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REVIEW ARTICLE

Bacteria From Marine Sponges: A Source of New Drugs

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Abstract: Sponges are rich source of bioactive natural products synthesized by the symbiotic bacteria belonging to different phyla. Due to a competition for space and nutrients the marine bacteria associated with sponges could produce more antibiotic substances. To explore the proactive potential of marine microbes extensive research has been done. These bioactive metabolites have some unique properties that are pharmaceutically important. To date, majority of these metabolites have been identified from marine invertebrates of which sponges predominate. Sponges harbor abundant and diverse microorganisms, which are the sources of a range of marine bioactive metabolites. From sponges and their associated microorganisms, approximately 5,300 different natural compounds are known. Current research on sponge-microbe interaction and their active metabolites has become a focal point for many researchers. Various active metabolites derived from sponges are now known to be produced by their symbiotic microflora. In this review, we attempt to report the latest studies regarding capability of bacteria from sponges as producers of bioactive metabolite. Moreover, these sponge associated bacteria are an important source of different enzymes of industrial significance. In present review, we will address some novel approaches for discovering marine metabolites from bacteria that have the greatest potential to be used in clinical treatments.

Keywords: Marine sponges, sponge-associated bacteria, antimicrobial activity, secondary metabolites, hydrolytic enzymes.

1. INTRODUCTION

The discovery of penicillin in the mid-twentieth century revolutionized the treatment of infectious disease. Since then, antimicrobial agents have saved the lives and eased the suffering of millions of people. Multiresistant bacteria such as Meticillin Resistant *Staphylococcus aureus* and Extended Spectrum BetaLactamase *Escherichia coli* threaten to cause new epidemics. Microorganisms not only cause infection but also produce bioactive compounds that can treat a variety of infectious disease [1]. The search for new compounds is encouraged in the fight against the threat posed by the increasing number of drug-resistant infectious disease and more and more upcoming disorders.

Previously terrestrial resources have been extensively investigated, thus researchers are attempting to get novel molecules from the marine environment. Oceans are most primitive, important and unique form of life on the earth. It provides a huge diversity of living organisms inhabiting diverse microflora [2]. The marine resources are widely studied nowadays because of numerous reasons. One of the reason is, the oceans cover more than 70% of planet surface and among 36 living phyla known yet, 34 of them are found in marine environments with more than 300000 known species of fauna and flora [3]. The fundamental reason of searching for new drugs from marine environment in fact is due to adaptation of the marine plants and animals to all kind of marine environments. These organisms develop some adaptation mechanism for their defense and the result of these adaptations may be useful for human beings in many ways [2]. Example of such adaptation mechanism is the production of bioactive metabolites, which helps them in their survival from predators [4]. Some marine organisms are simple, sessile and delicate and have developed a relation with surrounding microorganisms to protect themselves from predators and pathogens in the marine environment. In this relation, both microorganisms and hosts have developed different chemical protection strategies for the intensely competitive environment [5].

Marine microorganisms have incredible abilities as producers of compounds having anti-cancer activity and secondary metabolites used against different diseases. However, despite their tremendous bioactive potential, marine microorganisms have not been given the attention they actually deserve. Pharmaceutical industries apart from synthetic products, are now concentrating on bioactive metabolites derived from marine microorganisms [2]. So far, more than 10,000 bioactive compounds have been screened from marine organisms [6]. Recently, many new bioactive compounds have been isolated from different marine animals like tunicates, soft corals, sponges, bryozoans, sea slugs and other marine organisms. Sponges (*Porifera*) and their mutualistic symbionts produce a plenty of secondary metabolites to repel and prevent predators and to compete for space [7]. In this review, we have made an effort to survey the

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discoveries and biomedical significance of secondary metabolites of sponge-associated bacteria discovered so far from different sponges. It is also important to highlight the compounds having significance potential to lead to pharmacologically important and clinically useful in treatment of different diseases.

2. CULTIVATION TECHNIQUES FOR SPONGE-ASSOCIATED BACTERIA

Sponges are characterized to be host for diverse groups of microorganisms which consist of up to 60% of the biomass of the sponge host [8]. Sponge symbionts are living both intra and extra cellularly and each symbiotic microorganism seems to have a particular habitat in the host [9]. Symbiotic association attributes benefits to associated microbes including nutrient intake, stabilization of sponge skeleton, removal of metabolic waste and production of secondary metabolite [8]. Sponges are the excellent source of bioactive metabolites and many novel metabolites were isolated from marine sponges [10]. The members of the class *Demospongiae* are major producer of pharmacologically important bioactive compounds in association with microbes. From the class *Demospongiae*, 26 families have been recognised as producer of medicinally important bioactive compounds of microbial origin [8].

The functions of these secondary metabolites are unknown, as there is some evidence that they provide chemical defence against predators. The potential role of microbes in sponge biology varies from mutualistic symbiosis to the nutritional source of sponge [11,12]. Recently, some studies primarily relying on 16S rRNA sequencing [13], and fluorescence in situ hybridization [14] indicate that most sponges harbor phylogenetically diverse microbial groups distinct other marine sources. It has been hypothesized that the bacteria in these communities synthesize many of the associated bioactive compounds [15]. For the isolation of natural compounds, cultivation of invertebrates is generally impossible whereas it is secure and inexpensive to cultivate microorganism for unlimited supply of active metabolites. However, despite considerable effort many sponges-associated bacteria have not been cultured [16], pointing for some alternative strategies. Culture-independent techniques such as Denaturing gradient gel electrophoresis (DGGE) of PCR-amplified 16S rDNA gene fragments, amplified (DNA) fragment length polymorphism (AFLP), fluorescent *in situ* hybridization (FISH), amplified ribosomal DNA restriction analysis (ARDRA) and clone libraries are widely used for analysis of microbial communities from different environment [17] when it is difficult to identify bacterial population using culture dependent methods. Current use of genomic approaches used to isolate the biosynthetic genes and expressing them in a host is another alternative method to isolate targeted genes or bioactivities [18].

Based on some new molecular techniques for bacterial community analysis such as Denaturing Gradient Gel Electrophoresis (DGGE), 16S rRNA gene sequencing and Fluorescence *In Situ* Hybridization (FISH), it has been known that the bacterial community associated with sponge mainly consists of at least ten different bacterial phyla such as *Proteobacteria*, *Nitrospira*, *Cyanobacteria*, *Bacteriodetes*, *Actinobacteria*, *Chloroflexi*, *Planctomycetes*, *Acidobacteria*, *Poribacteria* and *Verrucomicrobia* besides species of Archaea [18]. The major secondary metabolites producing bacteria from sponges belong to different phyla, including α, β, γ, δ- *Proteobacteria*, *Firmicutes*, *Actinobacteria* and *Cyanobacteria* [18]. In the production of therapeutic compounds, Phylum *Actinobacteria* is a dominant group followed by *Proteobacteria*, where *Firmicutes* and *Cyanobacteria* are yet to be explored for their bioactive importance.

There is chemical and biological diversity among bioactive compounds isolated from sponge-associated bacteria. There are various classes of natural compounds to date isolated from sponge associated bacteria such as polyketides, alkaloids, fatty acids, peptides and terpenes. Beside their antimicrobial action, most of them show antitumor and anticancer properties too. The isolation of active metabolites within sponge-associated bacteria opens up the opportunity of providing a constant supply of the biologically active compounds by laboratory cultivation of the bacteria [19].

3. BIOACTIVE METABOLITES FROM SPONGE ASSOCIATED BACTERIA

Search for clinically significant bioactive compounds from microbes associated with sponges have been discovered so far from geographically different regions such as the Great Barrier Reef of Australia, South China Sea, Mediterranean Sea, Indonesia, Papua New Guinea, Indo-Pacific region, *etc*. [11]. In the early 1950s, by the discovery of the nucleosides spongothymidine and spongouridine in the marine sponge *Cryptotethya crypta* search for medically important compounds has started [12]. These compounds were the basis for the synthesis of ara-C, the first marine-derived anticancer agent, and the antiviral drug ara-A [6]. So far different groups of antimicrobial bacteria have been isolated from different sponges. Here is the brief description of these bacteria.

3.1. Actinomycetes

Actinomycetes from marine sponges are targeted in drug discovery studies due to their potential as a huge resource of diverse natural products with unusual biological activity by using both, culture-independent and culture-dependent methods, previous studies have identified abundant *Actinomycetes* associated with marine sponges [13]. A marine sponge *Halichondria* associated *Streptomyces* sp. produces Mayamycin 53, exhibited strong activity against several human cancer cell lines and antibacterial activity against different human pathogenic bacteria including multidrug resistant bacteria (MDR) [20]. A *streptomyces* sp isolated from the sponge *Dendrilla nigra* exhibits its activity against pathogenic bacteria [21]. The compound nocapyrones was isolated from a marine sponge-associated bacterial strain *Nocardiopsis* sp., which exhibited antibacterial and cytotoxic activity against different cancer cell lines [22]. Another endophytic *Streptomyces* sp. isolated from sponge *Aplysina* was identified as producer of two known compounds antagonistic to wide range of fungi including some dermatophytes [23]. A broad continuum of bacteria was found in *halichondrid* sponges including *Actinobacteria*. These microbes associated with *halichondrid* sponges were identified as a true source of bioactive compounds exhibiting considerable therapeutic effects [8].

The presence of rifamycin B as well as the rifamycin SV was observed in many *Salinispora* strains associated with the sponge *Pseudoceratina clavata* which can be an alternate anti-bacterial source of rifamycin [24]. Manzamines are significant potential pharmaceuticals, which were produced by the *Micromonospora* sp. associated with sponge *Petrosiidae* and showed their activity towards tuberculosis, HIV and malaria [25].

Nocardiopsis dassonvillei was isolated from the sponge *Dendrilla nigra* capable of producing various compounds exhibiting antimicrobial, antioxidant, hypocholesterolemic, nematicidal, antiandrogenic, hemolytic, anti-inflammatory and anticancer activities [23]. In a previous study, eight different sponges have been studied for isolation of antimicrobial isolates. Of the isolated bacteria, 27.5% exhibited antimicrobial activity and 91% contained polyketide synthase and/or non-ribosomal peptide synthetase genes, indicating potential of these isolates to produce secondary metabolites [26]. A new anti-MRSA bioactive compound kocurin, a new member of the thiazolyl peptide family of antibiotics has been isolated from different strains related to genera *Kocuria* and *Micrococcus* associated with marine sponge [27]. In a recent study, the sponge associated actinomycete strain produces three new compounds, amycofuran, amycocyclopiazonic acid, and amycolactam having antimicrobial and anticancer activities [28].

3.2. Proteobacteria

Phylum *Proteobacteria* is the second dominant group producing bioactive metabolites from sponges after *Actinobacteria*. The members of γ-*Proteobacteria* and *α-Proteobacteria* are the dominant bioactive metabolites producing groups of this phylum. Majority of these compounds exhibit antimicrobial, antitumor and anticancer properties. A *pseudomonas* sp. isolated from sponge *Aplysinellidae* produced quinolones showing strong antibacterial activity [29]. Two compound α-pyrones produced by *Pseudomonas* species isolated from marine sponge showed their anti-microbial activity against gram positive pathogens, which include multi-drug resistant strains and a weak action toward the gram negative bacteria [30].

Norharman (β-carboline alkaloid) is one of the key antimicrobial metabolites, isolated from *Pseudoalteromonas piscicida,* associated with sponge *Hymeniacidon perleve.* Anti-microbial activity of norharman was observed against *Staphylococcus aureus, Agrobacterium tumefaciens* and *Bacillus subtilis* [31]. The *Psychrobacter* sp belongs to a gram negative γ-*Proteobacteria,* extracted from marine sponge *Stelletta* sp showed antibacterial, anitinflammatory and cytotoxic effects [32]. A compound bromoalterochromide A was isolated from *Pseudoalteromonas maricaloris* KMM 636T associated with a sponge *Fascaplysinopsis reticulata* [33]. A strain of *Pseudomonas putida* isolated from sponge *Mycale microsigmatosa* yielded an anti-microbial substance which showed its activity toward MDR [34].

A strain of *Ruegeria* associated with the sponge *Suberites domuncula* exhibited its anti-bacterial property toward *B. subtilis* [35]. Similarly, metabolites extracted from α-*Proteobacteria* strains associated with sponge *Suberites domuncula* were found to show anti-microbial, cytotoxic and anti-angiogenic activities and also inhibited the growth of different strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* [36]. Recently, different species of bacteria have been isolated from sponge *Phorbas tenacior* belonging to *Proteobacteria* and some *Actinobacteria* showing their antiplasmodial, antimicrobial and antioxidant activities [37]. A strain of *β-Proteobacteria, Alcaligenes faecalis* exhibiting antimicrobial property was isolated from sponge *Stelletta tenuis*[38]. In a recent study, three Arthrobacter strains associated with the Antarctic sponge showed antibacterial activity [39]. Recently, we have isolated 54 bacterial strains from sponge *Pione vastifica* (unpublished). These strains belong to different genera especially *Vibrio, Halomonas, Alteromonas, Pseudoalteromonas,* and *Spongiobacter* and most of them are new species. These all active bacteria inhibit fungi, bacteria and produce hydrolytic enzymes (Fig. **1**).

3.3. Firmicutes and Other Groups

Firmicutes, especially strains of *Bacillus,* isolated from different sponges were found to produce active secondary metabolites. A strain of *Bacillus cereus* extracted from *Halichondria japonica* produced two antibiotics [40]. Two more thiopeptides comprising pyridine and thiazole moieties were obtained from the *B. cereus* culture which was extracted from sponge *Halichondria japonica.* These thiopeptides showed anti-bacterial properties toward *Staphylococcus* and *Enterococcus* and were also active toward bacterial strains which were resistant to multiple-drugs. One of the bacterial strains *B. subtilis* A184 extracted from sponge *Aplysina aerophoba* produces different anti-microbial lipopeptides which include iturins, fengycins and surfactins. This bacterial strain showed its activity toward *S. aureus, E. coli, C. albicans S. epidermidis, Bacillus megaterium, Proteus vulgaris* [41]. An antimicrobial compound Apteniol A, isolated from a sponge associated *Bacillus* sp. exhibited potent activity against several clinically pathogenic bacteria [42].

An unknown bacterium associated with sponge *Dysidea avara* produces metabolite 2-methylthio-1,4-naphthoquinone with anti-microbial and anti-angiogenic activities [36]. Potent bacteria were extracted from the sponge *Haliclona simulans* related with genera *Halomonas, Psychrobacter Bacillus, Cytophaga, Rhodococcus, Pseudoalteromonas, Pseudomonas, Sulfitobacter, Pseudovibrio,* and *Salegentibacter.* These strains were found to be biologically active and 50% among these strains showed anti-microbial properties [32]. Strong antioxidants acyl glycol carotenoic acids including the diapolycopenedioic acid xylosyl esters A, B and C were extracted from the *Rubritalea squalenifasciens,* isolated from the sponge *Halichondria okadai* [43]. Recently, diverse group of antimicrobial bacteria have been isolated from marine sponge *Erylus deficiens* [44].

4. DIVERSITY OF ENZYME PRODUCING BACTERIA ASSCOIATED WITH SPONGES

Sponges are in direct contact with pollutants and other debris in seawater. It is obvious that some hydrolases producing microbes

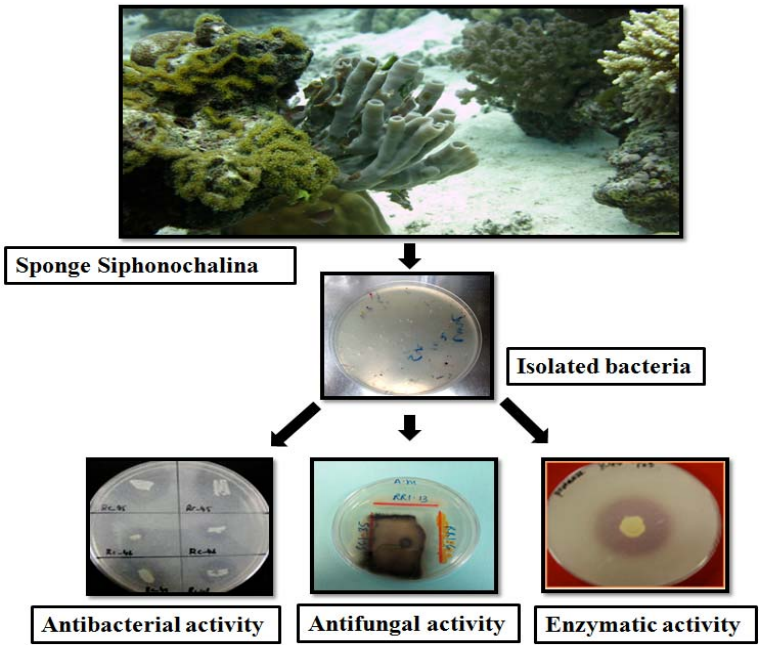

Fig. (1). Biotechnological potential of sponge-associated bacteria (adapted from our own study).

especially bacteria are present in sponges which help to breakdown these organic materials into nutrients. Bacterial species isolated from sponge *Halichondria panacea* mainly belong to genus *Cytophaga* were able to produce agarase enzyme [45]. A species of *Arthrobacter* associated with sponge *Spirastrella* sp. was able to produce an acetylcholinesterase [46]. Furthermore, several bacteria isolated from six different marine sponges were able to produce different enzymes such as protease, amylase and carboxymethylcellulase [47]. Bacteria associated with marine sponge *Aplysina aerophoba* were able to produce dehalogenase enzyme which degrades brominated phenolic compounds [48]. Similarly, bacteria from genus *Micrococcus* associated with *Spirastrella* sponge produced urethanase that can be used in beverage industry to remove cancer causing chemical from alcoholic beverages [49]. Chitinases play an important role in degradation of chitin and have different industrial and medical applications. *Streptomyces* sp. isolated from sponge *Craniella australiensis* produced chitinase showing antifungal activity [50]. Some previous studies also demonstrated the production of some industrially important enzymes from two marine sponges *Fasciospongia cavernosa* and *Dendrilla nigra* associated bacteria [51-53]. Recently, defence enzyme, Phospholipase A2 (PLA2) has been reported in sponge associated bacteria which helps host in protecting against different pathogens [54, 55]. There is report about production of PLA2 by both associated bacterium *Streptomyces dendra* and host sponge *Dendrilla nigra*.

Apart from chitinase, protease, amylase and other enzymes, cellulase is another important hydrolytic enzyme produced by sponge associated bacteria. Cellulase producing marine bacteria *Marinobacter* sp. has been isolated from sponge *Dendrilla nigra* [56]. Several classes of enzymes have been identified from sponge associated bacteria including: lipase [57], protease [58], amylase [59] and cellulase [60].

Esterase is an important industrial enzyme used in food, chemical and textile industry. A metagenomic library constructed from bacteria associated with sponge *Hyrtios erecta*, identified new esterases of industrial value [61]. Some enzymes produced by sponge-associated bacteria play an important role in neurodegenerative diseases like Alzheimer and Parkinson's disease. A strain of *Bacillus subtilis* isolated from marine sponge *Fasciospongia cavernosa* produced inhibitor of acetylcholinesterase (AChE) [62]. Microbes isolated from sponges also produce enzyme urease for the hydrolysis of urea in their environment into ammonia that in turn is utilized by sponge in protein synthesis. These results highlighted different roles of bacteria associated with marine sponge in their environment [63].

5. CONCLUDING REMARKS

Antimicrobial compounds isolated from different marine sponges associated bacteria exhibited different effects on their targets. This review brings out the information that sponge-associated bacteria are the richest source of bioactive compounds of clinical significance. Sponge-microbial associations are found to be very specific for the production of particular bioactive compounds. The phylum *Actinobacteria* encompasses microorganisms documented as possible candidates of pharmacologically relevant active secondary metabolites of sponges. Isolation of potent sponge-associated bacteria producing clinically beneficial compounds has opened up a new dimension in marine pharmacology. Various cultivation methods and approaches can be developed after understanding their optimum ecological conditions which compel the unbreakable production of bioactive compounds from sponge-associated bacteria as well as from clone libraries. The enzymes production by these bacteria may also be beneficial in medical and many industrial processes. It will help in developing new marine drugs from new genes, enzymes and bioactive compounds from sponge-associated microbes and their clone libraries.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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