IJPSR (2012), Vol. 3, Issue 12 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 June, 2012; received in revised form 16 November, 2012; accepted 28 November, 2012

PHARMACOLOGICAL PERCEPTION OF PEPTIDES FROM MARINE SPONGE: A REVIEW

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Keywords:
Sponges, Metabolites, peptides, anti-bacterial, anti- tumor

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ABSTRACT

Marine sponges, the sessile invertebrates of the *Phylum porifera* are invaluable tool in current research. They remain as a goldmine to chemist and pharmacologist due to its defensive weapons, the secondary metabolites. Endogenous peptides from marine sponges and associated microorganisms are promising lead compound for drug development. Some of the compounds are under clinical trials. These peptides can act against variety of diseases in humans including bacterial, fungal, protozoan, HIV, inflammatory and even tumor. This review focuses on sponge symbiotic association with other organisms, significance of peptides as secondary metabolites and its pharmacological effects by highlighting its role as ant-bacterial, anti- fungal, anti- HIV and anti- tumor agents. Sponge-microbial associations are found to be very specific in the production of particular bioactive compounds.

INTRODUCTION: More than two decades ago marine invertebrates have provided key structure and compounds that proved their potential in several fields, particularly as new therapeutic agent for a variety of diseases. Among marine invertebrates, Porifera (sponges) remain the most prolific phylum, concerning novel pharmacologically active compounds [1].

Pharmaceutical interest in sponges was aroused in the early 1950's by the discovery of a number of unknown nucleosides: spongothymidine and spongouridine in the marine sponge *Cryptotheca crypta* [2]. Sponges can provide potential drugs against many major world-wide occurring diseases. Of the 18,000 marine natural products described, they are responsible for more than 5300 different products and every year hundreds of new compounds are being discovered [3]. The antitumor natural product patent registrations in recent years over 75% are from sponges [4].

One among the well-established sector in the research of marine natural products is the search of bioactive peptides from marine sponges. The bioactive peptides are protein fragments which have a positive impact on the functions and conditions of living beings.

However, they are produced only in limited quantities by living species including marine sponges [5]. With respect to the diversity of the secondary metabolites produced marine sponges' remains as 'gold mine' to chemists and found their way in to pharmacological applications.

QUICK RESPONSE CODE

IJPSR:
ICV (2011)- 5.07

Website:
www.ijpsr.com

Marine Sponge Secondary Metabolites: With the variety of species inhabit the world's oceans, the intense concentration of species coexisting in these limited extent habitats necessarily makes them highly competitive and complex [6]. As a result of this intense competition, a high percentage of species have evolved chemical compounds to defend.

These chemical adaptations [7] generally take the form of so-called ''secondary metabolites. Marine invertebrates which are abundant in the Indo-Pacific regions are rich in secondary metabolites and are becoming targets of continuing search for bioactive compounds [8]. Researchers found that sponges have highest diversity of defensive chemical weapons *i.e.,* secondary metabolites [9, 10] to repel and deter predators [11], compete for space with other sessile species [12] and for communication and protection against infection.

Among marine organisms, the largest number of secondary metabolites isolated since 1965 have come from sponges [13]. The chemical diversity of sponge substances is remarkable. Sponge derived compounds are mostly nitrogen-containing ones and also non-nitrogenous compounds [14]. In addition to the unusual nucleosides, other classes of substances such as bioactive terpenes, sterols, cyclic peptides, alkaloids, fatty acids, peroxides, and amino acid derivatives (which are frequently halogenated) have been described from sponges or from their associated microorganisms [15, 16, 17, 18, 19].

The main biological activities of those sponge metabolites have been cytotoxic and antimicrobial while other activities (anti-inflammatory, immuno-suppressive, neurosuppressive, and antifouling activities) have been limited, suggesting the need for an evaluation of anti-cancer and anti-infective agents [20, 21]. The studies on sponge chemical ecology include three different aspects. First, diversity of chemical compounds produced by sponges; second, potential functions of these metabolites in nature and finally, the strategies for their use for human benefit [22].

Sponge Microbial Symbiosis: As marine sponges have been considered as a rich reservoir of bioactive compounds, a conceptual progress occurred focusing on sponges, highlighting the symbiosis of sponge-associated microorganisms (bacteria and fungi) in the host epibiotic defense [23]. Symbionts include archaea, bacteria, cyanobacteria, and microalgae. Bacteria associated with marine sponge *Theonella swinhoei* include unicellular cyanobacteria, unicellular bacteria and filamentous bacteria [24]. Many sponges contain large amounts of bacteria within their tissues, sometimes occupying 40 to 60% of the total biomass (equivalent to 108 to 1010 bacteria per gram) [25].

Therefore, it has often been proposed that associated bacteria might be the actual producers of many sponge-derived natural products [26]. Fungi associated with marine sponges are also known to produce many bioactive agents [27]. The members of the class Demospongiae are the richest producer of pharmacologically significant bioactive compounds in association with microbes [28].

In some cases, these microorganisms and not sponge cells are the likely source of the secondary metabolites of interest [29, 30, 31]. It is reported that sponge hosted diverse microorganisms are metabolically very active in their respective host and it was demonstrated by comparing 16S rRNA gene derived sequence [32]. The host (sponge) synthesizes bioactive compounds that provide protection against attacking microorganisms or eukaryotes, e.g., acetylenic compounds [33]. The symbiotic bacteria or fungi produce secondary metabolites that act as antibiotics, *e.g.*, cribrostatin [34], or as cytostatic agents, e.g. sorbicillactone-A [35].

Functionally, these compounds act only as defense molecules. Another functional class of secondary metabolites of sponges and their associated microorganisms play a dual role: they are involved in defense as well as in the activation of pathways crucial for self defense [9]. The occurrence of structurally similar substances in unrelated sponges, particularly those which were otherwise known exclusively from microorganisms, led to the hypothesis that such substances were of microbial origin including some already in drug trials [36].

An antibacillus compound, which was chemically identified as the peptide antibiotic andrimid was detected in the extract of the sponge *Hyatella* sp. A bacterial isolate M22-1, belonging to the genus *Vibrio* was also isolated from the homogenate of the same

sponge. The bacterium when cultured in marine agar also produced the same compound. This suggests that the origin of andrimid in the sponge is from the bacterium [36]. An epibiotic bacterial strain *Pseudoalteromonas maricaloris* KMM 636T, isolated from the Great Barrier Reef sponge *Fascaplysinopsis reticulata* was the source of two brominated chromopeptides such as bromoalterochromide A and bromoalterochromide A . They showed moderate cytotoxicity to the eggs of the sea urchin *Strongylocentrotus intermedius* [37, 38]. Leucamide A closely resembles the compound albeit, which is found frequently in cyanobacteria.

Scanning electromicrographs of *Leucetta microraphis* revealed the presence of microbial symbionts, including cyanobacteria in the tissue of the sponge *Leucetta microraphis*. The sponge-derived leucamide A might, therefore be produced by cyanobacteria associated with it and not by the invertebrate itself [39]. The fungus *Aspergillus versicolor*, isolated from *Petrosia* sp. (Jeju Island, Korea) yielded three known polyketides such as decumbenones A, B and versiol, and the cytotoxic lipopeptide fellutamide C [30].

Marine Sponge Peptides: Marine sponges are synthesizing a wide variety of peptidic and organic molecules with biological activities Natural peptides have been invaluable tools for pharmacological and biochemical investigations of a wide range of physiological functions [40]. Cyclic dipeptides (also known as diketopiperazines, DKPs) are known to have antibiotic, antiviral and antitumour properties, and are a relatively unexplored class of bioactive peptides that may hold great promise for the future [41].

Lithistid sponges are renowned among marine organisms for their ability to produce a diverse array of biologically active metabolites [42], including novel peptides characterized by a high proportion of D and/or *N*-methylated amino acids. The similarity between lithistid peptides and those from microorganisms leads to the speculation that lithistid peptides might arise from symbiotic microbes [43].

Polytheonamide-B (pTB), a highly cytotoxic polypeptide, is one of the most unusual nonribosomal peptides from sponge origin. pTB is a linear 48- residue peptide with alternating D- and l- amino acids and contains a total of eight type of non proteinogenic amino acids. The strong cytotoxicity can be ascribed to its ability to form single molecule channels through biological membranes [44]. Corticiamide A(1) and cyclocinamide B(2) represent the first peptides to be described from the genus Corticium [45].

A strain of *Penicillium brevicompactum* derived from the specimen of *Petrosia ficiformis* provided two new cyclopentadepsipeptides, petrosifungins A and B along with the known fungal metabolites brevianamide A, mycophenolic acid and asperphenamate. Since cyclodepsipeptides constitute new class of potential drugs, petrosifungins A and B, may serve as lead compounds for more pharmacologically potent and toxicologically safe derivatives [46].

TABLE 1: MARINE SPONGE DERIVED PEPTIDES

Substance	Class	Organism	Reference
Haliclonamides C, D and E	peptides	*Haliclona genus*	Sera et al., [47]
cyclo-(glycyl-L-prolyl-L- glutamyl)	cyclic peptides	*Suberites domuncula*	Mitova et al., [48]
mapacalcine; Mr 5 19,064 vastifica	dimeric peptide	*Cliona*	Morel et al., [49]
microsclerodermins C – E(3-4)	cyclic peptides	*Theonella sp*	Schmidt and Faulkner [50]
Koshikamide A1	linear peptide	*Theonella sp*	Fusetani et al., [51]
Euryjanicin A(1)	cycloheptapeptide	*Prosuberites*	Vicente et al., [52]
Phakellistatins 15−18 (**2**–**5**), Phakellistatins 13 (**1**), hymenistatin 1 and hymenamides G, H, and J	cyclopeptides	*Phakellia fusca*	Zhang et al., [53]
stylisin 1(**1**) and stylisin 2 (**2**), phakellistatin 13 (**3**)	Cyclic heptapeptides	*Stylissa caribica*	Mohammed et al., [54]
stylissamides E (3) and F (4)	Cyclic heptapeptides	*Stylissa caribica*	Cychon and Kock, [55]
corticiamide A (1) and cyclocinamide B(2)	cyclic peptide	Corticium sp	Laird et al., [45]

Anti-Bacterial Peptides: In the year 2007 alone 961 new compounds were described from marine microorganisms reflecting an increase of 24% compared with the number of compounds reported for 2006 Discodermines A-D have been isolated from *Discodermia kiiensis.* were proposed as antibacterial agents and two new cyclic peptides, cyclo-(glycyl-L-seryl-L-prolyl-L-glutamyl) and cyclo- (glycyl-L-prolyl-L-glutamyl), have been isolated from the cell extract of a *Ruegeria* strain associated with cell cultures of the sponge *Suberites domuncula* showed moderate activity against *B. subtilis*, with an MIC of 25 µg/ml and 50 µg/ml, respectively [48].

Cyclic lipopeptides are produced by different groups of bacteria, both Gram-positive and Gram-negative [55] and represent a unique class of bioactive microbial secondary metabolites [56]. The antibacterial peptide activity from the marine sponge Clathria *Indica* among the various strains maximum diameter of (12 mm) zone of inhibition was recorded in *Escheirchia coli* strain and minimum zone of inhibition of (6mm) was observed in *Salmonella typhi, Proteus mirabilis and Lactobacillus vulgaris* strain [57].

On the basis of TLC observations on further confirmations with ^{1}H NMR peptide presented in between (6-8ppm fractions) subjected to studies by using chromatography technique. This resulted in the identification of antimicrobial peptide [57].

Two cyclic thiopeptides containing thiazole and pyridine moieties, and several unusual amino acids, were obtained from a culture of *B. cereus* isolated from the marine sponge *Halichondria japonica*, which exhibited potent antibacterial activities against *Staphylococcus* and *Enterococcus* and were active against multiple drug resistant strains. These thiopeptides were only inactive against Gram-negative bacteria [58, 59].

The most promising antimicrobial substances appear to be 2-undecyl- 4-quinolone, DKPs, lipopeptides (surfactins, iturins and fengycins), manzamine-A, organo halogen (2,4,4'-trichloro- 2'-hydroxydiphenyl ether), phenazine, pyrone I, rifamycins and thio peptides. Among these substances, manzamine-A produced by an actinomycete appear to be great promise for the future.

Anti-Fungal Peptides: Two other peptides, discobahamin A and B, isolated from the Bahamian deep water marine sponge *Discodermia* sp., were evaluated as inhibitors of the growth of *C. albicans* [60]. The depsipeptides halicylindramides A–C , D and E [61, 62], with antifungal and cytotoxic properties (against P388), were obtained from the Japanese marine sponge *Halichondria cylindrata*. Halicylindramides A–C are tetradecapeptides with an N-terminus blocked by a formyl group and the C-terminus lactonized with a threonine residue. Halicylindramide D is a tridecapeptide also with antifungal and cytotoxic properties, while halicylindramide E is a truncated linear peptide with a C-terminal amide.

Other antifungal cyclic peptides from sponges are the aciculitins A–C [63] and the theonegramide [64]. The marine sponge *Theonella swinhoei* from Palau contains the bicyclic glycopeptide antifungal compound theopalauamide [65]. Another example is the Haligramides-A and B two new cytotoxic from hexapeptides from the sponge *Haliclona nigra* [66].

Anti- HIV Peptides: HIV-inhibitory peptides from sponges constitute a recent discovery. HIV-inhibitory peptides from sponges constitute a recent discovery. The cyclic depsipeptides papuamides A–D [67] isolated from sponges of the genus *Theonella* contain a number of unusual amino acids and are also the first marine derived peptides reported to contain 3- hydroxyleucine and homoproline residues, and 2, 3- dihydroxy-2, 6, 8-trimethyldeca-(4Z, 6E)-dienoic acid moiety N-linked to a terminal glycine residue.

Papuamides A and B inhibited the infection of human T-lymphoblastoid cells by HIV-1 sub (RF) *in vitro* with a 50% effective concentration (EC50) of approximately 4 ng/ml. Another anti-HIV candidate from the sponge *Sidonops microspinosa* is the microspinosamide [68], a cyclic depsipeptide incorporating 13 amino acid residues and the first naturally occurring peptide containing a beta- hydroxy-*p*-bromophenylalanine residue. Microspinos-amide inhibited the cytopathic effect of HIV-1 infection in an XTT-based *in vitro* assay.

A new sulfated cyclic depsipeptide, termed mutremdamide A, and six new highly *N*-methylated peptides, termed koshikamides C–H, were isolated from different deep-water specimens of *Theonella*

swinhoei and *Theonella cupola*. Mutremdamide A displays a rare 2-amino-3-(2-hydroxyphenyl)propanoic acid and a new *N*δ-carbamoyl-β-sulfated asparagine. Koshikamides C–E are linear undecapeptides, and koshikamides F–H are 17-residue depsipeptides containing a 10-residue macrolactone. Koshikamides F and G differ from B and H in part by the presence of the conjugated unit 2-(3-amino-5-oxopyrrolidin-2-ylidene)propanoic acid. Cyclic koshikamides F and H inhibited HIV-1 entry at low micromolar concentrations while their linear counterparts were inactive [69]. The origin and role of bioactive peptides inside the sponges in many cases is unclear.Several of these substances possess a great potential for drug development, but none has given origin to a commercial medication so far.

Six new depsipeptides belonging to two different structural classes, termed celebesides A–C and theopapuamides B–D, have been isolated from the marine sponge *Siliquariaspongia mirabilis*. Celebeside A neutralized HIV-1 in a single-round infectivity assay with an IC50 value of 1.9±0.4μg/mL while the nonphosphorylated analog celebeside C was inactive at concentrations as high as 50 μg/mL [69]. HIV cyclodepsipeptide, homophymine A, was isolated from a New Caledonian collection of the marine sponge *Homophymia* sp. Homophymine A contains 11 amino acid residues and an amide-linked 3-hydroxy-2,4,6-trimethyloctanoic acid moiety. In a cell-based XTT assay, homophymine A exhibited cytoprotective activity against HIV-1 infection with a IC50 of 75 nM [70].

Anti- Tumor Peptides: Koshikamide A2 (2) was isolated as a cytotoxic metabolite from a marine sponge of *Theonella* sp. Its structure was elucidated to be a linear undecapeptide by spectroscopic and chemical methods, together with enzymatic conversion to known koshikamide A1 (**1**). The new peptide moderately inhibited the growth of P388 murine leukemia cells [71].

Koshikamide B (**1**) has been isolated from two separate collections of the marine sponge *Theonella* sp. as the major cytotoxic constituent. Koshikamide B is a 17-residue peptide lactone composed of six proteinogenic amino acids, two d-isomers of proteinogenic amino acids, seven *N*-methylated amino acids, and two unusual amino acid residues.

It exhibits cytotoxicity against P388 murine leukemia cells and the human colon tumor (HCT-116) cell line with an IC50 value of 0.45 and 7.5 μg/mL, respectively [72].

Nonribosomal cyclic peptide leucamide A was isolated from the sponge *Leucetta microraphis*, obtained from the Great Barrier Reef of Australia. The compound was found to inhibit the growth of three tumor cell lines (stomach carcinoma, liver carcinoma and liver carcinoma with mutated p53) [32].

Keramamides B–D as well as Orbiculamide A, isolated from sponges of the genus *Theonella* [73] were cytotoxic against P388 murine leukemia cells (IC50 = 4.7 ng/ml).

Pakellistatin 12 (**1**) is a new cancer cell growth inhibitory (P388 ED50 2.8 μg/mL) cyclodecapeptide that was isolated from a marine sponge *Phakellia* sp [74]. Haliclona sp a marine sponge yielded Kendarimide A a novel peptide which reversed glycoprotein mediated multi drug resistanace in tumor cells. HTI-286 [61], a synthetic analog of the tripeptide, hemiasterlin, originally isolated from the South African sponge *Hemiasterella minor*, depolymerizes microtubules and blocks cell growth. HTI-286 has also shown antitumor activity in human tumor xenograft murine models [21].

Papuamides are representatives of a class of marine sponge derived cyclic depsipeptides, including callipeltin A, celebesides A and B, homophymine A, mirabamides, microspinosamide, neamphamide A and theopapuamides. They are thought to have cytoprotective activity against HIV-1 *in vitro* by inhibiting viral entry. Jasplakinolide, a representative member of marine sponge-derived cyclodepsipeptides that include arenastatin A, geodiamolides, homophymines, spongidepsin and theopapuamides, is a potent inducer of actin polymerization *in vitro.*

Although actin dynamics is essential for tumor metasasis, no actin targeting drugs have been used in clinical trials due to their severe cytotoxicity. Nonetheless, the actin cytoskeleton remains a potential target for anticancer drug development. These features imply the use of cyclodepsipeptides as molecular models in drug research [75].

CONCLUSION: Peptide compounds analysed here are obtained from very different marine organism of sponge exhibiting different chemicals and displaying the large variety of pharmacological effects of specific targets. The marine world has become an important source of therapeutic agents with novel mechanisms of action. A multidisciplinary and cooperative effort with the use of more sensitive and fast methods in the analysis of the structure of peptides, e.g. exact description of the molecular weight and the sequence, as well as in the pharmacological evaluation, will speed up drastically the discovery of novel active peptides from marine sources.

From another side, these compounds seem to be very useful and promising for biomedical research to clarify many normal and pathological mechanism of action in the human body as well as in the design of very specific and potent new pharmaceuticals for a wide variety of diseases. The discovery of the bio-regulatory role of different endogenous peptides in the marine sponges as well as the understanding of the molecular mechanisms of action as anti-bacterial, antifungal, anti-HIV and anti- tumor contributed to consider peptides also as promising lead drug candidates.

AKNOWLEDGEMENTS: The authors gratefully acknowledged Fr. Prem Kumar, Correspondent, Malankara Catholic College for his constant encouragement and the anonymous reviewers for their valuable comments in the preparation of this review.

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How to cite this article:
Joseph B, Nair VM and Sujatha S: Pharmacological Perception of Peptides from Marine Sponge: A Review. *Int J Pharm Sci Res*. 3(12); 4689-4696.