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Review
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Marine Sponges as a Drug Treasure

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Abstract

Marine sponges have been considered as a drug treasure house with respect to great potential regarding their secondary metabolites. Most of the studies have been conducted on sponge's derived compounds to examine its pharmacological properties. Such compounds proved to have antibacterial, antiviral, antifungal, antimalarial, antitumor, immunosuppressive, and cardiovascular activity. Although, the mode of action of many compounds by which they interfere with human pathogenesis have not been clear till now, in this review not only the capability of the medicinal substances have been examined *in vitro* and *in vivo* against serious pathogenic microbes but, the mode of actions of medicinal compounds were explained with diagrammatic illustrations. This knowledge is one of the basic components to be known especially for transforming medicinal molecules to medicines. Sponges produce a different kind of chemical substances with numerous carbon skeletons, which have been found to be the main component interfering with human pathogenesis at different sites. The fact that different diseases have the capability to fight at different sites inside the body can increase the chances to produce targeted medicines.

Key Words: Sponges, Pharmacokinetics, Antitumor, Antiviral, Pathogenesis, Microbes

INTRODUCTION

Sponges are spineless animals belong to phylum, "the pore bearers" (Porifera), serve as most primitive multicelled animals, existing for millions of year ago. Marine sponges are soft bodied, sessile and filter feeders assembling small particles of food from sea water rising through their bodies (Hadas *et al*., 2009; Ramel, 2010). All over the world, marine sponges are the member of benthic communities of a marine environment, including its biomass as well as its ability to promote pelagic and benthic processes (Maldonado *et al*., 2005), also provide habitat for other organisms (Hultgren and Duffy, 2010). Marine life is a massive source for the synthesis of novel molecules and it need to be studied. According to evolutionary history, marine microorganisms are more diversified than terrestrial microorganisms. Marine sponges frequently produce bioactive compounds as compared to other living microorganisms. Because sponges cannot move and lack physical defenses, they are highly susceptible to marine predators such as fish, turtles, and invertebrates. Thus, it is not surprising that sponges have developed a wide suite of defensive chemicals to deter predators (Thomas *et al*., 2010). They also use their defensive chemicals to keep the offspring of small plants and animals (fouling organisms) from settling onto their outer surfaces (Mol *et al*., 2009; Hertiani *et al*., 2010). These sessile animals are a prolific source of a huge diversity of secondary metabolites that has been discovered over the past 50 years (Faulkner, 2002; Blunt *et al*., 2005; Laport *et al*., 2009; Hertiani *et al*., 2010; Proksch *et al*., 2010). The bioactive compounds are very diverse in both structure and bioactivity. The known species of sponges are more than 8000 (Van soest *et al*., 2014) widely distributed in sea and freshwater environment (Hooper and van Soest, 2002).

In the early 1950s, pharmaceutical interest among sponges have been started and it has started by the investigation of the nucleosides spongouridine and spongothymidine in the marine sponge i.e. *Cryptotethya crypta* (Bergmann and Feeney, 1950; 1951). These nucleosides were the basic root for the synthesis of ara-A, an antiviral drug and ara-C, the first marine-derived anticancer agent (Proksch *et al*., 2002). Currently,

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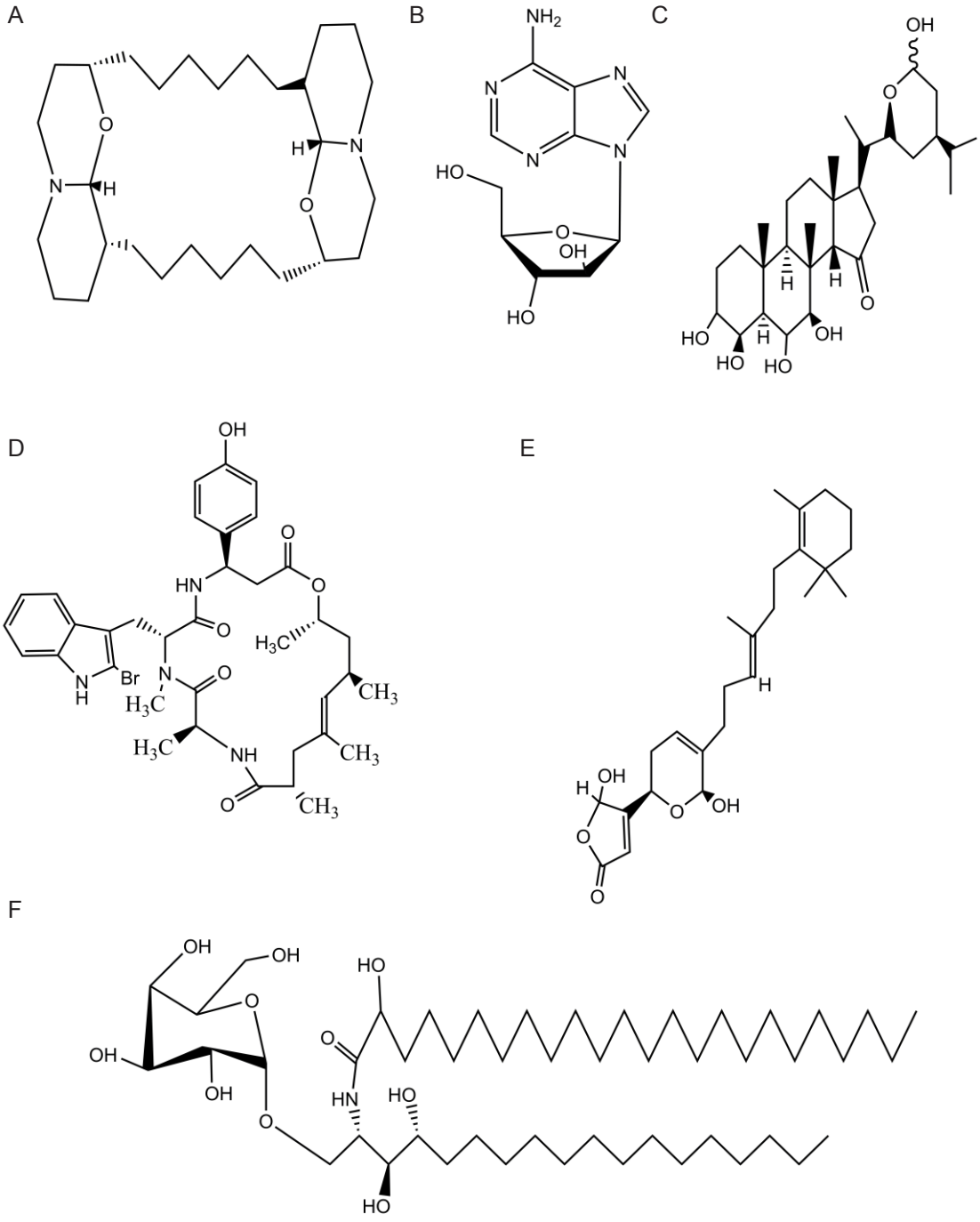

Fig. 1. The chemical structure of sponge derived molecules. (A) Xestospongin C (Xestospongia sp./macrocyclic bis-oxaquinolizidine. (B) Ara-A (Cryptotethia crypta/unusal nucleoside). (C) Contignasterol (Petrosia contignata/oxygenated sterol). (D) Jaspamide (Hemiastrella minor/macrocyclic lactam/lactone). (E) Manolide (Sesterterpenoids/*Luffariella variabilis* sp). (F) Agelasphin (Agelas mauritianus/agalactosyceramide).

ara-C used in the treatment of lymphoma and leukemia, a part of this one of its fluorinated derivative also permitted for the treatment of lung, pancreatic (Momparler, 2013), breast and bladder cancer (Schwartsmann, 2000). On the other hand, it also been revealed that lower invertebrates have more lipid components such as sterols, fatty acids and other unsaponifiable elements as compared to vertebrate animals (Bergmann and Swift, 1951; Piel, 2004). Up till now approximately 20,000 bioactive compounds have been found in marine organisms (Hu *et al*., 2011). However, most of these biologically active compounds, which are predominantly terpenoids and alkaloids, have been isolated from sponges (Leal *et al*., 2012).

Regarding the diversity of marine compounds, sponges are the most important producer. Every year around 5300 different natural products and new compounds have been isolated from marine sponges (Faulkner, 2000; 2001; 2002). Sponges are most abundantly produce novel compounds, including more than 200 novel metabolites, every year (Blunt *et al*., 2006; Turk *et al*., 2013). About 300 novel compounds were reported in 2011 from the phylum Porifera (Blunt *et al*., 2013). Moreover, some of the sponge-derived substances are however in a process of a clinical and pre-clinical trial (e.g., as anti- inflammatory or anticancer agents) in comparison of those substances that derived from different marine phylum (Blunt *et al*., 2005: Martins *et al*., 2014).

Sponge-derived or other marine microorganism's associated bioactive substances have possessed antibacterial, antiviral, antifungal, antimalarial, anthelminthic, immunosuppressive, muscle relaxants and anti-inflammatory activities. Sponge substances have remarkable chemical diversity. A part of uncommon nucleosides, marine sponges also able to produce other classes of amino acid derivatives including cyclic peptides, alkaloids, sterols, terpenes, fatty acids, peroxides, etc. (Fig. 1) (Donia and Hamann, 2003; Blunt *et al*., 2005, 2006; Sipkema *et al*., 2005; Piel, 2006). Although few representatives from sponges are approved as drugs, hundreds of new compounds with interesting pharmacological activities are discovered from sponges every year. Several sponge-derived compounds are already in clinical trials as agents against cancer, microbial infections, inflammation and other diseases. However, in many cases drug development is severely hampered by the limited supply of the respective compounds, as they are often present only in minute amounts in the sponge tissue. These reasons have moved the pharmaceutical drug discovery programs away from natural products in favor of synthetic approaches. However, the abundance of synthetic compounds with similar chemical functional groups and, therefore, limited chemical diversity has renewed interest in nature as a good resource for finding new fascinating leads to be applied to design the next generation of drugs.

In most cases development and production of sponge-derived drugs is hindered by environmental concerns and technical problems associated with harvesting large amounts of sponges. The presence of possibly producing microbial symbionts is therefore especially intriguing, as a sustainable source of sponge-derived drug candidates could be generated by establishing a symbiont culture or by transferring its biosynthetic genes into culturable bacteria. For example, Manzamine alkaloids, the promising leads for extended preclinical assessment against malaria, tuberculosis and HIV, have been previously isolated from sponge *Acanthostrongylophora* sp. and have also been isolated from the associated microorganism *Micromonospora* sp. (Hill *et al*., 2005). A dinoflagellate *Prorocentrum lima* produces okadaic acid (Morton *et al*., 1998), first isolated from the host sponge *Halichondria okadai* (Kobayashi and Ishibashi, 1993). A *Vibrio* sp. produces peptide, andrimid and brominated biphenyl ethers (Maria *et al*., 2011) that was purified from the *sponge Hyatella* sp. extract (Oclarit *et al*., 1994) and sponge *Dysidea sp*. (Elyakov *et al*., 1991).Thus, the microbial association that occurs on or in sponges could be of great interest as a solution of the supply problem of most of pharmaceutical compounds produced by sponges.

Therefore, the main focus of this review is to highlight the survey of discoveries of products derived from marine sponges which displayed *in vivo* potency or effective *in vitro* activity against infectious and parasitic diseases, including protozoal, bacterial, fungal and viral infections and their mode of action by which they interpose with the pathogenesis of human diseases. The knowledge of mechanisms of actions is very necessary for the development of the drug from a bioactive compound. For example, many secondary metabolites inhibit the growth of cancer cell lines or show the highest degree of antibiosis activity, but they do not prove that they are fit as anti-cancer or anti-microbial agents because they may exhibit severe adverse effects. Our objective was to highlight the compounds by disease type, their mode of action and the greatest potential to drive towards clinically useful treatments.

ANTIBACTERIAL ACTIVITY

At the beginning of the twenty century, the first antibiotics detection left the scientific and social society untrained, when the antibiotic-resistant bacteria emerged. This antibiotic-resistance bacterium has multiplied very swiftly and creates a considerable problem while both *Staphylococcus aureus* and some pathogenic bacteria are involved in causing the infections. According to Davies and Davies (Rice, 2006), lately vancomycin became ineffective to cure the infections caused by methicillin-resistant *S. aureus* (MRSA). The importance of drug-resistant bacterial infection has produced an imperative requirement for the quick and sustained development of new antibiotics classes, which may keep pace with the varying face of bacterial antibiotic vulnerability. Therefore, the first precedence of a biochemical research community is the innovation and improvement of new antibiotics.

The marine sponges crude extracts exhibited a low level of anti-bacterial activity against marine bacteria while a high level of antibacterial activity was exhibited against terrestrial bacteria (Amade *et al*., 1982; 1987; McCaffrey and Endeau, 1985; Uriz *et al*., 1992; Xue *et al*., 2004). The antimicrobial screenings of crude extracts from 101 Arctic sponges against bacteria associated with opportunistic infections showed that about 10% of the sponges yielded significant antimicrobial activities, with IC_{50} values from 0.2 to 5 μg/mL (Turk *et al*., 2013). In every year, some new molecules containing antibiotic properties are introduced, but in marine sponges, their ubiquity is on the top.

After an early screening test by Burkholder and Xue (Burkholder and Ruetzler, 1969; Xue *et al*., 2004), it was noted that 18 sponges out of 31 exhibited antibacterial effect while some of them were very strong against Gram-positive and Gram-negative bacteria. It was observed that marine sponges screening test for an antibacterial activity directed to both the isolation and characterization of a wide range of active substances, containing some promising therapeutic (Mayer and Hamann, 2004; Moura *et al*., 2006; Mayer *et al*., 2011) . Marine sponges produced up to 800 antibiotic substances (Torres *et al*., 2002), while some other antibacterial agents have also been identified from sponges by marine natural products community. However, no antibacterial product was reported yet in the discovered marine natural product but many of them are under investigation in current research. More or less isolated marine sponges substances with antibacterial activity are shown in (Table 1). Manoalide, one of the first sesterterpenoids to be isolated from a marine sponge *Luffariella*

Table 1. Examples of antibacterial compounds

Substance	Chemistry	Species	Activity Spectrum	MIC Value	References
Discodermins B, C and D	Cyclic peptide	*Discodermia kiiensis/Lithistida*	Antibacterial (*B. subtilis*)	3 μg/ml	Matsunaga *et al*., 1985
Arenosclerins A-C	Alkyl pepridine alkaloid	*Arenosclera brasiliensis*	*S. aureus, P. aeruginosa, M. tuberculosis*	16 μg/ml*, 30 μg/ml**	Torres *et al*., 2002
Haliclona cyclamine E	Alkylpiperidine alkaloids	*Arenosclera brasiliensis*	*S. aureus, P. aeruginosa*	8 μg/ml*	Torres *et al*., 2002
CvL	Lectine	*Cliona varians*	*S. aureus, B. subtilis*	16 μg/ml*	Moura *et al*., 2006
Axinellamines B-D	Imidazo-azolo-imidazole alkaloid	*Axinella sp./Halichondrida*	*H. Pylori, M. Luteus*	16.7 μg/ml***	Urban *et al*., 1999
Caminosides A-D	Glycolipids	*Caminus sphaeroconia*	*E. coli, S. aureus*	16 μg/ml*	Linington *et al*., 2006
6-hydroxymanzamine E	Alkaloid	*Acanthostrongylophora sp.*	*M. tuberculosis*	0.9 μg/ml**	Rao *et al*., 2004
Cribrostatin 3	Alkaloid	*Cribrochalina sp.*	*N.gonorrheae* (antibiotic resistant strain)	-	Petit and Knight, 2002
Cribrostatin 6	Alkaloid	*Cribrochalina sp.*	*S. pneumoniae* (anitibiotic resistant strain)	≤2	Pettit *et al*., 2004
Isojaspic acid, cacospongin D and jaspaquinol	Merditerpenes	*Cacospongia sp.*	*S. epidermidis*	20 μg/ml	Rubio *et al*., 2007
Isoaaptamine	Alkaloid	*Aaptos aaptos*	*S. aureus*	3.7 μg/ml	Jang *et al*., 2007
(–)-Microcionin-1	Terpenoid	*Fasciospongia sp*	*M. Luteus*	6 μg/ml	Gaspar *et al*., 2008

*S. aureus, **M. tuberculosis, ***M. luetus

variabilis, was found to be an antibiotic (Fig. 1) (de Silva and Scheuer, 1980). This is the only example of antibiotic sesterterpenoid discovered so far.

ANTIVIRAL ACTIVITY

The officially approved antiviral drug armamentarium for clinical use contains approximately 40 substances and most of them were discovered recently. It was reported that half of the recently discovered substances are used for the human immunodeficiency virus (HIV) infection treatment (De Clercq, 2004; Yasuhara-Bell and Lu, 2010). The significance of new antiviral agents development help to increase the number of available drugs becomes clear. It was observed that the adenovirus serotype 5 (AdV-5) is much constant in the environment for long time, and connected to respiratory infections with no special cure (Wiedbrauk and Johnston, 1992; Sipkema *et al*., 2005). There are some viruses such as rotaviruses, which are mainly responsible for sever gastroenteritis in human and animals. The treatment of diarrhea is only possible by symptomatic, which may cause the infection of children and immune compromised patients even it can lead to death (White and Fenner, 1986; Grimwood and Lambert, 2009).

Some new approaches being use to introduce new antiviral agents from marine sources and many promising therapeutic leads because sponges are one of the rich source of antiviral property compounds (Table 2). Maximum quantities of HIV-inhibiting compounds were introduced, while they do not reflect greater potential of sponges to fight against AIDS compared with other viral diseases. Researchers use screening techniques for anti-HIV activity has led to introducing of different compounds, although the system of inhibition is still not clear. It has been reported recently by many researchers that HIV-inhibiting compounds were produced by different sponges (Ford *et al*., 1999; Qureshi and Faulkner, 1999; Yasuhara-Bell and Lu, 2010; Sagar *et al*., 2010). For instance, avarol is a compound which inhibits the progression of HIV infection up to some extent. The data form *in vitro* experiment and animal show that avarol combines have very useful properties and increase humoral immune response (Muller *et al*., 1987; Amigó *et al*., 2007). HIV inhibits completely by avarol and blocking the production of natural UAG suppressor glutamine transfer tRNA. After viral infection, the production of tRNA is up-regulated, which is necessary for the viral protease and viral proliferation synthesis. The low Concentration of avarol 0.3 and 0.9 μM resulted in 50 and 80% of inhibition of virus released from infected cells (Muller *et al*., 1987). Moreover, the derivatives of avarol such as 6'- hydroxy avarol and 3'-hydroxy avarone were noted as very strong inhibitors of HIV reverse transcriptase (Fig. 2). Avarol play very important role during the early stages of HIV infection and it also has a specific target for antiviral drugs, while it convert the viral genomic RNA into proviral double-stranded DNA, and later on it integrated into the host chromosomal DNA (Loya and Hizi, 1990).

Another important antiviral discovery from marine source reported is the nucleoside ara A (vidarabine) which was isolated from *Cryptotethya crypta* sponge and was first synthesized in 1960 (Walter, 2005). Ara-A is an arabinosyl nucleosides which inhibits viral DNA synthesis (Bergmann and Swift, 1951; Blunt *et al*., 2006; Sagar *et al*., 2010). Research proved that our biological systems can recognize nucleoside base just after sug-

Table 2. Examples of antiviral compounds

Substances	Chemistry	Species	Action spectrum	References
4-Methylaaptamine	Alkaloid	*Aaptos aaptos*	Anti-viral (HSV-1)	Souza *et al*., 2007
Papuamides A–D	Cyclic depsipeptides	*Theonella* sp.	Anti-viral (HIV-1)	Ford *et al*., 1999
Ara-A	Nucleoside	*Cryptotethya crypta*	HSV-1, HSV-2, VZV	Faulkner, 2002
Avarol	Sesquiterpene hydroquinone	*Dysidea avara*	HIV-1,UAG suppressor Glutamine tRNA inhibitor	Muller *et al*., 1987
Haplosamates A and B	Sulfamated steroid	Xestospongia sp./ Haplosclerida	Anti-viral (HIV-1Integrase inhibitor)	Qureshi and Faulkner, 1999
Dragmacidin F	Alkaloid	*Halicortex* sp.	HIV-1	Cutignano *et al*., 2000
Hamigeran B	Phenolic Macrolide	*Hamigera tarangaensis*	Anti-viral (herpes and polio virus)	Wellington *et al*., 2000
Mycalamide A-B	Nucleosides	*Mycale* sp.	A59 coronavirus, (HSV-1)	Perry *et al*., 1990
Mirabamides A, C and D	Peptide	*Siliquariaspongia mirabilis*	Antiviral (HIV-1)	Plaza *et al*., 2007
Oroidin	Alkaloid	*Stylissa carteri*	Antiviral (HIV-1)	O'Rourke *et al*., 2016

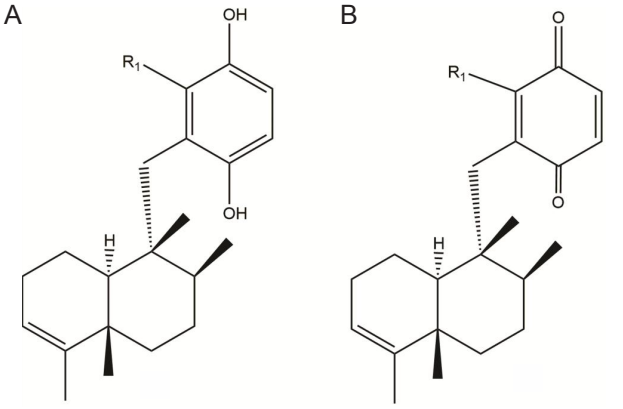

Fig. 2. Molecular structures of avarol (a: R1 = H) and 6¢- hydroxy avarol (A: R1 = OH) and avarone (B: R1 = H) and 3¢- hydroxy avarone (B: R1 = OH).

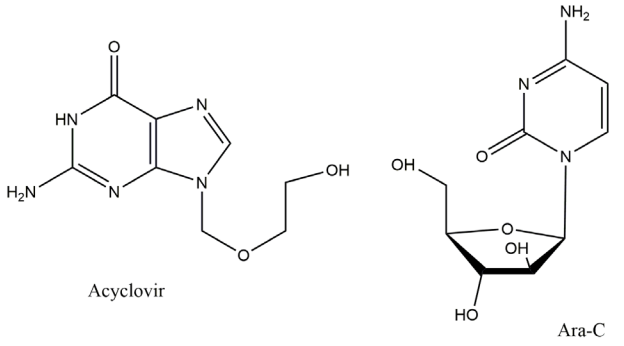

Fig. 3. Molecular structure of Acyclovir and Ara-c (Acyclovir is a drug of choice for Herpes virus).

ar moiety modifications, then chemists started to replace the pentoses by acyclic entities or with sugar molecules, it lead to the development of azidothymidine (zidovudine) drug. An examples of semisynthetic arabinosyl nucleosides modification are Ara-A, acyclovir, ara-C (Fig. 1, 3) and azidothymidine are in clinical use (De Clercq *et al*., 2002; Sagar *et al*., 2010).

ANTIFUNGAL ACTIVITY

In the last decades, the fungal infection (especially invasive mycoses) dramatically increased in those individuals suffering from AIDS, immune depressants, hematological malignancies, and transplant recipients, increased the need of new antifungals (García-Ruiz *et al*., 2004; Pontón *et al*., 2000). Fungal infection remains a major direct cause of death for those patients who are treated for malignant disease (Sandven, 2000; Ellis *et al*., 2000). Fungal causing malignant diseases are a major cause of life threatening diseases as well as resistance to them is a major problem (García-Ruiz *et al*., 2004; Giusiano *et al*., 2004; Walsh *et al*., 2004; Giusiano *et al*., 2005). Immunocompromised patients are mainly infected by *Candida*, *Aspergillus*, *Cryptococcus* and other opportunistic fungi. Currently using fungicides are less diversified than antimicrobial substances and their use is restricted because of biological system toxicity (Rahden-Staron, 2002).

Jaspamide is the first example of cyclodepsipeptide 19-membered macrocyclic depsipeptide (Fig. 1) isolated from the sponges *Jaspis sp* has a selective *in vitro* antifungal activity with MIC of 25 μg/ml against *C. albicans* while *in vivo* topical activity of a 2% solution against *Candida* vaginal infection in mice (Zabriskie *et al*., 1986; Ebada *et al*., 2009). The other examples of important antifungals examined *in vitro* with MIC values have been listed (Table 3).

ANTIMALARIAL PROPERTIRES

In sub- Saharan Africa, malaria is a predominant disease including that it is also serious public health problem in some areas of South America and Southeast Asia. Most of the malaria related deaths are caused by *Plasmodium falciparum* parasite (Mishra *et al*., 1999; Caraballo and King, 2014; WHO, 2015). Recently, most widely disseminated malarial species all over the world is *Plasmodium vivax*. *P. vivax* is the predominant specie in the Asia and America, while in Brazil this species represents around 80% of clinical issue annually (Brazilian Health Ministry, 2002). Sub-Saharan Africa carries a disproportionately high share of the global malaria burden. In 2015, the region was home to 88% of malaria cases and 90% of malaria deaths (Baird, 2013; WHO, 2015). During last decades,

Table 3. Examples of antiviral compounds

Substances	Chemistry	Species	Action spectrum	MIC value	References
Jaspamide	Macrocyclic depsipeptide	*Jaspis sp*	*C.albicans*	25 μg/ml*	Zabriskie *et al*., 1986
Eurysterols A-B	Sterols	*Eurypongia sp*	*C.albicans, Amphoterician B- resistant*	62.5 μg/ml*, 15.6 μg/ml	Boonlarppradab and Faulkner, 2007
Naamine D	Imidazole alkaloid	*Leucetta cf. chagosensis*	*C.neoformans*	6.25 μg/ml**	Dunbar *et al*., 2000
Mirabilin B	Tricyclic guanidine alkaloid	*Monanchora unguifera*	*C.neoformans*	7.0 μg/ml**	Hua *et al*., 2004
Hamacanthin A	Indole alkaloid	*Spongosorities sp.*	*C.albicans*	6.25 μg/ml*	Oh *et al*., 2006
Macanthins A-B	Indole alkaloid	*Spongosorities sp.*	*C.albicans, C.neoformans*	1.6 μg/ml*, 6.2 μg/ml**	Oh *et al*., 2006
Agelasines and agelasimines	Purine derivative	*Agelas sp.*	*C.krusei*	15.6 μg/ml	Vik *et al*., 2007

MIC: Minimum Inhibitory Concentration, **C. albicans*, ***C. neoformans*.

Table 4. Examples of anti-malarial compounds

Substances	Chemistry	Species	Action spectrum	IC_{50} value	References
Monamphilectine A	Antimalarial β-lactam	*Hymeniacidon sp*	*P. falciparum*	0.6 μM***	Avilés and Rodriguez, 2010
Manzamine A	Alkaloids	*e.g., Haliclona sp./ Haplosclerida Cymbastela hooperi/ Halichondrida Diacarnus levii/ Poecilosclerida*	*T. gondii, P. berghei, P. falciparum*	4.5 ng/ml***	D Ambrosio *et al*., 1998
Kalihinol A	Isonitril-containing kalihinane diterpenoid	*Acanthella sp./ Halichondrida*	*P. falciparum*	0.0005 μg/ml**	Ang *et al*., 2001
Diisocyanoadociane	Tetracyclic diterpene	*Cymbastela hooperi*	*P. falciparum*	0.005 μg/ml**	Miyaoka *et al*., 1998
Halichondramide	Macrolides		*P. falciparum*	0.002 μg/ml**	Konig *et al*., 1996
Sigmosceptrellin-B	Norsesterterpene acid	*Diacarnus erythraeanus*	*T. gondii, P. falciparum*	1200 ng/ml*	Konig *et al*., 1996
(E)-Oroidin	Alkaloids	*Agelas oroides*	*P. falciparum*	0.30 μg/ml**	Yousaf *et al*., 2002
Plakortin and dihydroplakortin	Cycloperoxidase	*Plakortis simplex*	*P. falciparum*	1263-1117 nM*	Tasdemir *et al*., 2007

IC_{50}: Inhibitory Concentration, **P. falciparum* (D10), ***P. falciparum* (D6 clone), ****Chloroquine-resistant P. falciparum* (W2).
[h] Fattorusso *et al*., 2002.

some of the antimicrobial compounds have been derived from sponges (Table 4, Fig. 4). Increasing resistance among Plasmodium strains created a need to discover new antimalarial compounds. *Plasmodium falciparum* has become resistant toward chloroquinone, pyrimethamine, and sulfadoxine (Bwijo *et al*., 2003). *In vitro*, selective antimalarial activity against *Plasmodium falciparum* has been recorded by different isonitrilese, isothiocyanates and terpenoid isocyanates from *Cymbastela hooperi* (Konig *et al*., 1996). Including that a number of free carboxylic acids (*Diacarnus levii*) after esterification were used as precursors to synthesize some new cyclic norditerpene peroxides. These epidioxy-substituted norsesterterpenes and norditerpenes endoperoxides from marine sponge *Diacarnus megaspinorhabdosa* showed antimalarial activity against both chloroquine- resistant *P. falciparum* and chloroquine-sensitive (D Ambrosio *et al*., 1998; Yang *et al*., 2014).

The most capable and promising antimalarial compound, manzamines have been isolated from a number of sponges (Sakai *et al*., 1986; Yousaf *et al*., 2002; Fattorusso and Taglialatela, 2009). Manzamine A displayed a potent *in vitro* activity against *P. falciparum* (D6clone), with MIC of 0.0045 μg/ml (Sakai *et al*., 1986; Ashok *et al*., 2014). According to research antimalarial activity of manzamine A is due to enhancing immune response (Ang *et al*., 2001).

ANTI-INFLAMMATORY ACTIVITY

Body inflammation is caused by physical or chemical damage or due to infection. In this case, blood is oozing out from blood vessels into tissues (Tan *et al*., 1997; Franceschi and Campisi, 2014). Manolide is the first sesterterpenoids anti-inflammatory drug derived from marine sponges with several other pharmaceutical properties (Mayer and Jacobs, 1998). Its Anti-inflammatory action is basically an irreversible inhibition of the release of arachidonic acid from phospholipid mem-

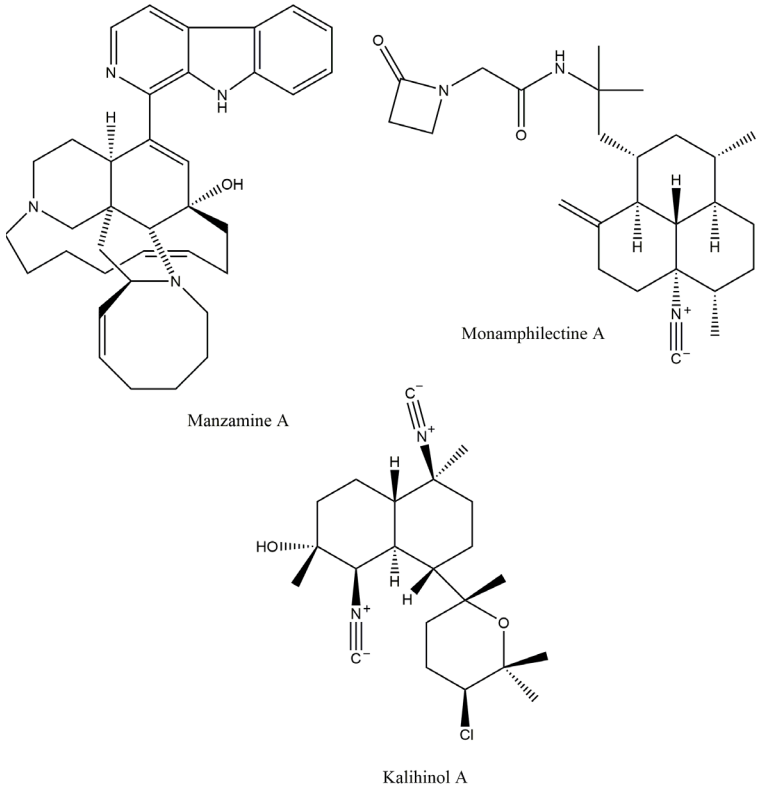

Fig. 4. Structure of Antimalarial compounds; Manzamine A; Monamphilectine A; Kalihinol A.

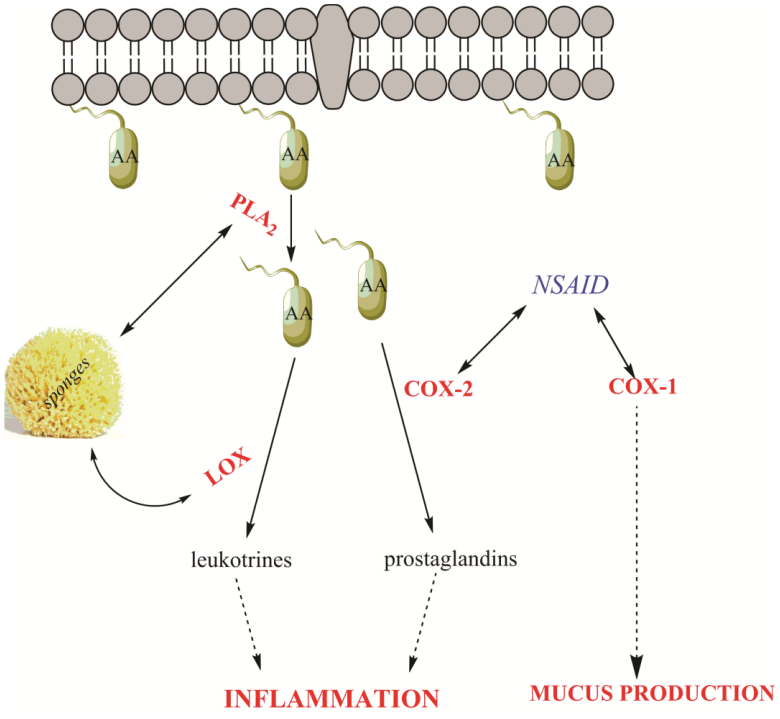

Fig. 5. Diagrammatic process of Inflammatory cascade inside the cell. Phospholipase A2 (PLA2) catalyzes the release of membrane-bound arachidonic acid (AA) to free arachidonic acid. Arachidonic acid is then converted to leukotrienes and prostaglandins by lipoxygenase (LOX) and cyclooxygenase-2 (COX-2), respectively. Sponge derived anti-inflammatory substances are mainly inhibitors of PLA2 or LOX, while nonsteroidal anti- inflammatory drugs (NSAID) inhibit COX-2, but also the constitutive COX-1.

Table 5. Examples of anti-tumor compounds

Compound	Chemistry	Species/order	Mode of action	References
Isoaaptamine	Benzonaphthyridine alkaloid	*Aaptos aaptos/Hadromerida*	Protein kinase C inhibitor	Fedoreev *et al*., 1988
Debromohymenialdisine	Pyrrole-guanidine alkaloid, prenylhydroquinone derivative	*Hymeniacidonaldis/Halichondrida*	Protein kinase C inhibitor	Kitagawa *et al*., 1983
Adociasulfates	Triterpenoid hydroquinones	*Sarcotragus sp./ Dictyoceratida Haliclona (aka Adocia) sp./ Haplosclerida*	A1, 3-fucosyltransferase inhibitor Kinesin motor protein inhibitors	Zapolska-Downar *et al*., 2001
Discodermolide	Linear tetraene lactone	*Discodermia dissolute/ Lithistida*	Stabilization of microtubules	Ter Haar *et al*., 1996
Peloruside A	Macrocyclic lactone	*Mycdle hentschett/ Poecilosclerida*	Stabilization of microtubules	Hood *et al*., 2002
Elenic acid	Alkylphenol	*Plakinastrella sp./ Homosclerophorida*	Topoisomerase II inhibitor	Hood *et al*., 2002
Naamine D	Imidazole alkaloid	*Leucetta cf. chagosensis*	Nitric oxide synthetase inhibitor	Juagdan *et al*., 1995
Agelasphin (KRN7000)	a-Galactosylceramide	*Agelas mauritianus / Agelasida*	NKT cell activator	Shimosaka, 2002
Crambescidins 1-4	Pentacyclic guanidine derivative	*Crambe crambe/Poecilosclerida*	Ca2+/channel blocker	Jares-Erijman *et al*., 1991
Discorhabdin D	Fused pyrrolophenanthroline alkaloid	*Latrunculia brevis/Poecilosclerida; Prianos sp./Haplosclerida*	Unknown	Perry *et al*., 1990
Glaciasterols A and B	9, 11-Secosterol	*Aplysilla glacialis/Dendroceratida*	Unknown	Pika *et al*., 1992
Durumolides A-C	Terpenoid	*Lobophytum duru*	Inducible NOS and COX-2 inhibition	Cheng *et al*., 2008
Plakortide P	Polyketide	*Plakortis angulospiculatus*	TXB2 inhibition	Kossuga *et al*., 2008
24-methoxypetrosaspongia C	Sesterterpenes	*Hyrtios erectus*	Unknown	Elhady *et al*., 2016

brane by the mechanism of preventing the phospholipase A2 enzyme from the binding to the membrane of phospholipid, the reason is that it increases the concentration of intracellular arachidonic acid that results in the upregulation of the inflammation mediators synthesis as a leukotrienes and prostaglandins. The Mode of action of sponge-derived anti-inflammatory substances has different from other non-steroidal anti-inflammatory drugs (NSAIDS). Only a few of sponge-derived substances have the capability to inhibit lipoxygenase, another enzyme which is involved in the inflammatory response (Carroll *et al*., 2001) (Fig. 5).

ANTITUMOR ACTIVITY

In the tumor development protein kinase C (PKC) is an essential factor (Bradshaw *et al*., 1993; Kang, 2014). Many of the sponge-derived substances are PKC inhibitors. Worldwide, PKC inhibitors have attracted interest because of providing evidence, that extreme levels of PKC enzymes are involved in the pathogenesis of psoriasis, arthritis and especially in the development of tumor (Bradshaw *et al*., 1993; Kang, 2014). PKC serve as a receptor for tumor-promoting phorbol esters by the binding prevention of carcinosarcoma cells with Endothelium (Liu *et al*., 1991; Kang, 2014).

Fucosyltransferase inhibitors, like octa and nonaprenylhydroquinone sulfates, which were derived from *Sarcotragus sp*. (Wakimoto *et al*., 1999), may be capable candidates for regulating inflammatory processes like arthritis or for opposing tumor growth.

There are many other sponge derived compounds having anti-tumor potency with different kind of mechanisms of actions (Table 5). These are divided into three types.

Non-specific inhibitors

Nonspecific anti-tumor inhibitors are important compounds to treat cancer but in unusual conditions because these compounds also have toxic effects on healthy cells of a body. Example is adociasulfates (titerpenoid hydroquinones), isolated from *Haticlona sp*. Etc (Blackburn *et al*., 1999; Zapolska-Downar *et al*., 2001) and they are protein inhibitors by binding to microtubule binding site “locking up” protein motor function and there by blocking cell division.

Specific inhibitors

Specific inhibitors are specifically active against the tumor. For example, agosterol A derived from marine spongia can reverse the over appearance of membrane glycoproteins. These proteins are responsible for multidrug resistance in human carcinoma cells. Another example belongs to these inhibitors group is salicylihamide A. The first natural isolated from *cinachyrella spp*. is 6- hydroximino-4-en-3 (Griffith and Gross, 1996).

Inhibitors of a cancer cell of certain types

Growth inhibitory active compounds against tumor cell line have been isolated but its mechanism of action is still unknown. For example Discorhabdin D (Perry *et al*., 1990) etc.

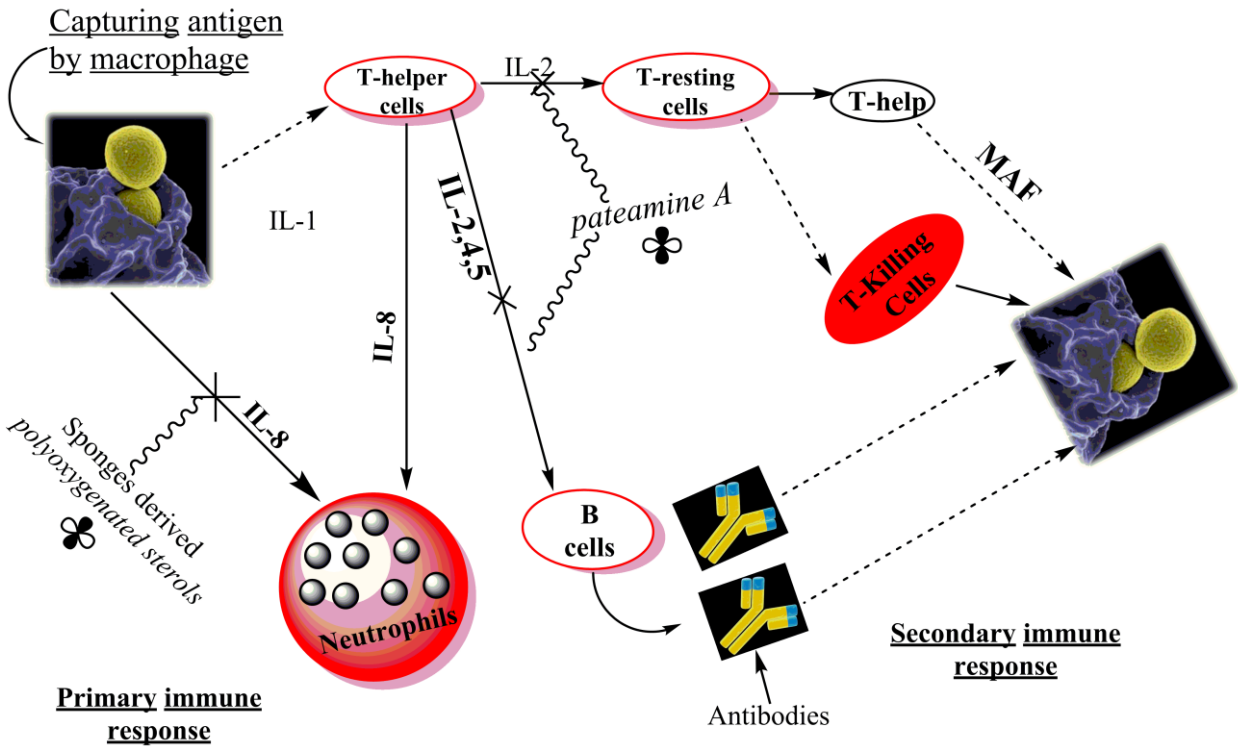

Fig. 6. Diagrammatic representation of body immune response towards antigen capturing by Macrophages. The macrophages and T-helper cells secrete many interleukins (IL-x) or macrophage activation factor (MAF), to trigger primary immune response with the help of neutrophils, or the secondary immune response by activating the B and resting T-cells. The activated B cells secrete antibodies which bind to macrophages that already have phagocytized an antigen, and then killed by T-killer cells. The ♣ sign shows the sponge derived substances.

Table 6. Examples of immunosuppressive compounds

Compounds	Chemistry	Species/ order	Mode of action	References
Simplexides	Glycolipids	*Plakortis simplex*/ Homosclerophorida	Inhibitors of T cell proliferation	Costantino *et al*., 1999
Polyoxygenated sterols	Sterol	*Dysidea sp.*/ Dendroceratida	IL 8 inhibitor	de Almeida Leone *et al*., 2000
Contignasterol	Oxygenated sterol	*Petrosia contignata*/ Haplosclerida	Histamine release inhibitor	Takei *et al*., 1994
Pateamine A	Thiazole macrolide	*Mycale sp./Poecilosclerida*	IL-2 inhibitor	Northcote *et al*., 1991
Iso-iantheran A	Polyketide	*Ianthella quadrangulata*	Ionotropic $P2Y_{11}$ receptor activation	Greve *et al*., 2007

IMMUNE SUPPRESSIVE ACTIVITY

Nitric oxide synthetase inhibitors, as anti-cancer agents are also responsible for the immune system suppression by downregulating the T-cells (Griffith and Gross, 1996). The ratio of Immune system suppression is very highly desired in case of hypersensitivity to antigens (e.g. allergies) medicines or organ transplantations. The cases in which patients receive any donor organ have to persist on life-long medication to prevent rejection by the body immune system as a foreign agent, and for that reasons, it is very important that these medicines should be specific suppressors. To prevent this autoimmune body defensive response and rejection of the donor organ, therefore, now it is a very crucial need for new specific immunosuppressors. A number of new biomolecules with strong immunosuppressive activities, which interfere at different sites of the immune response system have been discovered in marine sponges.

Dysidea sp have a large contribution in the portion of biomolecules (Mayer *et al*., 2000; 2004; 2011). 3 polyoxygenated sterols derived from *Dysidea sp*. in North Australia having a strong selective immunosuppressive capability of blocking the binding of interleukin 8 (IL-8), a cytokine that attracts neutrophil into tissue injury site, to the IL-8 receptor (de Almeida Leone *et al*., 2000). Thus, these polyoxygenated sterols have a specific selective inhibition on primary immune response

Table 7. Cardiovascular compound examples

Compounds	Chemistry	Species/ order	Mode of action	References
Cyclotheonamide A	Cyclic pentapeptide	*Theonella sp.*/Lithistida	Serine protease inhibitor	Maryanoff *et al*., 1993
Eryloside F	Penasterol disaccharide	*Eryltus formosus*/Astrophorida	Thrombin receptor antagonist	Stead *et al*., 2000
Halichlorine	Cyclic aza Polyketide	*Halichondria okadai*/Halichondria	VCAM 1* inhibitor	Arimoto *et al*., 1998

*VCAM: vascular cell adhesion molecule.

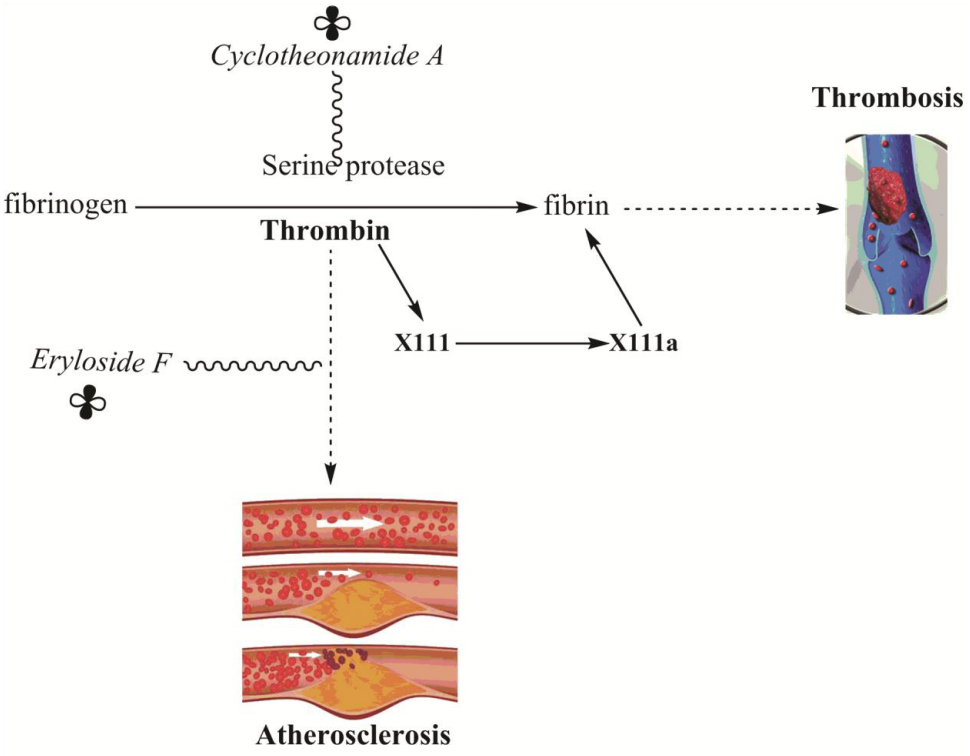

Fig. 7. Blood coagulation (Thrombosis) and atherosclerosis (arterial disease characterized by the deposition of plaques of fatty material on their inner walls) pathway *in vivo* showing central role played by Thrombin. X111 represent *fibrin stabilizing factor* (enzyme responsible for blood coagulation). The ✣ Sign shows the sponge derived compounds.

(Fig. 6). Correspondingly, Pateamine A derived from *Mycale sp*., are the selective inhibitors of the production of interleukin 2 (IL-2), IL-2 helps in activation of B cells and T resting cells leading to cause antigen-antibody reaction and produce Secondary immune response.(Romo *et al*., 1998; Pattenden *et al*., 2004). Some examples for these suppressants are mentioned in Table 6, Fig. 6.

CARDIOVASCULAR AGENTS

Some of the very common blood-related diseases like diabetes, thrombosis, atherosclerosis etc. have been treated by some marine sponge's derived substances (Table 7, Fig. 7). The mechanism of blood coagulation is managed by a complex photolytic cascade that leads to the production of fibrin. Fibrin, a major component responsible for blood coagulation has been generated by the peptide cleaving of fibrinogen by thrombin (Kołodziejczyk and Ponczek, 2013). Cyclotheonamide A, isolated from marine sponges Theonella sp (Maryanoff *et al*., 1993) is an unusual class of Serine protease (an enzyme responsible for the conversion of fibrinogen into fibrin) inhibitor and is a drug of choice for thrombosis (Maryanoff *et al*., 1993; Schaschke and Sommerhoff, 2010). Eryloside F derived from *Eryltus formosus sp*. was found to be a potent Thrombin-receptor antagonist (Shuman *et al*., 1993; Stead *et al*., 2000; Kalinin *et al*., 2012). Thrombin receptor plays a central role not only in thrombosis but also the main agent to cause atherosclerosis (Fig. 7) (Chackalamannil, 2001; Ikenaga *et al*., 2016). Atherosclerosis is a disease in which plaque (fats, cholesterol, and calcium etc.) builds up layer by layer inside the arteries and resulting by narrowing of the arteries, causing a barrier to blood circulation leading to serious problems including heart attack, stroke or maybe death (Zapolska-Downar *et al*., 2001; Ikenaga *et al*., 2016).

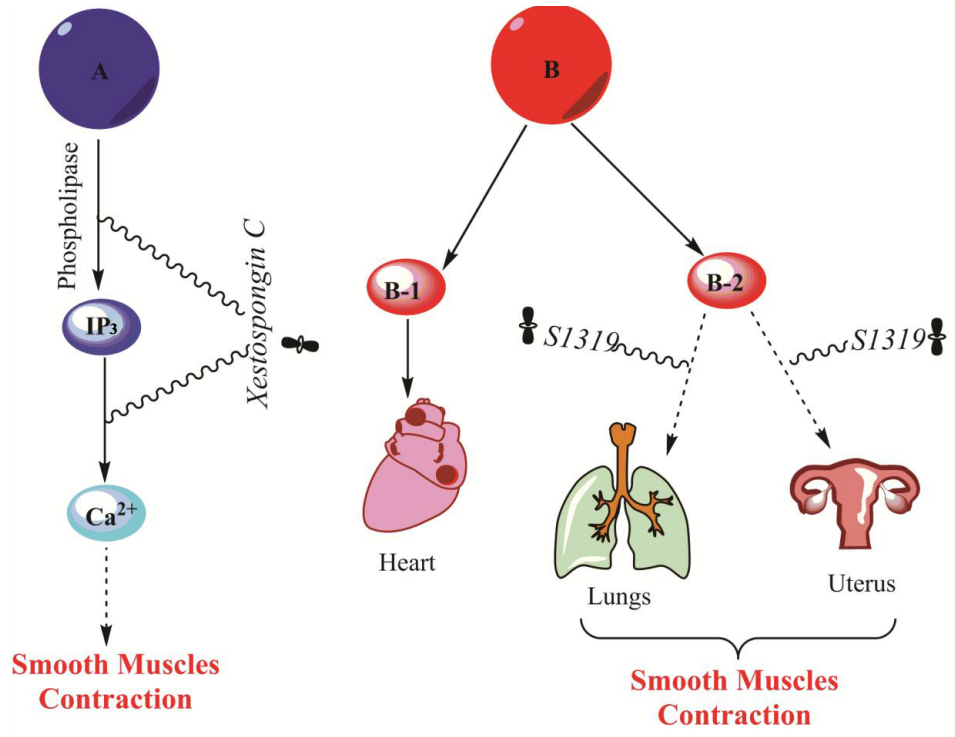

Fig. 8. The mechanism of adrenergic receptors. A represent α-receptors and trigger the IP_3 (Inositol triphosphate) which then increase the Ca^{2+} level in cytoplasm and causing muscles contraction. B represents β-adrenoreceptors. The ⁑ represents Marine compounds. *Xestospongin C* inhibit the phospholipase enzyme which play a key role in activation of IP_3 (Inositol triphosphate) and block Ca^{2+} channels. *S1319* B-2 receptor agonist resulting Bronchodilation and uterus relaxation.

ANTIHELMINTHIC ACTIVITY

A new macrocyclic polyketide lactam tetramic acid, geodin A Magnesium salt, isolated from the marine sponge *Geodia sp*. exhibited a remarkable nematocidal activity with (LD99=14 μg/ml) against *Haemonchus contortus* (Capon *et al*., 1999). The mode of action of the pure Geodin A is not explored yet. Two more studies contributed to the search of novel *anthelmintic* marine sponge derived products during 2005-6. Two novel alkaloidal betaines (-)-echinobetaine A (1) and (+)-echinobetaine B (2), isolated from marine sponge Echinodictyum sp proved to be a nematocidal with (LD_{99}=83 and 8.3 μg/mL, respectively) against commercial livestock parasite *Haemonchus contortus* (Capon *et al*., 2005). Unfortunately, the mode of action of these compounds was also undetermined. (+)-echinobetaine B's nematocidal potency was comparable to that of "two commercially available synthetic anthelmintic, closantel and levamisole" (Capon *et al*., 2005).

MUSCLE RELAXANT

Continuous muscles activation caused by disturbances in the neuromuscular communication that result in muscular stress (Lundberg *et al*., 1995; Edgar *et al*., 2002; Hibbs and Zambon, 2011). Muscle relaxants are divided into two parts; centrally and peripherally active. Centrally active can mediate neuromuscular communication while peripherally relaxants are used for local muscle relaxation like stroke or during surgery (Frakes, 2001; Hibbs and Zambon, 2011) Xestospongin C (Fig. 1) isolated from marine sponge *Xestospongia sp* is a potent α-receptor's IP_3 (Inositol triphosphate) inhibitor and Ca^{2+} (calcium channel) blocker (Quinn *et al*., 1980; Gafni *et al*., 1997; Miyamoto *et al*., 2000). IP_3 is a secondary messenger molecule used in signal transduction and it diffuses throughout the cell and increases the Ca^{2+} level and resulting cause's smooth muscles contraction (Fig. 8) (Quinn *et al*., 1980; Nausch *et al*., 2010). S1319 isolated from a *Dysidea sp*. (Suzuki *et al*., 1999) is another substance with a remarkable muscle relaxing capability. Its mechanism of action is to agonist the β-Adrenoreceptor. β-Adrenoreceptors are of two types β-1 and β-2. β-1 receptors are available in heart increases heart rate, myocardial contractility and increases conduction velocity while β-2 receptors are available in lungs and uterus responsible for dilation of bronchial smooth muscles, dilation of blood vessels in skeletal smooth muscles and relaxation of uterus muscles (Dennedy *et al*., 2002; Barrese and Taglialatela, 2013). S1319 have the uterus relaxing capability which can be therapeutically used at infant's delivery time (Dennedy *et al*., 2002) and bronchodilation property which can be used as antiasthmatic (Suzuki *et al*., 1999). However, because of their low selectivity, they have some side effects like activation of β-1 receptors resulting arterial hypertension, tachycardia and coronary heart disease (Borchard, 1998). Therefore, there is a desired continued research in interest to find selective β-agonists.

CONCLUSION

Sponge-derived substances span a wide range of chemistry (e.g., alkaloid, peptide, terpenoid and polyketides) with an equally variety of biotechnological properties (e.g., Antibacterial, antifungal, antiviral, immunosuppressive, cardiovascular and anti-parasitic) (Ang *et al*., 2001; Torres *et al*., 2002). The relationship between the chemistry of the secondary metabolites originated from marine sponges and their mode of action on disease *in vivo* is mostly not obvious (interaction with DNA to combat tumors, or inhibition of α/β receptors to provide muscle relaxation). Moreover, in drug discovery, it is frequently observed that a certain series of compounds that exhibited the most potent inhibitors *in vitro* turned out not to be the drug of choice *in vivo*. It is likely that for every compound prior to coming out to the market, its profile should be with a distinct chemistry, improved bioavailability with lesser side effects.

Now, there are some significant reports of activities from a particular class of metabolites, the manzamines from marine sponges as potential drugs that might be effective against HIV (Muller *et al*., 1987), malaria (Konig *et al*., 1996), tuberculosis (Schwartsmann, 2000) and some other diseases. Other substances with best anti-pathogenic profiles like ara-A, ara-C, acyclovir are in clinical use and are all examples of products originated from marine sponges (Muller *et al*., 1987).

The potency of sponge-derived medicines lies in the fact that each of these thousands of metabolites and their derivatives has its own specific dose-related efficacy, inhibitory effect, and potential side effects that determine its suitability for medicinal use. Unfortunately, these secondary metabolites are usually present in very trace amounts, and natural stocks are too small which is one of the major obstacles in sustaining the development of widely available medicines. An example is avarol (*D.avara* sponge), a potent anti-HIV drug (Muller *et al*., 1987), that was in preclinical assessment. However, further studies on this natural product stopped due to an insufficient amount of sponge for its isolation (Müller *et al*., 2004). In addition, the active core or skeleton of these compounds may be used as a vehicle to generate derivatives with their own distinct efficacy and side effects. Therefore, the most significant challenge in the transformation of bioactive molecules into medicines is now to screen the drug treasure house of sponges and elect those that illustrate a precise mode of action with the desired characteristics towards a disease. A major question for the future still persists, how to actually prepare the potential novel drugs in a bulk quantity.

REFERENCES

Amade, P., Charroin, G., Baby, C. and Vacelet, J. (1987) Antimicrobial activity of marine sponges of Mediterranean. *Sea. Mar. Biol*. **94**, 271-275.

Amade, P. H., Pesando, D. and Chevolot, L. (1982) Antimicrobial activities of marine from French Polynesia and Brittany. *Mar. Biol.* **70**, 223-228.

Amigó, M., Terencio, M. C., Payá, M., Iodice, C. and De Rosa, S. (2007) Synthesis and evaluation of diverse thio avarol derivatives as potential UVB photoprotective candidates. *Bioorg. Med. Chem. Lett.* **17**, 2561-2565.

Ang, K. K., Holmes, M. J. and Kara, U. A. (2001) Immunemediated parasite clearance in mice infected with *Plasmodium berghei* following treatment with manzamine A. *Parasitol. Res.* **87**, 715-721.

Arimoto, H., Hayakawa, I., Kuramoto, M. and Uemura, D. (1998) Absolute stereochemistry of halichlorine; a potent inhibitor of VCAM-1 induction. *Tetrahedron Lett.* **39**, 861-862.

Ashok, P., Ganguly, S. and Murugesan S. (2014) Manzamine alkaloids: isolation, cytotoxicity, antimalarial activity and SAR studies. *Drug Discovr. Today* **19**, 1781-1791.

Avilés, E. and Rodríguez, A. D. (2010) Monamphilectine A, a Potent Antimalarial β-Lactam from Marine Sponge *Hymeniacidon* sp: Isolation, Structure, Semisynthesis, and Bioactivity. *Org. Lett*. **12**, 5290-5293.

Baird, J. K. (2013) Evidence and implications of mortality associated with acute *Plasmodium vivax* malaria. *Clin. Microbiol. Rev*. **26**, 36-57.

Barrese, V. and Taglialatela, M. (2013) New advances in beta-blocker therapy in heart failure. *Front. Physiol*. **4**, 323.

Bergmann, W. and Feeney, R. J. (1950) The isolation of a new thymine pentoside from sponges. *J. Am. Chem. Soc.* **72**, 2809-2810.

Bergmann, W. and Feeney, R. J. (1951) Contribution to the study of marine products. *J. Org. Chem.* **16**, 981-987.

Bergmann, W. and Swift, A. N. (1951) Contributions to the study of marine products. XXX. Component acids of lipids sponges. I. *J. Org. Chem.* **16**, 1206-1221.

Blackburn, C. L., Hopmann, C., Sakowicz, R., Berdelis, M, S., Goldstein, L. S. B. and Faulkner, D. J. (1999) Adociasulfates 1-6, inhibitors of kinesin motor proteins from the sponge Haliclona (aka Adocia) sp. *J. Org. Chem.* **64**, 5565-5570.

Blunt, J. W., Copp, B. R., Keyzers, R. A., Munroa, M. H. and Prinsep, M. R. (2013) Marine natural products. *Nat. Prod. Rep.* **30**, 237-323.

Blunt, J. W., Copp, B. R., Munro, M. H., Northcote, P. T. and Prinsep, M. R. (2005) Marine natural products. *Nat. Prod. Rep.* **22**, 15-61.

Blunt, J. W., Copp, B. R., Munro, M. H., Northcote, P. T. and Prinsep, M. R. (2006) Marine natural products. *Nat. Prod. Rep.* **23**, 26-78.

Boonlarppradab, C. and Faulkner, D. J. (2007) Eurysterols A and B, cytotoxic and antifungal steroidal sulfates from a marine sponge of the genus Euryspongia. *J. Nat. Prod.* **70**, 846-848.

Borchard, U. (1998) Pharmacological properties of b-adrenoreceptor blocking drugs. *J. Clin. Basic Cardiol*. **1**, 5-9.

Bradshaw, D., Hill, C. H., Nixon, J. S. and Wilkinson, S. E. (1993) Therapeutic potential of protein kinase C inhibitors. *Agents Actions* **38**, 135-147.

Brazilian Health Ministry (2002) Epidemiological survey of malaria in Brazil, Funasa, Brasília. Available from: http://www.funasa.gov.br/.

Burkholder, P. R. and Ruetzler, K. (1969) Antimicrobial activity of some marine sponges. *Nature* **222**, 983-984.

Capon, R. J., Skene, C., Lacey, E., Gill, J. H., Wadsworth, D. and Friedel, T. (1999) Geodin A magnesium salt: a novel nematocide from a southern Australian marine sponge, Geodia. *J. Nat. Prod*. **62**, 1256-1259.

Capon, R. J., Vuong, D., McNally, M., Peterle, T., Trotter, N., Lacey, E. and Gill, J. H. (2005) (+)-Echinobetaine B: isolation, structure elucidation, synthesis and preliminary SAR studies on a new nematocidal betaine from a southern Australian marine sponge, Echinodictyum sp. *Org Biomol. Chem.* **3**, 118-122.

Caraballo, H. and King, K. (2014) Emergency department management of mosquito-borne illness: malaria, dengue, and west nile virus. *Emerg. Med. Pract.* **16**, 1-23.

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

Chackalamannil, S. and Xia, Y. (2006) Thrombin receptor (PAR-1) antagonists as novel antithrombotic agents. *Expert Opin. Ther. Pat.* **16**, 493-505.

Cheng, S., Wen, Z., Chiou, S., Hsu, C., Wang, S., Dai, C., Chiang, M. Y. and Duh, C. (2008) Durumolides A-E, anti-inflammatory and antibacterial cembranolides from the soft coral Lobophytum durum. *Tetrahedron* **64**, 9698-9704.

Costantino, V., Fattorusso, E., Mangoni, A., Di Rosa, M. and Ianaro, A. (1999) Glycolipids from sponges, VII: simplexides, novel immunosuppressive glycolipids from the Caribbean sponge *Plakortis simplex*. *Bioorg. Med. Chem. Lett.* **9**, 271-276.

Cutignano, A., Bifulco, G., Bruno, I., Casapullo, A., Gomez-Paloma, L. and Riccio, R. (2000) Dragmacidin F: A New Antiviral Bromoindole Alkaloid from the Mediterranean Sponge *Halicortex* sp. *Tetrahe-*

dron **56**, 3743-3748.
D Ambrosio, M., Guerriero, A., Deharo, E., Debitus, C., Munoz, V. and Pietra, F. (1998) New types of potentially antimalarial agents: epidioxy-substituted norditerpene and norsesterpenes from the marine sponge Diacarnuslevii. *Helv. Chim. Acta* **81**, 1285-1292.
de Almeida Leone, P., Redburn, J., Hooper, J. N. and Quinn, R. J. (2000) Polyoxygenated dysidea sterols that inhibit the binding of [I125] IL-8 to the human recombinant IL-8 receptor type A. *J. Nat. Prod.* **63**, 694-697.
De Clercq, E. (2002) New anti-HIV agents and targets. *Med. Res. Rev.* **22**, 531-565.
De Clercq, E. (2004) Antiviral drugs in current clinical use. *J. Clin. Virol.* **30**, 115-133.
Dennedy, M. C., Houlihan, D. D., McMillan, H. and Morrison, J. J. (2002) b2- and b3-Adrenoreceptor agonists: human myometrial selectivity and effects on umbilical artery tone. *Am. J. Obstet. Gynecol.* **187**, 641-647.
de Silva, E. D. and Scheuer, P. J. (1980) Manoalide, an antibiotic sesterterpenoid from the marine sponge *luffariella variabilis* (polejaeff). *Tetrahedron. Lett.* **21**, 1611-1614.
Donia, M. and Hamann, M. T. (2003) Marine natural products and their potential applications as anti-infective agents. *Lancet Infect. Dis.* **3**, 338-348.
Dunbar, D. C., Rimoldi, J. M., Clark, A. M., Kelly, M. and Hamann, M. T. (2000) Anti-cryptococcal and nitric oxide synthase inhibitory imidazole alkaloids from the calcareous sponge Leucetta cf chagosensis. *Tetrahedron* **56**, 8795-8798.
Ebada, S. S., Wray, V., de Voogd, N. J., Deng, Z., Lin, W. and Proksch, P. (2009) Two new jaspamide derivatives from the marine sponge *Jaspis splendens*. *Mar. Drugs* **7**, 435-444.
Edgar, V. A., Cremaschi, G. A., Sterin-Borda, L. and Genaro, A. M. (2002) Altered expression of autonomic neurotransmitter receptors and proliferative responses in lymphocytes from a chronic mild stress model of depression: effects of fluoxetine. *Brain Behav. Immun*. **16**, 333-350.
Elhady, S. S., El-Halawany, A. M., Alahdal, A. M., Hassanean, H. A. and Ahmed, S. A. (2016) A new bioactive metabolite isolated from the red sea marine sponge *Hyrtios erectus*. *Molecules* **21**, 82.
Elyakov, G. B., Kuznetsova, T., Mikhailov, V. V., Maltsev, I. I., Voinov, V. G. and Fedoreyev, S. A. (1991) Brominated diphenyl ethers from a marine bacterium associated with the sponge Dysidea sp. *Experientia* **47**, 632-633.
Faulkner, D. J. (2000) Marine natural products. *Nat. Prod. Rep.* **17**, 7-55.
Faulkner, D. J. (2001) Marine natural products. *Nat. Prod. Rep.* **18**, 1-49.
Faulkner, D. J. (2002) Marine natural products. *Nat. Prod. Rep.* **19**, 1-48.
Fedoreev, S. A., Prokof'eva, N. G., Denisenko, V. A. and Rebachuk, N. M. (1988) Cytotoxic activity of aaptamines from suberitid marine sponges. *Pharm. Chem. J.* **22**, 615-618.
Ford, P. W., Gustafson, K. R., McKee, T. C., Shigematsu, N., Maurizi, L. K., Pannell, L. K., Williams, D. E., De Silva, E. D., Lassota, P., Alien, T. M., Van Soest, R., Andersen, R. J. and Boyd, M. R. (1999) Papuamides A-D, HIV-inhibitory and cytotoxic depsipeptides from the sponges *Theonella mirabilis* and *Theonella swinhoei* collected in Papua New Guinea. *J. Am. Chem. Soc.* **121**, 5899-5909.
Frakes, M. A. (2001) Muscle relaxant choices for rapid sequence induction. *Air Med. J*. **20**, 20-21.
Gafni, J., Munsch, J. A., Lam, T. H., Catlin, M. C., Costa, L. G., Molinski, T. F. and Pessah, I. N. (1997) Xestospongins: potent membrane permeable blockers of the inositol 1,4,5-triphosphate receptor. *Neuron* **19**, 723-733.
García-Ruiz, J. C., Amutio, E. and Pontón, J. (2004) Invasive fungal infection in immunocompromised patients. *Rev. Iberoam. Micol.* **21**, 55-62.
Gaspar, H., Santos, S., Carbone, M., Rodrigues, A. S., Rodrigues, A. I., Uriz, M. J., Savluchinske Feio, S. M., Melck, D., Humanes, M. and Gavagnin, M. (2008) Isomeric furanosesquiterpenes from the Portuguese marine sponge Fasciospongia sp. *J. Nat. Prod.* **71**, 2049-2052.
Giusiano, G., Mangiaterra, M., Rojas, F. and Gámez, V. (2004) Yeasts species distribution in Neonatal Intensive Care Units in northeast Argentina. *Mycoses* **47**, 300-303.
Giusiano, G., Mangiaterra, M., Rojas, F. and Gámez, V. (2005) Azole Resistance in Neonatal Intensive Care Units in Argentina. *J. Chemother.* **17**, 347-350.
Greve, H., Meis, S., Kassack, M. U., Kehraus, S., Krick, A., Wright, A. D. and Konig, G. M. (2007) New iantherans from the marine sponge Ianthella quadrangulata: novel agonists of the P2Y(11) receptor. *J. Med. Chem.* **50**, 5600-5607.
Griffith, O. W. and Gross, S. S. (1996) Inhibitors of nitric oxide synthases. In Methods in nitric oxide research (J. Stamler and M. Feelish, Ed.), pp. 187- 208. Wiley & Sons, New York.
Grimwood, K. and Lambert, S. B. (2009) Rotavirus vaccines: opportunities and challenges. *Hum. Vaccin.* **5**, 57-69.
Hadas, E., Shpigel, M. and Ilan, M. (2009) Particulate organic matter as a food source for a coral reef sponge. *J. Exp. Biol.* **212**, 3643-3650.
Hertiani, T., Edrada-Ebel, R., Ortlepp, S., van Soest, R. W., de Voogd, N. J., Wray, V., Hentschel, U., Kozytska, S., Muller, W. E. and Proksch, P. (2010) From anti-fouling to biofilm inhibition: New cytotoxic secondary metabolites from two Indonesian Agelas sponges. *Bioorg. Med. Chem.* **18**, 1297-1311.
Hibbs, R. E. and Zambon, A. C. (2011) Control of muscle spasms and rigidity. Agents acting at the neuromuscular junction and autonomic ganglia. In Goodman & Gilman's the pharmacological basis of therapeutics (L. L. Brunton, B. A. Chabner, B. C. Knollman, Ed.), pp. 266-276. McGraw-Hill, New York.
Hill, R. T., Hamann, M., Peraud, O. and Kasanah, N., inventors; University of Maryland Biotechnology Institute, assignee. Manzamine-producing actinomycetes. United States patent US 20050244938 A1. 2005 Nov 3.
Hood, K. A., West, L. M., Rouwe, B., Northocote, P. T., Berridge, M. V., Wakefield, S. J. and Miller, J. H. (2002) Peloruside A, a novel antimitotic agent with paclitaxel-like microtubule-stabilizing activity. *Cancer Res.* **62**, 3356-3360.
Hooper, J. N. A. and van Soest, R. W. M. (2002) Systema porifera: a guide to the classification of sponges. Kluwer Academic/Plenum Publishers, New York.
Hu, G. P., Yuan, J., Sun, L., She, Z. G., Wu, J. H., Lan, X. J., Zhu, X., Lin, Y. C. and Chen, S. P. (2011) Statistical research on marine natural products based on data obtained between 1985 and 2008. *Mar. Drugs* **9**, 514-525.
Hua, H. M., Peng, J., Fronczek, F. R., Kelly, M. and Hamann, M. T. (2004) Crystallographic and NMR studies of antiinfective tricyclic guanidine alkaloids from the sponge Monanchora unguifera. *Bioorg. Med. Chem.* **12**, 6461-6464.
Hultgren, K. M. and Duffy, J. E. (2010) Sponge host characteristics shape the community structure of their shrimp associates. *Mar. Ecol. Prog. Ser.* **407**, 1-12.
Ikenaga, M., Higaki, Y., Saku, K. and Uehara, Y. (2016) High-Density Lipoprotein Mimetics: a Therapeutic Tool for Atherosclerotic Diseases. *J. Atheroscler. Thromb.* **23**, 385-394.
Jang, K. H., Chung, S. C., Shin, J., Lee, S. H., Kim, T. I., Lee, H. S. and Oh, K. B. (2007). Aaptamines as sortase A inhibitors from the tropical sponge Aaptos aaptos. *Bioorg. Med. Chem. Lett.* **17**, 5366-5369.
Jares-Erijman, E. A., Sakai, R. and Rinehart, K. L. (1991) Crambescidins: new antiviral and cytotoxic compounds from the sponge *Crambe crambe*. *J. Org. Chem.* **56**, 5712-5715.
Juagdan, E. G., Kalindindi, R. S., Scheuer, P. J. and Kelly-Borges, M. (1995) Elenic acid, an inhibitor of topoisomerase II, from a sponge, Plakinastrella sp. *Tetrahedron Lett.* **36**, 2905-2908.
Kalinin, V. I., Ivanchina, N. V., Krasokhin, V. B., Makarieva, T. N. and Stonik, V. A. (2012). Glycosides from marine sponges (Porifera, Demospongiae): structures, taxonomical distribution, biological activities and biological roles. *Mar. Drugs* **10**, 1671-1710.
Kang, J.-H. (2014) Protein kinase C (PKC) isozymes and cancer. *New J. Sci.* **2014**, 231418.
Kitagawa, I., Kobayashi, M., Kitanaka, K., Kido, M. and Kyogoku, Y. (1983) Marine natural products, XII: on the chemical constituents of the Okinawan marine sponge *Hymeniacidon aldis*. *Chem. Pharm. Bull.* **31**, 2321-2328.

Kobayashi, J. and Ishibashi, M. (1993) Bioactive metabolites of symbiotic marine microorganisms. *Chem. Rev*. **93**, 1753-1769.

Konig, G. M., Wright, A. D. and Angerhofer, C. K. (1996) Novel potent antimalarial diterpene isocyanates, isothiocyanates, and isonitriles from the tropical marine sponge *Cymbastela hooperi*. *J. Org. Chem*. **61**, 3259-3267.

Kossuga, M. H., Nascimento, A. M., Reimao, J. Q., Tempone, A. G., Taniwaki, N. N., Veloso, K., Ferreira, A. G., Cavalcanti, B. C., Pessoa, C., Moraes, M. O., Mayer, A. M., Hajdu, E. and Berlinck, R. G. (2008) Antiparasitic, antineuroinflammatory, and cytotoxic polyketides from the marine sponge Plakortis angulospiculatus collected in Brazil. *J. Nat.Prod*. **71**, 334-339.

Kołodziejczyk, J. and Ponczek, M. B. (2013) The role of fibrinogen, fibrin and fibrin (ogen) degradation products (FDPs) in tumor progression. *Contemp. Oncol. (Pozn.)* **17**, 113-119.

Laport, M. S., Santos, O. C. and Muricy, G. (2009) Marine sponges: potential sources of new antimicrobial drugs. *Curr. Pharm. Biotechnol.* **10**, 86-105.

Leal, M. C., Puga, J., Serodio, J., Gomes, N. C. M. and Calado, R. (2012) Trends in the discovery of new marine natural products from invertebrates over the last two decades - where and what are we bioprospecting? *PLoS ONE* **7**, e30580.

Linington, R. G., Robertson, M., Gauthier, A., Finlay, B. B., MacMillan, J. B., Molinski, T. F., van Soest, R. and Andersen, R. J. (2006) Caminosides BD, Antimicrobial Glycolipids Isolated from the Marine Sponge Caminus s phaeroconia. *J. Nat. Prod*. **69**, 173-177.

Liu, B., Timar, J., Howlett, J., Diglio, C. A. and Honn, K. V. (1991) Lipoxygenase metabolites of arachidonic and linoleic acids modulate the adhesion of tumor cells to endothelium via regulation of protein kinase C. *Cell Regul*. **2**, 1045-1055.

Loya, S. and Hizi, A. (1990) The inhibition of human immunodeficiency virus type 1 reverse transcriptase by avarol and avarone derivatives. *FEBS Lett.* **269**, 131-134.

Lundberg, U. (1995) Methods and applications of stress research. *Technol. Health Care* **3**, 3-9.

Maldonado, M., Carmona, C., Velasquez, Z., Puig, A., Cruzado, A., Lopez, A. and Young, C. M. (2005) Siliceous sponges as a silicon sink: An overlooked aspect of the benthopelagic coupling in the marine silicon cycle. *Limnol. Oceanogr*. **50**, 799-809.

Maria, M., Lone, G. and Thomas, O. L. (2011) Production of bioactive secondary metabolites by marine vibrionaceae. *Mar. Drugs* **9**, 1440-1468.

Martins, A., Vieira, H., Gaspar, H. and Santos, S. (2014) Marketed marine natural products in the pharmaceutical and cosmoceutical industries: tips for success. *Mar. Drugs* **12**, 1066-1101.

Maryanoff, B. E., Qiu, X., Padmanabhan, K. P., Tulinsky, A., Almond, H. R., Andrade-Gordon, P., Greco, M. N., Kauffman, J. A., Nicolaou, K. C., Liu, A., Brungs, P. H. and Fusetani, N. (1993) Molecular basis for the inhibition of human alpha-thrombin by the macrocyclic peptide cyclotheonamide A. *Proc. Natl. Acad. Sci. U.S.A.* **90**, 8048-8052.

Matsunaga, S., Fusetani, N. and Konosu, S. (1985) Bioactive marine metabolites, VII: structures of discodermins B, C, and D, antimicrobial peptides from the marine sponge *Discodermia kiiensis*. *Tetrahedron Lett.* **26**, 855-856.

Mayer, A. M., Rodriguez, A. D., Berlinck, R. G. and Fusetani, N. (2011) Marine pharmacology in 2007-8: Marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous system, and other miscellaneous mechanisms of action. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **153**, 191-222.

Mayer, A. M. and Hamann, M. T. (2004) Marine pharmacology in 2000: marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiplatelet, antituberculosis, and antiviral activities; affecting the cardiovascular, immune, and nervous systems and other miscellaneous mechanisms of action. *Mar. Biotechnol.* **6**, 37-52.

Mayer, A. M. S. and Jacobs, R. S. (1988) Manoalide: an anti-inflammatory and analgesic marine natural product. *Mem. Calif. Acad. Sci*. **13**, 133.

Mayer, A. M. S. and Lehmann, V. K. B. (2000) Marine pharmacology in 1998: marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, anthelmintic, antiplatelet, antiprotozoal, and antiviral activities; with actions on the cardiovascular, endocrine, immune, and nervous systems; and other miscellaneous mechanisms of action. *Pharmacologist* **42**, 62-69.

McCaffrey, E. J. and Endeau, R. (1985) Antimicrobial activity of tropical and subtropical sponges. *Mar. Biol*. **89**, 1-8.

Mishra, S. K., Satpathy, S. K. and Mohanty, S. (1999) Survey of malaria treatment and deaths. *Bull. World Health Organ*. **77**, 1020.

Miyamoto, S., Izumi, M., Hori, M., Kobayashi, M., Ozaki, H. and Karaki, H. (2000) Xestospongin C, a selective and membrane-permeable inhibitor of IP_3 receptor, attenuates the positive inotropic effect of α-adrenergic stimulation in guinea-pig papillary muscle. *Br. J. Pharmacol.* **130**, 650-654.

Miyaoka, H., Shimomura, M., Kimura, H., Yamada, Y., Kim, H. S. and Wataya, Y. (1998) Antimalarial activity of kalahinol A and new relative diterpenoids from the Okinawan sponge, Acanthella sp. *Tetrahedron* **54**, 13467-13474.

Mol, V. P. L., Raveendran, T. V. and Parameswaran, P. S. (2009) Antifouling activity exhibited by secondary metabolites of the marine sponge, Haliclona exigua (Kirkpatrick). *Int. Biodeterior. Biodegrad.* **63**, 67-72.

Momparler, R. L. (2013) Optimization of cytarabine (ARA-C) therapy for acute myeloid leukemia. *Exp. Hematol. Oncol*. **2**, 20.

Morton, S. L., Moeller, P. D., Young, K. A. and Lanoue, B. (1998) Okadaic acid production from the marine dinoflagellate Prorocentrum belizeanum Faust isolated from the Belizean coral reef ecosystem. *Toxicon.* **36**, 201-206.

Moura, R. M., Queiroz, A. F., Fook, J. M., Dias, A. S., Monteiro, N. K., Ribeiro, J. K., Moura, G. E., Macedo, L. L., Santos, E. A. and Sales, M. P. (2006) CvL, a lectin from the marine sponge *Cliona varians*: Isolation, characterization and its effects on pathogenic bacteria and *Leishmania* promastigotes. *Comp. Biochem. Physiol., Part A Mol. Integr. Physiol.* **145**, 517-523.

Muller, W. G., Sobel, C., Diehl-Seifert, B., Maidhof, A. and Schroder, H. C. (1987) Influence of the antileukemic and anti-human immunodeficiency virus agent avarol on selected immune responses *in vitro* and *in vivo*. *Biochem. Pharmacol.* **36**, 1489-1494.

Müller, W. E., Schröder, H. C., Wiens, M., Perovic-Ottstadt, S., Batel, R. and Müller, I. M. (2004) Traditional and modern biomedical prospecting: Part II-the benefits. *Evid. Based Complement. Alternat. Med*. **1**, 133-144.

Nausch, B., Heppner, T. J. and Nelson, M. T. (2010) Nerve-released acetylcholine contracts urinary bladder smooth muscle by inducing action potentials independently of IP_3-mediated calcium release. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **299**, R878-R888.

Northcote, P. T., Blunt, J. W. and Munro, M. H. G. (1991) Pateamine: a potent cytotoxin from the New Zealand marine sponge, mycale sp. *Tetrahedron Lett.* **32**, 6411-6414.

Oclarit, J. M., Okada, H., Ohta, S., Kaminura, K., Yamaoka, Y., Iizuka, T., Miyashiro, S. and Ikegami, S. (1994) Anti-bacillus substance in the marine sponge, Hyatella species, produced by an associated Vibrio species bacterium. *Microbios* **78**, 7-16.

Oh, K. B., Mar, W., Kim, S., Kim, J. Y., Lee, T. H., Kim, J. G., Shin, D., Sim, C. J. and Shin, J. (2006) Antimicrobial activity and cytotoxicity of bis (indole) alkaloids from the sponge Spongosorites sp. *Biol. Pharm. Bull.* **29**, 570-573.

O'Rourke, A., Kremb, S., Bader, T. M., Helfer, M., Schmitt-Kopplin, P., Gerwick, W. H., Brack-Werner, R. and Voolstra, C. R. (2016) Alkaloids from the sponge *Stylissa carteri* present prospective scaffolds for the inhibition of human immunodeficiency Virus 1 (HIV-1). *Mar. Drugs* **14**, 28.

Pattenden, G., Critcher, D. J. and Remuiñán, M. (2004) Total synthesis of ()-pateamine A, a novel immunosuppressive agent from Mycale sp. *Can. J. Chem.* **82**, 353-365.

Perry, N. B., Blunt, J. W., Munro, M. H. G. and Thompson, A. M. (1990) Antiviral and antitumor agents from a New Zealand sponge, Mycale sp. 2. Structures and solution conformations of mycalamides A and B. *J. Org. Chem*. **55**, 223-227.

Petit, G. R. and Knight, J. C., inventors; Arizona Board of Regents, assignee. Cribrostatins 3-5. United States patent US 6437128 B1. 2002 Aug 20.

Pettit, R. K., Fakoury, B. R., Knight, J. C., Weber, C. A., Pettit, G. R., Cage, G. D. and Pon, S. (2004) Antibacterial activity of the marine sponge constituent cribrostatin 6. *J. Med. Microbiol.* **53**, 61-65.

Piel, J. (2004) Metabolites from symbiotic bacteria. *Nat Prod Rep*. **21**, 519-538.

Piel, J. (2006) Bacterial symbionts: prospects for the sustainable production of invertebrate-derived pharmaceuticals. *Curr. Med. Chem.* **13**, 39-50.

Pika, J., Tischler, M. and Andersen, R. J. (1992) Glaciasterols A and B, 9,11-secosteroids from the marine sponge Aplysilla glacialis. *Can. J. Chem.* **70**, 1506-1510.

Plaza, A., Gustchina, E., Baker, H. L., Kelly, M. and Bewley, C. A. (2007) Mirabamides A-D, depsipeptides from the sponge Siliquariaspongia mirabilis that inhibit HIV-1 fusion. *J. Nat. Prod.* **70**, 1753-1760.

Pontón, J., Rüchel, R., Clemonds, K. V., Coleman, D. C., Grillot, R., Guarro, J., Aldebert, D., Ambroise-Thomas, P., Cano, J., Carrillo-Muñoz, A. J., Gené, J., Pinel, C., Stevens, D. A. and Sullivan, D. (2000) Emerging pathogens. *Med. Mycol.* **38**, 225-236.

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

Proksch, P., Putz, A., Ortlepp, S., Kjer, J. and Bayer, M. (2010) Bioactive natural products from marine sponges and fungal endophytes. *Phytochem. Rev.* **9**, 475-489.

Quinn, R. J., Gregson, R. P., Cook, A. F. and Bartlett, A. F. (1980) Isolation and synthesis of 1-methylisoguanisine, a potent pharmacologically active constituent from the marine sponge *Tedania digitata*. *Tetrahedron Lett.* **21**, 567-568.

Qureshi, A. and Faulkner, D. J. (1999) Haplosamates A and B: new steroidal sulfamate esters from two haplosclerid sponges. *Tetrahedron* **55**, 8323-8330.

Rahden-Staron, I. (2002) The inhibitory effect of the fungicides captan and captafol on eukaryotic topoisomerases *in vitro* and lack of recombinagenic activity in the wing spot test of *Drosophila melanogaster*. *Mutat. Res*. **518**, 205-213.

Ramel, G. (2010) Phylum Porifera [cited 2013 Jan]. Available from: http://www.earthlife.net/inverts/porifera.html/.

Rao, V. K., Kasanah, N., Wahyuono, S., Tekwani, B. L., Schinazi, R. F. and Hamann, M. T. (2004) Three new manzamine alkaloids from a common indonesian sponge and their activity against infectious and tropical parasitic diseases. *J. Nat. Prod.* **67**, 1314-1318.

Rice, L. B. (2006) Antimicrobial resistance in gram-positive bacteria. *Am. J. Infect. Control* **34**, S11-S19.

Romo, D., Rzasa, R. M., Shea, H. A., Park, K., Langenhan, J. M., Sun, L., Akhiezer, A. and Liu, J. O. (1998) Total synthesis and immunosuppressive activity of (-)-pateamine A and related compounds: implementation of a b-lactambased macrocyclization. *J. Am. Chem. Soc*. **120**, 12237-12254.

Rubio, B. K., van Soest, R. W. and Crews, P. (2007) Extending the record of meroditerpenes from Cacospongia marine sponges. *J. Nat. Prod.* **70**, 628-631.

Sagar, S., Kaur, M., Minneman, K. P. (2010) Antiviral lead compounds from marine sponges. *Mar. Drugs* **8**, 2619-2638.

Sakai, R., Higa, T., Jefford, C. W. and Bernardinelli, G. (1986) Manzamin, A., a novel antitumor alkaloid from a sponge. *J. Am. Chem. Soc.* **108**, 6404-6405.

Sandven, P. (2000) Epidemiology of candidemia. *Rev. Iberoam. Micol.* **17**, 73-81.

Schaschke, N. and Sommerhoff, P. C. (2010) Upgrading a natural product: inhibition of human β-tryptase by cyclotheonamide analogues. *Chem. Med. Chem.* **5**, 367-370.

Schwartsmann, G. (2000) Marine organisms and other novel natural sources of new cancer drugs. *Ann. Oncol.* **11**, 235-243.

Shimosaka, A. (2002) Role of NKT cells and a-galactosyl ceramide. *Int. J. Hematol.* **76**, 277-279.

Shuman, R.T., Rothenberger, R. B., Campell, C. S., Smith, G. F., Gifford-Moore, D. S. and Gesellchen, P. D. (1993) Highly selective tripeptide thrombm inhibitors. *J. Med. Chem.* **36**, 314-319.

Sipkema, D., Osinga, R., Schatton, W., Mendola, D., Tramper, J. and Wijffels, R. H. (2005) Large scale production of pharmaceuticals by marine sponges: Sea, cell, or biosynthesis. *Biotechnol. Bioeng.* **90**, 201-222.

Souza, T. M., Abrantes, J. L., de A Epifanio, R., Leite Fontes, C. F. and Frugulhetti, I. C. (2007) The alkaloid 4-methylaaptamine isolated from the sponge *Aaptos aaptos* impairs Herpes simplex virus Type 1 penetration and immediate early protein synthesis. *Planta Med.* **73**, 200-205.

Stead, P., Hiscox, S., Robinson, P, S., Pike, N. B., Sidebottom, P. J., Roberts, A. D., Taylor, N. L., Wright, A. E., Pomponi, S. A. and Langley, D. (2000) Eryloside F, a novel penasterol disaccharide possessing potent thrombin receptor antagonist activity. *Bioorg. Med. Chem. Lett.* **10**, 661-664.

Suzuki, H., Shindo, K., Ueno, A., Miura, T., Takei, M., Sakakibara, M., Fukamachi, H., Tanaka, J. and Higa, T. (1999) S1319: A novel β2-adrenoceptor agonist from a marine sponge Dysidea sp. *Bioorg. Med. Chem. Lett.* **9**, 1361-1364.

Takei, M., Burgoyne, D. L. and Andersen, R. J. (1994) Effect of contignasterol on histamine release induced by anti-immunoglobulin E from rat peritoneal mast cells. *J. Pharm. Sci.* **83**, 1234-1235.

Tan, P., Luscinskas, F. W. and Homer-Vanniasinkam, S. (1997) Cellular and molecular mechanisms of inflammation and thrombosis. *Eur. J. Vasc. Endovasc. Surg.* **17**, 373-389.

Tasdemir, D., Topaloglu, B., Perozzo, R., Brun, R., O'Neill, R., Carballeira, N. M., Zhang, X., Tonge, P. J., Linden, A. and Rüedi, P. (2007) Marine natural products from the Turkish sponge *Agelas oroides* that inhibit the enoyl reductases from *Plasmodium falciparum*, *Mycobacterium tuberculosis* and *Escherichia coli*. *Bioorg. Med. Chem.* **15**, 6834-6845.

Ter Haar, E., Kowalski, R. J., Hamel, E., Lin, C. M., Longley, R. E., Gunasekera, S. P., Rosenkranz, H. S. and Day, B. W. (1996) Discodermolide, a cytotoxic marine agent that stabilizes microtubules more potently than taxol. *Biochemistry* **35**, 243-250.

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

Torres, Y. R., Berlink, R. G., Nascimento, G. G., Fortier, S. C., Pessoa, C. and de Moraes, M. O. (2002) Antibacterial activity against resistant bacteria and cytotoxicity of four alkaloid toxins isolated from the marine sponge *Arenosclera brasiliensis*. *Toxicon.* **40**, 885-891.

Turk, T., Ambrožič Avguštin, J., Batista, U., Strugar, G., Kosmina, R., Čivovič, S., Janussen, D., Kauferstein, S., Mebs, D. and Sepčič, K. (2013) Biological activities of ethanolic extracts from deep-sea antarctic marine sponges. *Mar. Drugs* **11**, 1126-1139.

Urban, S., De Almeida Leone, P., Carroll, A. R., Fechner, G. A., Smith, J., Hooper, J. N. and Quinn, R. J. (1999) Axinellamines A-D, novel imidazo-azolo-imidazole alkaloids from the australian marine sponge *Axinella* sp. *J. Org. Chem.* **64**, 731-735.

Uriz, M. J., Martin, D. and Rosell, D. (1992) Relationships of biological and taxonomic characteristics to chemically mediated bioactivity in Mediterranean littoral sponges. *Mar. Biol.* **113**, 287-297.

Vik, A., Hedner, E., Charnock, C., Tangen, L. W., Samuelsen, O., Larsson, R., Bohlin, L. and Gundersen, L. L. (2007) Antimicrobial and cytotoxic activity of agelasine and agelasimine analogs. *Bioorg. Med. Chem.* **15**, 4016-4037.

Wakimoto, T., Maruyama, A., Matsunaga, S., Fusetani, N., Shinoda, K. and Murphy, P. T. (1999) Octa- and nonaprenylhydroquinone sulfates, inhibitors of a1,3-fucosyltransferase VII, from an Australian marine sponge Sarcotragus sp. *Bioorg. Med. Chem. Lett*. **9**, 727-730.

Walsh, T. J., Groll, A., Hiemenz, J., Fleming, R., Roilides, E. and Anaissie, E. (2004) Infections due to emerging and uncommon medically important fungal pathogens. *Clin. Microbiol. Infect.* **10**, 48-66.

Walter, S. (2005) Drug discovery: a history. p. 258. Wiley, New York.

Wellington, K. D., Cambie, R. C., Rutledge, P. S. and Bergquist, P. R. (2000) Chemistry of Sponges. 19. Novel Bioactive Metabolites from *Hamigeratarangaensis*. *J. Nat. Prod*. **63**, 79-85.

White, D. E. and Fenner, F. J. (1986) Medical Virology. Academic Press., San Diego.

WHO (2015) World Malaria report. World Health Organization, Geneva.

Wiedbrauk, D. L. and Johnston, S. L. G. (1992) Manual of Clinical Virology. Raven Press., New York.

Xue, S., Zhanga, H. T., Wua, P. C., Zhanga, W. and Yuana, Q. (2004)

Study on bioactivity of extracts from marine sponges in Chinese Sea. *J. Exp. Mar. Biol. Ecol.* **298**, 71-78.

Yasuhara-Bell, J. and Lu, Y. (2010) Marine compounds and their antiviral activities. *Antiviral Res*. **86**, 231-240.

Yousaf, M., El Sayed, K. A., Rao, K. V., Lim, C. W., Hu, J. F., Kelly, M., Franzblau, S. G, Zhang, F., Peraud, O., Hill, R. T. and Hamann, M. T. (2002) 12,34-Oxamanzamines, novel biocatalytic and natural products from rnanzamine producing Indo-Pacific sponges. *Tetrahedron* **58**, 7397-7402.

Zabriskie, T. M., Klocke, J. A., Ireland, C. M., Marcus, A. H., Molinski, T. F., Faulkner, D. J., Xu, C. and Clardy, J. C. (1986) Jaspamide, a modified peptide from a Jaspis sponge, with insecticidal and antifungal activity. *J. Am. Chem. Soc*. **108**, 3123-3124.

Zapolska-Downar, D., Zapolska-Downar, A., Markiewski, M., Ciechanowicz, M., Kaczmarczyk, M. and Naruszewicz, M. (2001) Selective inhibition by procubol of vascular cell adhesion molecule 1 (VCAM-1) expression in human vascular endothelial cells. *Atherosclerosis* **155**, 123-130.