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Marine Sponge: Natural Reservoir of a Myriad of Bioactive Compounds

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ABSTRACT

Biodiversity in the marine environment exceeds that of the terrestrial environment. But exploration of marine natural products is still in the infant stage. Among the diverse bioactive compounds which are discovered from marine organisms, sponges have been assigned a high priority as they have been accepted as a promising organism for the discovery of pharmacologically active drug leads. Marine sponges have provided successful examples that prove natural products derived from them had the therapeutic potential to develop as future drugs against different types of cancer, viral diseases, malaria, inflammation etc. All these findings attract the pharmaceutical field to involve in marine sponge research though more research is required to confirm promising results. Today scientists engage in studying the mode of action of the compounds from sponges at molecular level and also their possible role in treating diseases as the fascinating marine life continues to give natural products. This review aims at covering the new developments in the field of marine sponge research and bioactive compound discovery.

INTRODUCTION

Discovery of marine derived natural products began in the 1950s with the discovery of nucleoside derivatives in the sponge *Tethya crypta* by Bergmann and Feeney. But it was only by the end of 1960, marine organisms were utilized for deriving bioactive compounds. Marine habitat is blessed with a plethora of bioactive compounds that are considered to be a source of potential drugs. 70% of the earth's area is comprised of ocean and 95% of the biosphere is represented by the marine ecosystems. 33-34% animal phyla live in marine environment. Marine bioactive compounds mainly produced by microbes, sponges, gorgonians, soft and hard corals seaweeds, and other marine organisms could be divided into steroids, terpenoids, isoprenoids, norisoprenoids, quinones, brominated compounds, nitrogen heterocyclics, and nitrogen sulfur heterocyclics. It is believed that secondary metabolites, a diverse array of compounds are produced due to factors like self defense, nutrition and competition for space. Secondary metabolites are regarded as communication molecules that are used by animals for intercommunication between themselves and their environment. These communication molecules evolved within the scope of symbiotic interrelationship (Sima and Vetvicka, 2011) have become the new interest of pharmaceutical industry for new drug leads. Bioactive compounds produced by phylogenetically diverse organisms are small molecules up to 3000 Daltons.

In the largely unexplored marine ecosphere, microorganisms form highly specific and symbiotic relationships with sessile, soft bodied and morphologically defenseless filter-feeding organisms like sponges. Microbial symbionts usually produce bioactive natural products. Marine bioactive natural products could be secondary metabolites, enzymes, lipids or heteropolysaccharides (Proksch *et al.*, 2002). Metabolites are mainly of two types, primary and secondary. Primary metabolites that are formed by a limited number of metabolic reactions are considered essential for growth and life in all living systems. When primary metabolites serve as building blocks for the synthesis of macromolecules, proteins, nucleic acids, carbohydrates and lipids, secondary metabolites such as terpenes, polyketides, and alkaloids are not essential for the producing organism and are formed from primary metabolites. Majority of the secondary metabolites play a role in enhancing the survival fitness of the organism and form best examples as chemical weapons used against bacteria, fungi, insects and large animals. Secondary metabolites have captured the attention and interest of pharmaceutical companies. Swift progress has occurred in the field of novel marine natural product discovery from marine organisms (Blunt 2013). Sponges contribute to nearly 30% of all marine natural products discovered so far. This makes them a prolific producer of bioactive compounds and this is mainly due to the diversity of microbes living inside the sponge body.

Overview of marine sponges, symbionts and bioactive compounds

Marine sponges are multicellular pore bearing invertebrates that belong to the phylum porifera. They have been living on the earth for millions of years and are the simplest and oldest organisms. Regardless of extreme temperatures, they can be found 5-50 meters deep. Sponges have the ability to filter up to 2000 liters of seawater each day and are very efficient in taking up nutrients as well as microorganisms from the seawater. They mainly dominate in many benthic habitats. Sponges are sessile without any tissues or sensory organs but possess different types of cells that help to perform all types of bodily functions.

Complex microbial communities of sponges are renowned for biotechnological and ecological importance. Microbial communities such as bacteria, fungi, microalgae etc. are usually found in sponges comprising more than 40% of sponge body (Wang 2006). Bacteria and fungi are the common symbionts in sponges where bacterial symbionts outnumber fungal symbionts (Taylor *et al*, 2007). The major bacterial phyla that are associated with marine sponge include Cyanobacteria, Bacteriodetes, Actinobacteria, Chloroflexi, Proteobacteria, Nitrospira, Poribacteria, Verrucomicrobia Planctomycetes, Archaea and Acidobacteria. Fungi, microalgae and viruses also inhabit sponge body, though little is known about viruses. Among the microbes associated with marine sponges, it has been identified that the prime producers of bioactive compounds belong to the bacterial phylum Actinobacteria and the fungal division Ascomycota (Kennedy *et al.*, 2009). The three main classes of sponges are Calcarea, Demospongiae and Hexactinellida. Among these, the abounding sources of bioactive compounds have been recognized in the class Demospongiae and the orders Halichondrida, Poecilosclerida and Dictyoceratida.

Many studies have shown that secondary metabolites produced by sponges often have defensive roles of protecting themselves from microbial infections, biofouling, predator attacks, and overgrowth by other sessile organisms. Five compounds isolated from the sponges have successfully used for medicinal purposes, and 13 anticancer compounds are in clinical trial and almost 100 compounds are under preclinical trial till 2014 (Mayer *et al.*, 2010). Marine invertebrates are the prolific producers of natural compounds and among them phylum porifera occupies the top position due to the sheer amount of novel pharmacologically active metabolites produced, that are of immense use in the treatment of human diseases (Lee *et al.*, 2001) (Jensen 1994) (*Taylor et al.*, 2007). Due to the potential of sponge associated symbionts to produce natural compounds against many diseases like cancer, autoimmune diseases, viral diseases, inflammations and malaria (Molinski *et al.*, 2009) (Simmons *et al.*, 2005) (Gordaliza 2010) (Alcaraz 2006) they have become a major field of interest to scientists from different disciplines.

Bioactive sponge metabolites

Sponges have been considered as the topmost producers of natural products since the chemical diversity of sponge products is remarkable and they include bioactive terpenes, fatty acids, sterols, peroxides, nucleosides and derivatives of amino acids that are halogenated. Some of the major bioactive compounds discovered from marine sponges include anti-tumour, anti-malarial, anti-viral, antibiotic, immunosuppressive, neuro suppressive, anti-inflammatory and antifouling agents (Blunt *et al.*, 2013) and a few important compounds have been described below.

Anti-oxidants and anti-inflammatory compounds

Several bioactive compounds from marine sponges that possess anti-inflammatory, antioxidant and radical scavenging properties have been discovered in the last few years. A recent study on the antioxidant property of *Tedania anhelans* confirmed the antioxidant potential of its associated bacteria *Bacillus* species (D.Balakrishnan *et al.*, 2014).

Table 1: Closest match of *Tedania angels* associated bacteria showing anti-oxidant activity (Reference D. Bal akrishnan *et al.*, 2014)

Strain	Source	Nearest relative	Identity [%]	Phylogenetic affiliation (Phylum)
Bacillus licheniformis KDRSS1	*Tedania anhelans*	*Bacillus licheniformis* DSM 13 (CP000002)	97	*Firmicutes*
Bacillus subtilis KDRSS4	*Tedania anhelans*	*Bacillus subtilis* DSM 10 (AJ276351)	97	*Firmicutes*
Bacillus subtilis KDRSS6	*Tedania anhelans*	*Bacillus subtilis* strain 168 (AL009126)	97	*Firmicutes*

In another study Ageloline A, new antioxidant and antichlamydial quinolone from the marine sponge-derived bacterium *Streptomyces* sp. SBT345 was derived that showed the antioxidant potential of the novel compound (Cheng *et al.*, 2016). Phorbaketal A, isolated from the marine sponge *Phorbas* sp., was shown to inhibit the production of inflammatory mediators via down-regulation of the NF-κb pathway and up-regulation of the HO-1 pathway (Yun-Ji Seo *et al.*, 2015).

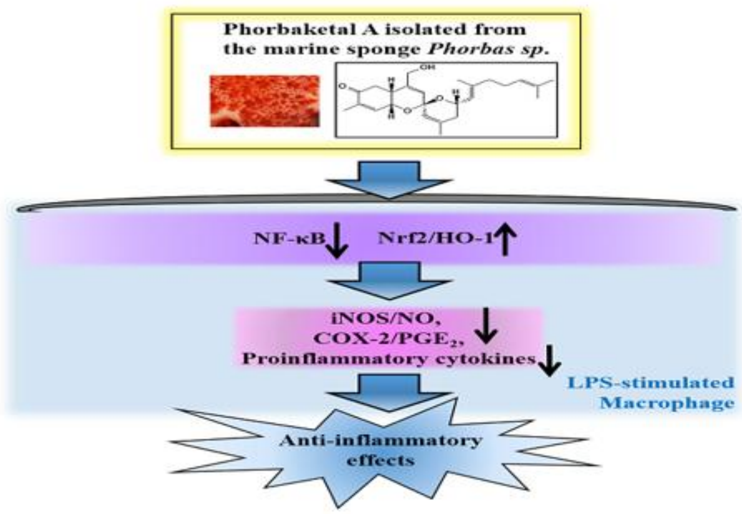

Figure 1. Mode of action of Phorbaketal A (Reference Yun-Ji Seo et al., 2015)

A study on the anti-inflammatory activities of extracts from bacteria associated with marine sponge *Theonella sp* proved the cytotoxicity and anti-inflammatory activity of secondary metabolites produced by these bacteria when studied using macrophage cell lines (Siti Aisha Mohd Radzi *et al.*, 2015).

The extracts of sponges *Callyspongia, Niphates and Stylissa* collected from the Red sea showed potent reducing power and inhibitory effects on oxidative stress (Shaaban M *et al.*, 2012). A scientific study in the sponge *Pandaros acanthifolium* showed cytoprotective as well as antioxidant properties (Berrué F *et al.*, 2012). Another study proved the presence of metabolites like phenolic compounds, alkaloids and polyketides that exhibited antioxidant properties (Longeon A *et al.*, 2011).

Anti-tumour compounds

A derivative of the nucleosides spongothymidine and spongouridine isolated from *Tectitethya crypta* known as Ara-C is considered as the pioneer anticancer agent that can be used against leukemia (Proksch P *et al.*, 2002).It has been currently used in clinical trials against myeloid neoplasms along other anticancer drugs (Feldman *et al.*, 2011). Almost 39 compounds from sponges that can induce apoptosis and that can act as anticancer agents have been identified (Essack *et al.*, 2011).

Renieramycin isolated from the sponge genera *Reniera* has shown to induce apoptosis in lung cancer cells (Halim *et al.*, 2011).

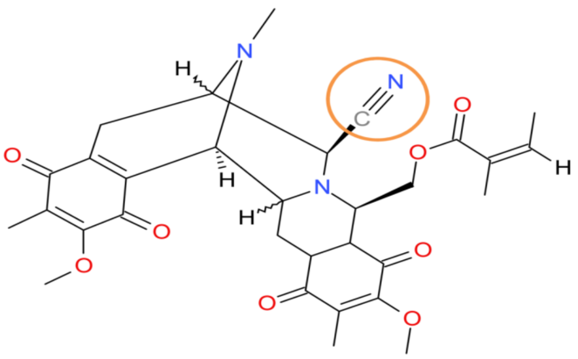

Figure 2. Structure of Renieramycin (Reference Magbubah Essack et al., 2011)

Researchers have proven that a lectin from the sponge *Cinachyrella apion* has the ability to induce cell death in tumor cells (Valeriote *et al.*, 2012).

From the marine sponge *Monanchora pulchra*, a novel polycyclic guanidine alkaloid isolated is Monanchocidin that induced cell death in human monocytic leukemia, human cervical cancer (HeLa) and mouse epidermal cells (Guzii *et al.*, 2010).

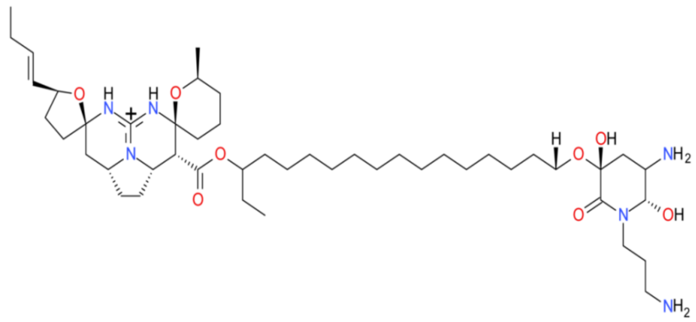

Figure 3. Structure of Monanchocidin (Reference Magbubah Essack et al., 2011)

Antitumour effect of cyclodepsipeptides jasplakinolide isolated from the marine sponge *Jaspis splendens* and its analogs neamphamides and geodiamolides are generally accepted as actin-polymerising and actin-stabilising drug and were tested to possess potent cytotoxic activities (Rosa Lemmens-Gruber 2014).

Another study investigated the anticancer properties of marine sponge *Hyattella cribriformis* ethyl acetate (EA) fraction in various cancer and normal cell lines that showed potent anticancer activity by promoting tubulin polymerization as evidenced mitotic arrest and induction of apoptosis (Pazhanimuthu Annamalai *et al*., 2015).

Guanidine Alkaloids from the marine sponge *Monanchora pulchra* was found to show cytotoxic properties and prevented EGF-Induced neoplastic transformation *in vitro* and this study proved that guanidine marine alkaloids hold potential to eliminate human cancer cells and prevent cancer cell formation and spreading (Sergey *et al*., 2016). Four new tetracyclic meroterpenes, dysiherbols A–C and dysideanone E isolated from a *Dysidea sp.* marine sponge were found to possess NF-κB inhibitory and cytotoxic activity (Wei-Hua Jiao *et al*., 2016).

Four triterpenes, isolated and identified as sipholenone A, sipholenol A, neviotine A and sipholenol L from the Red Sea Sponge, *Siphonochalina siphonella* were found to be cytotoxic to MCF-7 and HepG-2 cancer cell lines (SM Al-Massarani *et al.*, 2015). Methanol extracts of *Haliclona species* indicated that it could induce apoptosis via the JNK-p53 pathway and caspase-8 in nonsmall cell lung cancer A549 cells (Woori Bae *et al.*, 2015).

Immunosuppressive compounds

Promising immunomodulating activities have been attributed to marine natural compounds. Immunomodulators may be biological or synthetic substances, that can suppress, modulate or stimulate, the immune system including both adaptive and innate immunity of the immune response. Immune system suppression is desired in cases of hypersensitivity to certain antigens or organ transplantations. It was by the end of 1980s, immunosuppressive compounds from marine sponges were derived. Two compounds with important immunosuppressive activity were discovered in *Agelas flabellrformis* whose structures determined were found to be effective in suppressing the response of murine splenocytes (Gunasekara *et al.*, 1989). In a study conducted on the marine sponge *Callyspongia difusa* almost 10 marine bacterial strains were isolated that showed antagonistic activity against clinical bacterial pathogens.This led researchers to suggest that the sponge associated bacterial strain *Virgibacillus species* may possess the potential to contribute to the discovery of novel antibiotics against infections and also for the production of potential immunomodulators (Kalirajan *et al.*, 2013). Immunomodulatory potential exhibited by the marine sponge *Aurora globostellata* was proven by oral administration to Wistar rats. The results obtained indicated that extracts possess immunosuppressant activity (Chairman K *et al.*, 2013)

Solomonsterol A, considered as a selective pregnane X receptor (PXR) agonist has been isolated from the marine sponge *Theonella swinhoei*. It has been found to possess anti-inflammatory activity that could attenuate systemic inflammation and immune dysfunction in mouse models of rheumatoid arthritis (Andrea Mencarelli *et al.,* 2014).

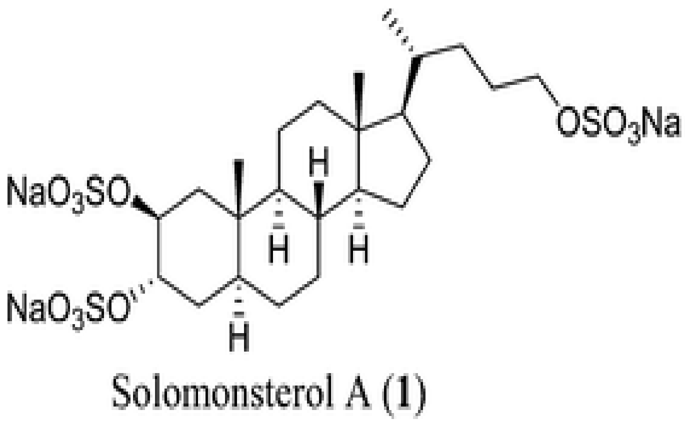

Fig 4.Structure of Solomonsterol A (Ref: Valentina Sepe *et al.*,2012)

Studies of Mayer *et al*., 2000; 2004; 2011, has shown that the polyoxygenated sterols identified from Dysidea species possess immunosuppressive ability to block the binding of interleukin 8 (IL-8), to the IL-8 receptor (de Almeida Leone *et al*., 2000). Likewise, from Mycale species, Pateamine A that can act as the selective inhibitors of the production of (IL-2) has been derived. Interleukin 2 plays a role in antigen-antibody reaction through the activation of B cells and T resting cells thus producing secondary immune response (Pattenden *et al*., 2004).

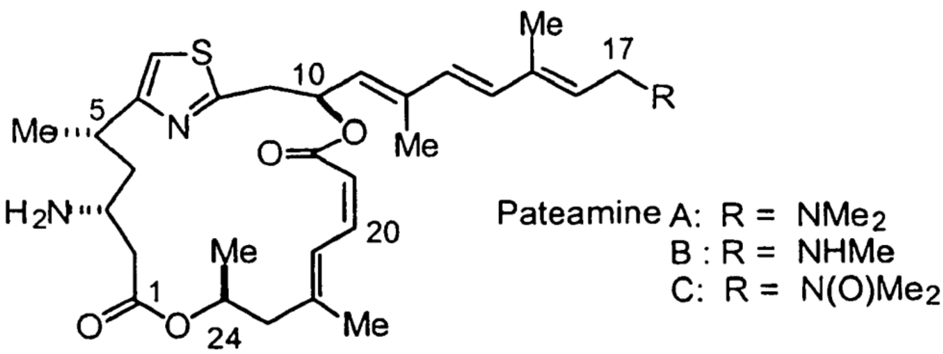

Fig 5.Structure of Pateamine (Ref: Gerald Pattenden 2004)

A novel family of closely related N-acyl dopamine glycosides from the Icelandic marine sponge *Myxilla incrustans* were tested for immunomodulating activity in an in vitro dendritic cell model (Einarsdottir E *et al*., 2016).

Antiviral and antimalarial compounds

Ara-A (vidarabine) isolated from sponge *Tethya crypta* has been considered as the most important antiviral agent as it inhibits DNA synthesis of herpes, vaccinia and varicella viruses. Such compounds are produced by enzyme clusters in sponges (Villa 2010).

The extracts from sponge *Petromica citrina* produced by the *Bacillus sp*ecies gives promising results for the treatment of hepatitis C (Santiago *et al.*, 2013). Psammaplin derivatives identified in the Indonesian marine sponge *Aplysinella strongylata* showed antimalarial activity against *falciparum* malaria parasites (Mudianta *et al.*, 2012). Diterpenes from the sponge *Stylissa* exhibit antimalarial activity (Chanthathamrongsiri *et al.*, 2012).

From the marine sponge *Verongula rigida*, Bromo tyrosine derived compounds were screened for *in vitro* activity against parasitic protozoa such as *Leishmania panamensis, Plasmodium falciparum and Trypanosoma cruzi.* Some of the compounds showed potent and selective anti-parasitic activity (Galeano *et al.*, 2011).

A diterpenoid showing potent anti-malarial activity was isolated from the marine sponge *Hymeniacidon sp* (Avilés 2010).

In a study conducted on the marine sponge *Stylissa carteri* alkaloids, debromohymenialdisine (DBH), hymenialdisine (HD), and oroidin exhibited the ability to inhibit HIV-1 replication (Aubrie O'Rourke *et al.*, 2016).

Two novel asteltoxins named asteltoxin E and F, and a new chromone, together with four known compounds isolated from the marine sponge *Callyspongia sp.*, erived fungus, Aspergillus sp. SCSIO XWS02F40 was found to possess antiviral activities against H1N1 and H3N2 (Yong-Qi Tian *et al.*, 2016).

Batzelladine- and Crambescidin-like guanidine alkaloids isolated from *Poecilosclerida* marine sponge were found to exhibit antiviral activity against different viruses such as Human immunodeficiency virus (HIV-1), Herpes simplex virus (HSV-1), and Human hepatitis B virus (HBV) (Estelle Sfecci *et al.*, 2016).

A polyketide endoperoxide, Plakortin, isolated from the sponge *Plakortis simplex* was found to show oxidative stress mediated antiparasitic activity against malaria parasite *Plasmodium falciparum* (Oleksii A. Skorokhod *et al.*, 2015). A compound stachybotrin D, isolated from a sponge associated fungus *Stachybotrys chartarum*, was found to exhibit anti-HIV activity and this was found to be possible by targeting reverse transcriptase (Ma *et al*., 2013). Li *et al.* studied the property of another anti-HIV compound from *Stachybotrys chartarum* and found that the compound chartarutine B resulted in 50% inhibition of HIV-1.

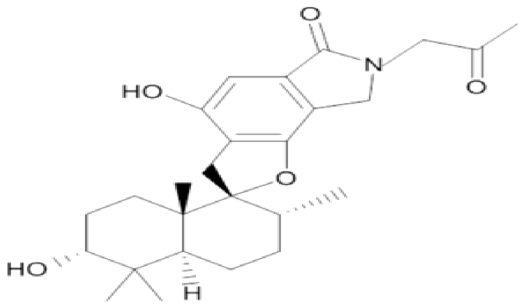

Figure 6: Structure of Stachybotrin D (Modified from Anak Agung Gede Indraningrat et al.,2016)

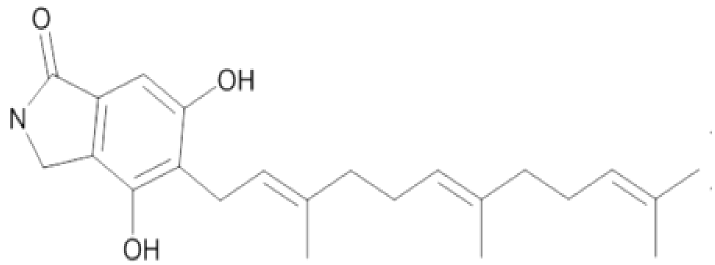

Figure 7: Structure of chartarutine B (Modified from Anak Agung Gede Indraningrat et al., 2016)

Antibiotics

Halogenated alkaloids from the marine sponge *Lotrochota purpurea* exhibited inhibitory activity against diseases related to fungi and bacteria (Shen *et al.*, 2012). Alkaloids isolated from the marine sponge *Agelas mauritiana* showed antifungal activity against *Cryptococcus neoformans*, antileishmanial activity *in vitro* and antibacterial activity against *Staphylococcus aureus* and methicillin-resistant *S. aureus in vitro* (Yang *et al.*, 2012).

Diterpene isonitriles isolated from the marine sponge *Cymbastela hooperi*, and the sesquiterpene axisonitrile-3, isolated from the sponge *Acanthella kletra*, were evaluated in a series of bioassays including anti-algal, anti-photosynthetic, antibacterial, antifungal, and anti-tubercular. The results showed that the majority of the tested compounds were active in at least two of the applied test systems (Wright *et al.*, 2011).

In another study, marine sponge's sediments and sponge-derived actinomycetes were isolated and tested for bioactive metabolites with antimicrobial and antifungal activity. Nine of the fifteen active extracts were active against multiresistant gram-positive bacteria and/or fungal indicator organisms, including vancomycin-resistant Enterococcus faecium and multidrug-resistant *Candida albicans* (Engelhardt *et al.*, 2010).

In an extensive study using marine sponge, *Neopetrosia exigua* it was concluded that the antimicrobial activities of *N. exigua* fractions evaluated using disc diffusion and microdilution methods showed that the active metabolites were present in n-hexane, CH_2Cl_2, nBuOH, and water fractions and *Staphylococcus aureus* was the most susceptible microbe evaluated (Ibrahim Majali *et al.,* 2015). A new anti-MRSA (Methicillin resistant *Staphylococcus aureus*) compound producing *Streptomyces* strain isolated from a sponge was found to show cell wall destructing property (Appadurai Muthamil Iniyan *et al.*, 2016).

A study on the marine sponge *Dysidea granulose* proved that polybrominated diphenyl ether, 2-(2′,4′-dibromophenoxy)-3,5-dibromophenol proved that they exhibit potent and broad antibacterial activity against methicillin resistant *Staphylococcus aureus* (MRSA), methicillin sensitive *Staphylococcus aureus* (MSSA), *Escherichia coli* O157:H7, and *Salmonella* (Shi Sun *et al.*,2015).

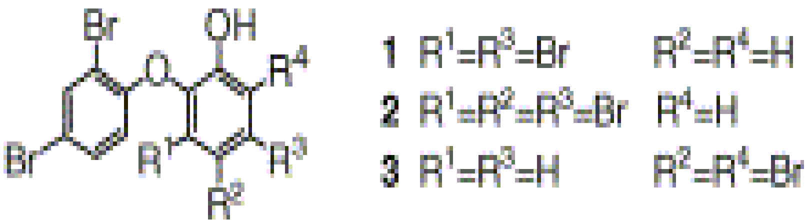

Figure 8: Structure of polybrominated diphenyl ether from sponge *Dysidea granulose* (Reference Shi Sun *et al.*, 2015)

CONCLUSION

Since marine invertebrates are found to produce significant number of natural products and secondary metabolites, isolation of new microbes with potential to produce secondary metabolites from the largely unexplored marine environment requires extensive research. Among them, marine sponges exhibit tremendous capability to produce diverse secondary metabolites. Sponge associated marine microorganisms are the prolific producers of natural compounds with potential against different diseases. These products possess anticancer, antimalarial, antiviral, immunosuppressive properties and other medicinal effects. Plethora of bioactive compounds from the marine life is greatly useful for developing new effective drugs with fewer side effects. In this context, marine sponges offer a promising source for developing new drugs that can be expected to benefit the human kind and the society. In this review, the most important and highly cited reviews for marine sponge bioactive compounds have been included.

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