological activities. Marine invertebrates and microbial communities are the primary producers of such metabolites. Among the richest sources of these metabolites, class Demospongiae and the order Haplosclerida and genus Xestopongiae from family Petrosiidae are of interest. This review summarizes the research that has been conducted on two classes, eight orders, twelve families and fourteen genera of marine sponges available in the South East Asia region, covering the literature of the last 20 years. Ninety-five metabolites including alkaloids, sterols, terpenoids, quinones isolated from marine sponges collected in South East Asia along with their bioactivities especially cytotoxicity and antibacterial activities were reported in this review. Chemistry and biology are highly involved in studying marine sponges. Thus, tight collaboration is needed for understanding their taxonomy aspects. This

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review will outline chemistry and biological aspects, challenge, limitation, new idea and a clear future perspective on the discovery of new drugs from South East Asia's marine sponges.

Keywords: Bioactivities, chemistry, marine sponges, South East Asia

INTRODUCTION

The world's biodiversity is a wellspring for new discoveries. As a result of life's having developed multiple solutions to recurring challenges, organisms have produced billions of diverse compounds to enhance their chance of survival, and many of these compounds are potentially useful to mankind (Bhakuni & Rawat, 2005). In addition to its huge inventory of flora, fauna and other forms of life, the world's biodiversity also contains all of the interactions, energy pathways, symbioses and other elements that contribute to the lives of these species. The oceans, which comprise 95% of the Earth's hydrosphere, are the greatest centers of biodiversity (Jaksha, 2010). Within the realm of these oceans lies a treasure trove of undiscovered metabolites with novel chemical structures. These molecules demonstrate diverse biological properties of potential medical interest, such as anticancer, anti-inflammatory, anti-HIV, anti-infectives and treatments for a myriad of other diseases (El-Amraoui et al., 2013; Youssef et al., 2013; Blunt et al., 2007; Keyzers & Davies-Coleman, 2005; Simmons et al., 2005; Phuwapraisirisan et al., 2003).

Marine organisms are amazing living chemical factories. They produce primary metabolites (include sugars, fats, nucleic acids and proteins). These organisms are needed for life-sustaining and simple physiological functions, such as growth, metabolism and respiration. They are also important in energy storage, transfer, and genetic information management. In addition, molecular structural diversity of marine organism was higher than their terrestrial counterparts due to their longer evolutionary history. Similar to the terrestrial plants and animals, marine organisms also contain secondary metabolites that are essential contributors to their fitness and survival. Certain invertebrates that contain specific natural product compounds in their tissues may have less chance to be attacked by grazers and predators compared to similar organisms, which do not have such compounds. For example, the predators may be able to overcome the built-in defenses of their food source by sequestering the defense metabolites in their own tissues for their own protection.

Marine plants and animals have been drawn attention worldwide biomining effort to isolate useful natural product compounds from the marine environment in the past 30-40 years. A slight number of marine plants, microbes, and animals was reported to provide more than 13000 novel natural product molecules (Blunt et al., 2011). Since then, hundreds of new compounds have been yearly discovered. The interest in marine natural

products is further fueled by the fact that marine natural products tend to be more potent than those isolated from terrestrial organisms. This is probably as an essential arsenal in their chemical defense systems, marine organisms have to produce toxins that are potent at very low concentrations to overcome the enormous dilution factors that result from the dispersal of chemicals into the sea. Thus, the most potent cytotoxins known, such as apratoxin A and theopederins A to E, have been found in marine organisms (Huang et al., 2016; Fusetani et al., 1992).

In reality, the number of marine natural products that has made it to commercial application is still small compared to the terrestrial organism-derived bioproducts (Newman & Cragg, 2016). However, this is more likely to have been due to the relative infancy of marine bioprospecting activities than to a lack of potential for discovery. However, in the last two decades biodiscovery programs on marine natural products have indeed resulted in significant enrichment of marine natural product chemical libraries as exemplified by the two most notable marine databases, The Dictionary of Marine Natural Products (DMNP) and MarinLit. The biodiversity in marine species is extremely rich on coral reefs, where there are approximately 1000 species per m^2 especially in the Indo-Pacific Ocean where the marine diversity is maximal (Brahmachari, 2012; National Research Council, 2002). In fact, the Indo-Pacific oceans in particular, in which Malaysia is so opportunely situated, house the world's greatest tropical marine biodiversity. Despite this great promise, however, many vast ocean regions of the world, especially in the tropics, remain almost entirely unexplored. There is now a growing concern that many of the oceans' unknown resources are under threat from both climatic and human-effected changes on the earth's ecosystem. These bioresources may forever be lost, even before they could be fully understood let alone harnessed for the benefit of mankind. This calls for a more concerted, coordinated and sustainable effort to explore this valuable bioresources.

MARINE SPONGES AS A SOURCE OF MARINE NATURAL COMPOUNDS

Marine sponges (Porifera) have found for more than 700 million years and are claimed to be the most primitive of the multicellular animals. Taxonomically, there are four classes of Porifera*:* the Demospongie, Hexactinellida, Calcarea and Sclerospongie. Globally, there are more than 10000 species of marine sponges and most are classified as Demospongie (Koziol et al., 1997; Kruse et al., 1998). Marine sponges exclusively inhabit the marine environment and are widely found in the intertidal zones to areas of thousands of meters deep. They have a very strong pumping ability to filter large volumes of water via their tissues for the consumption of food and oxygen. Marine scientists believed that they have well-developed and efficient defenses against foreign organisms that may attack them. It is hence not unexpected that sponges are able to survive in a nutrient-poor environment and have evolved special chemical resistance strategy to defend against possible predators.

Marine sponges contain novel compounds on the basis that they yield the biggest quantity of structurally diversified natural products (Blunt et al., 2009; Rifai et al., 2005). They are indeed the top source of marine bioactive compounds, which serve as an important feedstock for the pharmaceutical industry. The bioactive compounds isolated from marine sponge species (*Neopetrosia* sp.) can interact with multiple key aspects of the cell cycle, enzymes and other targets, contributing to antidiabetic, antimicrobial, antifungal and cytotoxic activities (Ramanjooloo et al., 2015; Qaralleh et al., 2010). These interactions provide insights and potential inroads into the development of new therapeutics that have significant biological activities (Qaralleh et al., 2016; Ramanjooloo et al., 2015; Guzmán et al., 2011; Qaralleh et al., 2010; Takei et al., 2010; Coello et al., 2009; Rao et al., 2006; Lucas et al., 2003). These studies have deeply impacted the progress of drug discovery in the field of pharmacology, where new applications and potentials of certain compounds from the marine sponge can be more thoroughly characterized through studies of the interactions between the drugs and human systems (Dembitsky et al., 2005; Kim & Park, 2002).

OCCURRENCE OF MARINE SPONGES IN SOUTH EAST ASIA

Studies on the diversity of South East Asia sponges have been conducted by several groups, who have reported on the discovery and taxonomic identification of many species of sponges in the Indo-Pacific region. Among these were 168 species identified around the Derawan Islands, Indonesia (De Voogd et al., 2009), 118 species from Jakarta Bay, Indonesia (De Voogd & Cleary, 2008), 45 species from the Mo Ko Thale Tai National Park in the Gulf of Thailand (Putchakarn, 2007), 33 species from Cebu, Philippines (Longakit et al., 2007), 128 species from the Mariana Islands (Kelly et al., 2003), 126 species from the Eastern Gulf of Thailand (Kritsanapuntu et al., 2001), 151 species from Southwest of Sulawesi (de Voogd et al., 1999) and 3 species from Malaysia (Qaralleh et al., 2011). Table 1 shows the classification of the marine sponges.

Table 1

Classification of marine sponges

Class	Order	Family	Genus	Location
Demospongiae	Hadromerida	Suberitidae	*Aaptos*	Malaysia
	Haplosclerida	Petrosiidae	*Xestospongia*	Indonesia, Phillipines, Thailand and Vietnam
		Calafibrospongiidae		
		Callyspongiidae		

Table 1 *(Continue)*

Class	Order	Family	Genus	Location
		Chalinidae	*Haliclona*	Indonesia, Malaysia, Philippines and Thailand
		Niphatidae		
		Phloeodictyidae		
	Halichondrida	Axinellidae	*Axinella*	
		Halilchondriidae	*Axinyssa*	Thailand
	Poecilosclerida	Mycalidae	*Mycale*	Thailand
		Isodictyidae	*Isodictya*	Indonesia
	Dictyoceratida	Spongiidae	*Lendenfeldia*	Indonesia
			Spongia	Vietnam and Malaysia
	Verongiidae	Aplysinellidae		Indonesia
		Lanthellidae	*Lanthella*	Vietnam
Homoschleromorpha	Homosclerophorida	Plakinadae	*Plakortis*	
			Penares	Vietnam
Calcarea	Clathrinida	Leucettidae	*Leucetta*	Indonesia

In this review, the metabolites isolated from 12 families and 13 genera together with their bioactivities are summarized. The current review is intended to present an overview of the findings done by other researchers on South East Asia marine sponges, which reflect the rich structural diversity of the sponges in the South East Asia region as well as their great potential to yield lead compounds for future drug discovery. The information summarized herein will be useful in planning future research and development activities on the marine bio-resources of the South East Asia region.

Metabolites from the Genus *Aaptos*

Sponges of the genus *Aaptos* (family; Suberitidae, order; Hadromerida, and class; Demospongiae) are greyish-yellow or dark reddish-brown in color, with irregular and hispid surfaces but without prominent papillae (Boxshall et al., 2016). With firm and hard character traits, they are commonly 3 to 5 cm in diameter, occasionally larger to fist-sized and are described as lumpy and bluntly lobate. Sponges of this genus are typically found in deep waters, but they are also sometimes found in shallow sublittoral areas. The class of compounds reported from several *Aaptos* sp. includes alkaloids and sterols. Table 2

summarizes the compounds isolated from this genus and their bioactivities. The structures of the compounds are presented in Figure 1.

Aaptamine (1) and two other aaaptaminoids, 3-(phenythylamino)demethyl(oxy) aaptamine (2) and 3-(isopentylamino) demethyl(oxy)aaptamine (3) were isolated from an *Aaptos sp.* collected from the coastal waters of Terengganu, Malaysia (Shaari et al., 2008). These compounds were isolated from the chloroform fraction through bioassay-guided isolation in which the preliminary screening showed significant cytotoxic activities towards a range of cancer cell-lines, including human promyelocytic leukemia cells (HL-60), human T4-lymphoblastoid cells (CEM-SS), human breast cancer cells (MCF-7), human cervical cancer cells (HeLa), human colon cancer cells (HT-29) and mouse fibroblast cells (L929) with CD_{50} values, ranging from 3.2 to 24.1 µg/mL. Aaptamine was also isolated from another *Aaptos sp*. collected from Pulau Bidong, Terengganu (Mohamad et al., 2009).

The sterol cholestanol known as cholestan-3β-ol (4) was isolated from the non-polar fraction whereas aaptamine was isolated as greenish-yellow crystal from a semi-polar fraction during the screening of methanol extracts that showed strong antibacterial activity towards *Bacillus subtilis*, *Streptococcus fecalis* and *Streptococcus agalata* and weak antibacterial activity against *Bacillus proteus* and *Escherichia coli* as well as strong free-radical scavenging activity at 78.8% with IC_{50} value of 0.12 mg/mL (Mohamad et al., 2009).

Table 2

The bioactivity and isolated compounds from Genus Aaptos

Class	Compound	Bioactivity	References
Alkaloids	3-(phenythylamino) demethyl(oxy)aaptamine 3-(isopentylamino) demethyl(oxy)aaptamine	cytotoxic activities towards human promyelocytic leukaemia cells (HL-60), human T4-lymphoblastoid cells (CEM-SS), human breast cancer cells (MCF-7), human cervical cancer cells (HeLa), human colon cancer cells (HT-29) and mouse fibroblast cells (L929)	Shaari et al. (2008)
Cholestanol	cholestan-3β-ol	antibacterial activity against *Bacillus subtilis*, *Streotococcus fecalis* and *Streptococcus agalata* and weak antibacterial activity against *Bacillus proteus* and *Escherichia coli* strong free radical scavenging activity	Mohamad et al. (2009)

Aaptos species collected from Pulau Kapas, Pulau Perhentian and Pulau Redang were found to exhibit anti-amoebic capacity against the morbific *Acanthamoeba castellanii* (IMR isolate) (Nakisah et al., 2012). The study concentrated on cell growth inhibition, membrane penetrability and morphological features determined using scanning electron microscopy (SEM). The sponge extracts, whose anti-amoebic IC_{50} values ranged from 0.615 to 0.876 mg/mL, induced extensive cell blebbing, surface morphology changes, cell size reduction, cystic appearance, and reduction of the acanthapodia as well as the food cup. From the SEM analysis, it was found that the extracts not only affect the viability of *A. castellanii* but also induced apoptotic cell death. The sponge extracts were also shown to be genotoxic, inducing significant DNA damage in *A. castellanii*. The metabolites that were isolated from this species showed cytotoxicity, antibacterial properties and strong free radical-scavenging activity, and the extracts also exhibited potential anti-amoebic activity and genotoxicity.

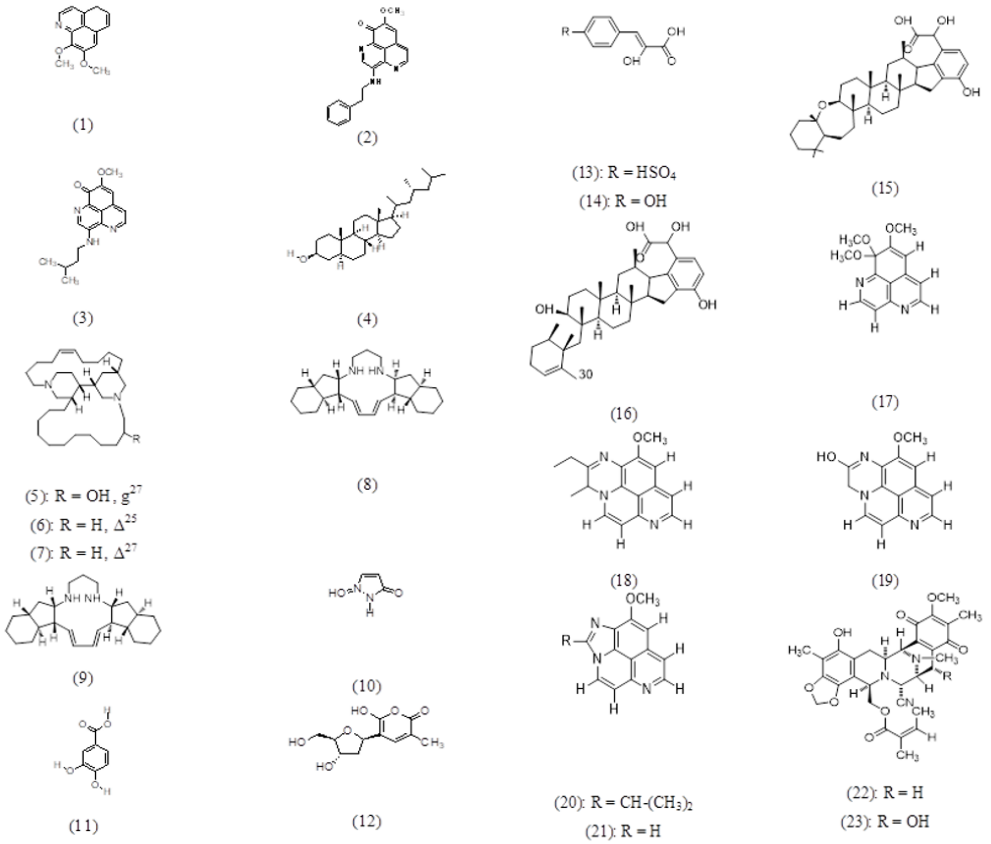

Figure 1. Chemical structures of isolated compounds from South East Asia marine sponges from genus *Aaptos* for (1)-(4), from genus *Haliclona* for (5)-(16), from genus *Petrosiidae* or *Xestospongia* for (17)-(23)

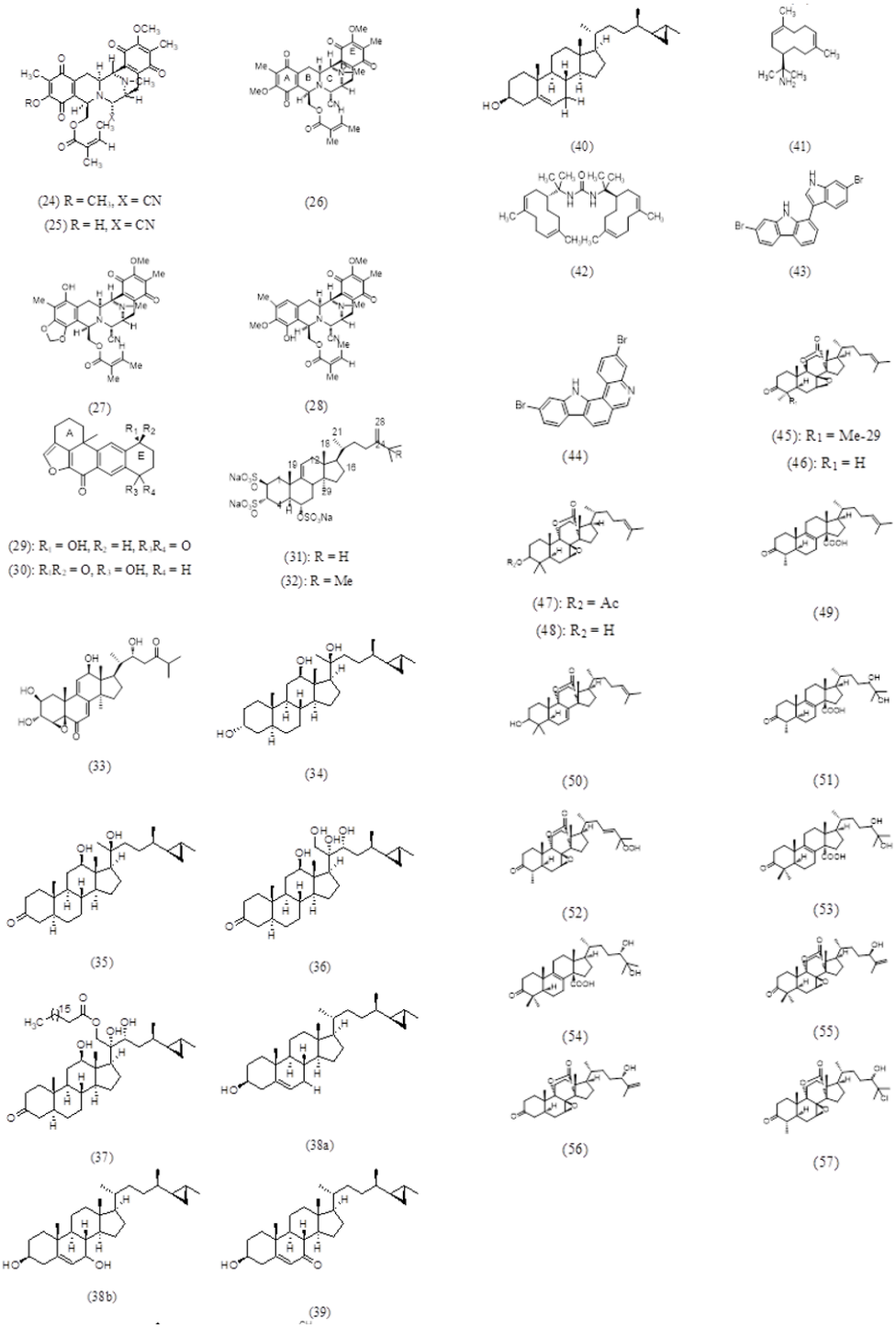

Figure 1. Chemical structures of isolated compounds from South East Asia marine sponges from genus *Petrosiidae* or *Xestospongia* for (24)-(40), from genus *Axinyssa* for (41)-(42), from genus *Penares* for (43)-(57)

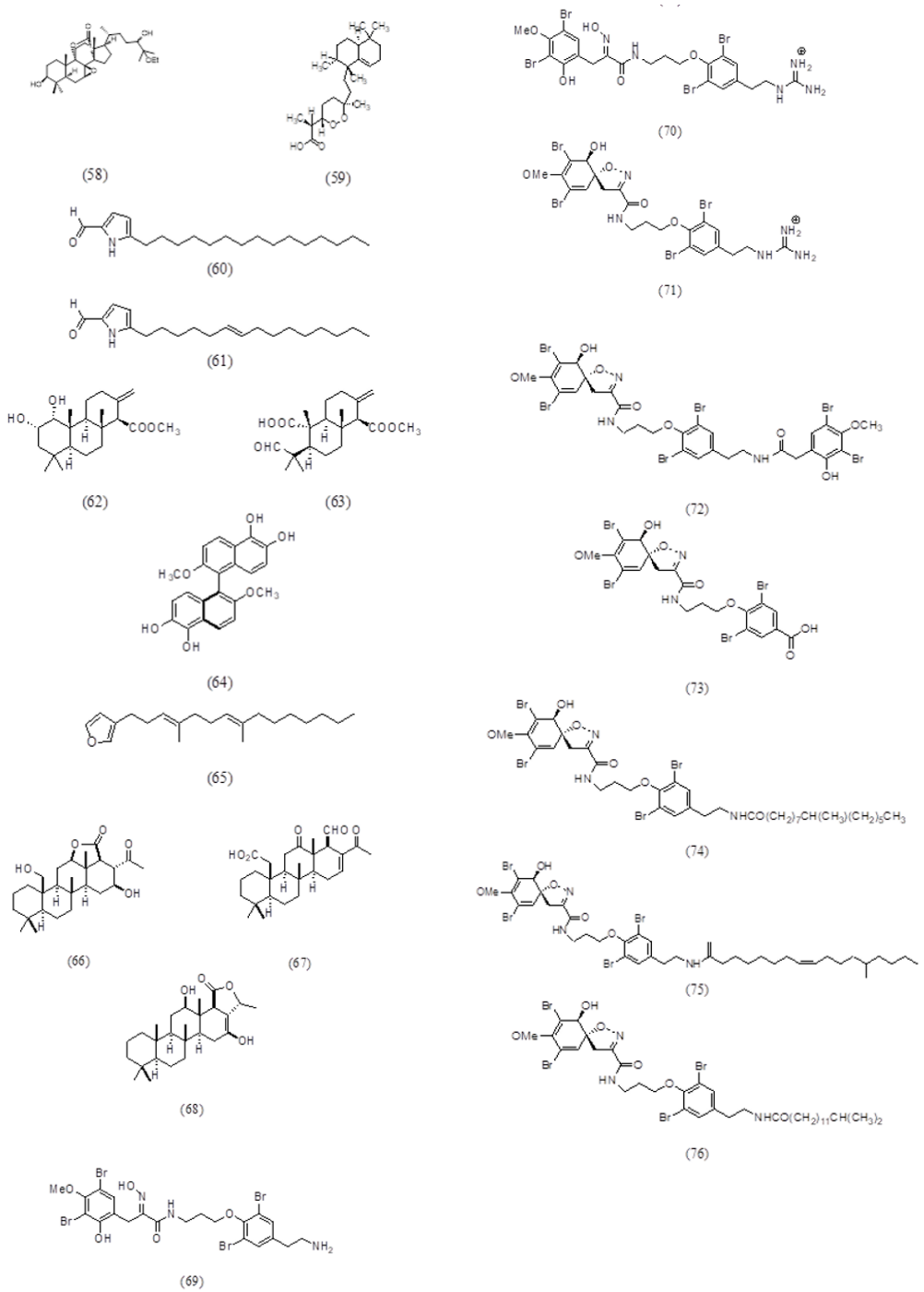

Figure 1. Chemical structures of isolated compounds from South East Asia marine sponges from genus *Penares* for (58), from genus *Mycale* for (59)-(61), from genus *Isodictya* for (62)-(63), from genus *Lendenfeldia* for (64)-(68), from family Aplysinellidae for (69)-(76)

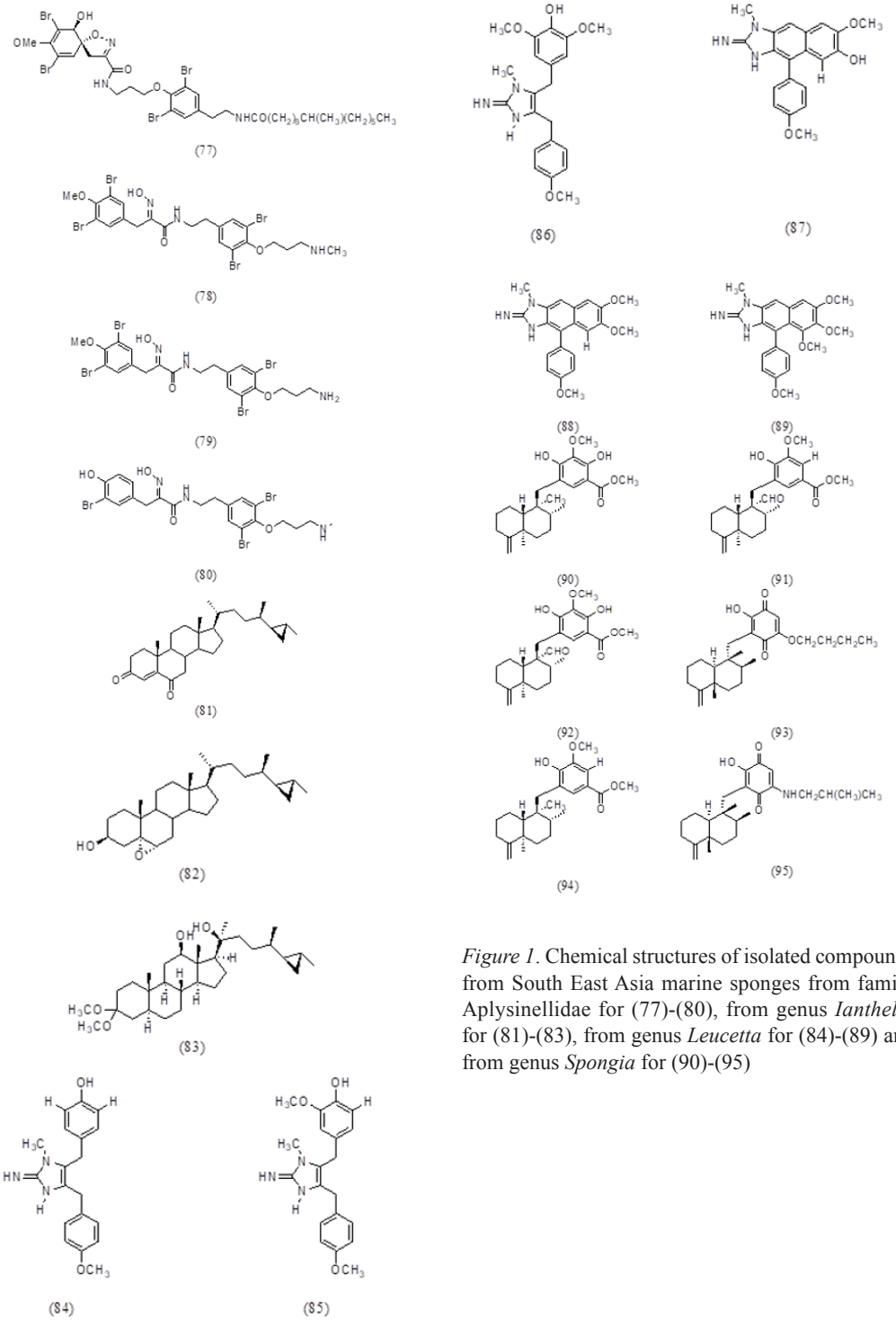

Figure 1. Chemical structures of isolated compounds from South East Asia marine sponges from family Aplysinellidae for (77)-(80), from genus *Ianthella* for (81)-(83), from genus *Leucetta* for (84)-(89) and from genus *Spongia* for (90)-(95)

Metabolites from the Genus *Haliclona*

Haliclona sponges (family; Chalinidae, order; Haplosclerida, and class; Demospongiae) are typically clumps of hollow cylinders that appear smooth and delicate on the surface (Beedessee et al., 2012). With firm and corky characteristic traits, they are commonly found under the stones with flat crusts and on rocks from the intertidal zone downwards to 30 m, where they serve as homes to baby starfish or echinoderms. The genus *Haliclona* has been chemically studied quite extensively since it has been discovered in many areas of the world. It elaborates a diverse array of compounds comprising alkaloids, hemiketals, polyacetylenes, quinones, terpenoids and sterols. Many of the *Haliclona* metabolites have been displayed to have significant biological activities, such as cytotoxicity, antibacterial, antifungal, anti-tumor and enzyme inhibition (Damodaran et al., 2013; Williams et al., 2012; Lakshmi et al., 2010; Casapullo et al., 2009; Jang et al., 2009; Abdo et al., 2007). *Haliclona* species are also common to the South East Asia region, and studies on them have yielded a myriad of compounds with interesting biological activities (Table 3).

A tetracyclic alkylpiperidine alkaloid, 22-hydroxyhaliclonacyclamine B (5) and haliclonacyclamines A (6) and B (7) were isolated from *Haliclona* sp. obtained from Flores Island, Indonesia (Arai et al., 2009). The alkaloids revealed strong anti-mycobacterial activity under aerobic and hypoxic (oxygen-depleted) conditions towards *Mycobacterium smegmatis* and *M. bovis* with MIC values of 2.5 μg/mL and 1.0 μg/mL, respectively, for both conditions. In contrast, the positive control (isoniazid) gave much weaker MIC values for the two strains (25 and >100 μg/mL, respectively) under hypoxic condition whereas it demonstrated similar or more potent MIC values (2.5 and 0.03 μg/mL, respectively) under aerobic conditions. Furthermore, 22-hydroxyhaliclonacyclamine B exhibited a bactericidal effect only on *M. bovis* under both aerobic and hypoxic states using colony-forming-unit (CFU) assay.

Papuamine (8) was isolated from a *Haliclona* sp. that was collected from Indonesia. The crude extract of the marine sponge displayed strong cytotoxicity and stimulation of apoptosis against human solid tumor cells (Kanno et al., 2013). The cytotoxicity effects of papuamine on human breast tumor cells (MCF-7) were found to be time- and concentration-dependent. Further studies showed that papuamine's mechanism of action was related to autophagy and is time-dependent. In this process, the mitochondrial membrane prospective showed a concentration- and a time-dependent reduction due to exposure to papuamine, which eventually caused dysfunction of the mitochondria. Furthermore, exposure to papuamine increased the phosphorylation or activation of c-Jun N-terminal protein kinase (JNK) through the release of cytochrome C that was also caused by the decrease in the membrane potential of mitochondria, which contributed to the reduction of cell survival and the activation of apoptotic cell death.

Papuamine (8) and haliclonadiamine (9) were also isolated from another *Haliclona* sp. obtained from Indonesia waters. In the preliminary screening, the ethanol extract of the marine sponge was cytotoxic to MCF-7 (MIC value 1.40 µg/mL), LNCap (MIC value 1.80 µg/mL), Caco-2 (MIC value 2.39 µg/mL) and HCT-15 (MIC value 2.25 µg/mL) cells (Yamazaki et al., 2013). The purified compounds were further found to be cytotoxic to six human cancer cell lines, i.e., breast cancer MCF-7, *liver cancer* Huh-7, prostate cancer PC-3, colorectal adenocarcinoma HCT-15, histiocytic lymphoma U937 and human Jurkat leukemia cells. The compounds were notably very potent against U937, with IC_{50} values of 0.93 µg/mL and 1.00 µg/mL, respectively. Further investigation on the mechanism of action revealed that the compounds trapped U937 cells at the sub-G1 phase, which contributed to condensation of chromatin and fragmentation of the nuclei (apoptosis of U937 cells).

Maleimide-5-oxime (10), 3,4-dihydroxybenzoic acid (11) and tetillapyrone (12) were isolated from *Haliclona baeri* collected in the coastal area of Chonburi Province, Thailand (Wattanadilok et al., 2007). Maleimide-5-oxime was isolated from the ethyl acetate extract as a viscous yellow mass. The isolated compounds showed potential antifungal activities tested on 7 yeasts, including *Candida albicans*, *C. krusei*, *C. glabata*, *C. parapsilosis C. dubliniensis*, *C. tropicalis*, and *Cryptococcus neoformans*. Moreover, 3 non-dermatophyte filamentous fungi known as *Aspergillus fumigatus*, *A. flavus* and *A. niger* were also inhibited as well as 5 dermatophyte fungi, including *Microsporum gypseum*, *M. canis*, *Trichophyton mantagrophytes*, *T. rubrum*, and *Epidermophyton floccosum*. Furthermore, the *in vitro* growth inhibition was examined against 3 cancer cell lines, the human breast adenocarcinomas (estrogen-dependent ER(+) MCF-7 and estrogen-independent ER(-) MDA-MB-231) and a non-small cell lung cancer cells (NCI-H460). However, maleimide-5-oxime showed very weak activities with MIC > 250 µg/mL for the antifungal assay and GI_{50} > 200 µM for the growth inhibition assay.

The marine sponge *Haliclona cymaeformis* collected in Mahatao, Batanes, Philippines yielded *p*-sulfooxyphenyl-pyruvic acid (13) as a mixture with *p*-hydroxyphenylpyruvic acid (14) (Bugni et al., 2002). Attempts at purification via HPLC were not successful and the compounds were therefore evaluated as the mixture. However, the mixture showed a very weak bioactivity for tyrosine kinase inhibition in the ^{3}H-thymidine incorporation assay.

Halicloic acid A (15) and halicloic acid B (16) were two merohexaprenoids isolated from the Philippines marine sponge *Haliclona* sp. collected in Culasian Point, Leyte (Williams et al., 2012). Both acids inhibited indoleamine 2,3-dioxygenase (IDO), which plays a central role in tumor cell evasion of T-cell-mediated immune rejection, with IC_{50} values of 10 µM and 11 µM, respectively, in an *in vitro* assay of the inhibition of purified recombinant human IDO. Overall, the secondary metabolites isolated from *Haliclona sp.* show great potential for antibacterial, cytotoxicity and antifungal activities in which the results showed that each compound is selective.

Table 3

The bioactivity and Isolated gompounds from genus Heliclona

	Compound	Bioactivity	References
Alkaloids	haliclonacyclamines A and B	strong anti-mycobacterial activity under aerobic and hypoxic conditions	Arai et al. (2009)
	22-hydroxyhaliclonacyclamine B	bactericidal effect against *M. bovis* Bacille de Calmette ed Guerin (BCG) under aerobic and hypoxic conditions	Arai et al. (2009)
	papuamine	potent cytotoxicity, induce apoptosis against human solid cancer cells	Kanno et al. (2013)
	papuamine and haliclonadiamine	cytotoxicity against MCF-7, hepatoma Huh-7, prostate fencer PC-3, HCT 15, histolytic lymphoma U937 & Jurkat cells	Yamazaki et al. (2013)
	haliscosamine	antifungal	El-Amraoui et al. (2013)
Malaimides	maleimide-5-oxime	antifungal	Erickson et al. (1995); Wattanadilok et al. (2007)
Terpenoids	*p*-sulfooxyphenyl-pyruvic acid		Bugni et al. (2002)
	halicloic acid A and B	Indoleamine 2,3-dioxygenase (IDO) inhibition	Williams et al. (2012)

Metabolites from the Genus *Xetospongia*

The genus *Xestospongia* (family; Petrosiidae, order; Haplosclerida, and class; Demospongiae) consists of tubular sponges of oscules or large openings at the apex with a rough surface (Beedessee et al., 2012). Appearing as a massive vase or volcano-like shape, some of which are encrusted and bulbous, these stony and brittle sponges are commonly found on the wall of sea cliffs or caves, in the reef and at the sea bed (Qaralleh et al., 2011). These species are also known to contain more siliceous spicules than spongin. There have been many chemical investigations on *Xetospongia* collected from many parts of the world, which revealed it to elaborate a diverse array of compounds which includes alkaloids, macrolides, polyacetylenes, quinones, terpenoids and sterols (Lorente et al., 2015; Mejia et al., 2013; Laurent et al., 2006). Some of the reported bioactivities and compounds isolated from *Xestospongia* collected in the South East Asia region are summarized in Table 4.

Table 4

The bioactivity and isolated compounds from genus Petrosiidae or Xestospongia

	Compound	Bioactivity	References
Alkaloids	8,9,9-trimethoxy-9H-benzo[*de*][1,6]-naphthyridine and four new compounds	cytotoxic	Calcul et al. (2003)
	renieramycins T and U	cytotoxic to human colon carcinoma (HCT 116), human lung carcinoma (QG 56), human pancreatic adenocarcinoma (AsPC1) and human ductal breast epithelial tumor (T47D)	Daikuhara et al. (2009)
	renieramycins W, X and Y		Tatsukawa et al. (2012)
Quinones	xestosaprol D and E	Xestosaprol D weakly inhibits the aspartic protease BACE-1	Millán-Aguiñaga et al. (2010)
Sterols	ibisterol sulfates B and C and 4β,5β-epoxy-2β,3α,12β,22S-tetrahydroxy-14α-methylcholest-7,9(11)-dien-6,24-dione	Inhibitors of HIV-1 integrase	Lerch & Faulkner (2001)
	aragusterol I, aragusterol B, xestokerol A, 21-*O*-octadecanoyl-xestokerol A, 7α-hydroxypetrosterol, 7β-hydroxypetrosterol, 7-oxopetrosterol and petrosterol	Antifouling	Nguyen et al. (2013)

Aaptaminoids were isolated from an Indonesian *Xestospongia* collected off the Jakarta coast (Calcul et al., 2003). The methanolic extract of the sponge revealed a potent antimicrobial activity against bacteria of Gram-negative (*Escherichia coli* and *Vibrio anguillarum*) and Gram-positive (*Staphylococcus aureus*). It was also tested against fungi (*Candida tropicalis*) and showed potential activity. Thus, it was subjected to bioassay-guided isolation to yield the alkaloids 8,9,9-trimethoxy-9H-benzo[de][1,6]-naphthyridine (17), 2-ethyl-3-methyl-10-methoxy-3H-1,3a,6-triazapyrene (18), 11-methoxy-1H-[1,6]naphthyridino[6,5,4-def]quinoxalin-2(3H)-one (19), 2-isopropyl-10-methoxybenzimidazo[6,7,1-def][1,6]naphthyridine (20) and 10-methoxybenzimidazo[6,7,1-

def][1,6]naphthyridine (21). Various compounds from the aaptamine class were isolated together with the previously found aaptamine, isoaaptamine and demethyl(oxy)aaptamine from Indonesian marine sponge *Xestospongia* sp. obtained off Jakarta. All the isolated compounds were examined for antimicrobial against Gram-negative bacteria of *Escherichia coli* and *Vibrio anguillarum* as well as Gram-positive bacteria of *Staphylococcus aureus*. The *Candida tropicalis* fungi was also tested. In addition, the compounds were cytotoxic against human buccal carcinoma KB cells. Aaptamine, isoaaptamine, demethyl(oxy) aaptamine and 10-methoxybenzimidazo[6,7,1-def][1,6]naphthyridine displayed moderate antibacterial activity with MIC values ranging from 6 to 100 µg/mL. In particular, the compounds were more active against *Vibrio anguillarum* with MIC values of 12 µg/mL for both aaptamine and isoaaptamine, and 100 µg/mL for both demethyl(oxy)aaptamine and 10-methoxybenzimidazo[6,7,1-def][1,6]naphthyridine. With respect to the antifungal activity, only aaptamine and isoaaptamine showed activity against *Candida tropicalis* with MIC values of 25 µg/mL and 12 µg/mL, respectively. As for cytotoxicity, 8,9,9-trimethoxy-9H-benzo[de][1,6]-naphthyridine as well as aaptamine, isoaaptamine and dimethyl(oxy) aaptamine showed cytotoxic activities with ID_{50} values of 3.5 µg/mL, 3.7 µg/mL, 0.5 µg/mL and 1.8 µg/mL, respectively.

Two bistetrahydroisoquinoline marine natural products, renieramycins T (22) and U (23) were isolated together with renieramycins M (24) and S (25) from a Thai *Xestospongia* sp. collected in the vicinity of Sichang Island (Daikuhara et al., 2009). These compounds were isolated from the methanolic extract pretreated with KCN through partitioning and column chromatography. Both renieramycins T and U were isolated as amorphous powders. All of the isolated compounds were tested for cytotoxicity against human colon carcinoma (HCT 116), human lung carcinoma (QG 56), human pancreatic adenocarcinoma (AsPC1) and human ductal breast epithelial tumor (T47D) cells. Renieramycin T, showed strong cytotoxicity with IC_{50} values ranging from 4.7 to 98 nM while renieramycin M showed the strongest cytotoxicity with IC_{50} values ranging from 0.84 to 20 nM.

Three bistetrahydroisoquinoline marine natural products, including renieramycins W (26), X (27) and Y (28) and two renieramycins M (24) and T (22) were identified from a Philippine *Xestospongia* sp. collected in the vicinity of Puerto Galera at Oriental Mindoro of Mindoro Island (Tatsukawa et al., 2012). These compounds were isolated from the ethyl acetate extract pretreated with KCN via column chromatography. Renieramycin W was isolated as pale-yellow amorphous powder, renieramycin X as a pale yellow amorphous solid, and renieramycin Y as a pale-yellow solid. These renieramycins W and X were examples of tiglic acid esters derivatives at the C-1 side chain, while renieramycin Y is the example, having pentasubstituted phenol in the A-ring.

Xestosaprol D (29) and E (30), two xestosaprol derivatives, and a series of pentacyclic compounds, including adociaquinones A and B, xestosaprol A,

13,14,15,16-tetrahydroxestoquinol and 3,13-dideoxo-1,2,13,15-tetrahydro-3-13-dihydroxyhalenaquinone were isolated from *Xestospongia* sp. obtained from Turtle Bay, Sangalaki, Indonesia (Millán-Aguiñaga et al., 2010). Xestosaprol D was isolated as an optically active yellow solid, while xestosaprol E was identified as an optically dynamic solid through bioassay-guided fractionation. In a preliminary screening, an ethyl acetate extract showed potent antimicrobial activity against multi-drug resistant *Staphylococcus aureus* (ATCC 43300). However, pure xestosaprol D only poorly inhibited the aspartic protease BACE-1, a key enzyme in the etiology of Alzheimer's disease, with an IC_{50} value of 30 μg/mL. In addition, neither xestosaprol D nor E displayed any appreciable antimicrobial activity against Vancomycin-Resistant Enterococci, *Escherichia coli*, Methicillin-resistant *Staphylococcus aureus* or *Staphylococcus aureus* or cytotoxicity against SKOV-3 cells (IC_{50}> 50 μg/mL), which is a human ovarian tumor cell line.

Two sulfated sterols, ibisterol sulfates B (31) and C (32) and an extraordinary non-sulfated sterol, 4β,5β-epoxy-2β,3α,12β,22*S*-tetrahydroxy-14α-methylcholest-7,9(11)-dien-6,24-dione (33) together with halistanol sulfate and ibisterol sulfate were elucidated in a Philippines *Xestospongia* sp. obtained off Boracay Island (Lerch & Faulkner, 2001). These compounds were isolated through bioassay-guided fractionation and column chromatography since the methanolic extract showed some selectivity in initial cytotoxicity screening against a 25-cell-line panel. All compounds were obtained as white powders in which the sulfated sterols ibisterol sulfates B and C were the major metabolites while the non-sulfated 4β,5β-epoxy-2β,3α,12β,22S-tetrahydroxy-14α-methylcholest-7,9(11)-dien-6,24-dione was a minor metabolite. All isolated compounds were tested in an HIV-integrase inhibition assay in which they exhibited mild inhibition with IC_{50} values of 0.4 μg/mL, 2.3 μg/mL, 1.8 μg/mL and 26 μg/mL for halistanol sulfate, ibisterol sulfate B, ibisterol sulfate C and 4β,5β-epoxy-2β,3α,12β,22S-tetrahydroxy-14α-methylcholest-7,9(11)-dien-6,24-dione, respectively. This species yields compounds with strong cytotoxicity properties regardless of geographical area of origin, which may be further targets for study for drug development.

Three new sterols, aragusterol I (34), 21-*O*-octadecanoyl-xestokerol A (37) and 7β-hydroxypetrosterol (38b) and five known compounds, aragusterol B (35), xestokerol A (36), 7α-hydroxypetrosterol (38a), 7-oxopetrosterol (39) and petrosterol (40) were isolated from *Xestopongia testudinaria* collected in Truong Sa archipelago, Khanh Hoa, Vietnam (Nguyen et al., 2013). Aragusterol B and 21-*O*-octadecanoyl-xestokerol A showed the most active antifouling activity with EC_{50} value (60 and 10 μM, respectively) where EC_{50} value of 21-*O*-octadecanoyl-xestokerol A is comparable to tributyltin oxide (EC_{50} = 12 μM), a current marine anti-biofouling agent while not exhibiting toxicity up to 200 μM in growth inhibition and viability assay on *Polaribacter* sp., TC5.

Metabolites from the Genus *Axinyssa*

The genus *Axinyssa* (family; Halilchondriidae, order; Halichondrida, and class; Demospongiae) are digitate cushion-shaped sponges with hispid and conulose surfaces (Boxshall et al., 2016). This genus is commonly found in soft sediment in deeper water ranging from 40 m to 80 m. *Axinyssa* is known for having sesquiterpenes that contain unusual nitrogenous functional groups and that usually possess anthelmintic, antimalarial and antifouling properties. The compounds isolated, and bioactivities reported from genus *Axinyssa* are presented in Table 5.

A Thai *Axinyssa sp*. collected from the Andaman Sea yielded two new nitrogenous germacrane sesquiterpenes identified as (1*Z*,4*Z*)-7α*H*-11-aminogermacra-1(10),4-diene (41) and *N*,*N*-11-bis-[(1*Z*,4*Z*)-7α*H*-germacra-1(10),4-dienyl]urea (42) from the ethyl acetate extract (Satitpatipan & Suwanborirux, 2004). (1*Z*,4*Z*)-7α*H*-11-aminogermacra-1(10),4-diene showed strong antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis* with inhibition zones 23 mm and 22 mm, respectively. The compound also exhibited potent antifungal activity against *Candida albicans* with an inhibition zone of 27 mm. However, *N*,*N*-11-bis-[(1*Z*,4*Z*)-7α*H*-germacra-1(10),4-dienyl]urea did not show any antimicrobial activity at the same test concentration.

Table 5

The bioactivity and isolated compounds from genus Axinyssa

	Compound	Bioactivity	References
Terpenoids	(1*Z*,4*Z*)-7α*H*-11-aminogermacra-1(10),4-diene (1) and *N*,*N*-11-bis-[(1*Z*,4*Z*)-7α*H*-germacra-1(10),4-dienyl]urea	antimicrobial against *Staphylococcus aureus* and *Bacillus subtilise and* anti fungal against *Candida albicans*	Satitpatipan and Suwanborirux (2004)

Metabolites from the Genus *Penares*

Sponges of the genus *Penares* (family; Plakinadae, order; Homosclerophorida, and class; Demospongiae) usually consist of several rounded parts joined at their bases. Sometimes these sponges are also described as shapeless (Lyakhova et al., 2012). They may be structurally hard or slightly compressible and whitish-beige or greyish in color. This genus is well known to elaborate triterpenoids, indole and azetidine alkaloids, sphingolipids, macrolides and fatty acids. Some of the reported bioactivities and compounds isolated from genus *Penares* are presented in Table 6.

Two unusual bromine-containing alkaloids, 7-bromo-1-(6-bromo-1*H*-indol-3-yl)-9*H*-carbazole (43) and 3,11-dibromo-13*H*-indolo[3,2-*k*]phenanthridine (44) were elucidated

from a South China Sea *Penares* sp. obtained from the Vietnamese waters (Lyakhova et al., 2012). 7-bromo-1-(6-bromo-1*H*-indol-3-yl)-9*H*-carbazole was observed as pale yellow amorphous powder while 3,11-dibromo-13*H*-indolo[3,2-*k*]phenanthridine was obtained as light brown solid. Compound (43) showed moderate inhibition of the human cancer cell lines, human promyelocytic leukemia HL-60 (IC_{50} of 16.1 μM) and human cervical carcinoma HeLa (IC_{50} of 33.2 μM). However, compound (44) was inactive.

Six triterpenoids (45 - 50) together with penasterone, acetylpenasterol and ergosta-4,24(28)-dien-3-one were identified from the non-polar fractions of a *Penares sp*. collected from Vietnamese waters (Kolesnikova et al., 2013). Cytotoxic activity for all of these triterpenoids compounds were tested against numerous human cancer cell lines, including human promyelocytic leukemia (HL-60), Ehrlich ascites carcinoma, and human cervical carcinoma (HeLa). It was also examined on normal murine epithelial cells (JB6 C141). The results showed that compound 50 was cytotoxic against human HL-60 cells with an IC_{50} value of 9.7 μM.

Eight tritepenes, derivatives of oxidized lanostane and *nor*-lanostane (51 - 58) were isolated from the non-polar extract of another *Penares sp*. collected from the Vietnam waters (Lyakhova et al., 2015). The compounds were identified as 29-*nor*-24(*R*),25-dihydroxypenasterone (51), 29-*nor*-25-hydroperoxy-3-oxo-7β,8β-epoxy-5α-lanost-23(*E*)-en-30,9α-olide (52), 24(*R*),25-dihydroxypenasterone (53), 24(*S*)-25-dihydroxypenasterone (54), 24(*R*)-hydroxy-3-oxo-7β,8β-epoxy-5α-lanost-25-en-30,9α-olide (55), 24(*S*)-hydroxy-3-oxo-7β,8β-epoxy-5α-lanost-25-en-30,9α-olide (56), 29-*nor*-24ξ-hydroxy-25-chloro-3-oxo-7β,8β-epoxy-5α-lanost-30,9α-olide (57) and 3β,24-dihydroxy-7β,8β-epoxy-5α-lanost-24-en-30,9α-olide (58).

Table 6

The bioactivity and isolated compounds from genus Penares

	Compound	Bioactivity	References
Alkaloids	7-bromo-1-(6-bromo-1*H*-indol-3-yl)-9*H*-carbazole	cytotoxic against human tumour cell lines, human promyelocytic leukaemia HL-60 and human cervical carcinoma HeLa	Lyakhova et al. (2012)
	3,11-dibromo-13*H*-indolo[3,2-*k*]phenanthridine		Lyakhova et al. (2012)
Terpenoids	Six new triterpenoids, penasterone, acetylpenasterol and ergosta-4,24(28)-dien-3-one	cytotoxic against human promyelocytic leukaemia HL-60	Kolesnikova et al. (2013)
	Eight oxidised lanostane and *nor*-lanostane derivatives, penasterol and 24-ethylcholesta-4,24(28)-dien-3-one		Lyakhova et al. (2015)

Metabolites from the Genus *Mycale*

The genus *Mycale* (family; Mycalidae, order; Poecilosclerida, and class; Demospongiae) comprises yellow or yellowish sponges that look like cushions or sheets, which are found either under the littoral boulders or under rocks and shells in the sublittoral areas (Boxshall et al., 2016). This genus has a soft to firm consistency, occasionally compressible, with a fibrous interior. It has few but large oscules at the summit of the lobes. This genus is known for producing secondary metabolites that exhibit antiviral and antitumor activities (Habener et al., 2016). Some of the compounds and their bioactivities are presented in Table 7.

A cyclic norsesterterpene peroxide, mycaperoxide H (59), as well as a known norsesterterpene peroxide, mycaperoxide B, were isolated from a Thai *Mycale* sp. collected from Sichang Island (Phuwapraisirisan et al., 2003). These peroxides were isolated from the polar fractions of the sponge via bioassay-guided isolation. Mycaperoxide H exhibited cytotoxicity against HeLa cells with an IC_{50} value of 0.8 μg/mL while mycaperoxide B is a known compound with cytotoxic properties.

5-Pentadecyl-1*H*-pyrrole-2-carbaldehyde (60) and (6'E)-5-(6'pentadecenyl)-1*H*-pyrrole-2-carbaldehyde (61) were isolated as a mixture from ethyl acetate fraction through column chromatography and DAD-HPLC. It was based on the results from bioassay guided fractionation of *in vitro* growth inhibition screening on mouse lymphoma cell line (L5178Y) (Hertiani et al., 2009).

Table 7

The bioactivity and isolated compounds from genus Mycale

	Compound	Bioactivity	References
Carbaldehydes	5-pentadecyl-1*H*-pyrrole-2-carbaldehyde and (6'E)-5-(6'pentadecenyl)-1*H*-pyrrole-2-carbaldehyde	Growth inhibition of mouse lymphoma cell line (L5178Y)	Hertiani et al. (2009)
Norsesterterpenes peroxide	mycaperoxide H and B	cytotoxic against HeLa cells	Phuwapraisirisan et al. (2003)

Metabolites Isolated from the Genus *Isodictya*

Sponges from genus *Isodictya* (family; Isodictyidae, order; Poecilosclerida, and class; Demospongiae) are being described as colourful (bright yellow, brownish, maroon, greenish and black) daisy-like, large, and hard but chalky sponge. Typically found in narrow opening of rocks in shallow waters to 40 m deep waters, these sponges have many small, branch-like fistules on an exhalant-liked perforated large subhemisperical body (Lim et al., 2008; Fattorusso et al., 2006). Compounds isolated, and their bioactivities are summarized in Table 8.

Table 8
The bioactivity and isolated compounds from genus Isodictya

	Compound	Bioactivity	References
ent-isocopalane diterpenes	coelodiol and coeloic acid	cytotoxic against human gastric adenocarcinoma	Fattorusso et al. (2006)

Coelodiol (62) and coeloic acid (63), both are rare *ent*-isocopalane diterpenes were isolated from the ethyl acetate fractions of the *Isodictya* genus (Fattorusso et al., 2006). For cytotoxicity screening, both isolated compounds showed inhibition in *in vitro* growth of human gastric adenocarcinoma cell line (MKN-45) with 20 μg/mL for coelodiol and 40 μg/mL for coeloic acid.

Metabolites Isolated from the Genus *Lendenfeldia*

Sponges from genus *Lendenfeldia* (family; Spongiidae, order; Dictyoceratida, and class; Demospongiae) are less described with details and it is mostly found near Australian waters with ample of cytotoxic compounds isolated from it. However, few of this genus were reported in South East Asia and the isolated compounds and their bioactivities for *Lendenfeldia* sp. found in South East Asia are summarized in Table 9.

A new naphthalene dimer, (S)-2,2′-dimethoxy-1,1′-binaphthyl-5,5′,6,6′-tetraol (64), a new furanolipid, 3-[(3E,7E)-4,8-dimethylpentadeca-3,7-dienyl]-furan (65) and three known homoscalarane sestertepenes, 16β,22-dihydroxy-24-methyl-24-oxoscalaran-25,12β-olactone (66), 24-methyl-12,24,25-trioxoscalar-16-en-22-oic acid (67), and 12,16-dihydroxy-24-methylscalaran-25,24-olide (68) were isolated from marine sponge, *Lendenfeldia* sp. collected from Indonesia (Dai et al., 2007). The bioassay-guided isolation was performed using column chromatography to yield the new colourless gum, (S)-2,2′-dimethoxy-1,1′-binaphthyl-5,5′,6,6′-tetraol, and oil, 3-[(3E,7E)-4,8-dimethylpentadeca-3,7-dienyl]-furan besides obtaining the three known homoscalarane sestertepenes. All isolated compounds showed inhibition in hypoxia-induced HIF-1 activation and iron chelator (1, 10-phenanthroline)-induced HIF-1 activation in T47D breast tumour cells except 3-[(3E,7E)-4,8-dimethylpentadeca-3,7-dienyl]-furan with IC_{50} values ranges from 0.64 to 6.90 μM with 24-methyl-12,24,25-trioxoscalar-16-en-22-oic acid, which was the most potent compound. Besides, the naphthalene dimer and homoscalarane sestertepenes showed similar results on both human breast tumour cell lines (T47D and MDA-MB-231) under normoxic conditions (containing 21% oxygen).

Table 9

The bioactivity and isolated compounds from genus Lendenfeldia

	Compound	Bioactivity	Reference
Naphthalene dimer	(S)-2,2′-dimethoxy-1,1′-binaphthyl-5,5′,6,6′-tetraol	inhibit hypoxia-induced HIF-1 activation and reduction of the viability of breast tumor cells (T47D and MDA-MB-231)	Dai et al. (2007)
Furanolipid	3-[(3E,7E)-4,8-dimethylpentadeca-3,7-dienyl]-furan		
Homoscalarane sestertepenes	16β,22-dihydroxy-24-methyl-24-oxoscalaran-25,12β-olactone, 24-methyl-12,24,25-trioxoscalar-16-en-22-oic acid, and 12,16-dihydroxy-24-methylscalaran-25,24-olide		

Metabolites Isolated from the Family Aplysinellidae

Sponges originated from the family Aplysinellidae of the Order Verongiidae have a dendritic fibrous skeleton (Bergquist & de Cook, 2002). The skeleton of sponges from this family is typically made up of fibres with bark and pith elements of different proportion of fibre-mass to soft tissues volume from one species to another. However, sponges from this family are well-known for its alkaloids containing bromotyrosine residues (Dai et al., 2016). The compounds isolated and their bioactivities reported are presented in Table 10.

Seven new bromotyrosine-derived metabolites and six known compounds were isolated from the family Aplysinellidae collected from Manta Point, Sangalaki, Indonesia (Dai et al., 2016). The new metabolites isolated were purpuramine M (69), purpuramine N (70), araplysillin VII (71), araplysillin VIII (72), araplysillin IX (73), araplysillin X (74) and araplysillin XI (75). In the same study, there was also six known compounds, namely hexadellin A (8), araplysillin II (76), araplysillin IV (77), purpurealidin I (78), aplysamine 4 (79), and purpuramine G (80). They are isolated together with the new compounds from the methanol extract through silica flash column chromatography and reversed-phase HPLC. The isolated compounds were tested for inhibition of aspartic protease, BACE-1 (memapsin-2) and differential cell viability in five cancer cell lines, ovarian cancer A2780S and cisplatin-resistant variant A2780CP (SCP5), non-small cell lung cancer A549, human breast cancer MCF-7, and glioma U251MG cells and a control cell line of normal mouse fibroblasts of NIH3T3. Araplysillin X and purpurealidin I showed the most significant activity while purpuramine M had inhibition of growth in ovarian cancer cell lines (A2780S

and A2780CP (SCP5)) and glioma cancer cell line U251MG with IC_{50} values 20, 40 and 50 μM respectively.

Table 10

The bioactivity and isolated compounds from family Aplysinellidae

	Compound	Bioactivity	Reference
Bromotyrosine-derived metabolites	purpuramine M, purpuramine N, araplysillin VII, araplysillin VIII, araplysillin IX, apaplysillin X, araplysillin XI, hexadellin A, araplysillin II, araplysillin IV, purpurealidin I, aplysamine 4, and purpuramine G	moderate inhibition of the aspartic protease (BACE1), cytotoxicity	Dai et al. (2016)

Metabolites Isolated from the Genus *Ianthella*

Normally being found in shallow waters attached to dead or alive coral head, sponges from genus *Ianthella* (family; Lanthellidae, order; Verongiidae, and class; Demospongiae) are known to be bright-coloured and tube-liked (Brunt and Davies, 1994). Compounds isolated from sponges of this genus and their bioactivities are summarized in Table 11.

Petrosterol-3,6-dione (81) and 5α,6α-epoxy-petrosterol (82) are two new cycloprapane ring sterols isolated together with a known compound, petrosterol (40) from a Vietnamese sponge, *Ianthella* sp. collected from Namyet Island in Khanh Hoa province in Vietnam (Tung et al., 2009a). The isolated compounds exhibited cytotoxicity activities against multiple cancer cell lines (A549, HL-60, MCF-7, SK-OV-3 and U937) with IC_{50} ranges from 8.4 to 22.6 μM especially in HL-60 cells. Apoptosis events (chromatin condensation and increase of the amount of sub-G1 hypodiploid cells) were observed in treated cells, suggesting the possibility of potential leukemia treatment.

In addition, aragusteroketal B (83) and aragusterol B (35) were isolated from ethyl acetate soluble fractions through silica gel and resins column chromatography from *Ianthella* sp. obtained from Vietnam waters (Tung et al., 2009b). Cytotoxicity activities against three human tumour cell lines (MCF-7, SK-Hep-1 and HeLa) were conducted on isolated compounds presenting moderate activities with aragusterolketal B giving lower IC_{50} against HeLa (24.6 μM). Aragusterol B had lower IC_{50} against MCF-7 (12.8 μM) and SK-Hep-1 (18.5 μM).

Table 11

The bioactivity and isolated compounds from genus Ianthella

	Compound	Bioactivity	References
Sterols	petrosterol-3,6-dione, 5α,6α-epoxy-petrosterol and petrosterol	cytotoxic against A549, HL-60, MCF-7, SK-OV-3 and U937	Tung et al. (2009a)
	aragusteroketal B and aragusterol B	cytotoxic against MCF-7, SK-Hep-1 and HeLa	Tung et al. (2009b)

Metabolites Isolated from the Genus *Leucetta*

With massive, subspherical or pear-shaped outline, sponges from genus *Leucetta* (family; Leucettidae, order; Clathrinida, and class; Calcarea) usually consists of large oscules surrounded by elevated margin with visible subcortical cavities (Hooper, 2014). Mostly found on the hard substrate on the outer reef slope, the sponges of this genus are often being described in bright coloured and with compact or firm structure but chalky or friable. Due to presence of imidazole alkaloids with interesting bioactivities profile, this genus is frequently being studied. Table 12 summarizes the compounds isolated from genus *Leucetta* with their bioactivities.

New imidazole alkaloids, naamine F (85), naamine G (86), kealiinine A (87), kealiinine B (88) and kealiinine C (89) were isolated together with known compound, naamine A (84) from sponges of *Leucetta chagosensis* collected near the coast of Kapoposang Island, Indonesia (Hassan et al., 2004). These alkaloids were isolated from the ethyl acetate and butanol fractions of methanol crude extract using reversed-phase silica and Sephadex LH20. Isolated compounds were tested on antimicrobial assays and antiproliferative assay against human cervix carcinoma cell line (HeLa), mouse lymphoma cells L5178Y and rat brain tumour cell line PC12. Naamine G exhibited strong antifungal activity against *Clasdosporium Herbarum* and weak cytotoxicity against L5178Y and HeLa cell lines and inactive against the PC12 cell lines. However, for brine shrimp assay, kealiinine A showed the most active result, contributing to a mortality rate of 50 % at 20 µg/mL.

Table 12

The bioactivity and isolated compounds from genus Leucetta

	Compound	Bioactivity	Reference
Imidazole alkaloids	naamine A, naamine F, naamine G, kealiinine A, kealiinine B and kealiinine C	antifungal and cytotoxicity	Hassan et al. (2004)

Metabolites Isolated from the Genus *Spongia*

With firm, rubbery and compressible texture, sponges of genus *Spongia* (family; Spongiidae, order; Dictyoceratida, and class; Demospongiae) are identified as dark cream or brownish coloured sponge of subspherical, fig-shaped and stalk tapered with wide base found in lagoons on top of rocks or pinnacles (Hall, 2012). Meroterpenoids from this genus showed a variety of interesting bioactivities. Table 13 presents the bioactivity and isolated compounds from genus *Spongia*.

Three new sesquiterpene phenols (langconol A (90), langconol B (91), and langconol C (92)) and a new sesquiterpene hydroxyquinone (langcoquinone C (93)) were isolated from marine sponge *Spongia* sp. obtained from Vietnam waters. In addition, two others known meroterpenoids, polyfibrospongol A (94) and smenospongorine (95) were identified from this sponge (Nguyen et al., 2017). Langcoquinone C and smenospongorine exhibited strong antibacterial activity against Gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus* (MIC values ranges from 6.25 to 12.50 μM) which is comparable with positive control (amplicillin, MIC: 6.25 μM). Langconol A and langconol C showed moderate antibacterial activity against *Bacillus subtilis* (MIC value of 12.50 and 25.00 μM, respectively). For cytotoxicity testing against three cancer cell lines, lung cancer (A549), breast cancer (MCF-7) and cervix cancer (HeLa) and one human normal cell line, fibroblast (WI-38), langconol C, langcoquinone C and smenospongorine had strong to moderate cytotoxicity against all tested cell lines including both cancer cell lines and normal cell line. However, langconol A, langconol B and polyfibrospongol A exhibited weak cytotoxicity (IC_{50} > 50 μM) for all cell lines.

Table 13

The bioactivity and isolated compounds from genus Spongia

	Compound	Bioactivity	References
Meroterpenoids	langconol A, langconol B, and langconol C	antibacterial and cytotoxicity	Nguyen et al. (2017)
	langcoquinone C		
	polyfibrospongol A and smenospongorine		
	scalarolide acetate, scalarolide, 12-*O*-deacetyl-12-*epi*-19-*O*-methylscalarin and methyl 18-hydroxy-19-norscalar-16-en-20-carboxylate	Cytotoxic against T-cell leukemia (ATL), S1T cells	Phan et al. (2018)

CONCLUSION

In summary, the marine environment of South East Asia has great potential to yield new insights on novel bioactive sponge metabolites because of the wide array of compounds of diverse structures isolated from only a small number of sponge species collected from this region. Although marine organisms are potential sources of many bioactive compounds and are expected to provide more that could combat various chronic diseases, research in this area is still scarce. The discovery of compounds with potential bioactivities from marine organisms is valuable to pharmaceutical research and industry. Many of these compounds show interesting and potent biological activities that suggesting that they may have potential uses as therapeutic agents. Certainly, exploration of the wealth of these marine organisms using cutting-edge technologies needs to be pursued with greater coordination and vigor to fully tap their real value for the betterment of health and the regional economy. Many marine organisms are found in various locations, and some of them show great potentiality, regardless of their geographical origin. In view of the high significance of these marine organisms for pharmaceutical research, further exploration and identification of precious metabolites that may serve as the important basis for the future of drug development require more efforts.

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