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. Cryptotheca 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,
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).

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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, antimarial, antihelminthic, 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, steroids, 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 *Acanthostrongyliphora* 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 (Oclari 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 sponge-
Examples of antibacterial compounds

Table 1.

| Substance                                      | Species                        | Activity Spectrum                     | MIC Value       | References                          |
|------------------------------------------------|--------------------------------|---------------------------------------|-----------------|-------------------------------------|
| Discodermins B, C and D                        | Cyclic peptide                | Antibacterial (S. aureus, P. aeruginosa) | 3 μg/ml*        | Matsunaga et al., 1985              |
| Arenosclerins A-C                              | Alkyl pepridine alkaloid      | Antibacterial (S. aureus, P. aeruginosa) | 16 μg/ml*, 30 μg/ml** | et al., 2002                      |
| Haliclona cyclamine E                          | Alkylpiperidine alkaloids     | Antibacterial (S. aureus, P. aeruginosa) | 8 μg/ml*        | Torres et al., 2002                 |
| Caminus sphaeroconia E                         | Alkaloid                       | Antibacterial (E. coli, S. aureus)     | 16 μg/ml*       | Linington et al., 2006              |
| 6-hydroxymanzamine E                           | Alkaloid                       | Antibacterial (M. luteus)              | 0.9 μg/ml**     | Rao et al., 2004                    |
| Cribrostatin 6                                 | Alkaloid                       | Antibacterial (M. luteus)              | ≤2 μg/ml        | Pettit et al., 2004                 |
| Cribrostatin 3                                 | Alkaloid                       | Antibacterial (N. gonorrheae)          | 3 μg/ml*         | Petit et al., 2004                  |
| Cribrochalina sp.                              | Terpenoid                      | Antibacterial (C. varians)             | 16 μg/ml*       | Moura et al., 2006                  |
| Cribrochalina sp.                              | Terpenoid                      | Antibacterial (C. varians)             | 16 μg/ml*       | Moura et al., 2006                  |
| Isoaaptamine                                   | Alkaloid                       | Antibacterial (S. aureus)              | 16 μg/ml*       | Jang et al., 2006                   |
| (–)-Microcionin-1                              | Meroterpenes                   | Antibacterial (M. luteus)              | 7 μg/ml         | Gaspar et al., 2008                 |
| Cacospongia sp.                                | Meroterpenes                   | Antibacterial (S. epidermidis)         | 20 μg/ml         | Rubio et al., 2007                  |
| Cribrochalina sp.                              | Meroterpenes                   | Antibacterial (C. varians)             | 3.7 μg/ml       | Jang et al., 2007                   |
| Faschiocarpus sp.                              | Meroterpenes                   | Antibacterial (C. varians)             | 6 μg/ml         | Cortes et al., 2005                 |
| 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 adenosine 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 rotavirus, which are mainly responsible for severe 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 Cryptothetya 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-
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 modifications 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 PROPERTIES

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,
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. Plasmadium falciparum has become resistant to chloroquine, pyrimethamine, and sulfadoxine (Bwijo et al., 2002). Manzamine A displayed a potent in vitro antimalarial activity against P. falciparum (D6 clone), with MIC of 0.0045 μg/ml (Sakai et al., 1986; Ashok et al., 2002; Fattorusso and Taglialetela, 2009). According to research antimalarial activity of manzamine A is due to enhancing immune response (Ang et al., 2001).

### Table 3. Examples of antiviral compounds

| Substances            | Chemistry                          | Species            | Action spectrum          | MIC value   | References       |
|-----------------------|------------------------------------|--------------------|--------------------------|-------------|------------------|
| Eurysterols A-B       | Sterols                            | Eurysspongia sp    | C. albicans, Amphoterician B-resistant | 62.5 μg/ml*, 15.6 μg/ml | Boonlarpreadap and Faulkner, 2007 |
| Naammine D            | Imidazole alkaloid                  | Leucceta cf. chagosensis | C. neoformans          | 6.25 μg/ml** | Dunbar et al., 2000 |
| Mirabiben B           | Tricyclic guanidine                 | Monanchora unguifera | C. neoformans          | 7.0 μg/ml** | Hua et al., 2004 |
| Hamacanthin A         | Indole alkaloid                     | Spongosoritites sp. | C. albicans            | 6.25 μg/ml*  | Oh et al., 2006  |
| Macanthins A-B        | Indole alkaloid                     | Spongosoritites sp. | C. albicans, C. neoformans | 1.6 μg/ml*, 6.2 μg/ml** | Oh et al., 2006  |
| Agelasines and agelasamines | 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 [i]-lactam             | Hymeniacidon sp    | P. falciparum            | 0.6 μM***     | Avilés and Rodriguez, 2010 |
| Manzamine A           | Alkaloids                           | e.g., Halicoma sp./ Halichondrida | T. gondii, P. berghei, P. falciparum | 4.5 ng/ml*** | D Ambrosio et al., 1998 |
| Kalihinol A           | Isonitril-containing kalinhinane diterpenoid | Acanthella sp./ Halichondrida | P. falciparum            | 0.0005 μg/ml** | D Ambrosio et al., 1998 |
| Diisocynaoacodine      | Tetracyclic diterpenic Macrolides   | Cymbastela hooperi | P. falciparum            | 0.005 μg/ml** | Miyonoka et al., 1998 |
| Siomosceptrelin-B      | Noristerpenic acid                  | Diacarnus erythraeaus | T. gondii, P. falciparum | 0.002 μg/ml** | Konig et al., 1996 |
| (E)-Oridin            | Alkaloids                           | Agelas oroides     | P. falciparum            | 0.30 μg/ml**  | Yousaf et al., 2002 |
| Plakortin and dihydroplakortin | Cycloprenoxidase                 | 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).

[1] Fattorusso et al., 2002.

### 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 lipooxygenase (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 | Hymeniacidonella/Halichondrida | Protein kinase C inhibitor          | Kitagawa et al., 1983         |
| Adociasulfates      | Triterpenoid hydroquinones       | Sarcodragna sp./Dicyocteratida | A1, 3-fucosyltransferase inhibitor  | Zapolka-Downar et al., 2001  |
|                    |                                  | Haliclona (aka Adocia) sp./Haplosclerida | Kinesin motor protein inhibitors   |                               |
| Discordemolide      | Linear tetraene lactone          | Discodermia dissolute/Lithistida | Stabilization of microtubules       | Ter Haar et al., 1996         |
| Pelorurside A        | Macrocyclic lactone              | Mycole hentschelli/Poecilosclerida | Stabilization of microtubules       | Hood et al., 2002              |
| Crambesclammins 1-4 | Alkylphenol                      | Leucetta cf. chagosensis        | Topoisomerase II inhibitor          | Hood et al., 2002              |
| Discorhabdin D       | Imidazole alkaloid               | Agelas mauniscus/Agelasida      | Nitric oxide synthetase inhibitor   | Juagdan et al., 1995          |
| Glaciasterols A and B | 9,11-Secosterol                  | Aplysilla glacialis/Dendroceratida | Ca2+/channel blocker                | Shimosako, 2002               |
| Durumolides A-C      | Terpenoid                        | Lobophytum durus                | Inducible NOS and COX-2 inhibition  | Cheng et al., 2008             |
| Plakortide P         | Polyketide                       | Plakortis angulosipilatus       | TXB2 inhibition                     | Kossuga et al., 2008          |
| 24-methoxypetrosaonpangia | Sesterterpenes                  | Hyrtios erectus                 | Unknown                             | Elhady et al., 2016           |

Non-specific inhibitors

- Specific inhibitors are specifically active against the tumor.
- Non-specific inhibitors are important compounds used in treating cancer because of their toxic effects on healthy cells. These proteins are responsible for multidrug resistance in human carcinogen binding in these proteins. Another example is the binding site of each protein group is salicylamide A, which is isolated from Thalassia sp. (Griffith and Gross, 1996).


tumor cell line.

The reason is that it increases the concentration of intracellular enzyme from the binding prevention of carcinosarcoma cells with Endoglycosidase Haticlona sp. Etc (Blackburn et al., 2001) and they are protein inhibitors by binding to microtubule binding sites blocking protein function and by there by blocking cell division.

ANTITUMOR ACTIVITY

The phosphatase A2 (PPA2) is an essential factor that increases the concentration of intracellular enzyme from the binding prevention of carcinosarcoma cells with Endoglycosidase Haticlona sp. Etc (Blackburn et al., 2001) and they are protein inhibitors by binding to microtubule binding sites blocking protein function and by there by blocking cell division.

Inhibitors of a cancer cell of a certain type.

1. Non-specific inhibitors

- There are many other sponge derived compounds having anti-tumor activity which are involved in the inflammatory response (Carroll et al., 2001) (Fig. 5).

2. Specific inhibitors

- There are many other sponge derived compounds having anti-tumor activity which are involved in the inflammatory response (Carroll et al., 2001) (Fig. 5).

3. Specific inhibitors

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5. Specific inhibitors

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6. Specific inhibitors

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7. Specific inhibitors

- There are many other sponge derived compounds having anti-tumor activity which are involved in the inflammatory response (Carroll et al., 2001) (Fig. 5).

8. Specific inhibitors

- There are many other sponge derived compounds having anti-tumor activity which are involved in the inflammatory response (Carroll et al., 2001) (Fig. 5).

9. Specific inhibitors

- There are many other sponge derived compounds having anti-tumor activity which are involved in the inflammatory response (Carroll et al., 2001) (Fig. 5).

10. Specific inhibitors

- There are many other sponge derived compounds having anti-tumor activity which are involved in the inflammatory response (Carroll et al., 2001) (Fig. 5).
**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
(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 Erytus 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).

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**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 | *Erytus formosus*/Astrophorida | Thrombin receptor antagonist | Stead et al., 2000      |
| Halichlorine    | Cyclic aza Polyketide | *Halichondria okada*/Halichondria | VCAM 1* inhibitor        | Arimoto et al., 1998    |

*VCAM: vascular cell adhesion molecule.
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 anthelminthic 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 anthelminthic, 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 IP3 (Inositol triphosphate) inhibitor and Ca2+ (calcium channel) blocker (Quinn et al., 1980; Gafni et al., 1997; Miyamoto et al., 2000). IP3 is a secondary messenger molecule used in signal transduction and it diffuses throughout the cell and increases the Ca2+ 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 Taglialetela, 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.

Fig. 8. The mechanism of adrenergic receptors. A represent α-receptors and trigger the IP3 (Inositol triphosphate) which then increase the Ca2+ level in cytoplasm and causing muscles contraction. B represents β-adrenoreceptors. The I represents Marine compounds. Xestospongin C inhibit the phospholipase enzyme which play a key role in activation of IP3 (Inositol triphosphate) and block Ca2+ channels. S1319 B-2 receptor agonist resulting Bronchodilation and uterus relaxation.
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, immuno-suppressive, 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 (Schwartmann, 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 (Muller 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.

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