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Bioprospecting of sponge and its symbionts: New tool for mosquitocidal & insecticidal metabolites

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ABSTRACT

Vector borne disease is a global threat and chemical, biopesticides have been employed for their control. Application of pyrethroid in Long Lasting Insecticide treated Nets (LLIN) for the prevention of mosquito bite and alarming resistance of this compound lead to global issue. Wide usage of chemical pesticides and its resistance in mosquito urged the research community to find better alternatives for mosquito control. Sponges (phylum Porifera) are primitive aquatic metazoans since 600 million years and comprised of 8600 species till date and existing in various habitats. Sponges symbiotic microbes are involved in nutrition, nitrogen fixation, nitrification, defense, skeleton stabilization of the invertebrate host. Many insecticidal molecules such as manzamine, Jaspamide, alkaloids and terpenoids have been identified from marine sponges and Mosquitocidal activity from several sponge extracts from *Dendrila nigra*, *Haliclona cribricutis* etc. were reported. In this connection, sponges and sponge associated microbes were really unexplored much for vector control. Ideally, novel leads from sponges and sponge associated microbes could be a prospective source for new vector control tool.

1. Introduction

The marine realm has been proved as a tremendous source of numerous beneficial metabolites and originated from the associated marine plants, Invertebrates and their microbial communities (Fenical and Jensen, 2006). Marine halophytes, such as mangroves and related species, are known to have many and various metabolites possessing antibacterial and antifungal (Behbahani et al., 2018) antiviral (Zhandi et al., 2008) antidiarrhoeal (Rouf et al., 2007), hepatoprotective (Gnanadesigan et al., 2017; Ravikumar et al., 2011), antifeedant (Wu et al., 2008), insecticidal (Calderon et al., 2008) cytotoxicity (Han et al., 2007) and antiplasmodial (Kim et al., 1997; Okai et al., 1997; Ravikumar et al., 2010) properties. Furthermore, 15,000 natural products for diverse application have been isolated from marine invertebrates and specifically 30% of its derived from marine sponges (Koopmans et al., 2009).

Sponges (phylum Porifera) are one among the oldest metazoan animals of aquatic environment since Precambrian period (Hentschel et al., 2002). Sponges are living in diversified habitats like polar, deep oceans, freshwater lakes and streams. Eighty-five percent of the 6000 formally described living species belong to the class Demospongiae (demosponges) and other species represented by the classes Hexactinellida (glass sponges), Calcarea (calcareous sponges) (Fieseler et al., 2004). COI (Cytochrome oxidase subunit I) sequence based Phylogeny of four different class of sponge represented (Fig. 1). Members of the class Demospongiae are the abundant producer of important bioactive compounds in association with microbes. Only one family from the class Calcarea has been identified as a source of pharmacologically significant bioactive compounds. None of the bioactive compounds has been reported from the class Hexactinellida (Thomas et al., 2010). 231 bioactive compounds have been obtained during the year 2017 from marine sponges and 277 compounds were reported from the year 2001–2010 and diversified metabolites such as Terpenoids, Alkaloids and Peptides reported from promising source such as marine sponge (Blunt et al., 2018).

Sponges occur in various shapes like encrusting, rope, ball, tube, barrel, vase and represented in different colours namely white, yellow, green etc. and variable in size (a few millimetres to nearly 2 m) are reported (Hentschel et al., 2006). Morphological identification of sponges was hard due to lack of consistent morphological parameters. Sponge associated microbes compose of up to 50% of sponge tissue volume. The bacterial load in sponges seems proportionally correlated with the irrigation status of the sponge. Sponges with a poor water circulating system contain high bacterial numbers while the well-

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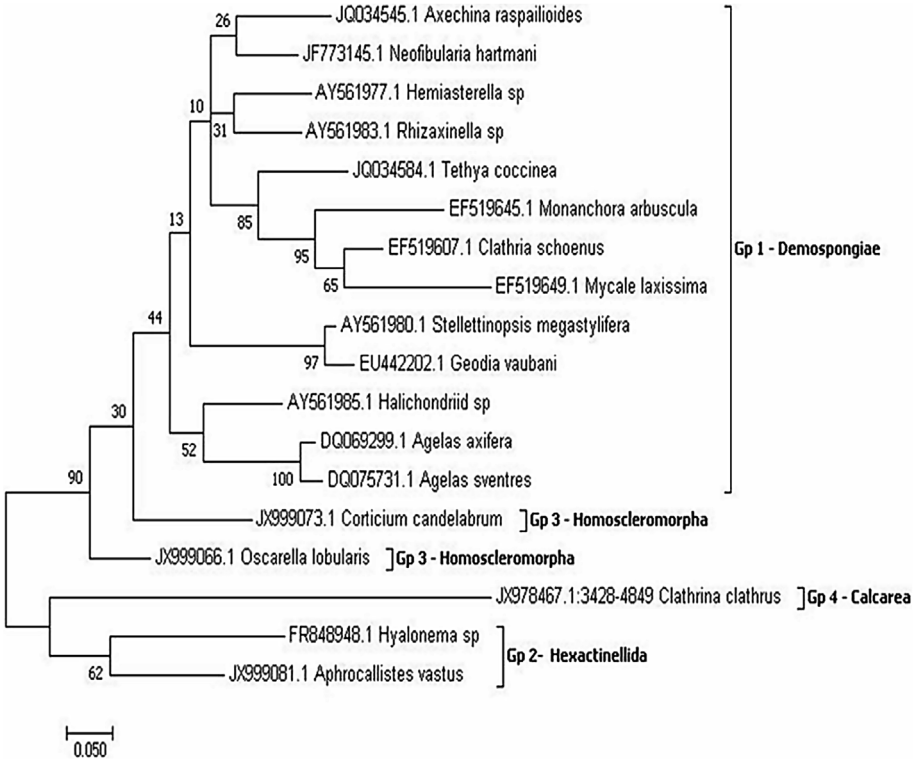

Fig. 1. COI gene based phylogenetic tree using maximum likelihood method showing sponge specific class.

irrigated sponges have fewer bacteria within their tissues (Wang, 2006). Mesophyll of 'High-Microbial-Abundance (HMA) sponges) consist of high load of bacterial community in contrary to the 'low-microbial-abundance (LMA) sponges with less microbial community (Hentschel et al., 2006). The presence of large numbers of bacteria within marine sponges was first established by microscopic studies. Early studies determined the association of bacteria with sponges based on bacterial morphology and recognized three types of associations of bacteria with sponges ie. Bacteria nonspecific to sponges, Intracellular bacteria and mesophyll living bacteria (Taylor et al., 2007). Coloration of the sponge host is due to cyanobacterial association (Hentschel et al., 2006). Fungal association with marine sponges is vital for an important role in nutrient regeneration cycles as decomposing of dead and decaying organic matter (Wang, 2006). Mesophyll of 'High-Microbial-Abundance (HMA) sponges) consist of high load of bacterial community in contrary to the 'low-microbial-abundance (LMA) sponges with less microbial community (Hentschel et al., 2006). The presence of large numbers of bacteria within marine sponges was first established by microscopic studies. Early studies determined the association of bacteria with sponges based on bacterial morphology and recognized three types of associations of bacteria with sponges ie. Bacteria nonspecific to sponges, Intracellular bacteria and mesophyll living bacteria (Taylor et al., 2007). Coloration of the sponge host is due to cyanobacterial association (Hentschel et al., 2006). Fungal association with marine sponges is vital for an important role in nutrient regeneration cycles as decomposing of dead and decaying organic matter (Wang, 2006).

2. Ecosystem services of sponges

Sponges play an important role in coral reef conservation, regeneration of damaged corals by providing temporary stabilization, nutrient recycling and primary production by microbial symbionts. Nitrification, calcification, alteration of water column and adaptation in benthic environment were influenced by sponges for coral reef management (Colman, 2015). Sponges contributed for formation of reef sediment by coral reef destruction. Bioerosion and accretion of coral reefs found to be equal for maintaining a balance in marine ecosystem. Genes involved in ammonia oxidation and denitrification (*amo*A, *nir*S, *nir*K, and *nxr*A) were characterized in seven different sponges and proved that nitrogen recycling is due to microbial association. (Han et al., 2013). Sponges feed on ultra plankton and contribute for carbon flow from lower level to higher trophic levels. Sponges contributed for digestion of diatom frustules to obtain silica and involved in global silicon cycling. The silicon deposition is a fundamental process in the production of the sponge skeleton in which siliceous spicules used for three dimensional structures connected by spongin and as a vital part of reef sediment (Bell, 2008).

3. Microbial association of sponges

As a living fossil, sponges may contain genetic fingerprints for the origin of their microbes and could be good hosts for study of microbial evolution and biogeography. Sponge metabolism produces ammonia and host phagocytosis resulted in carbohydrates and amino acids synthesis. So, microbial communities utilize this resource of nutrients and colonize in their respective habitat sponges. Microbial association in sponges involved in nutrition, nitrogen fixation, nitrification, defense, skeleton stabilization of the invertebrate host (Hentschel et al., 2002). Fluorescence In Situ Hybridization (FISH) revealed metabolically active microbes living in sponge. Coevolution of microbes in sponge habitat is revealed by mitochondrial cytochrome oxidase gene and other studies etc. Selective absorption of specific symbionts from marine environment or vertical transmission from parent sponge to larvae was documented. The necessity of microbial symbiont transmission in both female and male sponges has been documented (Webster and Taylor, 2012). Association of microbial communities in sponges were detected initially by electron microscopy and molecular techniques like 16SrRNA gene library, Denaturing Gradient Gel Electrophoresis (DGGE), FISH and metagenomics. Recent report of Pyrosequencing revealed that *Chloroflexei*, *Acidobacteria*, *Actinobacteria* and *Proteobacteria* as major communities associated with Great Barrier Reef sponges which coincide with the earlier conventional 16srRNA libraries

Table 1
List of Sponges with the associated Microorganisms.

Sponge- Phylum	Sponge - Class	Sponge - Order	Sponge associated Bacterial Phylum
Porifera	• Demospongiae	• Verongida • Dendroceratida • Dictyoceratida • Haplosclerida • Agelasida • Poecilosclerida • Chondrosiida • Chondrillida • Axinellida • Bubarida • Biemnida • Tetractinellida • Polymastiida • Merilida • Desmacilida • Clionaida • Tethyida • Trachycladida • Suberitida • Scopalinida • Polymastida •Desmacilida	• Cyanobacteria • Actinobacteria • Acidobacteria • Chloroflexi • Nitrospirae • Deferribacteres • Proteobacteria • Bacteriodetes • Firmicutes • Poribacteria • Tectomicrobia • Verrumicrobia • Planctomycetes • Lentisphaerae • Chlamydiae • Gemmatimonadetes • Thermus deinococcus • Spirochaetes • Fusobacteria • Archae
	• Hexactinellida	• Amphidiscosida • Lychniscosida • Lyssacinosida • Aulocalycoida • Hexactinosida	
	• Calcarea	• Murrayonida • Clathrinida • Leucosolenida • Lithonida • Baerida	
	• Homoscleromorpha	•Homosclerophorida	

reported by Taylor et al. (2007). Recent discovery of novel phylum'*Poribacteria*'was reported in verongid sponges (Fieseler et al., 2004) and later their specificity was disapproved in the recent study by Ian et al. (2014). Table 1 displayed the different class of sponges and its associated bacterial phylum. Analysis of 12 million 16SrRNA gene pyrotags concluded that the presence of sponge specific clusters like *Acidobacteria*, *Actinobacteria*, *Chloroflexei*, *Cyanbobacteria*, *Gemmatimonadetes*, *Alphaproteobacteria*, *gammaproteobacteria have been* associated with sponge host. Previously reported sponge specific clusters found in association with other than sponge host in the marine environment. Initiation of next-generation sequencing technologies will also evidence the same in near future (Taylor et al., 2013). Sponge associated bacterial phylum specific phylogenetic tree based on Cytochrome oxidase subunit I was shown (Fig. 2). Environmental stress like rise in temperature, heavy metals induce shift in normal microbial community associated with sponge host. Loss of symbiotic microbes and abundant growth of motile, nutrient scavenging bacteria noticed due to elevated temperature in the sponge *Rhopaloeides odorabile* (Fan et al., 2013). Functional mechanism due to symbiosis may be disturbed and is mandatory to understand the consequences of microbial shift in response to environmental stress. Role of marine sponges in marine eco system and being repository of different classes of pharmacologically important compounds has to be protected for future research.

4. Sponge as a source of novel metabolite leads

Nearly 65.71% Sponge associated fungus were found to produce bioactive compounds whereas only 34.28% of marine sponge-bacteria are bioactive. Among this bacterial population, *Actinobaceria* was major bioactive contributor followed by *Proteobacteria*, *Firmicutes* and *Cyanobacteria* in novel bioactive compounds synthesis. (Thomas et al., 2010). There was enormous reports strongly supporting the co-existence of diversified microbial community with marine sponges and discovery of novel compounds used as anti-inflammatory, anti-tumor, anti HIV active compounds etc. (Devi et al., 2010; Selvin et al., 2012). Previous research reports revealed that, the microbial population in sponges was responsible for bioactive compounds and microbe cultivation enhances the production of novel compounds. So, marine sponge symbionts could be exploited for novel compounds with mosquitocidal activity. Sponge and sponge associated bacteria have been explored for antimicrobial activity, anticancer activity etc … (Thiel et al., 2007; Radjasa et al., 2007; Gandhimathi et al., 2009; Selvin et al., 2009; Baker et al., 2009; Schneemann et al., 2010; Engelhardt et al., 2010; Devi et al., 2010; Inbaneson and Ravikumar, 2011; Zhou et al.., 2011; Ravikumar et al., 2011; Ravikumar and Jacob inbaneson, 2012; Kiran et al., 2014; Abdelmohesen et al., 2014; Prasanna kumar and Ravikumar, 2014; Inbaneson and Ravikumar, 2012a,b, c, d).

Symbiotic microorganisms associated with marine sponges were responsible for lot of bioactive compound synthesis. (Proksch et al., 2002; Zhang et al., 2005). *Dysideaherbacea,* a sponge was well studied for its antibiotic production and so the antibiotic was actually synthesized by the symbionts like *Cyanobacterium*, *Oscillatoria spongeliae.* Sponge associated microbes are immense source of novel compounds and have antimicrobial activity against fungi, bacteria, virus and parasite. α-*Proteobacteria*, *Pseudoalteromonas* and *Actinobacteria* are best example for such microbes. Diversified metabolites like protein phosphatase inhibitor okadaic acid, macrolactam antibiotics, antitumor compounds, antioxidants, antifungal compounds were produced by the genus *Halichondria* in association with sponges (Thomas et al., 2010). Presence of PKS (polyketide synthase) and NRPS (nonribosomal peptide synthetase) genes in *Actinobacteria*, *Bacillus*, *Sulfitobacter* and *Pseudovibrio* revealed the potential for secondary metabolite production. Synthesis of pharmacologically important compounds by marine sponges associated bacteria has been proven for its novelty.

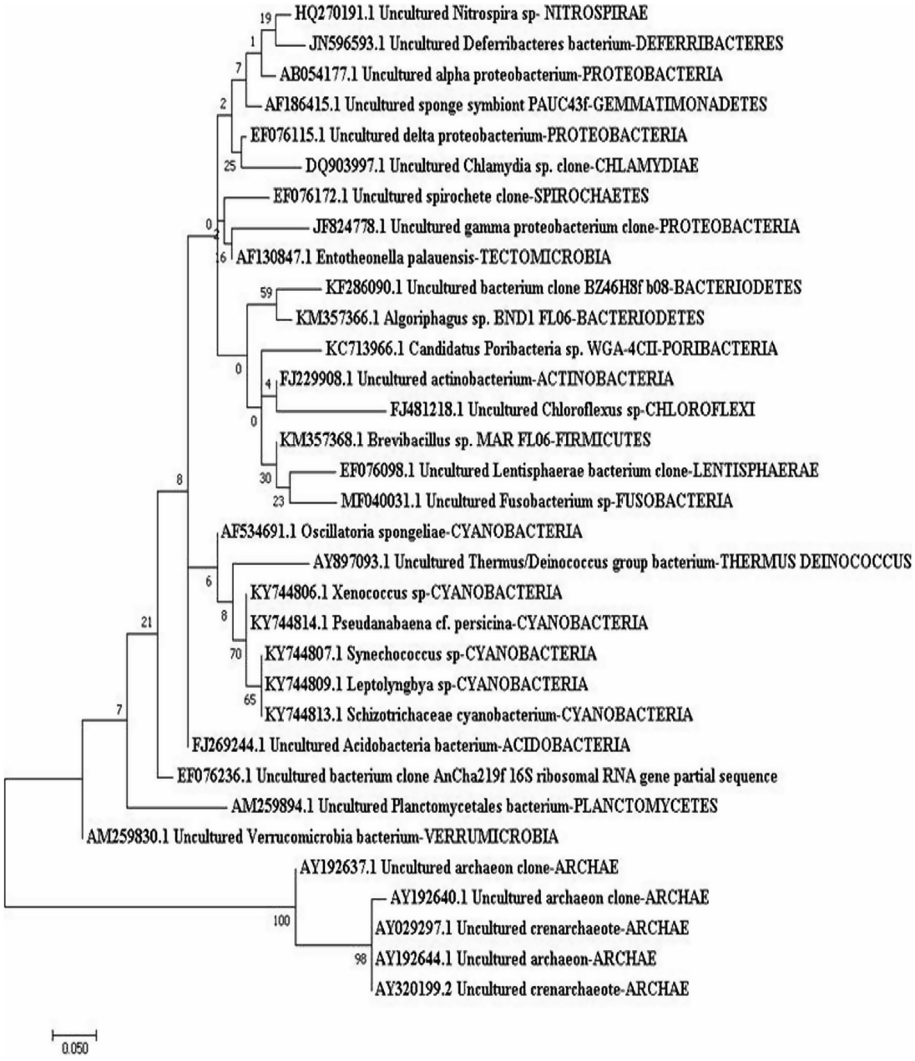

Fig. 2. COI gene based phylogenetic tree using maximum likelihood method showing sponge associated bacterial phylum.

4.1. Microbial transmission in sponges

Vertical transmission of microbes in sponges used to sustain the association for evolutionary longer period and was reported in many sponges like *Ircinia felix*, *Corticum* sp, *Svenzea zeai* (Hentschel et al., 2012). Four Kasumigamide gene clusters were detected in very different bacterial species, like '*Entotheonella*' *sp.* (a marine sponge symbiont), the free-living cyanobacterium *M. aruginosa*, the human oral bacterium *D. acidovorans* and a bacterium from tree endosphere *Herbaspirillum* sp. Phylogenetic tree analysis of keto synthease domains exposed close relationships among the *kas*-related gene clusters and proved the horizontal gene transfer between bacterial strains. Occurrence of putative kasumigamide biosynthetic gene clusters among different kinds of bacteria living in different ecological niches displayed horizontal gene transfer between different bacterial species.

Long terminal repeats flanking the *kas* gene was annotated as putative transposases was involved in the role of interspecies transfer of *kas* gene clusters. Sponge-associated bacteria reportedly contain high numbers of transposable insertion elements, expected to take part in the evolution of symbiont bacteria genomes (Nakashima et al., 2016).

4.2. Prospective source of novel leads by co cultivation & growth conditions

Sponge symbiont will be able to synthesize versatile bioactive compounds by changing the growth conditions and it was reported in marine fungus *Spicaria elegans* to synthesize novel spicochalasin A (Lin et al., 2009). Similarly, O-Glycosylated angucyclines, actinosporins were produced by *Actinokineospora* sp (Abdelmohsen et al., 2014) Sponge derived actinomycetes *Actinokineospora* and *Nocordiopsis* were grown as consortium and yielded bioactive compounds which was not reported while using a single organism (Brinkmann et al., 2017). Co-cultivation of sponge symbiont strains and optimizing its growth conditions will be applied as tool for drug discovery in future.

4.3. Approach for detection of Sponge bioactive compounds

Identification process is mandatory for obtaining novel lead compound for mosquito control. Dereplication process is used to screen the compound with the already reported compounds using morphological, molecular characterization and techniques like HPLC-MS, NMR spectrum (Rocha-Martin et al., 2014). Bioactivity guided screening has been used for direct detection of the antimicrobial, mosquitocidal activity using the culture supernatant or extract of cell pellet (Devi et al., 2010; Karthik et al., 2011; Saurav et al., 2013). Demerits like moderate quantity of bioactive compound and more time is needed in bioactivity based screening. Metabolomics used to identify and quantify all low molecular weight metabolites in an organism. The simultaneous detection of a wide range of secondary metabolites, known to be species specific, provides an immediate image of sponge metabolome profile and prioritization for bioactive compounds. The principal components

analysis was useful in analyzing the mass data in comparison with MarinLit (MarinLit database. http://pubs.rsc.org/marinlit/) and Scifinder (Scifinder Database. https://scifinder.cas.org/scifinder), found a good match with several 3-alkyl pyridine alkaloids, some of which are known to possess cytotoxic activity (Einarsdottir et al., 2017). LC-MS together with XCMS online data processing helped to identify several bioactive compounds. In addition, NMR data was also used to detect Furanosesterterpene and spongiolactam in *Spongia officinalis* (Bauvais et al., 2017). Gene-guided screening is a valuable tool to detect gene involved in the biosynthesis of the particular compound. For example, 24 out of 61 strains possess staD gene, which is essential for the synthesis of Staurosporine in *Streptomyces* sp and 15 strains were shown positive for KS domain involved in the synthesis of Salinosporamide (Freel et al., 2011). Biosurfactant encoding genes (*sfp*, *sfpO*, *srfA*) were used to screen sponge associated microbe such as *Bacillus licheniformis* to be used for bioremediation (Lawrance et al., 2014). Sponge associated *Streptomyces* sp were screened for NRPS and PKS genes and most of the isolates possess antifungal and antibacterial activity using microwell culture. Thiopeptide antibacterial antibiotic was reported from *Nocardiopsis* sp (Engelhardt et al., 2010; Zhou et al., 2011). The combined strategy of gene and bioactivity based screens creates a more powerful tool which allows us to obtain valuable strains with the potential to synthesize new bioactive compounds.

Metagenome mining is used for the discovery of polyketides and nonribosomal peptides from uncultured bacteria. Metagenomic analysis of the Japanese marine sponge *Discodermia calyx* has resulted in the identification of a hybrid type I polyketide synthase-nonribosomal peptide synthetase gene (*kas*) and bioinformatic analysis of the gene proved the biosynthesis of Kasumigamide by an symbiont bacteria *Entotheonella* (Nakashima et al., 2016). Comparative gene cluster analysis and structural prediction of NRPS/PKS products have been carried out by antiSMASH that helped for graphical display of query gene with the homolog in NCBI database and identification of gene cluster that encode for specific chemical moieties (Boddy, 2014). AntiSMASH analysis of a bacterium *Actinokineospora* sp associated from marine sponge revealed 996 genes in 36 gene clusters for secondary metabolites synthesis (Harjes et al., 2014) Genes for PKS, NRPS and hybrid NRPS-PKSII, lantipeptide, siderophore, ectoin, bacteriocin have been identified (Blin et al., 2013) Diverse natural products like actinorhodin, tetronomycin were identified by another bioinformatics tool called NaPDoS from the same bacterium (Harjes et al., 2014). Genome mining approach was used to analyze diverse biosynthetic pathways and metabolites (Ziemert et al., 2016). Genes encoding bacteriocin, lantipepetide, Terpene were identified in three isolates of *Streptomyces* sp associated with Norwagian marine sponges (Ian et al., 2014). Automated identification of Onnamide, Konbamides, Polytheonomaides encoding gene cluster was identified in sponge associated bacterium *Entotheonella* sp (Wilson et al., 2014).

5. Insecticidal activity of sponges

First report of the occurrence of bioactive manzamine N-oxides in marine sponge *Xestospongia ashmorica* reported for insecticidal activity toward neonate larvae of the polyphagous pest insect *Spodoptera littoralis* during larval feeding bioassay (Edrada et al., 1996). Manzamine alkaloids were also reported from sponges like Amphimedon sp and *Acanthostrongylophora* sp from different geographical locations like Philipines, South Africa and Italy. Asian countries such as Japan, Indonesia and Korea contributed more biochemical compounds from marine sponges (Mehbub et al., 2014). Jaspamide from Jaspis sponge exhibited insecticidal activity (Zabriskie et al., 1986). Ulosantoin from *Ulosa ruetzleri* has shown insecticidal activity against tobacco hornworm and cockroaches (VanWagenen et al., 1993). Bioactive sesquiterpenoid quinine like compound from the Mediterranean Sea marine sponge *Dysidea avara* exhibited insecticidal activity (Hamed et al., 2013). Crude metabolite from Jamaican sponge *Amphimedon compressa* exhibited moderate insecticidal activity towards sweet potato weevil (Thompson et al., 2010). Swinhoeiamide A from *Theonella swinhoei* exhibited insecticidal activity toward neonate larvae of the polyphagous pest insect *Spodoptera littoralis* larval feeding and was found to be fungicidal against *Candida albicans* and *Aspergillus fumigates* (Edrada et al., 2002). The Micronesian sponge *Oceanapia* sp. afforded three pyridoacridine alkaloids named kuanoniamine C, kuanoniamine D exhibited insecticidal activity toward neonate larvae of the polyphagous pest insect *Spodoptera littoralis* (LC_{50} of 156 and 59 ppm, respectively), when incorporated into artificial diet (Eder et al., 1998). Agelastatin A isolated from the Indian Ocean sponge *Cymbastela* sp. exhibited insecticidal activity against larvae of beet army worm, *Spodoptera exigua,* and corn rootworm, *Diabrotica undecimpunctata* (Hong et al., 1998). Two novel insecticidal metabolites, calyculin E and F which had insecticial activity against the German cockroach and mosquito larvae, were isolated from a Japanese marine sponge, *Discodermia* sp (Okada et al., 1991). Merosesquiterpenoids from Spongia sp and Sesquiterpenoids and their formamides were reported from Axinessa, Dysidea and *Halichondria* sp. Canadian *Phorbas* sponge, yielded eight new sesterpenoids with difference in the carbon skeleton (Blunt et al., 2018). Eribusinone, novel metabolite from Antartic sea sponge *Isodictya erinacea* found to inhibit moulting of arthropod and resulted in high mortality (Vankayala et al., 2017). Novel manzamine alkaloids were derived from sponges such as *Amphimedon*, *Lissodendoryx*. Mersosesquiterpenoids were reported from the genus *Hyrtois* and *Smenospongia* (Carroll et al., 2019). Sesquiterpenoids such as Axiriabilines A-D from *Axinessa variabilis* and Lamellodesidines from *Lamellodysidea herbacea* were reported recently (Carroll et al., 2019). Metabolites like Terpenoids or Alkaloids have shown insecticidal activity (Takahashi et al., 1989; Arasu et al., 2013). So, it is recommended to explore these compounds for insecticidal activity.

5.1. Mosquitocidal activity of sponge extracts

Marine novel compounds have been extracted from potent sponges such as *Psammaplysilla purpurea* and *Haliclona cribricutis with* LC_{50} at < 50 ppm against *A. aegypti* larvae whereas other sponges like *Dendrilla nigra*, *Petrosia testudinaria*, *Petrosia similes*, *Haliclona pigmentifera*, *Ircinia fusca*, *Sigmadocia fibulata* showed LC_{50} values at < 100 ppm. Notable activity was observed in both larvicidal and insecticidal assays with the sponge extracts of *P. purpurea, H. cribricutis, D. nigra, H. Pigmentifera*, *P. Testudinaria and* could be used as novel insecticidal molecules (Sesquiterpenes, Diterpenes) (Reegan et al., 2015). Sponges isolated from Indian coast such as *Dendrilla nigra, Clathria gorgonoides, Axiella donnanihas* had larvicidal potential against second instar larvae of *Culex* sp (Selvin and Lipton, 2004). Methanol Extracts of *Acanthella elongata* exhibited larvicidal activity. The sponge extracts of *Clathria longitoxa* and *Callyspongia diffusa* were reported to be highly active against *C. quinquefasciatus* larvae with the LC_{50} values at < 50 ppm. But, extracts from other sponges like *Dendrilla nigra* (Den.), *Petrosia similes*, *Haliclona pigmentifera*, *Ircinia fusa*, *Sigmadocia fibulata* revealed LC_{50} values only at < 100 ppm (Reegan et al., 2015). Methanol extract of the sponge *Cliona. celata* showed highest larvicidal activity at 500 ppm against *A agypti* and *C quinquefasciatus.* The LC_{50} and LC_{90} values of *C. celata* methanol extract were recorded for 95.63 and 242.16 ppm against *C. quinquefasciatus* larvae and 158.40 and 780.16 ppm against *A. aegypti* larvae, respectively. Ovicidal activity was performed using methanol extract of *C. celata* and it *showed* 100% ovicidal activity against *C quinquefasciatus* and 72% activity were noted in *A aegypti* at 500 ppm. Sponges when extracted with hexane were found to be effective protectant against the adult mosquitoes of both species. On average, the protection time recorded in hexane extract was up to 273 and 165 min at 5mg/cm2 dosage against *C. quinquefasciatus* and *A. aegypti*, respectively. Based on the observations in the study, *C. celata* could be a promising agent for novel lead for pesticidal activity (Reegan et al., 2013). Extracts of *N magnifica* and *C siphonella* were

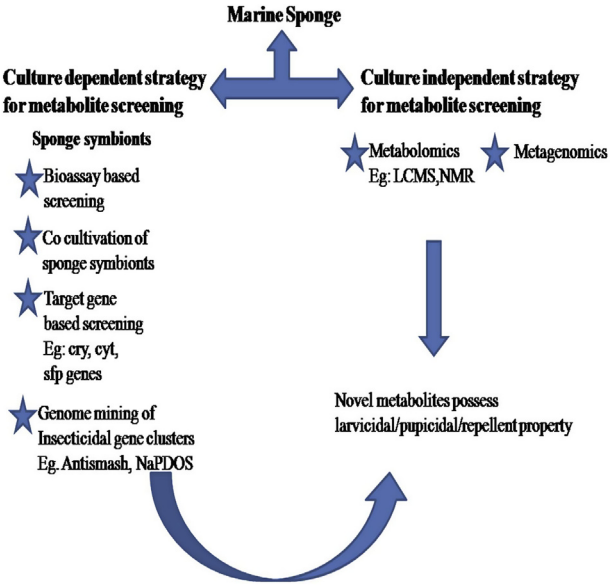

Fig. 3. Screening of Sponge & Sponge associated microbes for mosquitocidal metabolites.

shown activity against vitellogenin synthesis, ovarian development of *Culex pipiens*. Concentration dependent activity was observed at pupal mortality, adult emergence and fecundity of *C pipiens* (Hasaballah et al., 2017).

5.2. Sponge symbionts as potential source for vector control

Sponges have been well studied for their mosquitocidal compounds by the recent findings of Indian researchers (Rao et al., 2008; Sonia and Lipton, 2012; Reegan et al., 2013). There is no other spotlight on sponge associated microbes for mosquitocidal lead compounds (Mathivanan et al., 2014) Most of the reports from marine sponges revealed the activity of sponge extracts (Hasaballah et al., 2017; Reegan et al., 2013). It is mandatory to study the origin of the compound synthesis and possible role of microbial association needs to be investigated thoroughly. In this review, Screening of novel leads from sponge and sponge associated microbes for mosquitocidal activity is proposed (Fig. 3). Because most of marine natural products from marine realm and abundantly patented antitumor compounds originated from marine sponges (Koopmans et al., 2009). NRPS and PKS mega synthase enzyme complex was well known for the synthesis of diverse secondary metabolites and a conserved portion of this gene cluster used to screen potential symbiont associated with marine sponges (Schirmer et al., 2005) Potential isolate can be grown in optimized conditions in fermentor for the secondary metabolite of our interest (Fuerst, 2014). *Bacillus licheniformis*, sponge associated microorganism proved to synthesize biosurfactant surfactin and heterologous production of the biosurfactant increased from 2 to 3 fold than the original strain and could be used for bioremediation (Lawrance et al., 2014). Isolate from mangrove soil *B subtilis* exhibited mosquito pupicidal activity due to biosurfactant (Geetha et al., 2011, 2012). So, marine sponge symbionts could be explored for mosquito pupicidal or larvicidal activity to get novel lead molecule. PKS or NRPS module is involved in synthesizing of modular polyketide synthase (PKS) and nonribosomal peptide synthetases (NRPS) and able to predict the chemical structures of products derived from gene clusters of PKS/NRPS gene clusters. Microbial community associated with marine sponge were identified for the synthesis of Polyketides and NonRibosomal Peptides. Genome size of microbes more than 3 Mb has one or more PKS and NRP gene cluster (Boddy, 2014). Detection of PK or NRP biosynthetic gene cluster and investigation of a novel product encoding gene would be an ideal task (Bachmann et al., 2014). Metagenomic analysis enabled the discovery of novel gene clusters like polyketide synthases (PKS), non-ribosomal peptide synthases (NRPS), Isoprenoid synthases, and Terpenoid synthases.

Insecticidal antibiotic from *Streptomyces* sp from marine water and sediment showed activity towards *Helicovera armigera* and compound was similar to avermectin (Xiong et al., 2004). Novel polyketide metabolite isolated from marine *Streptomyces* sp revealed larvicidal and pupicidal activity against *Helicoverpa armigera* and *Spodoptera litura* (Arasu et al., 2013). Putative PirAB(vp) heterodimer from marine pathogen *Vibrio haemolyticus* have shown the similarity with the functional domains of the Cry protein in connection with its pore-forming activity. The gene organization of this toxin suggested that pirAB(vp) may be lost or acquired by horizontal gene transfer via transposition or homologous recombination (Lee et al., 2015). Broad spectrum of insecticidal activity was observed against larvae of *Culex quinquefasciatus*, *Anopheles subpictus, Haemophysalis bispinosa* and *Rhicipephalus microplus* from the synergistic action of multiple compounds (cyclopentanepropanoic acid, 3, 5-bis(acetyloxy)-2-[3-(methoxyimino)octyl etc.] of marine derived *Streptomyces* sp (Thenmozhi et al., 2013). Terpene named Altemicidin from marine *Streptomyces sioyaensis* SA-1758 displayed acaricidal activity (Takahashi et al., 1989). Surface layer protein from marine *Bacillus cereus* has shown mosquitocidal activity (Mani et al., 2018).

5.3. Current scenario of insecticide resistance

Pyrethroids replaced other pesticides like Organophosphorus, Carbamates, DDT and almost 23% of the chemical insecticides market. Pyrethroids are synthetic analogues of the chrysanthemic acid (pyrethrins I) and pyrethric acid (pyrethrins II) ester insecticides. Presently, malaria control is applying pyrtheroids for indoor residual spraying (IRS) (WHO report, 2006). IRS is an application of insecticide spray on the surface of walls and ceilings of house and lethal dose absorb by mosquito. Besides, pyrethroid is the only class approved by the World Health Organization Pesticide Scheme (WHOPES) for mosquito net impregnation (Insecticide Treated Net – ITN; Long Lasting Insecticide Treated Net - LLIN) (Silva et al., 2014). Pyrethroid is widely used for the Long Lasting Insectide treated Nets (LLIN) for the prevention of mosquito bite and alarming resistance of this compound lead to global issue (Churcher et al., 2016).

Initially plant extracts like Neem, Citronella, Cassia and Eucalyptus oil were used for mosquito control (Bunker and Hirschfelder, 1925). DEET and Picardin also considered as effective repellents (Leal, 2014) A natural product from lemon Eucalyptus, *Para*-menthane-3, 8 diol was approved by CDC. Short residual activity in plant based repellents during application is not ideal in comparison with volatile repellents like DEET, Picaridin (Traboulsi et al., 2005). Application of contact repellents such as DEET needs to be applied intermittently to avoid mosquito bite. Limited supply of repellents and perspiration will be highly challenging for the application of contact repellents in mosquito borne disease prone region. Spatial repellent are volatile and diffuse through air in treated area and induce aversive behavior or deleterious physiological response from the vector (Achee et al., 2012; Li et al., 2016).

In this connection, spatial repellent from synthetic pyrethroid origin or botanical origin induce different mechanism in mosquito and can be used for Integrated Vector Control Management (Norris and Coats, 2017). Plant based compounds has tremendous potential for the development of new repellents against pyrethroid-resistant mosquitoes. More numbers of odorant receptors have been identified in the binding of multiple botanical compounds eg. 50 odorant binding receptors isolated from *An. gambiae* (Carey et al., 2010). Furthermore, the efficacy and the safety in mammals have been well established (Isman et al., 2011). The presence of multiple odorant receptors was involved in mosquitoes and fruit flies revealed the slow resistance development

in comparsion with pyrethroid spatial repellents (De Bruyne et al., 2001; Maia and Moore, 2011).

The diverse mechanism of various terpenoid compounds involved in inhibition of acetylcholinesterase activity at octopamine and tyramine receptors, nicotinic acetylcholine receptor activity, and modulation of GABA-gated chloride receptors has been noticed in insects (Norris et al., 2015). It may be useful for getting new leads for repellents for the prevention of mosquito-borne disease transmission.

5.4. Limitations of existing biological control

Resistance to *B. sphaericus* has been reported in *C. pipiens* complex in Brazil and India and *C. pipiens pipiens* in France and China. *Bs* resistance has been observed during the last four years in Brazil (Silva-Filha et al., 1995), India (Rao et al., 1995) and France on *C. pipiens* (Charles and Nielsen-LeRoux, 2000). Only 2.78-fold increase in tolerance to B.t.i. was induced *in C. pipiens* as a result of 20 generations of selection. The tolerance of *C. pipiens* to B.t.i. decreased by about 58% after stopping the selection for three generations. Larval selection with B.t.i. caused a reduction in the reproductive potential of mosquito adult survivors but did not affect the adult longevity and the time of blood meal digestion ingested by female mosquitoes (Saleh et al., 2003).

5.5. Alternative strategy for vector control

Terpenoids are produced via the isoprene biosynthesis and phenylpropanoid pathways in plants. Sponges associated symbionts also involved in synthesis of terpenes and possess insecticidal activity (Ebada et al., 2010; Elissawy et al., 2015). Sesquiterpenoids were highly effective at repelling *Aedes aegypti* in a static air chamber (Paluch et al., 2009) and monoterpenoids that were capable of repelling a large variety of arthropod pest species (Misni et al., 2016). Monoterpenoids, possess more volatile and higher spatial repellency for the short period. Sesquiterpenoids, are larger molecules with slow volatization nature and providing a longer lasting repellent character (Norris and Coats, 2017). Ideally repellent with longer residual activity, safety and good efficacy would be preferable for future repellent synthesis. Use of chemical pesticides and increasing mosquito resistance should initiate the research community to find better alternatives for mosquito control.

6. Conclusions

Application of Insecticides and the available bio control tool such as *Bacillus thuringiensis* var *israelensis* or spinosad application, chemical and plant based repellents are currently used for vector control. Insecticide resistance and periodical application of larvicides and monitoring the breeding habitats are practical impediment in vector control measures. Adult mosquito control is considered a huge challenge and it involves the application of repellents, mosquito coils, Insecticide treated nets and Indoor residual spray. Issues associated with mosquito control are really in need of alternative and sustainable bio control tool for mosquito menace.

Alkaloids (20%), Terpenes (14.7%) and Peptides (8%) were produced from different marine sponges during last decade and the order Dictyoceratida was identified as highest producer of metabolites. 2400 new natural products were derived from 19 orders of marine sponges during the year 2001–2010 (Mehbub et al., 2014). Bacterial communities associated with marine sponges and diversity in sponges really would generate a new path for mosquito control. In this review, we recommend that sponges possess diverse community of microbes and potential mosquitocidal strain can be isolated with the available genomics, bioinformatics and metabolomics tools. In this connection, insecticidal activity containing terpenes or any novel metabolites from marine sponges or sponge associated symbionts will be explored for getting highly promising novel compounds for the control of vector borne diseases. Thus, novel metabolites could be tested for any form of mosquito stages like larval or pupal or adult mosquito and formulate the metabolite for further process. Uniqueness of this review lies in marine sponges and associated microbes have not been widely utilised for mosquitocidal actvitiy and it has tremendous potential in generating hub of novel metabolites for future vector control strategies.

Conflicts of interest

The authors declare that they have no conflict of interest.

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References

Abdelmohsen, U.R., Cheng, C., Viegelmann, C., Zhang, T., Grkovic, T., Ahmed, S., et al., 2014. Dereplication strategies for targeted isolation of new antitrypanosomal actinosporins A and B from a marine sponge associated-*Actinokineospora sp*. EG49. Mar. Drugs 12 (3), 1220–1244.

Achee, N.L., Bangs, M.J., Farlow, R., Killeen, G.F., Lindsay, S., Logan, J.G., Moore, S.J., Rowland, M., Sweeney, K., Torr, S.J., Zwiebel, L.J., Grieco, J.P., 2012. Spatial repellents: from discovery and development to evidence-based validation. Malar. J. 11, 164.

Arasu, M.V., Al-Dhabi, N.A., Saritha, V., Duraipandiyan, V., Muthukumar, C., Kim, S.J., 2013. Antifeedant, larvicidal and growth inhibitory bioactivities of novel polyketide metabolite isolated from *Streptomyces sp*. AP-123 against *Helicoverpa armigera* and *Spodoptera litura*. BMC Microbiol. 13 (1), 105.

Bachmann, B.O., Van Lanen, S.G., Baltz, R.H., 2014. Microbial genome mining for accelerated natural products discovery: is a renaissance in the making? J. Ind. Microbiol. Biotechnol. 41 (2), 175–184.

Baker, P.W., Kennedy, J., Dobson, A.D., Marchesi, J.R., 2009. Phylogenetic diversity and antimicrobial activities of fungi associated with *Haliclona simulans* isolated from Irish coastal waters. Mar. Biotechnol. 11 (4), 540–547.

Bauvais, C., Bonneau, N., Blond, A., Pérez, T., Bourguet-Kondracki, M.L., Zirah, S., 2017. Furanoterpene diversity and variability in the marine Sponge *Spongia officinalis*, from untargeted LC–MS/MS metabolomic profiling to furanolactam derivatives. Metabolites 7 (2), 27.

Behbahani, B.A., Yazdi, F.T., Shahidi, F., Noorbakhsh, H., Vasiee, A., Alghooneh, A., 2018. Phytochemical analysis and antibacterial activities extracts of mangrove leaf against the growth of some pathogenic bacteria. Microb. Pathog. 114, 225–232.

Bell, J.J., 2008. The functional roles of marine sponges. Estuar. Coast Shelf Sci. 79 (3), 341–353.

Blin, K., Medema, M.H., Kazempour, D., Fischbach, M.A., Breitling, R., Takano, E., Weber, T., 2013. antiSMASH 2.0—a versatile platform for genome mining of secondary metabolite producers. Nucleic Acids Res. 41, W204–W212.

Blunt, J.W., Carroll, A.R., Copp, B.R., Davis, R.A., Keyzers, R.A., Prinsep, M.R., 2018. Marine natural products. Nat. Prod. Rep. 35 (1), 8–53.

Boddy, C.N., 2014. Bioinformatics tools for genome mining of polyketide and non-ribosomal peptides. J. Ind. Microbiol. Biotechnol. 41 (2), 443–450.

Brinkmann, C.M., Marker, A., Kurtböke, D.İ., 2017. An overview on marine sponge-symbiotic bacteria as unexhausted sources for natural product discovery. Diversity 9 (4), 40.

Bunker, C., Hirschfelder, A., 1925. Mosquito repellents. Am. J. Trop. Med. Hyg. 5, 359–383.

Calderon, J.S., Cespedes, C.L., Rosas, R., Federico, G.G., Salazar, J.R., et al., 2008. Acetylcholinestrase and insect growth inhibitory activities of *Gutierrezia microcephala* on fall armyworm *Spodoptera frugiperda* JE Smith. Z. Naturforsch. 56 (5–6), 382–394.

Carey, A.F., Wang, G., Su, C.Y., Zwiebe, L.J., Carlson, J.R., 2010. Odorant reception in the malaria mosquito *Anopheles gambiae*. Nature 464 (7285), 66.

Carroll, A.R., Copp, B.R., Davis, R.A., Keyzers, R.A., Prinsep, M.R., 2019. Marine natural products. Nat. Prod. Rep. 36, 122–173.

Charles, J.F., Nielsen-LeRoux, C., 2000. Mosquitocidal bacterial toxins: diversity, mode of action and resistance phenomena. Memorias. Do. Instituto. Oswaldo. Cruz. 95, 201–206.

Churcher, T.S., Lissenden, N., Griffin, J.T., Worrall, E., Ranson, H., 2016. The impact of pyrethroid resistance on the efficacy and effectiveness of bednets for malaria control in Africa. Elife 22 (5), e16090.

Colman, A.S., 2015. Sponge symbionts and the marine P cycle. P.N.A.S. 112 (14), 4191–4192.

De Bruyne, M., Foster, K., Carlson, J.R., 2001. Odor coding in the *Drosophila* antenna. Neuron 30 (2), 537–552.

Devi, P., Wahidullah, S., Rodrigues, C., Souza, L.D., 2010. The sponge-associated bacterium *Bacillus licheniformis* SAB1: a source of antimicrobial compounds. Mar. Drugs 8

(4), 1203–1212.
Ebada, S.S., Lin, W., Proksch, P., 2010. Bioactive sesterterpenes and triterpenes from marine sponges: occurrence and pharmacological significance. Mar. Drugs 8 (2), 313–346.
Eder, C., Schupp, P., Proksch, P., Wray, V., Steube, K., Müller, C.E., et al., 1998. Bioactive pyridoacridine alkaloids from the Micronesian sponge *Oceanapia sp*. J. Nat. Prod. 61 (2), 301–305.
Edrada, R.A., Proksch, P., Wray, V., Christ, R., Witte, L., Van Soest, R.W.M., 1996. Bioactive isequinoline quinone from an undesrcribed Philippine marine sponge of the genus *Xestospongia*. J. Nat. Prod. 59, 973–976.
Edrada, R.A., Ebel, R., Supriyono, A., Wray, V., Schupp, P., Steube, K., et al., 2002. Swinhoeiamide A, a new highly active calyculin derivative from the marine Sponge *Theonella swinhoei*. J. Nat. Prod. 65 (8), 1168–1172.
Einarsdottir, E., Magnusdottir, M., Astarita, G., Köck, M., Ögmundsdottir, H.M., Thorsteinsdottir, M., et al., 2017. Metabolic profiling as a Screening tool for cytotoxic compounds: identification of 3-alkyl pyridine alkaloids from Sponges collected at a shallow water hydrothermal vent Site North of Iceland. Mar. Drugs 15 (2), 52.
Elissawy, A.M., El-Shazly, M., Ebada, S.S., Singab, A.B., Proksch, P., 2015. Bioactive terpenes from marine-derived fungi. Mar. Drugs 13 (4), 1966–1992.
Engelhardt, K., Degnes, K.F., Kemmler, M., Bredholt, H., Fjærvik, E., Klinkenberg, G., et al., 2010. Production of a new thiopeptide antibiotic, TP-1161, by a marine *Nocardiopsis species*. Appl. Environ. Microbiol. 76 (15), 4969–4976.
Fan, L., Liu, M., Simister, R., Webster, N.S., Thomas, T., 2013. Marine microbial symbiosis heats up: the phylogenetic and functional response of a sponge holobiont to thermal stress. ISME J 7 (5), 991.
Fenical, W., Jensen, P.R., 2006. Developing a New Resource for Drug Discovery: Marine Actinomycete Bacteria. Nat. Chem. Biol., vol. 2, 666–673.
Fieseler, L., Horn, M., Wagner, M., Hentschel, U., 2004. Discovery of the novel candidate phylum "*Poribacteria*" in marine sponges. Appl. Environ. Microbiol. 70 (6), 3724–3732.
Freel, K.C., Nam, S.J., Fenical, W., Jensen, P.R., 2011. Evolution of secondary metabolite genes in three closely related marine *Actinomycetes species*. Appl. Environ. Microbiol. 77 (20), 7261–7270.
Fuerst, J.A., 2014. Diversity and biotechnological potential of microorganisms associated with marine sponges. Appl. Microbiol. Biotechnol. 98 (17), 7331–7347.
Gandhimathi, R., Kiran, G.S., Hema, T.A., Selvin, J., Raviji, T.R., Shanmughapriya, S., 2009. Production and characterization of lipopeptide biosurfactant by a sponge-associated marine actinomycetes *Nocardiopsis alba* MSA10. Bioproc. Biosyst. Eng. 32 (6), 825–835.
Geetha, I., Manonmani, A.M., Prabakaran, G., 2011. *Bacillus amyloliquefaciens*: a mosquitocidal bacterium from mangrove forests of Andaman & Nicobar Islands, India. Acta Trop. 120 (3), 155–159.
Geetha, I., Paily, K.P., Manonmani, A.M., 2012. Mosquito adulticidal activity of a biosurfactant produced by *Bacillus subtilis* subsp. *subtilis*. Pest Manag. Sci. 68 (11), 1447–1450.
Gnanadesigan, M., Ravikumar, S., Anand, M., 2017. Hepatoprotective activity of *Ceriops decandra* (Griff.) Ding Hou mangrove plant against CCl4 induced liver damage. J. Taibah Univ. Sci. 11 (3), 450–457.
Hamed, A.N., Waetjen, W., Schmitz, R., Chovolou, Y., Edrada-Ebel, R., Youssef, D.T., et al., 2013. A new bioactive sesquiterpenoid quinone from the Mediterranean Sea marine *sponge Dysidea avara*. Nat. Prod. Commun. 8 (3), 289–292.
Han, L., Huang, X.S., Sattler, I., Fu, H.Z., Grabley, S., Lin, W.H.J., 2007. Two new constituents from mangrove *Bruguiera gymnorrhiza*. J. Asian Nat. Prod. Res. 9 (4), 327–331 2007.
Han, M., Li, Z., Zhang, F., 2013. The ammonia oxidizing and denitrifying prokaryotes associated with sponges from different sea areas. Microb. Ecol. 66 (2), 427–436.
Harjes, J., Ryu, T., Abdelmohsen, U.R., Moitinho-Silva, L., Horn, H., Ravasi, T., Hentschel, U., 2014. Draft genome sequence of the antitrypanosomally active sponge-associated bacterium *Actinokineospora sp*. strain EG49. Genome Announc. 2 (2) e00160-14.
Hasaballah, Ahmed, El-Naggar, Hussein, 2017. Antimicrobial activities of Some marine Sponges, and its biological, repellent effects against *Culex pipiens* (Diptera: Culicidae). Annu. Res. Rev. Biol. 12, 1–14.
Hentschel, U., Hopke, J., Horn, M., Friedrich, A.B., Wagner, M., Hacker, J., Moore, B.S., 2002. Molecular evidence for a uniform microbial community in sponges from different oceans. Appl. Environ. Microbiol. (9), 4431–4440.
Hentschel, U., Usher, K.M., Taylor, M.W., 2006. Marine sponges as microbial fermenters. FEMS Microbiol. Ecol. 55 (2), 167–177.
Hentschel, U., Piel, J., Degnan, S.M., Taylor, M.W., 2012. Genomic insights into the marine sponge microbiome. Nat. Rev. Microbiol. 10 (9), 641.
Hong, T.W., Jímenez, D.R., Molinski, T.F., 1998. Agelastatins C and D, new pentacyclic bromopyrroles from the sponge *Cymbastela sp*., and potent arthropod toxicity of (−)-agelastatin A. J. Nat. Prod. 61 (1), 158–161.
Ian, E., Malko, D.B., Sekurova, O.N., Bredholt, H., Rückert, C., Borisova, M.E., Albersmeier, A., Kalinowski, J., Gelfand, M.S., Zotchev, S.B., 2014. Genomics of sponge-associated Streptomyces spp. closely related to Streptomyces albus J1074: insights into marine adaptation and secondary metabolite biosynthesis potential. PLoS One 12 9(5):e96719.
Inbaneson, S.J., Ravikumar, S., 2011. In vitro antiplasmodial activity of marine sponge *Hyattella intestinalis* associated bacteria against *Plasmodium falciparum*. Asian. Pac. J. Trop. Biomed. 1 (1), S100–S104.
Inbaneson, S.J., Ravikumar, S., 2012a. *In vitro* antiplasmodial activity of *Clarthiria vulpina* sponge associated bacteria against *Plasmodium falciparum*. Asian. Pac. J. Trop. Dis. 319–323.
Inbaneson, S.J., Ravikumar, S., 2012b. *In vitro* antiplasmodial activity of Bacterium RJAUTHB 14 associated with marine sponge *Haliclona* Grant against *Plasmodium falciparum*. Parasitol. Res. 110 (6), 2255–2262.
Inbaneson, S.J., Ravikumar, S., 2012c. *In vitro* antiplasmodial activity of marine sponge *Stylissa carteri* associated bacteria against *Plasmodium falciparum*. Asian. Pac. J. Trop. Dis. 2, 370–374.
Inbaneson, S.J., Ravikumar, S., 2012d. *In vitro* antiplasmodial activity of marine sponge *Clathria indica* associated bacteria against *Plasmodium falciparum*. Asian. Pac. J. Trop. Biomed. 2 (2), S1090–S1095.
Isman, M.B., Miresmailli, S., Machial, C., 2011. Commercial opportunities for pesticides based on plant essential oils in agriculture, industry and consumer products. Phytochemistry Rev. 10, 197–204.
Karthik, L., Gaurav, K., Rao, K.B., Rajakumar, G., Rahuman, A.A., 2011. Larvicidal, repellent, and ovicidal activity of marine actinobacteria extracts against *Culex tritaeniorhynchus* and *Culex gelidus*. Parasitol. Res. 108 (6), 1447–1455.
Kim, J., Hudson, B., Huang, A.M., Bannistes, K., Jin, A., Choi, T.J., Towers, G.H.N., et al., 1997. Biological activity of seaweed extracts from British, Colombia, Canada and Korea. I. Antiviral activity. Can. J. Bot. Rev. 75 (10), 1656–1660.
Kiran, G.S., Sabarathnam, B., Thajuddin, N., Selvin, J., 2014. Production of glycolipid biosurfactant from sponge-associated marine actinobacterium *Brachybacterium paraconglomeratum* MSA21. J. Surfactants Deterg. 17 (3), 531–542.
Koopmans, M., Martens, D., Wijffels, R.H., 2009. Towards commercial production of sponge medicines. Mar. Drugs 7 (4), 787–802.
Lawrance, A., Balakrishnan, M., Joseph, T.C., Sukumaran, D.P., Valsalan, V.N., Gopal, D., Ramalingam, K., 2014. Functional and molecular characterization of a lipopeptide surfactant from the marine sponge-associated eubacteria Bacillus licheniformis NIOT-AMKV06 of Andaman and Nicobar Islands, India. Mar. Pollut. Bull. 82 (1–2), 76–85.
Leal, W.S., 2014. The enigmatic reception of DEET—the gold standard of insect repellents. Curr. Opin. Insect. Sci. 6, 93–98.
Lee, C.T., Chen, I.T., Yang, Y.T., Ko, T.P., Huang, Y.T., Huang, J.Y., et al., 2015. The opportunistic marine pathogen *Vibrio parahaemolyticus* becomes virulent by acquiring a plasmid that expresses a deadly toxin. Proc. Natl. Acad. Sci. USA. 112 (34), 10798–10803.
Li, H., Lydy, M.J., You, J., 2016. Pyrethroids in Indoor Air during Application of Various Mosquito Repellents: Occurrence, Dissipation and potential exposure risk. Chemosphere 144, 2427–2435.
Lin, Z., Zhu, T., Wei, H., Zhang, H., Wang, H., Gu, Q., 2009. Spicochalasin a and new aspochalasins from the marine-derived fungus *Spicaria elegans*. Eur. J. Org. Chem. 18, 3045–3051.
Maia, M.F., Moore, S.J., 2011. Plant-based insect repellents: a review of their efficacy, development and testing. Malar. J. 10, 1–15.
Mani, C., Selvakumari, J., Han, Y., Jo, Y., Thirugnanasambantham, K., Sundarapandian, S., Poopathi, S., 2018. Molecular characterization of mosquitocidal toxin (Surface layer protein, SLP) from *Bacillus cereus* VCRC B540. Appl. Biochem. Biotechnol. 184 (4), 1094–1105.
Mathivanan, A., Ravikumar, S., Abideen, S., Prasannakumar, S., 2014. Marine Sponges as Untapped Resource for Mosquitocidal Compounds – A Review Proceedings of the International Conference on Bioprospecting of Natural Resources for Human Health". pp. 165–172 978–93-80934–44-2.
Mehbub, M., Lei, J., Franco, C., Zhang, W., 2014. Marine sponge derived natural products between 2001 and 2010: trends and opportunities for discovery of bioactives. Mar. Drugs 12 (8), 4539–4577.
Misni, N., Nor, Z.M., Ahmad, R., 2016. New candidates for plant-based repellents against *Aedes aegypti*. J. Am. Mosq. Control Assoc. 32, 117–123.
Nakashima, Y., Egami, Y., Kimura, M., Wakimoto, T., Abe, I., 2016. Metagenomic analysis of the sponge *Discodermia* reveals the production of the cyanobacterial natural product kasumigamide by *'Entotheonella'*. PLoS One 11 (10), e0164468.
Norris, E.J., Coats, J.R., 2017. Current and future repellent technologies: the potential of spatial repellents and their place in mosquito-borne disease control. Int. J. Environ. Res. Public Health 14 (2), 124.
Norris, E.J., Gross, A.D., Dunphy, B.M., Bessette, S., Bartholomay, L., Coats, J.R., 2015. Comparison of the insecticidal characteristics of commercially available plant essential oils against *Aedes aegypti* and *Anopheles gambiae* (Diptera: Culicidae). J. Med. Entomol. 52, 993–1002.
Okada, A., Watanabe, K., Umeda, K., Miyakado, M., 1991. Calyculin E and F, novel insecticidal metabolites, from the marine Sponge, *Discodermia sp*. Agric. Biol. Chem. 55 (11), 2765–2771.
Okai, Y., Highasi, O.K., Ishizaka, S., Yamashita, U., 1997. Enhancing effect of polysaccharides from edible brown algae, *Hijikia furiform* (Hijki) on release of tumor necrosis factor alpha from macrophages of exndotoxin non responder C3H/HCl mice. Nutr. Canc. 27, 381–386.
Paluch, G., Grodnitzky, J., Bartholomay, L., Coats, J., 2009. Quantitative structure-activity relationships of botanical sesquiterpenes: Spatial and contact repellency to the yellow fever mosquito, *Aedes aegypti*. J. Agric. Food. Chem. 57, 7618–7625.
Prasanna kumar, S., Ravikumar, S., 2014. *In vitro* antiplasmodial activity of marine Sponge *Clathria vulpina* extract against Chloroquine sensitive *Plasmodium falciparum*. Asian. Pac. J. Trop. Dis. 4 (1), S162–S166.
Proksch, P., Edrada, R., Ebel, R., 2002. Drugs from the seas–current status and microbiological implications. Appl. Microbiol. Biotechnol. 59 (2–3), 125–134.
Radjasa, O.K., Sabdono, A., Junaidi, Zocchi, A., 2007. Richness of secondary metabolite producing marine bacteria associated with sponge *Haliclona sp*. Int. J. Pharmacol. 3 (3), 275–279.
Rao, D.R., Mani, T.R., Rajendran, R., Joseph, A.S., Gajanana, A., Reuben, R., 1995. Development of a high level of resistance to *Bacillus sphaericus* in a field population of *Culex quinquefasciatus* from Kochi, India. J. Am. Mosq. Control Assoc. 11 (1), 1–5.
Rao, J.V., Usman, P.K., Kumar, J.B., 2008. Larvicidal and insecticidal properties of some marine sponges collected in Palk Bay and Gulf of Mannar waters. Afr J Biotechnol 7 (2).
Ravikumar, S., Jacob inbaneson, S., 2012. *In vitro* antiplasmodial activity of marine

sponge *Stylissa carteri* associated bacteria against *Plasmodium falciparum*. Asian. Pac. J. Trop. Biomed 370–374.
Ravikumar, S., Jacob Inbaneson, S., Suganthi, P., Gnanadesigan, M., 2010. In vitro antiplasmodial activity of ethanolic extracts of mangrove plants from South East coast of India against chloroquine-sensitive. *Plasmodium falciparum*. Parasitol. Res. 108 (4), 873–878.
Ravikumar, S., Gnanadesigan, M., Jacob Inbaneson, S., Kalaiarasi, A., 2011. Hepatoprotective and antioxidant properties of *Suaeda maritima* (L.) Dumort ethanolic extract on concanavalin-A induced heaptotoxicity in rats. Indian J. Exp. Biol. 49 (6), 455–460.
Reegan, A.D., Kinsalin, A.V., Paulraj, M.G., Ignacimuthu, S., 2013. Larvicidal, Ovicidal, and Repellent Activities of Marine Sponge *Cliona celata* (Grant) Extracts against *Culex quinquefasciatus* Say and *Aedes aegypti* L.(Diptera: Culicidae). ISRN. Entomol Article id: 315389.
Reegan, A.D., Kinsalin, A.V., Paulraj, M.G., Ignacimuthu, S., 2015. Larvicidal, ovicidal and repellent activities of marine sponge *Cliona celata* (Grant) extracts against *Anopheles stephensi* Liston (Diptera: Culicidae) Asian. Pac. J. Trop. Med. 8 (1), 29–34.
Rocha-Martin, J., Harrington, C., Dobson, A.D., O'Gara, F., 2014. Emerging strategies and integrated systems microbiology technologies for biodiscovery of marine bioactive compounds. Mar. Drugs 12 (6), 3516–3559.
Rouf, R., Uddin, S.J., Shilpi, J.A., Alamgir, M., 2007. Assessment of antidiarrhoeal activity of the methanol extract of *Xylocorpus granatum* bark in mice model. J. Ethnopharmacol. 109 (3), 539–542.
Saleh, M.S., El-Meniawi, F.A., Kelada, N.L., Zahran, H.M., 2003. Resistance development in mosquito larvae *Culex pipiens* to the bacterial agent *Bacillus thuringiensis* var. *israelensis*. J. Appl. Entomol. 127 (1), 29–32.
Saurav, K., Rajakumar, G., Kannabiran, K., Rahuman, A.A., Velayutham, K., Elango, G., et al., 2013. Larvicidal activity of isolated compound 5-(2, 4-dimethylbenzyl) pyrrolidin-2-one from marine *Streptomyces* VITSVK5 sp. against *Rhipicephalus* (Boophilus) *microplus, Anopheles stephensi*, and *Culex tritaeniorhynchus*. Parasitol. Res. 112 (1), 215–226.
Schirmer, A., Gadkari, R., Reeves, C.D., Ibrahim, F., DeLong, E.F., Hutchinson, C.R., 2005. Metagenomic analysis reveals diverse polyketide synthase gene clusters in microorganisms associated with the marine sponge *Discodermia dissoluta*. Appl. Environ. Microbiol. 71, 4840–4849.
Schneemann, I., Kajahn, I., Ohlendorf, B., Zinecker, H., Erhard, A., Nagel, K., et al., 2010. Mayamycin, a cytotoxic polyketide from a *Streptomyces* strain isolated from the marine sponge *Halichondria panicea*. J. Nat. Prod. 73 (7), 1309–1312.
Selvin, J., Lipton, A.P., 2004. Biopotentials of Secondary Metabolites Isolated from Marine Sponges. Hydrobiologia, vol. 513, 231–238.
Selvin, J., Shanmughapriya, S., Gandhimathi, R., Kiran, G.S., Ravji, T.R., Natarajaseenivasan, K., Hema, T.A., 2009. Optimization and production of novel antimicrobial agents from sponge associated marine actinomycetes *Nocardiopsis dassonvillei* MAD08. Appl. Microbiol. Biotechnol. 83 (3), 435.
Selvin, J., Kennedy, J., Lejon, D.P., Kiran, G.S., Dobson, A.D., 2012. Isolation identification and biochemical characterization of a novel halo-tolerant lipase from the metagenome of the marine sponge *Haliclona simulans*. Microb. Cell Factories 11 (1), 72.
Silva, A.P.B., Santos, J.M.M., Martins, A.J., 2014. Mutations in the voltage-gated sodium channel gene of anophelines and their association with resistance to pyrethroids–a review. Parasites Vectors 7 (1), 450.
Silva-Filha, M.H., Regis, L., Nielsen-Leroux, C., Charles, J.F., 1995. Low-level resistance to *Bacillus sphaericus* in a field-treated population of *Culex quinquefasciatus* (Diptera: Culicidae). J. Econ. Entomol. 88 (3), 525–530.
Sonia, A.S.G., Lipton, A.P., 2012. Mosquito Larvicidal activity of marine sponge metabolites. Global J Pharmacology 6 (1), 1–3.
Takahashi, A., Ikeda, D., Nakamura, H., Naganawa, H., Kurasawa, S., Okami, Y., et al., 1989. Altemicidin, a new acaricidal and antitumor substance. J. Antibiot. 42 (11), 1562–1566.
Taylor, M.W., Radax, R., Steger, D., Wagner, M., 2007. Sponge-associated microorganisms: evolution, ecology, and biotechnological potential. MMBR (Microbiol. Mol. Biol. Rev.) 71 (2), 295–347.
Taylor, M.W., Tsai, P., Simister, R.L., Deines, P., Botte, E., Ericson, G., et al., 2013. 'Sponge-specific'bacteria are widespread (but rare) in diverse marine environments. ISME J. 7 (2), 438.
Thenmozhi, M., Kannabiran, K., Kumar, R., Khanna, V.G., 2013. Antifungal activity of *Streptomyces sp*. VITSTK7 and its synthesized Ag2O/Ag nanoparticles against medically important *Aspergillus* pathogens. J. Mycol. Med. 23 (2), 97–103.
Thiel, V., Leininger, S., Schmaljohann, R., Brümmer, F., Imhoff, J.F., 2007. Sponge-specific bacterial associations of the Mediterranean sponge *Chondrilla nucula* (Demospongiae, Tetractinomorpha). Microb. Ecol. 54 (1), 101–111.
Thomas, T.R.A., Kavlekar, D.P., LokaBharathi, P.A., 2010. Marine drugs from sponge-microbe association—a review. Mar. Drugs 8 (4), 1417–1468.
Thompson, M.N., Gallimore, W.A., Townsend, M.M., Chambers, N.A., Williams, L.A., 2010. Bioactivity of amphitoxin, the major constituent of the Jamaican sponge *Amphimedon compressa*. Chem. Biodivers. 7 (8), 1904–1910.
Traboulsi, A.F., El-Haj, S., Tueni, M., Taoubi, K., Nader, N.A., Mrad, A., 2005. Repellency and toxicity of aromatic plant extracts against the mosquito *Culex pipiens molestus* (Diptera: Culicidae). Pest Manag. Sci. 61 (6), 597–604.
Vankayala, S.L., Kearns, F.L., Baker, B.J., Larkin, J.D., Woodcock, H.L., 2017. Elucidating a chemical defense mechanism of Antarctic sponges: a computational study. J. Mol. Graph. Model. 71, 104–115.
VanWagenen, B.C., Larsen, R., Cardellina, J.H., Randazzo, D., Lidert, Z.C., Swithenbank, C., 1993. Ulosantoin, a potent insecticide from the sponge *Ulosa ruetzleri*. J. Org. Chem. 58 (2), 335–337.
Wang, G., 2006. Diversity and biotechnological potential of the sponge-associated microbial consortia. J. Ind. Microbiol. Biotechnol. 33, 545–551.
Webster, N.S., Taylor, M.W., 2012. Marine sponges and their microbial symbionts: love and other relationships. Environ. Microbiol. 14 (2), 335–346.
Wilson, M.C., Mori, T., Rückert, C., Uria, A.R., Helf, M.J., Takada, K., 2014. An environmental bacterial taxon with a large and distinct metabolic repertoire. Nature 506 (7486), 58.
World Health Organisation, 2006. The World Health report available from: http://www.who.int/whr/2006/en/.
Wu, J., Xiao, Q., Xu, J., Li, M.Y., Pana, J.Y., Yang, M., 2008. Natural products from the mangrove flora: source and bioactivities. Nat. Prod. Rep. 25 (5), 955–981.
Xiong, L., Li, J., Kong, F., 2004. *Streptomyces sp*. 173, an insecticidal micro-organism from marine. Lett. Appl. Microbiol. 38 (1), 32–37.
Zabriskie, T.M., Klocke, J.A., Ireland, C.M., Marcus, A.H., Molinski, T.F., Faulkner, D.J., 1986. Jaspamide, a modified peptide from a Jaspis sponge, with insecticidal and antifungal activity. J. Am. Chem. Soc. 108 (11), 3123–3124.
Zhandi, K., Taherzadeh, M., Tajbakhsh, S., Yaghoubi, R., Rastian, Z., Sartavi, K., 2008. Antiviral bactivity of *Avicennia marina* leaf extract on HSV-1 and vaccine strain of polio virus in vero cells. Int. J. Infect. Dis. 12 (1), e298.
Zhang, L., An, R., Wang, J., Sun, N., Zhang, S., Hu, J., Kuai, J., 2005. Exploring novel bioactive compounds from marine microbes. Curr. Opin. Microbiol. 8 (3), 276–281.
Zhou, K., Zhang, X., Zhang, F., Li, Z., 2011. Phylogenetically diverse cultivable fungal community and polyketide synthase (PKS), non-ribosomal peptide synthase (NRPS) genes associated with the South China Sea sponges. Microb. Ecol. 62 (3), 644–654.
Ziemert, N., Alanjary, M., Weber, T., 2016. The evolution of genome mining in microbes–a review. Nat. Prod. Rep. 33 (8), 988–1005.