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Review

Pharmacologically Important Natural products from Marine Sponges

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ABSTRACT

Present review describes research on novel natural pharmacological compounds isolated from marine sponges. More than 90 novel cytotoxic antitumor compounds and their synthetic analogs have shown confirmed activity in vitro tumor cell lines bioassay and are of current interest to NCI for further in vivo evaluation. A great problem, to use directly the reservoir of marine organisms for therapy is the very low availability and the isolation of only very small amounts of the biologically active substances from the natural materials. Sponges produce a wide array of secondary metabolites ranging from derivatives of amino acids and nucleosides to macrolides, porphyrins, terpenoids, aliphatic cyclic peroxides and sterols. The purpose of this article is to be present a structurally reviewed the pharmacological activities in marine sponge antitumor and cytotoxic properties of 143 marine natural products, many of them novel compounds that belongs to the family of porifera possessed the various species diverse structural classes, including polyketides, terpenes, steroids and peptides. Finally, this 2009 overview of the highlights the fact that the discovery of novel some pharmacologically important of novel naturally presented chemical compounds isolated from a wide variety of marine sponges. Naturally, the following pharmacological compounds such as Monomeric, oligomeric and polymeric 3-alkylpyridiniums, amino acids and nucleotides to macrolides, porphyrins, terpenoids to aliphatic cyclic peroxides and sterols, the majority of which are related to sponges and 3-alkylpyridines comprise a group of biologically active compounds found in several sponges. This review will present some of the aspects of the medicinal chemistry developed recently to introduce such modifications. The structures, origins, synthesis and biological activity of a selection of N-heterocyclic marine sponge alkaloids are reviewed. The emphasis is on compounds poised as potential anticancer drugs: pyrroles, pyrazines, imidazole, and other structural families.

Keywords: Marine sponge; Pharmacological activities; Secondary metabolites; Cytotoxic.

INTRODUCTION

Sponges have been considered as a gold mine for the chemists. More than 12,000 compounds have been isolated from marine sources with hundreds of new compounds still being discovered every year, with respect to the diversity of their secondary metabolites, elucidating the metabolisms of the sponges and investigating the possibility of being able to produce substances of interest synthetically. This overview resumes the state of the art of investigations about pharmacological activities in marine sponges. Reports of the isolation of natural products from marine sponges have been published from the early 1950's, and research activities on this topic have continued to increase (Munro, et al., 1999) and

(Faulkner, 2001) has published surveys on many more natural products recently isolated from sponges. Many of these natural products have interesting biomedical potential, pharmaceutical relevance and diverse applications also they provided the significant components of pharmacologically important chemical bioactive substances (Table-1). Structurally unique also secondary metabolites have been isolated, and a first compound was made available on the market in 2004, Marine sponges are rich source of Pharmacologically active compounds that can potentially be used as medicines to cure human diseases, and the isolation of bioactive compounds from sponge has been already reviewed extensively (Azevedo, et al., 2008). Antitumor pharmacological studies were conducted with 19 marine natural products in a number of experimental and clinical models that defined or further characterized their mechanisms of action (Alejandro, et al., 2003).

Potentially promising in vitro cytotoxicity data generated with murine and human tumor cell lines were reported for 124 novel marine chemicals accompanying with undetermined mechanisms of action. Noteworthy is the fact that marine sponge possessed pharmacological important compounds research clearly remains a multinational effort, involving researchers from Austria, Australia, Brazil, Canada, England, France, Germany, Greece, Indonesia, Italy, Japan, New Zealand, Russia, Spain, South Korea, Switzerland, Taiwan, the Netherlands and the United States. Polymeric 3-alkylpyridinium salts (poly-APS) present in the marine sponge *Reniera sarai* show a broad spectrum of biological activities.

Many of these natural products have interesting biomedical potential, pharmaceutical relevance and diverse applications. For example, arabinose-nucleosides with antiviral and anticancer activity isolated from sponge *Cryptotethya crypta*, are used clinically; manoalide obtained from sponge *Luffariella variabilis* is a candidate for new drugs with anti-inflammatory activity. Also, metabolites previously ascribed to sponges have been recently demonstrated to be biosynthesized by symbionts. If some compounds are derived from a symbiotic microorganism, culturing the microorganism could provide an improved source of the bioactive compound. Thus, we have focused on pharmacologically important natural products from marine sponges in this review.

Secondary metabolites in marine sponges: Marine invertebrates that are sessile organisms like sponges were provided the largest number of marine derived secondary metabolites including some of the most interesting pharmacological important drug candidates (West, et al., 2000). However, there are many difficulties regarding the origin of these natural compounds when sponges are studied in symbiotic relationships. Marine sponges are a rich source of biologically active secondary metabolites with novel chemical structures. Eighty four anti-inflammatory compounds have been isolated from marine sponges. This is the first comprehensive review presenting the pharmacological activities of marine sponge metabolites. Recently (Serrati, et al., 2008) reported sponge TGF betal antagonistic peptides inhibit TGF betal dependent angiogenesis. Previously number of researchers studied bioactive brominated metabolites from the red sea sponge *Suberea mollis*. Sponges produce a wide array of secondary metabolites ranging from derivatives of amino acids and nucleosides to macrolides, porphyrins, terpenoids, aliphatic cyclic peroxides and sterols (Tilvi, et al, 2004).

Elessek, 2008 analyzed Influence of polymeric 3-alkylpyridinium salts from the marine sponge *Reniera sarai* on the growth of algae and wood decay fungi. Sladic and Gasic, (2006) studied reactivity and biological activity of the marine sesquiterpene hydroquinone avarol and related compounds separated from the Dictyoptera order of sponges. Initially So far, more than 3,700 new natural products have been separated from these groups. The metabolic and physiological capabilities of marine micro-organisms that allow them to survive on their unique habitats also provide a great potential for production of metabolites (Table 1).

Biological activity and toxicity of 3-alkylpyridinium compounds in sponge: To date, around 30 and 50 structurally different 3-alkylpyridinium and 3-alkylpyridine compounds have been isolated from the marine sponges reported by Tom, et al. (2007). These include the alkylpyridines from different Haliclona spp, (Blunt, et al., 2006), ceramides from *H. koremella* (Hattori, et al., 1998), a hexapeptide from Haliclona sp. (Sera, et al., 2003). In general, the variety and potency of the biological effects of these compounds increased with

their degree of polymerisation, resulting in complex and unprecedented mechanisms of action of toxicity. 3-Alkylpyridinium polymers isolated from Haplosclerid marine sponges. Among them, polymeric 3-alkylpyridinium salts (poly-APS), isolated from crude extracts of the mediterranean marine sponge *Reniera sarai*, showed the highest degree of polymerisation. Afterwards this the pharmacologically active compounds and developed tools pore forming polyalkylpyridinium salts from marine sponges versus synthetic lipofection systems distinct tools for intracellular delivery of cDNA and siRNA.

In addition Koss, et al. (2007) and Scott, et al. (2004) has been made comparative study of the actions of alkylpyridinium salts from a marine sponge and related synthetic compounds in rat cultured hippocampal neurons. Tucker, et al. (2003) studied the influence of alkyl pyridinum sponge toxins on membrane properties, cytotoxicity, transfection and protein expression in mammalian cells. Chelossi, et al. (2006) studied comparative antibacterial activity of polymeric 3-alkylpyridinium salts isolated from the Mediterranean sponge *Reniera sarai* and their synthetic analogues. Tsukamoto, et al. (2000) discovered Hachijodines A-G: seven new cytotoxic 3-alkylpyridine alkaloids from two marine sponges of the genera Xestospongia and Amphimedon. Sponges, with their rich chemical defence mechanisms, are one of the most studied organisms for the isolation of NPAs (Thakur and Anil, 2000). Over the last few decades significant efforts have been made, by both pharmaceutical companies and academic institutions, to isolate and identify new marine sponge-derived, natural products. These initiatives have been accompanied by funding support from governmental agencies.

Novel marine sponge products with potential anti-tumor properties: The largest group of new chemical entities produced from marine sponge possessed natural product origin has anticancer indications (Newman and Cragg, 2007). Nakao, et al. (2004) reported the isolation of renieramycin-A was the new compound from the Japanese sponge *Neopetrosia* sp. That was mainly dose-dependently inhibited recombinant *Leishmania amazonensis* proliferation, while showing cytotoxicity at "*ten times higher concentration.* Isolation of new anticancer agents derived from marine sources has been based on the collection of marine micro-organisms of sponges with various types of extracts. Rashid, et al. (2002) identified the pellynol- I, a new cytotoxic polyacetylene from the sponge *Pellina sp.* Hirano et al., (2000) described pyrinodemins B-D, and Potent cytotoxic bis-pyridine alkaloids from marine sponge *Amphimedon sp*. Oku, et al. (2000) discovered the new isomalabaricane triterpenes from the marine sponge *Stelletta globostellata* that induce morphological changes in rat fibroblasts. Gauvin, et al. (2000) demonstrated isolation of bioactive 5 alphas, 8 alpha-epidioxy sterols from the marine sponge *Luffariella cf. variabilis.* Previously, Qureshi and Faulkner, (2007) reported alpha-hydroxytheonellasterol, cytotoxic 4-methylene sterol from the Philippines sponge *Theonella swinhoei.* Meanwhile, Watanabe (2000) studied strongylodiols A, B and C, new cytotoxic acetylenic alcohols isolated from the Okinawan marine sponge of the genus *trongylophora* as each enantiomeric mixture with a different ratio.

Thakur and Anil (2000) typically represented the antibacterial activity of the sponge, *Ircinia ramose i*mportance of its surface-associated bacteria. It has demonstrated significant antitumor activity in preclinical models against a wide spectrum of cell lines. For example, arabinose-nucleosides with antiviral and anticancer activity isolated from sponge *Cryptotethya crypta*, are used clinically. As a result of the National Cancer Institute's HIV-inhibitory natural product lead discovery program, a new HIV-inhibitory depsiundecapeptide neamphamide- A was isolated from the Papua New Guinea marine sponge *Neamphius huxleyi* (Oku, et al., 2004).

Marine sponge-derived compounds in clinical development: Specific programs directed towards the collection and characterization of marine natural products such as various types of sponges and evaluations of their biological activity have been established. This systematic investigation of marine environments is reflected in the large number of novel compounds especially reported in the literature over the past decade. Marine natural products especially sponges could yield new drugs to cure such diseases. The quest for drugs from the sea has yielded an impressive list of natural products mostly from invertebrates such as sponges that are either in the late stages of clinical trials, or have already entered the market. Some of the

sponge-derived bioactive compounds presently available in the market are Ara-A (antiviral), Ara-C (anticancer) and Manoalide (phospholipase A2 inhibitor), while IPL512602 (anti-inflammatory), KRN 7000 (anticancer), LAF389 (anticancer), Discodermolide (anticancer) and HTI286 (anticancer) are under clinical trial (Jimenz, et al., 2000; Nishimura, et al., 2003). Besides their pharmaceutical potential, sponges are an important to explain classification patterns and phylogenetic relationships.

During the year 1998 Hattori demonstrated new ceramide compound from marine sponge. Possible Biogenetic Relevance with Manzamine. (Schmidt, et al., 2000) portrayed novel Lipid contents of the sponge *Haliclona* sp. Sponges produce a wide array of secondary metabolites ranging from derivatives of amino acids and nucleosides to macrolides, porphyrins, terpenoids, aliphatic cyclic peroxides and sterols (Tilvi, et al., 2004). Consistently, Sera et al. (2004) proposed the new antifouling hexapeptide from a Palauan sponge, Haliclona sp. The antinociceptive and anti-inflammatory effects were investigated against different experimental models in mice described by Azevado et al. (2008) also this author explained the sponge Caissera possessed antinoceptive and anti-edematogenic effects.

Biological activities of polymeric 3-alkylpyridinium salts (poly-APS) from the marine Haliclona sponge of Reniera sarai: Since the structurally derived chemical compounds were (De Oliveira, et al., 2004) explained marine natural products halitoxin, toxic complex of several marine sponges of the genus *Haliclona.* Orabi, et al. (2002) and (Aoki, et al., 2004) demonstrated the valuable pharmacological compounds such as Araguspongines K and L, New Bioactive Bis, Oxaquinolizidine N-Oxide Alkaloids from Red Sea Specimens of *Xestospongia exigua.*

Microbiologically active compounds especially anti bacterial developed from the reef sponge *Amphimedon viridis* from the Red Sea published by Kelman, et al. (2001). Ankudy, et al. (2008) pointed out new bioactive bromotyrosine-derived alkaloid from a marine sponge *Aplysinella* sp. Elessek, et al. (2008) Influence of polymeric 3-alkylpyridinium salts from the marine sponge Reniera sarai on the growth of algae and wood decay fungi. In recent year the improvement in the marine sponge derived biopolymers is a vast resource of untapped.

Pharmacological oriented bioactive substances in sponge: Initially Hada, et al. (2000) studied chemistry of sponges 19 novel bioactive metabolites from *Hamigera tarengenesis*. Furthermore, (Chilli, et al., 2004) recorded in the case of medicinal properties consisted new sesquterpenes from Madagascan *Lendenfeldia* sponge. Specic (2001) synhesised bioactive compounds that was alkylpyridinum from marine sponge. Besides, Keyzers, et al. (2003) contributed a novel anti-inflammatory sterol, clathriol B from the New Zealand sponge *Clathria lissosclera*. Clathriol B was shown to moderately inhibit production of superoxide anion from agonist-stimulated human peripheral blood neutrophils. As a result of an effort to identify small molecules that disrupt protein-protein interactions involved in HIV-1 cellular entry, a new polycyclic guanidine alkaloid Crambescidin 826 (Chang, et al., 2003; Tilvi, et al., 2007) has been reported from the marine sponge *Monanchora* sp.

According to Carroll et al., (2004) reported three new peptides, dysinosins B, C (30) and D**,** isolated from the sponge *Lamellodysidea chlorea,* that inhibited the blood coagulation cascade serine proteases factor VIIa and thrombin. Furthermore, the study revealed that two structural motifs of the dysinosins contributed to the binding of these compounds to factor VII-a and thrombin proteases. Amphitoxin, a new high molecular weight antifeedant pyridinium salt from the Caribbean sponge *Amphimedon compressa* (Albrizio, et al.,1995).

In the year of 1993 Davies and co-workers recorded a new EGF active polymeric pyridinium alkaloid from the *Callyspongia fibrosa* sponge. Consequently, Sakai, et al. (2003) contributed to the search for novel ionotropic glutamate receptor ligands by reporting the isolation of the novel amino acid cribronic acid from the marine sponge *Cribrochalina olemda*. Furthermore, Wang, et al. (2003) reported thirteen novel tetramic acids isolated from the marine sponge *Melophlus sarassinorum.* A southern Australian marine sponge, *Trachycladus laevispirulifer*, has been yielded a potent new nematocide with antifungal activity which has been identified as onnamide. The structure was assigned by detailed spectroscopic analysis and chemical conversion to the methyl ester 2. Onnamide F contains a common structural motif previously described in a number of natural products exhibiting

interesting pharmacological activities, and the sponge metabolites the onnamides, mycalamides, and theopederins (Keyzers, et al., 2004).

Pharmaceutically important Phytochemicals originated from sponge (Groud, et al., 2003) reported inhibition of HIV by two bis-quinolizidine alkaloids petrosins isolated from the Indian marine sponge *Petrosia similis*. The extensive investigation determined that both petrosins inhibited HIV-1 replications. It has been repoted the Cribrostatin 6 showed antibacterial activity against Gram-positive bacteria, and it was most active against *S. pneumoniae*. Bugni, et al. (2004) and Lu, et al. (2007) investigated a series of kalihinols, diterpenes isolated from the Philippine marine sponge *Acanthella cavernosa*, as potential bacterial folate biosynthesis inhibitors. Very recently, Han (2009) studied Charecterization of antifungal chitinase from Streptomyces sp. DAII associated with South China Sea sponge *Craniella australiensis.*

CONCLUSION

Marine sponges have been excellent sources for natural products that are bio-activity which includes the enzyme inhibitors, cell division–inhibitors, anti-viral, anti-fungal, antimicrobial, anti-inflammatory, anti-tumour, ctotoxic or cardiovascular properties. Several brominated natural products and other aminoacid derivatives are present in complex structures such as cyclic peptides, polymere alkylpyridinum, sesquiterpenequinones, onamides, mycalamides, nucleotides to macrolides, porphyrins, terpenoids to aliphatic cyclic peroxides and sterols also other important cytotoxic secondary metabolites and its responsible marine sponges also been mainly focused this review.

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Table-1: Sponges and their natural products showing various bioactivities.

S.N.	Sponge	Bioactive metabolites	Biological activity
1	*Acanthella* sp	Kalihinol - A	Antibiotic
2	*Agelas dispar*	Aminozooanemonin	Antibacterial
3	*Agelas dispar*	Pyridinebetaine - A	Antibacterial
4	*Agelas mauritiana*	Agelasimine	Cytotoxic
5	*Agelas mauritiana*	Sceptrin	Antimicrobial
6	*Agelas nakamurai*	Ageliferine	Antibacterial
7	*Agelas nakamurai*	Debromosceptrin	Antibacterial
8	*Agelas novaecaledoniae*	Ageliferine	Somatostatin/VIP inhibitor
9	*Agelas novaecaledoniae*	Sceptrin	Somatostatin/VIP inhibitor
10	*Agelas novaecaledoniae*	Xestospongine - B	Somatostatin/VIP inhibitor
11	*Agelas* sp	Agelasine	Antileukemic
12	*Agelas* sp.	Agelasine - F	Antituberculosis
13	*Agelas* sp.	Agelasine - 1	Antimicrobia
14	*Amphimedon* sp	Pyrinodemin	Cytotoxic
15	*Aplysina aerophoba*	Aeroplysinin - I	Cytotoxic
16	*Batzella* sp	Discorhabdin	Cytotoxic, enzyme inhibitor
17	*Crella* sp	Crellastatins	Cytotoxic
18	*Discodermia calyx*	Calyculin - A	Antitumor
19	*Disidea avara*	Avarol	Cytotoxic
20	*Druinella purpurea*	Psammaplysin C	Cytotoxic
21	*Echinoclathria* sp	Echinoclathrines	Immunosuppressive
22	*Erylus lendenfeldi*	Eryloside A	Antitumor
23	*Halichondria okadai*	Halichondrin B	Antitumor
24	*Haliclona tulearensis*	Halitulin	Cytotoxic
25	*Ircinia* sp.	Haterumalides	Cytotoxic
26	*Jaspis johnstoni*	Jasplakinolide	Cytotoxic
27	*Jaspis johnstoni*	Toyocamycin	Cytotoxic
28	*Jaspis johnstoni*	Tubercidin	Cytotoxic
29	*Jaspis* sp	Bengamides	Antitumor
30	*Jaspis* sp	Jaspisamides	Cytotoxic
31	*Jaspis splendans*	Jaspamide	Antitumor
32	*Latrunculia magnifica*	Latrunculin A	Neurotoxin
33	*Neosiphonia superstes*	Sphinxolides	Cytotoxic
34	*Pandaros acanthifolium*	Acanthifolicin	Antitumor
35	*Petrosia* sp	Petrocortynes	Cytotoxic enzyme inhibitor
36	*Petrosia* sp	Petrotetrayndiols	Cytotoxic
37	*Petrosia* sp	Petrosiacetylenes	Na+/K+-ATPase inhibitor
38	*Plakinastrella* sp	Elenic acid	Topoisomerase II ihibitor
39	*Psammaplysilla purpurea*	Purealidin A	Cytotoxic
40	*Spongia* sp.	Spongianolide	Cytotoxic
41	*Spongionella gracilis*	Gracilin B	Cytotoxic
42	*Stronglyophora hartmani*	Puupehenone	Cytotoxic
43	*Stylinos*n. sp	Mycalamides	Cytotoxic
44	*Tedania digitata*	1-methylisoguanosine	Cardiovascular effector
45	*Tethya crypta*	Spongouridine, Spongothymidine	Antiviral, antitumor
46	*Verongia aerophoba*	Dienone	Cytotoxic
47	*Verongia spengelii*	Aplysinopsin	Cytotoxic
48	*Tedania ignis*	Tedanolide	Cytotoxic
49	*Zyzzya fuliginosa*	Sceptrin Somatostatin/VIP	Cytotoxic
50	*Xestospongia* sp	Sceptrin	Somatostatin/VIP inhibitor
51	*Zyzzya fuliginosa*	Veiutamine	Cytotoxic