Chapter 10

Biological and Medicinal Importance of Sponge

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Additional information is available at the end of the chapter

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Abstract

Sponges are multicellular, heterotrophic parazoan organisms, characterized by the possession of unique feeding system among the animals. They are the most primitive types of animals in existence, featuring a cell-based organization where different cells have different tasks, but do not form tissues. Sponges (Porifera) are a predominantly marine phylum living from the intertidal to the abyssal (deepest ocean) zone. There are approximately 8500 described species of sponges worldwide with a prominent role in many reef coral communities. Several ecological studies reported have shown that secondary metabolites isolated from sponges often serve defensive purposes to protect them from threats such as predator attacks, biofouling, microbial infections, and overgrowth by other sessile organisms. In the recent years, interest in marine sponges has risen considerably due to presence of high number of interesting biologically active natural products. More than 5300 different natural products are known from sponges and their associated microorganisms, and every year hundreds of new substances are discovered. In addition to the unusual nucleosides, other classes of substances such as bioactive terpenes, sterols, fatty acids, alkaloids, cyclic peptides, peroxides, and amino acid derivatives (which are frequently halogenated) have been described from sponges or from their associated microorganisms. Many of these natural products from sponges have shown a wide range of pharmacological activities such as anticancer, antifungal, antiviral, anthelmintic, antiprotozoal, anti-inflammatory, immunosuppressive, neurosuppressive, and antifouling activities. This chapter covers extensive work published regarding new compounds isolated from marine sponges and biological activities associated with them.

Keywords: sponges, anticancer, antibacterial, chemical constituents

1. Introduction

Sponges are the ancient, efficient designed multicellular parazoan organisms and show relatively little differentiation and tissue coordination. A sponge is a sessile, sedentary, filter-feeding

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primitive aquatic invertebrate animal which attaches itself to solid surfaces from intertidal zone to depths of 29,000 ft (85000m) or more, where they can get sufficient food to grow [1, 2]. Sponges feed on microscopic organisms (protozoa, bacteria and other small organisms in water) and organic particles [3]. There are about 10,000 known species inhabit a wide variety of marine and fresh water habitats and are found throughout deep ocean depths to rock pools, warm tropical seas to frozen arctic seas, rivers and streams [3, 4]. They are very diverse and occur in various colors, sizes and shapes such as tubular (tube-like), globular (ball-shaped), caliculate (cup-shaped), arboresecent (plant-shaped), flabellate (fan-shaped) and amorphous (shapeless). The scientific term for sponges is Porifera meaning "pore-bearing" and has bodies full of pores and channels allowing water to circulate through them, consisting of jelly-like mesohyl sandwiched between two layers of cells [5]. The shapes of their bodies are adapted for maximal efficiency of water flow through the central cavity, where it deposits the nutrients, and leaves through a hole called the osculum. Several sponges have spicules of silicon dioxide or calcium carbonate and a mesh of proteins called spongin as an internal skeleton. One of the remarkable properties of sponges is their ability to suffer damage and regenerative capacity [6–8]. Marine sponges have attracted growing attention as a source of overwhelming structurally diverse secondary metabolites with potential biological activities and were placed at the top with respect to discovery of biologically active chemical constituents [9, 10]. Although thousands of chemical compounds have been reported in the literature from these sponges, only few of them are clinically described. Many studies revealed that sponge-derived metabolites are used directly in therapy or as a prototype of bioactive leads to develop more active and less toxic analogs [11, 12]. Sponges are most primitive type of aquatic animals in existence which are dominating many benthic habitats, featuring a cell-based organization where different cells conduct all forms of bodily function, but do not form tissues [13]. They consume food and excrete waste products within cells without a body cavity [14]. Several ecological studies reported that high quantity of bioactive constituents produced by sponges often serve defensive against environmental threats such as predation, microbial infection, competition for space or overgrowth by fouling organisms [15, 16]. For this reason marine sponges are the subject of attraction for chemists due to the sheer number of metabolites produced, the novelty of structure encountered, and the therapeutic potential of these compounds in the treatment of human diseases. Scientists working in the field of natural product chemistry and research suggest that these sponges have promising potential to provide future drugs which can serve various diseases. In this chapter, we describe main isolated chemical entities from sponges and their pharmacological application.

2. Anticancer agents

In the recent years, marine natural products bioprospecting has yielded a considerable number of drug candidates, most still being in preclinical or early clinical development, with only a limited number already in the market [17]. A typical example of marine anticancer drugs is eribulinmesylate, a derivative of halichondrin B isolated from the marine sponge. *Halichondria okadai* has achieved success in phase III clinical trials. Literature studies have shown sponge-derived discodermolides antitumor compounds can play remarkable role in future to treat cancer. Plethora of secondary metabolites is produced by marine sponges and their symbionts. The spongothymidine and spongouridine nucleosides were the first successful sponge-derived

pharmaceutical drugs isolated from *Tectitethya crypta* [18]. Ara-C (cytarabineor1-beta-D-Arabinofuranosylcytosine) recently used for the cure of leukemia [19, 20] and its combination with Daunoribicin and other anticancer drugs, is screened in clinical trials for the treatment of acute myeloid neoplasms [21] During the last few years several marine derived natural compounds are in the pipeline for evaluation in Phase I–III clinical trials for various cancers treatment [22]. A review in 2003 listed the most important anticancer candidate from marine natural compounds undergoing preclinical and clinical (I, II, III) trials and following compounds were from sponge origin: Isohomohalichondrin B, Halichondrin B, Laulimalide/Fijianolide,5-methoxyamphimedine(alkaloid)Discodermolide, Hemiasterlins A and B, Fascaphysins (alkaloid), modified halichondrin B, KRN-70000, Alipkinidine (alkaloid), and Variolin (alkaloid) [23]. Moreover marine sponges are the important source for vital diverse bioactive constituents including alkaloids, terpenoids, sterols and macrolides. Renieramycins, members of tetrahydroiso-quinoline family were isolated from marine sponges from genus Reniera with promising anticancer potential. The preclinical results reported that Renieramycin M, a natural constituent from sponge induced lung cancer cells apoptosis through p53-dependent pathway and may inhibit progression and metastasis of lung cancer cells [24]. A novel polycyclic guanidine alkaloid monanchocidin isolated from *Monanchora pulchra* marine sponge reported to induce cell death in human cervical cancer (HeLa),human monocytic leukemia (THP-1) and mouse epidermal (JB6 Cl41) cells [25]. In the early 1987, as esquiterpene aminoquinone, Smenospongine extracted from *Smenospongia* sp. reported to induces cytotoxic, antiproliferetive, antiangiogenic, and antimicrobial activities [26]. Spongistatin a macrocyclic lactone polyether isolated from *Spongia* sp. marine sponge in 1993 was shown to inhibit microtubule assembly, mitosis, and the binding of tubulin to vinblastine thereby inducing cytotoxic cell death in numerous cancer cell lines [27, 28]. Recently a very important compound named lectin has been isolated from *Cinachyrella apion* marine sponge was evaluated for antiproliferative, hemolytic, and cytotoxic properties, besides the ability to induce cell death in tumor cells. Results showed that the lectin induces cell death by apoptosis activation by pro-apoptotic protein Bax, promoting permeabilization of mitochondrial membrane, S phase cell cycle arrest and acting as both dependent and/or independent of caspases pathway. These results indicate the potential of lectin for treating cancer [29]. Another marine sponge component, heteronemin a sesterterpene isolated from *Hyrtios sp*. has attracted the interest of researchers as an antimour agent especially for its pharmacological effects on chronic myelogenous leukemia cells. Results revealed that heteronemin affected the various cellular processes such as cell cycle, nitrogen-activated protein kinases pathways, apoptosis, and nuclear factor kappa B signaling cascade. Thus the compound has shown anti-inflammatory as well as anticancer agent [30]. A collaborative program between experimental therapeutics laboratory of Henry Ford Hospital in Detroit and University of California Santa Cruz initiated in 1990 focused on the development and discovery of anticancer drugs from sponge extracts. About 2036 extracts from 683 individual sponges were examined by using novel *in vitro* assay led to the identification pure bioactive compounds from many sponges for treating solid tumors. The collaborative efforts and analogs led to the isolation of number of constituents with of anticancer potential [31].

Thus the possibility of development of new anticancer drugs for curing or reducing cancer is promising. Until now, *in vitro* antitumor activity studies of sponge-derived compounds were tested. Thus, the detailed pharmaceutical studies to investigate the mechanism of action and clinical trials are needed. Moreover, the extensive ongoing research on sponges and development

of new advanced techniques have made it possible to access deep sea, new anticancer marine isolates with unprecedented carbon skeleton and inhibitory activities of human cancer cell continued to be discovered and developed, which will offer in future the new candidate for cancer therapy. The chemical constituents so far reported for anticancer activity include (**Table 1**).

Categories	Species	Active agents	Antitumor tested	References
Alkaloids	*Papua*	Hyrtiocarboline	H522-T1, MDA-MB- 435, U937 tumor cell lines	[31]
	Penares sp.		HL-60, HeLa	[32]
	Aaptos suberitoides	Aaptamine	L5178Y	[33]
	Monanchora arbuscula	Norbatzelladine		
		Dinorbatzelladine	MDA-MB-231 breast cancer	[34]
		Dinordehy-drobatzelladine		
		Dinorbatzelladine		
		Dihomodehy-drobatzelladine	MDA-MB-231 breast cancer	[34]
	Clathria calla	Norbatzelladine		
		Clathriadic acid		
	Xestospongia sp.	Renieramycin T	HCT116, QC56, AsPC1	[35]
			T47D tumor cell lines	
	Smenospongia sp.	6′-Iodoaureol	MOLT-3, HepG2 cells	[36]
	Hyrtios sp.	Hyrtimomine A	Human epidermoid carcinoma KB, murine leukemia L1210	[37]
	Pseudoceratina verrucosa	Aplysamine	HeLa, NFF cells	[38]
	Amphimedon sp.	Pyrinodemin G	P388 murine leukemia cells	
		Pyrinodemin H		[39]
	Oceanapia sp.	Sagitol C	PC12, L5178Y, HeLa cells	[40]
	Monanchora pulchra	Monanchocidins B		
		Monanchocidins C	HL-60 human leukemia cells	[41]
		Monanchocidins D		
		Monanchocidins E		
	Agelas sp.	Hexazosceptrin		
		Agelestes A-B	U937, PC9 human	
		(9S, 10R, 90S, 100R)-nakamuric acid	Cancer cell lines	[42]
Sterols	*Ianthella sp.*	Petrosterol-3,6-dione	A549 (lung), HT-29 (colon),	
		5α,6α-epoxy-petrosterol	SK-OV-3 (ovary), MCF-7 (breast) HL-60 and U937	[43]
	Lissodendryx fibrosa	Manadosterol A-B	Ubc13–Uev1A complex	[44]
Terpenoids	*Carteriospongia* sp.	Homoscalarane sesterterpenes	A2780, H522-T1, A2058	[45]
	Monanchora sp.	9Sesterterpenoids	A498, ACHN (renal cancer)	[46]
			MIA-paca, and PANC-1 (pancreatic cancer)	[47]
	Psammocinia sp.	Scalarane sesterterpenes	A498, ACHN MIA-paca,PANC-1	[48]
	Pseudoaxinella flava	Diterpene isonitrile	PC3(prostate cancer cell line)	[49]
	Agelas axifera	Three axistatins (pyrimidine diterpenes)	P338, BXPC-3 MCF-7, SF-268 NCI-H460, KML20L2, and DU-145 cell lines growth	[50]

Categories	Species	Active agents	Antitumor tested	References
	Thorectare ticulate	Metachromins U Metachromins V	SF-268, H460,MCF-7, HT-29, and CHOK1 (mammalian cell line)	[51]
	Dactylospongia elegans	Nakijinol B and CHO-K1	SF-268, H460, MCF-7, HT-29	[51]
	Coscinoderma sp.	Sesterterpenes coscinolactams C	K562 and A549 (human cancer cells)	[52]
		Coscinolactams D,		
		Coscinolactams E		
		Coscinolactams F		
		Coscinolactams G		[53]
Macrolide	*Cinachyrella enigmatica*	Enigmazole A	NCI 60 human tumor cells	[54]
	Jaspis splendans	Jaspamide M	MCF-7and HT-29	[55]
		Jaspamide N	(antimicrofilament)	
		Jaspamide O		
		Jaspamide P		
	Mycale hentscheli	Peloruside A	P388 HL-60 cells	[56]
		Peloruside B		
	Pipestela candelabra	Pipestelide A	KB cell lines	[57]
		Pipestelide B		
Polyketone	Plakortis simplex	Simplextone C	HeLa, K562, A-549 cell lines	
		Plakortoxide A		[58]
	Plakortis halichondrioides	Epiplakinidioic acid	DU-145, A2058	[59]
		Plakortoxide A	tumor cell lines	
	Lithoplocamialithistoides	Polyketides PM050489	HT-29, A549, MDA-MB-231	
		Polyketides PM060184	Human tumor cell lines	[60]
Peptides	*Homophymia* sp.	Homophymines B	KB, MCF7, MCF7R, HCT116	
		Homophymines E	HCT15, HT29, OVCAR 8, OV3,	
		Homophymines A1-E1	PC3, Vero, MRC5, HL60, HL60R, K562, PaCa, SF268, A549, MDA231, MDA435, HepG2, and EPC human tumor cells	[61]
	Neamphius huxleyi	Neamphamide B	A549,HeLa, LNCaP,	
		Neamphamide C	PC3, NFF human tumor	
		Neamphamide D	cell lines	[62]
	Eurypon laughlini	Rolloamide A	LNCap, PC3MM2, PC3, DU145 (Prostrate), MDA361, MCF7, MDA231 (breast), OVCAR3, SKOV3, U87MG (Glioma), (ovarian), A498 (renal)	[63]
	Stylissa caribica	Stylissamide H	HCT-116.	[64]
	Homophymia lamellose	Pipecolidepsin A	A549, HT-29 MDA-MB-231	
		Pipecolidepsin B	Human tumor cells	[65]
Glycosides	*Pandaros acanthifolium*	Acanthifoliosides A–E	L6 cell lines	[66]
	Rhabdastrella globostellata	Rhabdastin E-G	HL-60	[67]
Quinones	*Dysidea avara*	Dysidavarone A	HeLa, A549, MDA231, QGY7703	
		Dysidavarone D	HeLa tumor cells	[68]
	Dactylospongia metachromia	5 Sesquiterpene aminoquinones	L5178Y mouse cancer cell lines	[69]

Categories	Species	Active agents	Antitumor tested	References
	Dactylospongia avara	3 Dysideanones A–C	HeLa HepG2 cancer cell lines	[70]
Miscellaneous	*Petrosia* sp.	3(−) Petrosynoic acids A–D	A2058, H522-T1,	
			H460 human tumor cell line	
			IMR-90 human fibroblast cells	[71]
	Subereamollis	Subereaphenol D	HeLa cell lines	[72]
	Mixture of *Smenospongia aurea*	(E)-10-benzyl-5,7-dimethylun-1 deca,5,10-trien-4-ol	HL-60 human leukemia	
	Smenospongia cerebriformis			
	Verongula rigida			[73]
	Myrmekioderma dendyi	Myrmekioside E-2	NSCLC-N6 and A549 tumor cell lines	[74]
	Genus *Suberea*.	Four novel Psammaplysin analogs	Cytotoxicity	[75]

Table 1. Marine sponge-derived anticancer compounds and their effects.

3. Antibacterial active agents

Marine sponges are among the richest sources of interesting chemicals produced by marine organisms. Exploitation of bioactive metabolites by natural product chemist from marine sources by using antimicrobial or cytotoxic assays started back in 1970s. Later, various reputed pharmaceutical companies joined hands for this effort using more advance assay systems, including enzyme inhibition assays. As a result several new promising bioactive candidates have been discovered from marine sponges [76]. Bioactive constituents are claimed for potent *in vivo* or *in vitro* activity against infectious and parasitic diseases, such as bacterial, fungal, viral and protozoan infections. Studies revealed that the crude extracts of marine sponge have shown high incidences of antibacterial activity against terrestrial pathogenic bacteria, but very low incidences of antibacterial activity against marine bacteria [77, 78]. Very few cases of sponge infection by exogenous microorganisms are known, presumably due to the accumulation/or product by the marine sponges of substances which have antimicrobial activity [1]. A number of new metabolites with antibiotic applications are discovered every year, but in marine sponges their ubiquity is remarkable. Antibacterial screening of marine sponges led to identification and characterization of wide range of active chemical constituents, including some with promising therapeutic leads [79, 80]. Around 850 antibiotic constituents are reported from marine sponges [81]. Various antibacterial substances were identified from marine sponges by continuous efforts of marine natural product community. Despite of discovery of huge number of natural product from marine sponges, none of them has yet led to antibacterial product, but currently several are under investigation. Examples of some isolated substances from marine sponges with antibacterial activity are shown in **Table 2**. The first discovered antibiotic from a marine sponge was manoalide, a seterterpenoid isolated from *Luffariella variabilis* [82]. The most promising constituents with antibacterial properties reported from marine sponges include: agelasine D, cribrostatin 3 and 6, petrosamine B, psammaplin A and alkylpyridines (haliclonacyclamine E, arenosclerins) and among these constituents, manzamine A and psammaplin A are in preclinical trials. Many of these have excellent potential for drug development, but no commercial medication has been originated from them so far.

Categories	Species	Active agents	Antibacterial tested	References
Alkaloids	*Axinella* sp.	Axinellamines B-D	*H. pylori* Gram-(-ve)	[83]
	Acanthostrongylophora sp.	12,34-Oxamanzamine E,	*M. tuberculosis*	[84]
		8-Hydroxymanzamine J		
		6-Hydroxymanzamine E		
	Arenosclera brasiliensis	Haliclonacyclamine E,	*S. aureus, P. aeruginosa*	
		Arenosclerins A-C		[85]
	Spongosorites sp.	Deoxytopsentin, bromotopsentin	*S. aureus* (MRSA strain)	
		4,5-Dihydro-6″-deoxybromotopsentin, bis(indole)		[86]
	Cribrochalina sp.	Cribrostatin 3	*N. gonorrheae*	[87]
	Cribrochalina sp.	Cribrostatin 6	*S. pneumonia*	[88]
	Spongosorites sp.	Hamacanthin A	*S. aureus* (MRSA strain)	[86]
	Oceanapia sp.	Petrosamine B	*H. pylori*	[89]
	Latrunculia sp.	Discorhabdin R	*S. aureus, M. luteus*	[90]
			S. marcescens, E. coli	
	Hamacantha sp.	Hamacanthin A 1	*C. albicans*	
		Hamacanthin B 2	*C. neoformans*	[91]
Nitrogenous	*Pachychalina* sp.	Cyclostellettamines A-I,	*S. aureus* (MRSA strain),	[92]
		Cyclostel K-L	*P. aeruginosa* (antibiotic-resistant strain), *M. tuberculosis*	[93]
	Pachychalina sp.	Ingenamine G	*S. aureus* (MRSA strain)	
			E. coli, *M. tuberculosis*	[92]
	M. sarassinorum	Melophlin C	*B. subtilis, S. aureus*	[47]
	Agelas sp.	Agelasine D	*M. tuberculosis Gram (+ve, -ve)*	[94]
Terpenoids	*Cacospongia* sp.	Isojaspic acid, cacospongin D, jaspaquinol	*S. epidermidis*	[95]
	Myrmekiodermastyx	(S)-(+)-curcuphenol	*M. tuberculosis*	[96]
Miscellaneous	*Oceanapia* sp.	C14 acetylenic acid	*E. coli, P. aeruginosa, B. subtilis, S. aureus*	[97]
	C. sphaeroconia	Caminosides A-D	*E. coli*	[98]
	A. coralliphaga	Corallidictyals A-D	*S. aureus*	[99]
	C. varians	CvL	*B. subtilis, S. aureus*	[100]
	N. magnifica	Latrunculins	*S. aureus* and *B. cereus*	[101]
	Discodermia sp.	Polydiscamide A	*B. subtilis*	[93]
	Psammaplysilla	Psammaplin A	*S. aureus* (MRSA strain)	[102]

Table 2. Marine sponge-derived antibacterial compounds and their effects.

4. Antiviral compounds and their efficacy

The search for new antiviral substances from marine sources led to the isolation of several promising therapeutic leads which are presented in **Table 3**. The literature presents a good number of reports about different biological activities of marine sponges. Several papers

Categories	Species	Active agents	Antiviral tests	References
Alkaloid	*Aaptosa aptos*	4-Methylaaptamine	HSV-1	[110]
	Halicortex sp.	Dragmacidin F	HSV-1	[111]
	Indo-Pacific	Manzamine A, 8-hydroxymanzamine A, 6-deoxymanzamine X neokauluamine	HIV-1	[112]
Nucleosides	*Mycale* sp.	Mycalamide A-B	A59 coronavirus, HSV-1	[113]
	Hamacantha sp.	Coscinamides 60-62,		
		Chondriamides 63-65	Anti-HIV	[91]
Cyclic depsipeptides	*Theonella* sp.	Papuamides A-D	HIV-1	[114]
	S. microspinosa	Microspinosamide	HIV-1	[115]
Sterols	Haplosclerid sponges	Haplosamates A	HV-1	
		Haplosamates B		[116]
Terpenoids	*D. avara*	Avarol 6′-hydroxy avarol, 3′-hydroxy avarone	HV-1	[117]
Nucleoside	*Cryptotethya crypta*	Ara-A	HSV-1, HSV-2, VZV	[105]
	Mycale sp.	Mycalamide A-B	A59 coronavirus, HSV-1	[118]
Miscellaneous	*Dysidea avara*	Callyspongymic acid	HIV, hepatitis B virus	[119]
		2′-5′ Oligoadenylates	Viral replication	[120]
	H. tarangaensis	Hamigeran B	Herpes, polio viruses	[121]
	Petrosia weinbergi	Weinbersterols A-B	Leukemia virus, mouse influenza virus, mouse corona virus	[122]

Table 3. Antiviral compounds from marine sponges and their effects.

reports the screening results of marine organisms for antiviral activity, and a diverse range of active constituents have been isolated and characterized from them [80, 103, 104]. For some of these isolated substances important antiviral activities were reported. Perhaps the most important antiviral lead of marine origin reported thus far is the nucleoside ara-A (vidarabine) isolated from the sponge *Cryptotethya crypta*. Ara-A is a semisynthetic compound, based on the arabinosyl nucleosides, that inhibits viral DNA synthesis [105]. Once it was realized that biological systems would recognize the nucleoside base after modifications of the sugar moiety, chemists began to substitute the typical pentoses with acyclic entities or with substituted sugars, leading to the drug azidothymidine (zidovudine). Ara-A, ara-C (1-β-Darabinosyl cytosine, cytarabine), acyclovir, and azidothymidine are in clinical use and are all examples of products of semisynthetic modifications of the arabinosyl nucleosides [106]. Several of these substances have a great potential for drug development. Ara-A has been used for the treatment of herpes virus infections, but it is less efficient and more toxic than acyclovir [107, 108]. However, ara-A is capable of inhibiting a cyclovir-resistant HSV and VZV (varicella-zoster virus) [109]. The most promising antiviral substances from sponges appear to be 4-methylaaptamine, avarol, manzamines, mycalamide A and B. Among these substances, preclinical assessments were started for avarol and manzamine A. In general, antiviral molecules from sponges do not give protection against viruses, but they may result in drugs to treat already infected individuals. In addition, broad-based antiviral agents such as 2-5A and α-glucosidase inhibitors may be useful in cases of sudden outbreaks of (less familiar) viruses such as SARS and Ebola [80].

5. Antifungal compounds

Marine sponges have been considered a gold mine for the discovery of marine natural products during the past 50 years. The need of new antifungals in clinical medicine due to various kinds of mycoses, in particular invasive mycoses have become serious health problems as their incidences has increased dramatically during last few years in relation to AIDS, transplant recipients, hematological malignancies, transplant recipients and other immunosuppressed individuals. One of the major causes of death in patients suffering from malignant disease is fungal infections and emerging resistance is also an important problem. Immunocompromised patients are mainly infected by *Aspergillus*, *Cryptococcus*, *Candida*, and other opportunistic fungi. *Candida albicans* is most often associated with serious invasive fungal infections, but other *Candida* species and yeast-like organisms (*Blastoschizomyces*, *Trichosporon* and *Malassezia*) have emerged as etiological agents of severe mycoses problem [123–126]. Fungicides which are presently being used are less diverse than antimicrobials, and the usage of many of them is restricted because of their toxic effects to animals, plants and humans. Moreover the progress in this area is slow as comparison to antibacterial agents [126]. Antifungal compounds isolated from marine sponges are listed in **Table 4**.

Categories	species	Active agents	Antifungal tests	References
Alkaloids	*A. brasiliensis*	Arenosclerins A-C	*C. albicans*	
		Haliclonacyclamine E		[127]
	Acanthostrongylophora sp.	Manzamine A	*C. neoformans*	[112]
	Leucetta cf.	Naamine D	*Chagosensis C. neoformans*	[128]
	Pseudoceratina sp.	Ceratinadins A-C	*C. albicans*	[129]
	A. citrina	(−)-Agelasidine F,	*C. albicans*	
		(−)-Agelasidine C		[130]
	M. arbuscular	Batzelladine L	*A. flavus*	[131]
Terpenoids	*L. variabilis*	Secomanoalide	*C. glabrata, C. krusei*	
			C. albicans	[132]
	M. herdmani	Microsclerodermins A-B	*A. fumigatus*	[133]
	Hyrtios sp.	Puupehenonol	*C. neoformans*, *C. krusei*	[134]
Sterols	*Euryspongia* sp.	Eurysterols A-B	*C. albicans*	[135]
	Topsentia sp	Geodisterol-3-O-sulfite, 29-demethylgeodisterol-3-OCl-sulfite	*S. cerevisiae, C. albicans*	
			C. albicans	[136]
Peptides	*Discodermia* sp.	Discobahamin A-B	*C. albicans*	[137]
	Jaspis sp.	Jasplakinolide or jaspamide	*C. albicans*	[138]
	Latrunculia sp.	Callipeltins F-I	*C. albicans*	[139]
	Latrunculia sp.	Callipeltin J-K	*C. albicans*	[42]
	T. swinhoei	Theonellamide G	*C. albicans*	[140]
	Theonella sp.	Theonellamide TNM-F	*Candida* spp, *Trichophyton* spp, *Aspergillus* sp.	[141]
Purine derivatives	*Agelas* sp.	Agelasines, agelasimines	*C. krusei*	[142]

Categories	species	Active agents	Antifungal tests	References
Miscellaneous	*P. reticulate*	Crambescin A2 392	*C. albicans*	
		Crambescin A2 406	*C. neoformans var. gattii,*	
		Crambescin A2 420	*C. glabrata, C. krusei*	
		Sch 575948		[143]
	Sponge	Theonellamides	Antifungal	[144]
	Melophlus sp.	Aurantoside K	*C. albicans* (wild-type)	[145]
	P. halichondrioides	Plakortide F	*C. albicans*, *C. neoformans*, *A. fumigatus*	[146]
	H. viscosa	Haliscosamine	*C. neoformans*, *C. albicans*	[147]
	D. herbacea	3,5-Dibromo-2-(3,5-dibromo-2-methoxyphenoxy) phenol	*Aspergillus*	[148]
	P. onkodes	Two α and β1,2-dioxolane peroxide acids	*C. albicans*	[149]
	T. laevispirulifer	Nematocide, onnamide F	*S. cerevisiae*	[150]
	T. swinhoei	Swinhoeiamide A	*C. albicans*, *A. fumigates*	[151]
	Family *Neopeltidae*	Neopeltolide	*C. albicans*	[152]
	Plakinastrella	Epiplakinic acid F	*C. albicans*	[153]
	H. communis	(−)-Untenospongin B	*C. albicans*, *C. tropicalis*, *F. oxysporum*	[154]
	H. lachne	Hippolachnin A	*C. neoformans*, *T. rubrum*, *M. gypseum*	[155]

Table 4. Antifungal compounds from marine sponges and their effects.

6. Anti-inflammatory compounds

Marine organisms and microorganisms have provided a large proportion of the anti-inflammatory and natural antioxidants products over the last years. Reports suggest that marine invertebrates represent new marine resources for the isolation of novel agents which are active on inflammatory conditions have also been found in the literature. Herencia and coworkers [156] studied the effects of dichloromethane and methanol extracts from some Mediterranean marine invertebrates on carrageenan-induced paw edema in mice. Extracts partially decreased elastase activity and PGE2 levels measured in homogenates from inflamed paws, without affecting the levels of this prostanoid present in stomach homogenates. Within the framework of the European MAST III Project, extracts of different polarity from sponges, ascidians and cnidarians have been screened for immunomodulating activities [157]. It was demonstrated that endotoxin-free samples of marine origin possess effects on certain components of the immune system. As a result of all these investigations, bioassay-directed separation of active extracts identified many structurally diverse compounds as future leads. Anti-inflammatory compounds found in the marine environment include terpenes and steroids, alkaloids, peptides and proteins, polysaccharides and others. Examples of anti-inflammatory compounds marine sponge origin are presented in **Table 5**. Also includes diterpenes of (8*E*, 13*Z*, 20*Z*)-strobilinin and (7*E*, 13*Z*, 20*Z*)-felixinin from a marine sponge *Psammocinia* sp. [158], and novel anti-inflammatory spongian diterpenes from the New Zealand marine sponge *Chelonaplysill aviolacea* [159].

Categories	species	Active agents	Anti-inflammatory tests	References
Terpenoids	*F. cavernosa*	Cavernolide	TNF-α, NO and PGE2 production	[160]
	Axinella spp.	6-Cycloamphilectenes	NO, PGE2 and TNF-α production	[161]
		2-Cycloamphilectenes	Inhibit NF-KB pathway	[161]
	Psammocinia spp.	Chromarols A-E	Inhibition of 15-LOX	[162]
	Psammocinia spp.	(8*E*, 13*Z*, 20*Z*)-strobilinin	Anti-inflammatory	
		(7*E*, 13*Z*, 20*Z*)-felixinin	Anti-inflammatory	[158]
	C. violacea	Spongian	Anti-inflammatory	[163]
	D. avara	Avarol, avarone,	Inhibition of eicosanoid release	[164]
		Spongiaquinone, ilimaquinone	and depression of superoxide generation	[165]
	Dysidea spp.	Dysidotronic acid	Inhibited production of TNF-α, IL-1 PGE2, and LTB4	[166]
	Plakortis spp.	Plakolide A	Inhibit iNOS	[167]
	D. elegans	Cymopol	DNA binding of NF-KB	[168]
	L. variabilis	Manoalide, scalaradial	Inhibited IL-1 and TNF-α	[169]
	F. cavernosa	Cacospongiolide B	Inhibited PLA2	[170]
	Dysidea spp	Dysidenones A-B	Inhibited human synovial PLA2	[171]
	L. variabilis	Cladocorans A-B	Inhibition of secretory PLA2	[172]
	P. nigra	Petrosa spongiolides	Inhibitor of PLA2	[173]
	P. nigra	Petrosa spongiolide M	Inhibited LTB4 levels	[174]
	Cacospongia spp.	Scalaradial	Inactivate the enzyme PLA2	[175]
	G. sedna	Homoscalarane	Moderate activity to inhibit mammalian PLA2	[176]
	Hyrtios sp.	Puupehenone, hyrtenone	A high potency against 12-human, 15-human and 15-soybean LOX	[177]
	C. linteiformis	Cyclolinteinone	iNOS and COX-2 protein expression in LPS-stimulated J774 macrophages	[178]
	Callyspongia spp.	Akaterpin	Inhibitor of phosphatidylinositol-specific Phospholipase C	[179]
Steroids	*C. lissosdera*	Clathriol	*In vitro* anti-inflammatory activity against human neutrophil and rat mast cells	[180]
	Euryspongia spp.	Petrosterol, 3β-hydroxy-26-*nor*-campest-5-en-25 oic acid	Against 6-keto-PGF1α release in a human keratinocyte cell line HaCaT	[181]
Alkaloids	*X. testudinaria*	Hymenialdisine	Inhibitor of NF-KB and ILs production	[182]
	Agelas spp.	Nagelamides A-H	NF-KB in inflammatory diseases	[183]
	S. flabellate	Stylissadines A-B	Antiinflammatory activity	[184]

Table 5. Anti-inflammatory compounds from marine sponges and their effects.

7. Marine sponge-derived compounds with enzyme inhibitory activity

Derivatives of halenaquinone and xestoquinone showed various enzyme inhibitory activities besides the phosphatidylinositol 3-kinase and topoisomerase I and II inhibitory activities mentioned above. Compound xestoquinone inhibited both Ca^{2+} and K^{+}-ATPase of skeletal muscle myosin [185]. SAR Investigations showed that halenaquinone and three synthetic analogs with a quinone structure significantly inhibited Ca^{2+} ATPase activity. In contrast, four xestoquinone

Categories	Species	Active agents	Enzyme-inhibitory	References
Quinones	*X. exigua*	Halenaquinone	Ca^{2+} ATPase activity	[191]
	X. exigua	Xestoquinone	Ca^{2+} and K^{+}-ATPase activity	[192]
	X. sapra	Halenaquinol	Protein tyrosine kinase activity	[193]
	X. cf. carbonaria	14-Methoxyhalenaquinone	Protein tyrosine kinase activity	[187]
	Xestospongia sp.	Adociaquinone B	Protein tyrosine kinase activity	[194]
	Xestospongia sp.	3-Ketoadociaquinone B	Cdc25B phosphatase activity	[195]
	Xestospongia sp.	Adociaquinone A	Cdc25B phosphatase	[194]
	Xestospongia sp.	3-Ketoadociaquinone	Cdc25B phosphatase	[195]
Cyclostellettamines	*Xestospongia* sp.	Cyclostellettamine	A histone deacetylase derived inhibition	
		Cyclostellettamine G		
		Dehydrocyclostellettamine D		
		Dehydrocyclostellettamine E		[189]
Fatty acids	*X. testudinaria*	Xestospongic acid ethyl ester	inhibit the Na+/K+ ATPase	[190]

Table 6. Marine sponge-derived compounds showing enzyme-inhibitory activities.

analogs in which the quinine structure was converted to quinol dimethyl ether did not inhibit the Ca^{2+} ATPase activity [186]. The protein tyrosine kinase (PTK) inhibitory activities of halenaquinone, halenaquinol, and 14-methoxyhalenaquinone were the most remarkable with IC_{50} values <10 mm. The other analogs was either less potent or inactive, and a rationalization for this SAR pattern was also reported [187]. Xestoquinone also showed significant protein kinase inhibitory activity toward Pfnek-1, a serine/threonine malarial kinase, with an IC_{50} value of ca. 1 mm, and moderate activity toward PfPK5, a member of the cyclin-dependent kinase (CDK) family [188]. Adociaquinone B and 3-ketoadociaquinone B were the most potent inhibitors of the Cdc25 B phosphatase inhibitory activities, and the dihydro-benzothiazine dioxide in compounds Adociaquinone A, Adociaquinone B, 3-Ketoadociaquinone A, and 3-Ketoadociaquinone B appeared to be an important structural feature for this enhanced activity. Four cyclostellettamines, cyclostellettamine A, cyclostellettamine G, dehydrocyclostellettamine D and dehydrocyclostellettamine E inhibited histone deacetylase derived from K562 human leukemia cells with IC_{50} values ranging from 17 to 80 mm [189]. Xestospongic acid ethyl ester (207) was found to inhibit the Na+/K+ ATPase [190]. Compounds are listed in **Table 6**.

8. Sponge-derived immunosuppressive compounds and their efficacy

Recently natural constituents isolated from marine sponges were tested for immunosuppressive activities and in the end of 1980s, deep water marine sponges resulted in isolation of pure compounds with immunosuppressive properties. Two important compounds: 4a-merhyl-5a-cholest-8-en-3~-ol and 4,5-dibromo-2-pyrrolic acid discovered by American scientist from deep water sponge *Agelasfla bellrform is* showed significant immunosuppressive activity. Both compounds were found significantly active in suppression of the response of murine splenocytes in the two-way mixed lymphocyte reaction (MLR) with little to no demonstrable cytotoxicity at low doses [196]. Constituents isolated from the Aurora globostellata marine sponge showed

immunomodulatory potential. The immunomodulatory potential was evaluated by oral administration of ethyl acetate extract of marine sponge (200 mg/kg) to Wistar rats and the results obtained showed that extracts exhibited immunosuppressant activity and can further be studied [197]. A recent investigation on an Indian marine sponge aimed to isolate and characterize bacteria with immunomodulatory and antimicrobial activity. *Callyspongia difusa* (Gulf of Mannar province) a marine sponge resulted in isolation of 10 marine bacterial strains which exhibited remarkable antagonistic activity against clinical bacterial pathogens. These findings suggested that the sponge associated bacterial strain *Virgibacillus* sp. can contribute the search for novel antibiotics to overcome infections and also for the production of potential immunomodulators [109].

9. Hypocholesterolemic compounds

In the last decade studies reported that marine sponges could have been a source of hypocholesterolemic compounds. For example, lysophosphatidylcholines and lyso-PAF analogs derived from *Spirastrella abata* are reported as successful inhibitors of cholesterol biosynthesis in vitro study [198, 199]. Zhao et al. [200] extracted novel lysophosphatidylcholines from marine sponges with hypocholesterolemic properties and thereby aroused an interest of compounds from marine sponge due to short lifespan of conventional lysophosphatidylcholines *in vivo*.

10. Sponge–derived antibiotics

Also, over the years marine sponges are considered as a rich source of natural products and metabolites for antibiotics possessing strong inhibitory against bacteria, fungi and microbes. Several studies revealed that many natural bioactive components isolated from various marine sponges can be useful for the production of new antibiotics and antimicrobial drugs. In the recent years many scientific studies provided evidences for marine sponge metabolites with efficient antibiotic, antibacterials and antimicrobial properties. Purpuroines A-J, halogenated alkaloids isolated from *Lotrochota purpurea* marine sponge showed promising inhibitory activities against bacteria and fungi related diseases [201]. *Haliclona* sp. sponge from Korea resulted in isolation of novel cyclic bis-1,3-dialkylpyridiniums and cyclostellettamines, which showed moderate cytotoxic and antibacterial activities against A549 cell-line and Gram-positive strains, respectively [202]. A number of new alkaloids were isolated from the marine sponge *Agelas mauritiana*: (+)-2-oxo-agela-sidine C, (−)-8′-oxo-agelasine D,4-bromo-N-(butoxymethyl)-1H-pyrrole-2-carboxamide, ageloxime B, and (−)-ageloxime D and some of these isolated components exhibited antifungal activity against *Cryptococcus neoformans*, antileishmanial activity in vitro and antibacterial activity against *S. aureus* and methicillin-resistant *S. aureus in vitro* [203]. Extracts prepared from the sponge's species *Petromica citrina*, *Haliclona* sp. and *Cinachyrella* sp. exhibited antibacterial activity against 61% of the coagulase-negative staphylococci (CNS) strains, including strains resistant to conventional antibiotics. *P. citrina* extracts showed the largest spectrum of inhibitory activity. This current study according scientist shows potential of marine sponges to become new sources of antibiotics and disinfectants for the control of CNS involved in bovine mastitis in future [204]. Isolation of isonitriles ditepene from *Cymbastela hooperi*, tropical marine sponge and the axisonitrile-3 sesquiterpene isolated *Acanthella kletra*, from

the tropical marine sponge were tested for series of bioassays antibacterial, antiphotosynthetic, antifouling, antialgal, antifouling, antialgal, antiphotosynthetic, antifungal, and antitubercular. The results showed majority of the tested compounds were active against at least two of the applied test systems [152]. Recently, sponge-derived actinomycetes and sediments isolated from marine sponge were tested for bioactive constituents with antifungal and antimicrobial activity. Out of 15 prepared active extract nine were found active against *Enterococcus fascism* (vancomycin-resistant) and *Candida albicans* multidrug-resistant [132], including strains resistant to conventional antibiotics. Thus the bacterial actinomycetes from marine sponges and other marine organisms have been proved prolific producers of pharmacologically active compounds. Literature studies revealed that 70% of naturally derived antibiotics which are currently in clinical use have been derived from actinomycetes. In the recent study, *Streptomyces* sp. strains from Mediterranean sponges and secondary metabolite namely, cyclic depsipeptide valinomycin, indolocarbazole alkaloid staurosporine and butenolide, were screened for anti-infective activities. All the isolated compounds along with *Streptomyces* sp. exhibited antiparasitic activities. Researchers also claim the anti-infective potential of marine actinomycetes is very promising.

11. Marine sponges-derived antifouling and antibiofilm compounds

Bacterial biofilms are surface-attached microorganism's communities that are protected by an extracellular matrix of biomolecules. Continuous use of chemical antifoulants resulted in increased tributyltin concentration and created extensive pollution problems in marine organisms. Natural antifouling molecules from marine have been recently reviewed and researches hope that will provide more specific and less toxic antifouling activity in future. Antifouling compounds derived from sponges were found to be very effective, environmentally friendly biocides and less toxic [205]. In the last few years several studies were directed to find the most promising alternative technologies to antifouling in marine organisms, especially from sponges. In a recent study structurally different compounds containing 3-alkylpyridine moiety were evaluated for antifouling potential. The compounds, namely haminols, saraine and 3-alkylpyridinium salts extracted from *Reniera sarai, Haliclona* sp. and the mollusk *Haminoea fusar* is obtained by synthesis, showed very good antifouling potential larvae of the barnacle *Amphibalanus amphitrite*. Bromopyrrole or diterpene alkaloids derivatives isolated from *Agelas linnaei* and *Ageles nakamurai* Indonesian marine sponges exhibited cytotoxic activity. Moreover, agelasine derivatives inhibited settling of larvae of *Balanus improvisus* in an antifouling bioassay as well as the growth of planktonic forms of biofilm forming bacteria *S. epidermidis* [206].

12. Conclusion

Marine invertebrates (Porifera, Cnidaria, Mollusca, Arthropoda, Echinodermata, etc.) are considered as one of the major groups of biological organisms which gave huge number of natural products and secondary metabolites with interesting pharmacological properties and led in the formation of novel drugs. Among marine invertebrates, marine sponges (phylum: Porifera) is the most dominant responsible group for discovering significant number of natural components, which has been used as template to develop therapeutic drugs. These natural products

possesses vast range of therapeutic application, including antimicrobial, antihypertensive, antioxidant, anticancer, anticoagulant, anti-inflammatory, immune modulator, and wound healing and other medicinal effects. Therefore, marine sponges are considered a rich source of chemical diversity and health benefits for developing drug candidates, nutritional supplements, cosmetics, and molecular probes that can be supported to increase the healthy life span of humans. In this chapter we included the most important and biologically active marine sponge-derived compounds and presented selected studies of most important bioactive and promising natural products and secondary metabolites from marine sponges.

Conflict of interest

The authors declare that they have no conflict of interest.

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