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Marine Sponges: Repositories of Bioactive compounds with Medicinal applications

Sasireka Rajendran[1]

[1]Department of Biotechnology, Mepco Schlenk Engineering College, Sivakasi, India

Abstract : Marine Sponges and its associated symbiotic organisms are considered as the depositories of bioactive compounds and secondary metabolites naturally. Compounds in specific can be used for different applications as a drug candidate. It is believed that sponges have the potential to cure various diseases such as malaria, cancer and other viral infections. Eventhough the mechanism of action is still unclear for few cases, compounds in crude extracts interferes with the pathogenesis of different diseases. Based on the preliminary screening results of *in vitro* and *in vivo* studies, researchers are trying to formulate medicinal products out of this crude extract and to commercialize in the market. Chemical compounds of few sponges have varying carbon skeletons which have the ability to fight against different pathogens and may provide immunity to individuals affected by various diseases.
Key Words : Sponges, Bioactive Compounds, Secondary Metabolites, Malaria, Cancer.

Introduction:

Marine environment is a reservoir of natural bioactive products which is of having pharmaceutical importance. Marine organisms normally produce naturalbioactive compounds for protection, communication and reproduction against predation, infection and competition. These natural products serve as a source for invention of new molecules and are considered as the most important drug lead in different fields.

Marine sponges are sessile animals that look like plants which attached themselves to a rock, shell or seafloor when they are young and live there for the rest of their lives.Sponges belong to the phylum Porifera, are oldest and simplest of multicellular animals with bodies full of pores which show relatively little differentiation and tissue coordination[1]. 8000 species were identified which were found throughout tropical, temperate and polar regions. Sponges are considered as an important component of pharmaceutical bioactive compounds among other marine sources. Discovery of Marine based natural products began in 1950s by the identification of nucleosides products spongothymidine and spongouridine in the marine sponge *Cryptotheca crypta*[2,3].Marine sponges and its associated microbes, seaweeds, soft and hard corals, gorgonians, cnidarians, etc is considered as factories for several pharmaceutical drugs. Nucleosides, Alkaloids, Steroids, Peptides, Terpenoids, Isoprenoids, Prostaglandins, Quinones, Brominated Compounds and Toxins are the major products of marine sponges which are of having prime importance.

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Nowadays, bioactive compounds from marine sources are of great importance. Bioactive substances from marine sponges or other associated microbes posses antibacterial, antiviral, antifungal, antileishmanial activity, antihelmintic activity, anti-inflammatory, antimalarial, antifouling, antibiotics,analgesic, antiallergic activity, antithrombotic activity, antihypertensive, immunomodulatory, hepatoprotective activity and neurosuppressive function.

Marine sponges have the potential to provide future drugs against important diseases such as malaria, cancer and other viral diseases[4].Sponges are classified into three main classes such as Calcarea, Demospongiae and Hexactinellida. Among these, it was found that Demospongiae is the major source of bioactive compounds. In addition to bioactive substances, sponges produce secondary metabolites which help to defend themselves against foreign prokaryotic and eukaryotic organisms.

Microbes such as bacteria, fungi and microalgaeare also associated with marine sponges with beneficiary impact. Most common symbiont associated with marine sponges is bacteria and fungi whereas bacterial species outnumber fungal species. Cyanobacteria, Bacteriodetes, Actinobacteria, Chloroflexi, Proteobacteria, Nitrospira, Poribacteria, Verrucomicrobia Planctomycetes, Archaea and Acidobacteriaare the major bacterial species that are associated with marine sponges. Discovery of pharmaceutically active substances from symbionts associated with marine sponges is also of greater interest. Bacterial phylum actinobacteria and fungal division ascomycota are the prime producers of bioactive compounds among other species.

In this review, pharmacologically active substances as potential drug candidates from marine sponges were focused.

Antimicrobial activity (Antibacterial and Antifungal):

Antibiotic resistant bacterium like *Staphylococcus aureus* creates a considerable problem and is involved in causing major infections. Presently many antibiotics became resistant by many strains which led to the discovery of newer class of antibiotics. Crude extracts obtained from marine sponges exhibit varying antibacterial activity for marine and terrestrial bacteria[5,6,7,8,9]. Selected crude extracts obtained from sponges have antibacterial activity against Gram positive and Gram negative species. Nearly 800 potent antibiotic substances were identified from marine sponges[10]. Eventhough antibiotic substances were identified, no antibacterial product was reported yet in the discovered marine natural product but many of them are under investigation in current research.

Fungal infection is predominant in the case of patients suffering from AIDS, immune depressants, hematological malignancies and transplant recipients which led to the development of novel compounds with antifungal activity[11,12]. It remains a major cause of death in patients who are treated for malignant disease[13]. Immunocompromised persons are severely infected by *Candida*, *Aspergillus*, *Cryptococcus* and other opportunistic fungi. In order to provide solution to these fungal associated problems new anti-fungal agents has to be discovered. Several species of marine sponges were screened for antimicrobial activity and are listed in the table 1.

Table 1: Selected marine species with antimicrobial activity.

Sponge	**Compound/class**	**Function / Target Species**	**Reference**
Aplysia aerophoba, Verongia thiona	Aerothionin	Antibiotic, *M. tuberculosis*	14
Agelas oroides	4,5-dibromopyrrole-2-carboxylic acid (Carboxylic acid)	Alters cellular calcium signals	15
Phakellia flagellate	Dibromophakellin (Alkaloids)	Antibacterial	16
Halichondria mooriei	Halistanol (Sterol)	*Streptococcus* sp	17

Plakina sp.	Plakinamine A (Steroidal alkaloid)	*Staphylococcus aureus, Candida albicans*.	18
Plakina sp.	Plakinamine B (Steroidal alkaloid)	*Staphylococcus aureus, Candida albicans*.	18
Dysidea, *Euryspongia* and *Siphonodictyon* species.	Furanoid (sesquiterpenoids)	Anti-bacterial	19
Aplysina caissara	Bromotyrosine compounds such as Fistyralin-3 and 11-hydroxyaerothionin	Antibiotic activity *E. coli, P. aeruginosa* and *S. aureus*	*20*
Cliona varians	Lectins	Cytotoxic activity Gram positive bacteria, such as *Bacillus subtilis, Staphylococcusaureus* and agglutinated *Leishmania chagasi*, promastigotes	21
Ircinia sp.	Unknown	Antibiotic, analgesic and anti-inflammatory properties	*20*
Sigmadocia pumila	Unknown	Gram positive bacterial strains included *Bacillus thuringiensis* MTCC 4714, *Enterococci fecalis* MTCC 439, *Listeriamonocytogenes* MTCC 1143, *Staphylococcus aureus*, MTCC 737 and *Proteus vulgaris* MTCC 426. Gram negative strains such as the *E. coli* MTCC 443, *Klebsiellapneumonia* MTCC 109, *Pseudomonas putida* MTCC 1688 and *Serratia liquefaciens* MTCC 3039 Antifungal *Trichoderma viride* MTCC 2047, *Fuzarium sp*MTCC 284, *Aspergillus niger* MTCC 1344, *Candida albicans* MTCC 183, *Penicillium chrysogenum* MTCC 5108 and *Aspergillus flavis* MTCC 873	*20*
Aplysina cavernicola	Aeroplysinin and aerthionin and other dibromo and dichlorotyrosine derivatives	Antibiotic *Bacillus subtilis* and *Proteus vulgaris*	22
Stylotella aurantium	Unknown	*Bacillus cereus, Escherichia coli, Salmonella typhi*and *Staphylococcus aureus*.	23
Haliclona molitba	Unknown	*Bacillus cereus, Escherichia coli, Salmonella typhi*, and *Staphylococcus aureus*.	23

Luffariella variabilis	Manoalide	*Staphylococcus aureus* and *Bacillus subtilis*	24
Zygomycale sp	Unknown	*Bacillus subtilis, Proteus vulgaris, Escherichia coli*	24
Cinachyrella sp., *Haliclona* sp. and *Petromica citrina*	Unknown	Antibacterial activity coagulase-negative *Staphylococci* (CNS) strains (responsible for causing bovine mastitis), including strains resistant to conventional antibiotics	24
Discodermia kiiensis/Lithistida	Discodermins B, C and D (Cyclic peptide)	Antibacterial *B. subtilis*	25
Arenosclera brasiliensis	Arenosclerins A-C (Alkyl pepridine alkaloid)	Antibacterial *S. aureus, P. aeruginosa,*	10
Arenosclera brasiliensis	Haliclona cyclamine E (Alkylpiperidine alkaloids)	*S. aureus, P. aeruginosa*	10
Cliona varians	CvL (Lectin)	Antibacterial *S. aureus, B. subtilis*	21
Axinella sp./ Halichondrida	Axinellamines B-D (Imidazo-azolo-imidazole alkaloid)	Antibacterial *H. Pylori, M. Luteus*	26
Caminus sphaeroconia	Caminosides A-D (Glycolipids)	Antibacterial *E. coli, S. aureus*	27
Acanthostrongylophora sp.	6-hydroxymanzamine E (Alkaloid)	Antibacterial *M. tuberculosis*	28
Cribrochalina sp.	Cribrostatin 3 (Alkaloid)	Antibacterial *N.gonorrheae* (antibiotic resistant strain)	29
Cribrochalina sp.	Cribrostatin 6 (Alkaloid)	Antibacterial *S. pneumoniae* (antibioticresistant strain)	29
Cacospongia sp.	Isojaspic acid, cacospongin D and jaspaquinol Meroditerpenes	Antibacterial *S. epidermidis*	30
Aaaptos aaptos	Isoaaptamine (Alkaloid)	Antibacterial *S. aureus*	31
Fasciospongia sp	(–)-Microcionin-1 (Terpenoid)	Antibacterial *M. Luteus*	32

Haliclona exigua	Unknown	Antifungal *Candida albicans, Cryptococcus neofromans, Aspergillus fumigatus, Candida parapsilolis*.	*20*
Topsentia sp./Halichondrida	Topsentiasterol sulfates A–E (Sulfated sterol)	Antibacterial/antifungal (D and E)	33
Acanthodendrilla sp./ Dendroceratida	Acanthosterol I and J (Sulfated sterol)	Antifungal	34
Oceanapia phillipensis/ Haplosclerida	Oceanapiside (Bisaminohydroxylipid Glycoside)	Antifungal	35
Hyrtios erecta/ Dictyoceratida	Spongistatin (Polyether macrolide Lactone)	Antifungal	29
Leucascandra caveolata/ Calcarea	Leucascandrolide A (Oxazole-containing polyether macrolide)	Antifungal	36
Lotrochota purpurea	Halogenated alkaloids named purpuroines A-J	Inhibitory activity against diseases related to fungi and bacteria	37
Haliclona sp.	Novel cyclic bis-1,3-dialkylpyridiniums and cyclostellettamines	Moderate cytotoxic and antibacterial activities against A549 cell-line and Gram-positive strains	38
Agelas mauritiana	Alkaloids, (-)-8'-oxo-agelasine D, ageloxime B, (+)-2-oxo-agela-sidine C, 4-bromo-N-(butoxymethyl)-1H-pyrrole-2-carboxamide and (-)-ageloxime D	Antifungal activity *Cryptococcus neoformans*, antibacterial activity against *Staphylococcusaureus* and methicillin-resistant *S. aureusin vitro*	39

Antitumour Compounds:

Numerous sponge derived compounds are inhibitors of Protein Kinase C. High levels of PKC enzyme are involved in the pathogenesis of arthritis and psoriasis (owing to the regulation of phospholipase A2 activity), and in tumor development. PKC is considered as the receptor protein of tumour promoting phorbol esters while PKC inhibitors prevent binding of carcinosarcoma cells to the endothelium. Receptors glycosylation especially fucose containing residues play an important role in the binding of carcinosarcoma cells and leukocytes to the receptors present in the endothelium.

Fucosyltransferase inhibitors, like octa and nonaprenylhydroquinone sulfates which were isolated from a *Sarcotragus* sp, could be used as a promising candidate to control inflammatory processes such as arthritis or for combating tumor growth. Numerous anti-tumour compounds with different mode of action are identified and are listed in the table 2. Compounds of which can be classified into three classes.Non Specific Inhibitors, Specific Inhibitors and Inhibitors of cancer cells of certain type of Cancer.

Compounds considered as non specific inhibitors are valuable for treating cancers but the major drawback is that it also affects healthy cells. Considering this it has limited application with specific characteristics. The cytoskeleton is an important target for cancer therapy, since microtubules and microfilaments are directly involved in cellular organization during cell division. One such example is adociasulfates (triterpenoid hydroquinones) from a *Haticlona* sp. were the first discovered inhibitors of the kinesin motor protein. The compound selectively inhibits the protein by binding to the microtubule binding site, ''locking up'' the proteins motor function, and thereby blocking cell division. In addition to this lot of potent microtubule interfering compounds have been discovered.Specific Inhibitors are specifically active against

tumour. Compounds for inhibitors of cancer cells of certain type of Cancerhave been isolated but the mechanism of action is unclear.

Table 2: Compounds which exhibit high antitumour activity.

Sponge	**Compound**	**Function**	**Reference**
Hyrtios sp	Heteronemin (marine sesterterpene)	Affecting the cellular processes including apoptosis, cell cycle, MAPKs pathway(mitogen-activated protein kinases) and the nuclear factor kappa B (NF-kappaB) signaling cascade	40
oceanapia sagittaria	Kuanoniamines A and C (pyridoacrydine alkaloids)	A potent inhibitor of DNA synthesis and it was also found to cause an extensive reduction of the MCF-7 cells in G-2phase	41
Thorectandra	Thorectandrols	Anti Proliferative activity	42
Aaptos aaptos/ Hadromerida	Isoaaptamine (Benzonaphthyridine alkaloid)	Protein kinase C inhibitor	43
Hymeniacidonaldis/ Halichondrida	Debromohymenialdisine (Pyrrole-guanidine alkaloid)	Protein kinase C inhibitor	44
Sarcotragus sp./ *DictyoceratidaHaliclona (aka Adocia) sp./* Haplosclerida	Adociasulfates (Triterpenoid hydroquinones)	A1, 3-fucosyltransferase inhibitor Kinesin motor protein inhibitors	45
Discodermia dissolute/ Lithistida	Discodermolide (Linear tetraene lactone)	Stabilization of microtubules	46
Mycdle hentschett/ Poecilosclerida	Peloruside A (Macrocyclic lactone)	Stabilization of microtubules	47
Plakinastrella sp./ Homosclerophorida	Elenic acid (Alkylphenol)	Topoisomerase II inhibitor	47
Leucetta cf. chagosensis	Naamine D (Imidazole alkaloid)	Nitric oxide synthetase inhibitor	48
Agelas mauritianus / Agelasida	Agelasphin (KRN7000) (α-Galactosylceramide)	NKT cell activator	49
Crambe crambe/ Poecilosclerida	Crambescidins 1-4 (Pentacyclic guanidine derivative)	Ca^{2+}/channel blocker	50
Latrunculia brevis/Poecilosclerida; Prianos sp./Haplosclerida	Discorhabdin D (Fused pyrrolophenanthroline alkaloid)	Unknown	51
Aplysilla glacialis/ Dendroceratida	Glaciasterols A and B 9, 11-Secosterol	Unknown	52
Lobophytum duru	Durumolides A-C (Terpenoid)	Inducible NOS and COX-2 inhibition	53
Plakortis angulospiculatus	Plakortide P (Polyketide)	TXB2 inhibition	54
Hyrtios erectus	24-methoxypetrosaspongia C (Sesterterpenes)	Unknown	55
Calcareous sponge	BRS1 (Diamino-dihydroxy polyunsaturated lipid)	Protein kinase C inhibitor	56

Cacospongia mycofljiensis/ Dictyoceratida	Laulimalide (Macrocyclic lactone)	Stabilization of microtubules	57
Auletta sp./Halichondrida	Hemiasterlin (Unusual tripeptide)	Stabilization of microtubules	58
Corallistidae sp./Lithistida	Dictyostatin (Macrocyclic lactone)	Stabilization of microtubules	59
Halichondria okadai/ Halichondrida	Halichondrin B (Polyether macrolide)	Tubulin polymerisation inhibitor	60, 61
Macrocyclic lactan/ lactone	Arenastatin A	Dysidea arenaria/ Dendroceratida	62
Latrunculia magnified/ Poecilosclerida	Latrunculin A (Thiazole macrolide)	Actin-depolymerisation	63, 64
Theonella swinhoei/ Lithistida	Swinholide A (Macrocyclic lactone)	Actin-depolymerization	65
Mycale sp./Poecilosclerida	Mycalolide B (Oxazole macrolide)	Actin-depolymerization	66, 67
Xestospongia cf carbonaria/ Haplosclerida	Neoamphimedine (Pyridoacridine alkaloid)	Topoisomerase II inhibitor	68
Spongia sp./Dictyoceratida	Agosterol A (Sterol)	Reverses drug resistancy of cancer cells	69
Haliclona sp./Haplosclerida	Salicylihalamide A (Salicylate macrolide)	v-ATPase inhibitor	70
Chondropsis sp./Poecilosclerida	Chondropsin A and B (Macrolide lactam)	v-ATPase inhibitor	71, 72
Cinachyrella sp./Spirophorida	6-Hydroximino-4-en-3-one Steroids (Oximated steroid)	Aromatase inhibitor	73
*Haliclona nigra/*Haplosclerida	Haligramides A and B (Cyclic peptide)	Unknown	74
Latrunculia brevis/Poecilosclerida; Prianos sp./Haplosclerida	Discorhabdin D (Fused pyrrolophenanthroline alkaloid)	Unknown	75
*Callyspongia truncata/*Haplosclerida	Callystatin A (Polyketide)	Unknown	76
*Tedania ignis/*Poecilosclerida	Tedanolide (Macrocyclic lactone)	Unknown	77
*Aplysilla glacialis/*Dendroceratida	Glaciasterols A and B 9, 11-Secosterol	Unknown	52
*Axinella carter!/*Halichondrida	Axinellins A and B (Cyclic peptide)	Unknown	78
*Dysidea incrustans/*Dendroceratida	Incrustasterols A and B (Sterol)	Unknown	79

Anticancer compounds:

Table 3:Compounds with high anticancer activity.

Sponge	Compound	Function	Reference
Discodermolide	Modified halichondrin BKRN-70000 Hemiasterlins A & B, Fascaphysins (alkaloid),Alipkinidine (alkaloid), Isohomohalichondrin B, 5-methoxyamphimedine (alkaloid), Laulimalide/Fijianolide, Variolin (alkaloid).	Anticancer	41
Xestospongia sp	Renieramycin M (tetrahydroiso-quinoline) Genera - *Reniera*	Inhibitprogression and metastasis of lung cancer cells.	80
Monanchora pulchra	Monanchocidin (polycyclic guanidine alkaloid)	Induced cell death in human monocytic leukemia(THP-1), human cervical cancer (HeLa) and mouse epidermal (JB6 Cl41) cells.	81
Smenospongia sp.	Smenospongine (sesquiterpene aminoquinone)	Induces antiangiogenic activities, antimicrobial, antiproliferative and cytotoxic.	82
Spongia sp.	Spongistatin-I (macrocyclic lactone polyether)	Mitosis inhibition, assemblyof microtubule and the vinblastine binding to tubulinthereby inducing cytotoxic cell death in numerous cancercell lines.	83

Antifouling Effects:

Natural sponge derived compounds were recently reviewed for antifouling effects with less toxic effect. Compounds derived from sponge exhibit settlement of barnacle larvae also inhibit fouling by macroalgae, or repell the blue mussel Mytilus edulis galloprovincialis. Antifouling property based compounds are highlighted in table 4.

Table 4: Sponges exhibit antifouling property.

Sponge	Compound	Reference
Acanthella elongata	Unknown	84
Haliclona sp. and *Reniera sarai*	poly 3-alkylpyridinium salts, saraine, and haminols	85
Acanthella cavernosa/Halichondrida	Kalihinene X (Isocyanoterpenoid)	86
Acanthella cavernosa/Halichondrida	Kalihipyran B (Isocyanoterpenoid)	87
Acanthella cavernosa/Halichondrida	10b-Formarnidokalihinol Isocyanoterpenoid	88
Pseudoceratina purpurea/Verongida	Pseudoceratidine 2, Dibromopyrrole-containing spermidine derivative	89
Pseudoceratina purpurea/Verongida	Ceratinamide A and B (Bromotyrosine derivative)	90
Haliclona koremella/Haplosclerida	C22 ceramide (Ceramide)	91
Erylus formosus/Astrophorida Lendenfeldia chondrodes /Dictyoceratida	Formoside Striterpene glycoside, sterol diperoxide	92
Axinyssa sp./Halichondrida	AxinyssimidesSesquiterpene carbonimide Cdichlorides	93

Anti –Malarial activity:

Certain compounds listed in the table 5 exhibit antimalarial activity. *Plasmodium* strains are mainly responsible for malaria. Multi-drug resistant plasmodium strains are emerging nowadays and it is very difficult to treat since those strains are resistant to many antibiotics chloroquinone, pyrimethamine and sulfadoxine. To overcome this, new antimalarial drugs has to be emerged in order to fight against multidrug resistant plasmodium strains. Terpenoid isocyanates, isothiocyanates and isonitriles from sponges showed selective in vitro anti malarial activity against *Plasmodium falciparum*. Free carboxylic acids are used as precursors for synthesis of new cyclic norditerpene peroxidesafter esterification. These epidioxy-substituted norditerpenes and norsesterterpenes exhibit selective antimalarial activity against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* strains.

Table 5: Selective Sponges with anti malarial activity.

Sponge	**Compound**	**Target / Function**	**Reference**
Phakellia ventilabrum	Alkaloids	*P. falciparum*	*20*
Aplysinella strongylata	Psammaplysin derivatives	Chloroquine-sensitive (3D7) *P. falciparum*	94
Petrosid Ng5 Sp5 (family Petrosiidae)	Pentacyclic ingamine alkaloids [22(S)-hydroxyingamine A and dihydroingenamine D], together with the known compound ingamine A	Strong antiplasmodial activity against chloroquine-sensitive (D6) and resistant (W2) strains of *Plasmodium falciparum.*	95
Zyzzya sp.	Bispyrroloiminoquinone alkaloid, tsitsikammamine C	Inhibited both ring and trophozoite stages of the malaria parasite life cycle	96
Zyzzya sp.	Makaluvamines and damirones A	Potent growth inhibitory activity against both *P. falciparum* lines	96
Iotrochota sp	N-cinnamoyl-amino acids, iotrochamides A and B	Inhibit *Trypanosoma brucei*	97
Stylissa cf. massa	8-isocyanato-15-formamidoamphilect-11(20)-ene and 8-isothiocyanato-15-formamidoamphilect-11(20)-ene, (Diterpenes)	*P. falciparum*	98
Verongula rigida	Nine bromotyrosine-derived compounds	*Leishmania panamensis, Plasmodium falciparum and Trypanosoma cruzi*.	99
Hymeniacidon sp	Diterpenoid β-lactam alkaloid, Monamphilectine-A	*P. falciparum*	100
Mycale laxissima and *Clathria echinata*	Unknown	Exhibited promising antimalarial activities in the infection model of C57BL/6 mice with *Plasmodium berghei* ANKA	101
Haliclona sp./ Haplosclerida *Cymbastela hooperi*/ Halichondrida *Diacarnus levii*/ Poecilosclerida	Manzamine A (Alkaloids) diterpene isocyanates, isothiocyanates and isonitriles, norditerpenoid and norsesterterpenoid endoperoxides	*P. falciparum, T. gondii, P. berghei,*	102
Acanthella sp./ *Halichondrida*	Kalihinol A Isonitril-containing	*P. falciparum*	103

	kalihinane diterpenoid		
Cymbastela hooperi	Diisocyanoadociane Tetracyclic diterpene	*P. falciparum*	104
	Halichondramide Macrolides	*P. falciparum*	105
Diacarnus erythraeanus	Sigmosceptrellin-B Norsesterterpene acid	*T. gondii, P. falciparum*	105
Agelas oroides	(E)-Oroidin Alkaloids	*P. falciparum*	106
Plakortis simplex	Plakortin andDihydroplakortin Cycloperoxidase	*P. falciparum*	107
Acanthella klethra/ Halichondrida	Axisonitrile-3 Sesquiterpenoid isocyanide	*P. falciparum*	108

Larvicidal activity and Pesticidal Activity:

Table 6: Marine sponges exhibiting larvicidal and Pesticidal activity.

Sponge	**Function**	**Reference**
*Clathria gargonoids*and *callyspongia diffusa*	Larvicidal activity against culex and insecticidal properties.	*20*
Sigmodosia carnosa	Higher toxic effect on *Aedes egypti.*	*20*
Haliclona pigmentifera, Petrosia similies	Larvae of *A. janata* and *P. ricini*	*20*

Compounds from Marine Sponges with diverse property:

Table 11: Sponges with multiple applications.

Sponge	**Compound**	**Function**	**Reference**
Haliclona sp.	Manzamine A, beta-carboline alkaloid	Anti-inflammatory activity, antifungal, anti-HIV-I activities with moderate antitumor activities	83
Pachypellina species	8-hydroxymanzamine A	Antitumor and anti HSV-II activity	41
Axinyssa sp. *Halichondria* sp. and *Chondrosia reticulate*.	Unknown	Anti-M tuberculosis activity	*20*
Topsentia sp.	Unknown	Strong hemolytic activity on fresh bovine erythrocytes.	*20*
Myrmekioderma styx	Unknown	Hemagglutination activity	*20*
Spongia sp. and *Spirastrella* sp.	spongistatins	Antiprolific activity	*20*
Petrosia sp.	Polyacetylenenic alcohols, including (35,145)- petrocortyre A,	Cytotoxic activity against a small panel of human solid tumour cell liner by inhibiting DNA replication	109
Ircinia ramosa	Unknown	Possess antiviral, CNS stimulatory and antialgal properties	110
Haliclona exigua	Unknown	Antibacterial, Cytotoxic, Anti-inflammatory and Anti-oxidant activity	111

Hippospongia sp.	the pentacyclic sesterterpene, hippospongide A, and a scalarene sesterterpenoid, hippospongide B sesterterpenoids	Cytotoxic, Antispasmodic, and Antibacterial	112
Jaspis stellifera	stelletin A (Isomalabaricane triterpenoids)	Cytotoxic	113
Jaspis stellifera	stelliferins A-F	Antineoplastic activity against both murine lymphoma (L1210) and human epidermoid carcinoma (KB) cells	114
Stelletta globostellata	isomalabaricane triterpenoids globostellatic acids	Cytotoxic activity against murine leukemia P388 cells	115
Stylissa carteri	Carteramine A	Anti-inflammatory (Neutrophil Chemotaxis inhibitor)	116
Petrosia strongylata	Acetylenic alcohols, petrosiols	Interfering PDGF-Rβ signaling	117
Rhaphisia lacazei	Pyrazin-2(1H)-one	Interfering PDGF-Rβ signaling	118
Fasciospongia cavernosa	Cacospongionolide B	Interfering NF-κB pathway	119
Petrosaspongia nigra	Petrosaspongiolide M	Interfering NF-κB pathway	119
Hyrtios erectus	Hyrtiosal	Interfering TGF-β pathway	120
Pandaros acanthifolium	steroidal glycosides	Antioxidant and cytoprotective activities	121
Agelas flabellrformis Carter (Agelasidae)	4a-merhyl-5a-cholest-8-en-3-ol 4,5-dibromo-2- pyrrolic acid	Immunosuppressive compounds	122
Aurora globostellata	Unknown	Immunomodulatory potential	123
Cymbastela hooperi,	Diterpene isonitriles	Anti-fouling, anti-algal, anti-photosynthetic, anti-bacterial (Gram +ve and -ve), anti-fungal, and anti-tubercular activity	124
Agelas linnaei and *Ageles nakamurai*	alkaloid derivatives	Cytotoxic activity	125
Amphimedon viridi Neopetrosia sp.	Unknown	Antileishmanial activity	*20*

Anti-inflammatory activity:

Acute inflammations in the human body arise as a result of microbial infection, physical damage, chemical agents and allergens. Blood flow changes results in increasing the permeability of the blood vessels thereby allows escape of cells from blood into tissues. Chronic inflammation of the skin or joints results in severe damage to if it leads to psoriasis or rheumatic arthritis. Sponges have been proved as an interesting source for anti-inflammatory compounds. Manolide is the first identified anti-inflammatory compound from Marine sponge with proven benefits. Mechanism of action is based on irreversible inhibition of the release of arachidonic acid from membrane phospholipids by preventing the enzyme phospholipase A2 from binding to the membranes. Few sponge derived compounds were found to inhibit lipooxygenase, another enzyme which is

involved in inflammation. Increase in the intracellular concentration of arachidonic acid results in the synthesis of inflammation mediators like luekotrienes and prostaglandins.

Table 7: Species with anti inflammatory activity.

Sponge	Compound/class	Target / Function	Reference
Luffariella variabilis/ Dictyoceratida	Manoalide (Cyclohexane sesterterpenoid)	Phospholipase A2 inhibitor	126
Dysidea sp./ Dendroceratida	Dysidotronic acid (Drimane sesquiterpenoid)	Phospholipase A2 inhibitor	127
Ircinia oros/ Dictyoceratida	Ircinin-1 and -2 (Acyclic sesterterpenoid)	Phospholipase A2 inhibitor	128
Petrosaspongia nigra/ Dictyoceratida	Petrosaspongiolides M-R (Cheilantane sesterterpenoid)	Phospholipase A2 inhibitor	129
Spongia sp./ Dictyoceratida	Spongidines A-D (Pyridinium alkaloid)	Phospholipase A2 inhibitor	130
Topsentia genitrix/ Halichondrida	Topsentin (Bis-indole alkaloid)	Phospholipase A2 inhibitor	131
Cacospongia scalaris/ Dictyoceratida	Scalaradial (Scalarane sesterterpene)	Phospholipase A2 inhibitor	132
Jaspis splendens/ Astrophorida	Jaspaquinol (Diterpene benzenoid)	Lipoxygenase inhibitor	133
Suberea sp./Verongida	Subersic acid (Diterpene benzenoid)	Lipoxygenase inhibitor	133

Antiviral activity:

Several different sponges are rich source of bioactive compounds with antiviral properties. Screening and testing of anti-HIV agents from sponges led the researchers to gain interest to discover novel compounds. Eventhough lots of compound have been proved as anti-HIV agents the mechanism of action is still unclear. Despite of the introduction of HIV – inhibiting compounds from sponges, they do not have greater potential to fight against AIDS when compared with other viral diseases.

Table 8: Compounds with antiviral properties.

Sponge	Compound	Target / Function	Reference
Jaspis sp.	Jaspamide Macrocyclic depsipeptide	*C.albicans*	134
Euryspongia sp.	Eurysterols A-B (Sterols)	*C.albicans, Amphoterician B- resistant*	135
Leucetta cf. chagosensis	Naamine D (Imidazole alkaloid)	*C.neoformans*	136
Monanchora unguifera	Mirabilin B (Tricyclic guanidine Alkaloid)	*C.neoformans*	137
Spongosorities sp.	Hamacanthin A (Indole alkaloid)	*C.albicans*	138
Spongosorities sp.	Macanthins A-B (Indole alkaloid)	*C.albicans, C.neoformans*	138
Agelas sp.	Agelasines and Agelasimines Purine derivative	*C.krusei*	139
Aaptos aaptos	4-Methylaaptamine (Alkaloid)	Anti-viral (HSV-1)	140
Theonella sp.	Papuamides A–D (Cyclic depsipeptides)	Anti-viral (HIV-1)	141

Cryptotethya crypta	Vidarabine or Ara-A (Nucleoside)	HSV-1, HSV-2, VZV	142
Dysidea avara	Avarol Sesquiterpene hydroquinone	HIV-1,UAG suppressor Glutamine tRNA inhibitor	143
Xestospongia sp./ Haplosclerida	Haplosamates A and B (Sulfamated steroid)	Anti-viral (HIV-1Integrase inhibitor)	144
Halicortex sp.	Dragmacidin F (Alkaloid)	HIV-1	145
Hamigera tarangaensis	Hamigeran B (Phenolic Macrolide)	Anti-viral (herpes and polio virus)	146
Mycale sp.	Mycalamide A-B (Nucleosides)	A59 coronavirus, (HSV-1)	147
Siliquariaspongia mirabilis	Mirabamides A, C and D (Peptide)	Antiviral (HIV-1)	148
Stylissa carteri	Oroidin (Alkaloid)	Antiviral (HIV-1)	149
Sidonops microspinosa	Microspinosamide (cyclic depsipeptide)	Anti-HIV activity	150
Neamphius huxleyi	Neamphamide	Inhibits HIV growth	150
Monanchora	Crambescidin	Inhibits HIV-1 envelope fusion with normal cells	151
Lendenfeldia (Madagascan sponge)	Dehydrofurodendin	Inhibits the RT-RNA and DNA directed DNA polymerases like polyacetylenetriol	152
Petrosia similis	Petrosins	Inhibits HIV growth	153
Axinella cf. corrugata	Esculetin ethyl ester	Inhibits the protease 3CL of the SARS enzyme &effective against Corona virus	154
Order- Verongida	Mololipids (Tyramine lipid)	Antiviral (HIV-1)	155
Petrosia weinbergi/ Haplosclerida	Weinbersterols A and B (Sulfated sterol)	Antiviral (feline leukemia, mouse influenza, mouse corona)	156
Kirkpatrickia varialosa/ Poecilosclerida	Variolin B (Pyridopyrrolopyrimidine alkaloid)	Antiviral	51
2', 5' Linked oligonucleotide	2-5A	Interferon mediator	157
Polyfibrospongia sp./ Dictyoceratida	Hennoxazole A Bisoxazole	Antiviral	158

Neurosuppressives, Muscle Relaxants and Immunosuppressive Compounds:

Nitric oxide synthetase inhibitors downregulate Tcells and suppresses the immune system function thereby prevents the person from migraine attacks. Immune system suppression is the important process in case of hypersensitivity to certain allergens or other organ transplantations. In order to prevent rejection by the immune system, and also for several reasons compounds with medicinal value plays a significant role. Despite of several existing compounds, marine sponges are also considered as the source for development of immunosuppressive agents.

Neurosuppressive compounds interfere with neural communication which could be used as potent drug for neurologic disorders. Improper signaling in neuromuscular communication arises from stress which results in permanent muscle activation. Despite of these centrally acting muscle relaxants, which mediate neuromuscular communication, peripherally acting muscle relaxant can be used for local muscle relaxation. These can be applied for relief of strokes, or during intubations and surgery.

Table 9: Compounds with immunosuppressive, neurosuppressive and muscle relaxant property.

Sponge	Compound	Function/Mode of action	Reference
Plakortis simplex/ Homosclerophorida	Simplexides (Glycolopids)	Inhibitors of T cellProliferation	159
Dysidea sp./ Dendroceratida	Polyoxygenated sterols (Sterol)	IL 8 inhibitor	160
Petrosia contignata/ Haplosclerida	Contignasterol (Oxygenated sterol)	Histamine release inhibitor	161
Mycale sp./ Poecilosclerida	Pateamine A (Thiazole macrolide)	IL-2 inhibitor	162
Ianthella quadrangulata	Iso-iantheran A (Polyketide)	Ionotropic P2Y11 receptor activation	163
Dysidea herbacea/ Dendroceratida	Dysiherbaine (Unusual amino acid)	Glutamate receptor antagonist	164
Agelas sp. / Agelasida	Keramadine (Pyrrole-guanidine Alkaloid)	Serotonergic receptor antagonist	165
Tedania digitata / Poecilosclerida	1-Methylisoguanosine (Nucleoside analogue)	Unknown (muscle relaxant, antiallergic)	166
Xestospongia sp./ Haplosclerida	Xestospongin C (Macrocyclic bis-oxaquinolizidine)	IP3-inhibitor	167
Spongionella sp./ Dendroceratida	Okinonellin B Furanosesterterpenoid	Unknown (muscle relaxant)	168
Spongosorites sp./ Halichondrida	Bromotopsentin (Bis-indole alkaloid)	α1-Adrenergic receptor antagonist	169
Penares sp./ Astrophorida	Penaresidin A (Azetidine alkaloid)	Actomyosin ATPase inhibitor	170
Dysidea sp./ Dendroceratida	S1319 (Benzothiazole derivative)	Unknown (antiasthmatic, uterine relaxation)	171

Cardiovascular agents:

Sponge derived molecules has the ability to interfere with blood related diseases such as thrombosis, atherosclerosis or diabetes. Blood coagulation process is triggered by a complex proteolytic cascade which leads to the formation of fibrin. Thrombin, a serine protease cleaves a peptide fragment from fibrinogen, which then leads to the generation of fibrin, a major component of blood clots.

Table 10: Selective compounds from Marine sponges as cardiovascular agents.

Sponge	Compound	Function	Reference
Theonella sp./ Lithistida	Cyclotheonamide A Cyclic pentapeptide	Serine protease inhibitor and is a potential drug for the treatment ofThrombosis	172
Eryltus formosus/ Astrophorida	Eryloside F, Penasterol disaccharide	Thrombin receptor Antagonist	173
Halichondria okadai/ Halichondrida	Halichlorine, Cyclic aza-polyketide	VCAM-1 inhibitor	174
Callyspongia truncata/ Haplosclerida	Callyspongynic, Acid Polyacetylene	α-glucosidase inhibitor	175

Analgesic Agents:

Compound Ziconotide isolated from the marine snail *Conus magus*, recently approved by the FDA to treat pain. The mechanism of action of ziconotide is still unclear. Results in animal models suggest that ziconotide blocks the N-Type calcium channels on the primary nociceptive nerves in the spinal cord[176].

Anti-oxidant activity:

Subergargoria suberosa derived natural products exhibit anti oxidant activity. Bioactive diterpenes such as Subergorgic acid 1 presence in the marine sponge showed anti oxidant property[177].

Conclusion:

Marine sponges naturally produce enormous amount of bioactive compounds and secondary metabolites in association with other symbiotic species for its defense mechanisms. These bioactive compounds can be used as active metabolites to treat various infections as antimicrobial agents, antibiotic, anti-inflammatory compounds, immunosuppressive compounds and can also affect pathogenesis of many diseases. Compounds in nature target different substances in pathways or receptors and exhibits its inhibitory role. Inhibitory mechanism or its mode of action for certain compoundsfrom marine sponges can be found out but for most of the substances their exact mode of action is not well known. In addition to that, limited tests make the substances to get their exact mode of action and their origin. Most of the bioactive substances exhibit their potential of inhibiting certain enzymes and it mediate or it acts as a mediator of certain intracellular or intercellular messengers directly involved in the pathogenesis of diseases. Moreover in the drug discovery process, substances which exhibited as potent inhibitors *in vitro* turned not to commercialize as drug after experimenting *in vivo*. It is mandatory that substances which are proved with inhibitory activity *in vitro* should produce better results in the *in vivo* condition. Those substances can be screened to commercialize as drug with better bioavailability with lesser side effects. Few compounds from marine sponges are existing as drugs in the market for various diseases. Potency of sponge derived medicines lies in the fact based on their efficacy, bioavailability and their side effects.In addition, the active core area of these molecules can be found and it can be used as a vehicle to derive many compounds as derivatives with their own specific efficacy and side effects. Most important challenging job in transforming bioactive molecules into medicine is to screen the treasure house of sponge metabolites and to select those displaying specific functions against a particular disease. But it should be decided that how these bioactive molecules can be produced in a large scale remains a question.

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