Available online at www.ijpab.com

DOI: http://dx.doi.org/10.18782/2320-7051.7492

ISSN: 2320 – 7051
Int. J. Pure App. Biosci. **7 (3):** 58-66 (2019)

Review Article

Siderophores from Marine Bacteria with Special Emphasis on Vibrionaceae

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Received: 11.04.2019 | Revised: 18.05.2019 | Accepted: 25.05.2019

ABSTRACT

More than 500 siderophores have been isolated from a huge number of marine bacteria till date. With mankind's ever-increasing search for novel molecules towards industrial and medical applications, siderophores have gained high importance. These chelating ligands have immense potential in promoting plant growth, drug-delivery, treatment of iron-overload, etc. Many of the potential siderophores have been isolated from bacteria like Pseudomonas, Bacillus, Nocardia, etc. Bacteria belonging to the family Vibrionaceae have recently gained focus owing to their rich potential in secreting siderophores. Many of the vibrionales, viz. Vibrio harveyii, V. anguillarium, V. campbellii. etc. are aquatic pathogens. These bacteria require iron for their growth and virulence, and hence produce a wide variety of siderophores. The genetic basis of siderophore production by Vibrio sp. has also been largely studied. Further detailed genetic analysis of the mode of siderophore production by Vibrionaceae would be highly effective to treat aquaculture diseases caused by these pathogenic organisms.

Key words: *Marine bacteria; Siderophore; Vibrionaceae; Bioactivity; Vibrio campbellii.*

INTRODUCTION

The earth is mainly surrounded by the ocean[41]. The marine environment harbours huge biodiversity and is a potential source of marine microorganisms with extensive applications[5]. The fundamental sources for growth and survival of plants and animals are abundantly available in the marine environment. The sea water contains 1 million microorganisms per milliliter, which includes several thousands of microbial types. Marine bacteria are defined by bacteria living in a marine environment ranging from pelagic to benthic ecosystems, in which salinity plays a vital role[9]. The essential contribution of marine microbial communities is in global biomass, nitrogen cycling, and biodiversity[50]. The prokaryotic microbes lead a key role in Fe Cycling to release the energy and matter and to maintain ecosystem functioning[25,35].

Cite this article: Archana, V., Revathi, K., Limna Mol, V. P., Kirubagaran, R., Siderophores from Marine Bacteria with Special Emphasis on Vibrionaceae, *Int. J. Pure App. Biosci.* **7(3):** 58-66 (2019). doi: http://dx.doi.org/10.18782/2320-7051.7492

Marine microbes are involved in the fundamental aspects of controlling the environment based on biogeochemistry[44]. Marine microbes are free-living which supports research which exhibits the biogeographic pattern[30]. Approaches towards the marine microbes were significantly changed by researchers to isolate the various potential bioactive products[37].

Gram-negative bacteria can survive better in the rough oceanic environment because of the cell membrane Lipopolysaccharides (LPS). The outer membrane LPS triggers the immune response which leads to infection and even causes death[32,47]. Marine bacteria have been found to be a great source of novel bioactive compounds, with more than a thousand compounds being isolated and screened for the potential to produce contemporary medicine[22]. Metabolic activity of bacterium requires iron for its growth and survival. Iron exists in two forms, either as Ferrous Fe II or insoluble ferric Fe III, but in the oceanic environment, it is present in the ferric condition due to the neutral to alkaline pH[34]. Although the bacterium requires an easily soluble ferrous form, survival in the aerobic environment was a difficult task. However, in the aerobic condition under certain biological pH, ferrous is oxidized to ferric iron[34]. Further, to overcome this condition of low iron availability and to sustain in the aerobic condition, bacteria developed an interesting mechanism to assimilate the iron from any given environment by secreting iron-carrying or binding molecules, literally coined as siderophores[33].

Siderophore, literally coined as an iron chelating compound[19], are low -molecular weight ligands (20-2000 Da) produced to hydrolyze and metabolize iron by bacteria, fungi and plants[36]. The iron ligation groups were tentatively classified into three major chemical types: Hydroxamate, Catecholate, and Hydroxy carboxylates; However, other siderophore structures, including oxazoline, thiazoline, hydroxypyridinone, α- and β-hydroxy acids and α-keto acid components, have also been resolved[27]. Siderophore peptide backbone is usually made up of several analogs of nonprotein amino acids, including modified and D-amino acids[14]. Some bacteria produce one type of siderophore while many produce multiple types of siderophore that enable microbes to grow in different environments[7].

The objective of this review is to peruse the available literature to explain the importance of iron for bacterial growth and virulence, structure and general contour of the iron assimilation system, role of siderophores in marine ecosystem with special reference to siderophores from marine Vibrionaceae.

1. Siderophore : an overview

Most of the organisms require iron as an essential element in a variety of metabolic and cellular pathways due to its unique chemical properties. Iron-containing cofactors such as iron-sulfur clusters or heme groups are found to be present in over 100 enzymes that act in processes of primary and secondary metabolism. Its ability to coordinate and trigger oxygen and to get ideal oxidation chemistry for involvement in electron transport and metabolic processes makes iron most suitable for catalyzing broad spectrum of a redox reaction[29,36].

Fe (II) is soluble in aqueous solution at neutral pH and, if the reductive state is maintained, is, therefore, sufficiently available for living cells. In general, omnipresent divalent metal transporters can be taken over[8,3,29]. In bacteria[8] and fungi[16], specific Fe (II)) uptake systems are known. However, Fe (II) is oxidized to Fe (III)) in most microbial habitats either spontaneously by reacting in host organisms with molecular oxygen or enzymatically during assimilation and circulation. Knight *et al.*[42] Fe (III) forms ferric oxide complex in the environment. Fe (III)) forms complexes of ferric oxide hydrate in the presence of oxygen and water with neutral to basic pH. These complexes are very stable, resulting in a free concentration of Fe (III)[27,34].

Using multiples of membrane-bound iron siderophore receptors, iron-coordinated siderophore (III) are accumulated by microorganisms through facilitative transport. Iron is predominantly removed from siderophore by a redox-mediated process the affinity of iron (II) siderophore is much lower than that of iron (III)[38]. Some siderophores may be secreted to deprive the competing organisms of iron, which will in turn influence the ecology of the environment that the secreting colony occupies[17,23]. The correlation between siderophore production and virulence is strong for some microorganisms[12]. The fundamental role of siderophore is involved in the acquisition of high affinity and receptor-dependent ferric ion transport. Siderophore production regulation is based on iron concentration in the environment[24].

2. Types of Siderophores

Microbial products, especially secondary metabolites can be considered as siderophores when they possess characteristics such as iron chelating property. Iron level plays a vital role in the biosynthesis of siderophores and has the capability to transport across the membrane[48]. Including secondary metabolites, different and complex chemical structures within the siderophore are typical, preventing their unambiguous and universal classification. Even though siderophore biosynthesis and structural characteristics are diverse, a classification scheme will be arbitrary to some extent. Metrics may include source organisms (bacteria, fungi, plants), backbone character (peptide or nonpeptide, cyclic or open-chain), or chelating group character[15]. Given the considerable structural variation found in siderophores, their common feature is to form high thermodynamic stability six-coordinate complexes with iron (III). Ligating groups contain hydroxamate, catecholate, α-hydroxycarboxylic acids and α-keto carboxylic acids of oxygen atoms[39].

Additionally, siderophores with various binding groups of Fe (III) ions, such as salicylic acid, oxazoline, and thiazoline nitrogen, and even negative nitrogen as in the case of maduraferrin) were isolated[1]. Extensive reviews are available on the structural variety of siderophores[45]. Major types of siderophores are Catecholate, Hyroxymates, carboxylate and mixed ligands.

3. Sources of Siderophores

Most of the microorganisms produce a wide range of siderophores (iron-chelators) in iron-deficient marine ecosystems. Four significant environmental habitats occur naturally: soil and surface water, marine water, plant tissue (pathogens) and animal tissue (pathogen). For bacteria and fungi, the soil is a rich source of habitat. Generally, gram-positive species are those belonging to the *Bacillus*, *Arthobacter*, *Actinomycetales* and *Nocardia* genera. Almost all of these microbes produce and secrete ferrioxamines that promote growth not only of the producing organisms but also for other microbial population that can avail it. Aspergillus and Penicillium, which mainly produce ferrichromes are soil fungi. This group of siderophore is made up of cyclic hexapeptides and therefore highly resistant to environmental degradation due to the wide range of hydrolytic enzymes present in the soil[49]. The pH values of soils containing decaying plant materials are as low as 3-4. Because of the extreme acid stability of these molecules, organisms producing hydroxamate siderophore have an advantage under such conditions. Freshwater lakes also contain large *Pseudomonas*, *Azomonas*, *Aeromonas* and *Alcaligenes species* populations[6].

Unlike most freshwater sources, surface sea-water iron levels are extremely low (1nM to 1 μMin the upper 200 m) and much lower than those of V, Co, Ni, Cu and Zn. Almost all of this iron is in the state of iron (III) and complex to organic ligands Rue and Bruland[40]. The distinct nature of the marine pelagic atmosphere promotes large diffuse losses and poses a problem with the efficiency of normal siderophore based iron uptake strategies. Many heterotrophic marine bacteria, however, produce siderophore, although they have different properties than those produced by terrestrial organisms. Marine siderophores are active on the surface and tend to form molecular aggregates.

4. Applications of Siderophores

Only approximately 1% of marine bacteria can be cultured in the laboratory. Siderophore enhances the growth in artificial media of unculturable microorganisms. The siderophore based approach has made it possible to cultivate organisms that are only remotely related to microbes previously grown. For many strains from this habitat, the lack of growth in the laboratory stems from an inability to produce siderophore autonomously, and the resulting chemical dependence on other microbes regulates community establishment in the environment.

Siderophores are involved in the growth of plant species to increase the yield by enhancing the iron uptake to the plant. In agriculture, soil inoculation with *Pseudomonas putida,* which produces pseudobactin, increases the growth and yield of different plants demonstrated the presence of hydroxamate siderophore in variety. Siderophore type hydroxamate present in soil plays an important role in immobilizing the metals in these cases. Siderophore production activity plays a central role in determining the ability of various microorganisms to improve the development of plants in soil. Siderophore acts against harmful phytopathogen and holds the ability to substitute hazardous pesticides.

In the Medical field, Siderophore uses the Trojan strategy to form complexes with antibiotics and helps in the selective delivery of antibiotics to the antibiotic-resistant bacteria. Certain iron overload diseases, for example, Sickle cell anemia can be treated using siderophores. Deferiprone and Desferrioxamine combined chelation therapy of thalassemia major disease has also been reported. Reversed siderophore acts as an antimalarial activity. The synthetic ferrichromes antimicrobial activity correlated with their lipophilicity, and this antimalarial activity was averted when applied as iron (II) complexes to the chelators. Synthetic ferrichrome action sites are located in the intra-erythrocytic parasite and not in the serum or on normal components of erythrocytes. These agents have been effective against all parasite growth.

5. Siderophores from marine Vibrionaceae

Vibrionaceae family is widely distributed in the marine environment comprising of several species which cause diseases to human beings and animals[2]. Subsequently, Vibrios have a profound ability to produce bioactive secondary metabolites[28]. Like other pathogenic bacteria, Vibrios also require iron for their growth[31]. Although covering a limited chemical space, Vibrios produce compounds with attractive biological activities, including antibacterial, anticancer, and antivirulence activities. This review highlights some of this group of bacteria's most interesting structures. Many of the compounds found in vibrios have also been isolated from other bacteria that are distantly related. This cosmopolitan occurrence of metabolites indicates a high incidence of transferring horizontal genes, raising interesting issues. Some of these molecules have an ecological function. This account highlights the pending potential of exploring new bioactive compounds bacterial sources and the challenges associated with their research[28].

Vibrio campbellii is a marine gram-neagtive curved rod-shaped bacterium closely linked to its sister species, *Vibrio harveyi* In aquatic organisms, it is an emerging pathogen. Qurom sensing enables the bacterium to communicate with autoinducers, a secreted chemical signaling molecule. Some *V .campbellii* strains are known not to be luminescent; these strains are believed to be less virulent than the luminescent strains.

Siderophore is synthesized and secreted in their environment where they chelate ferric iron to overcome hunger. Once bound, the siderophore receptor recognizes the ferric iron- siderophore complexes and are transported via ABC transporters over the membrane using TonB complexes as energy transducers.

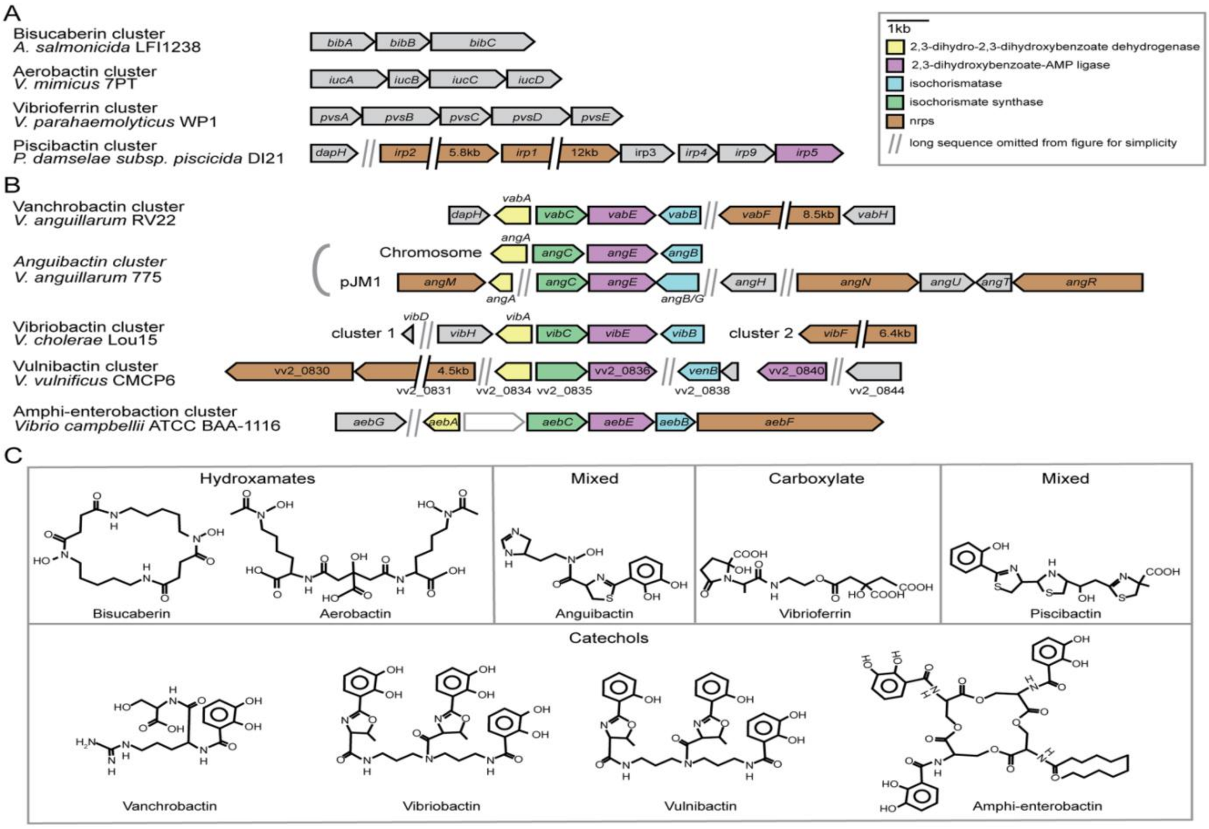

Fig. 1: The organisation of Vibrionaceae siderophore clusters of biosynthesis and the corresponding siderophore schematic structure.a)Biosynthesis clusters of Vibrionaceae and carboxylate and siderophore.b) Catecholatae Vibrionanaceae and biosynthesis cluster mixed catechol/hydroxamate siderophore c) Vibrionaceae siderophore with known biosynthesis gene cluster representation of schematic 2D structure[46].

Vibrionaceae siderophore biosynthesis, siderophore receptors and phylogenetic analyses were used to investigate their organization, distribution, origin and evolution. Identified nine different siderophore biosynthesis systems and 13 siderophore receptors in Vibrionaceae through literature search. Blast searches identified homologs and mapped the results to a phylogeny of Vibrionaceae. 81 biosynthetic system in 45 species of Vibrionaceae and 16 unclassified strains of Vibrionaceae and 409 receptors in 89 species of Vibrionaceae and 49 unclassified strains of Vibrionaceae have been identified[46]. Most taxa are associated with at least one type of siderophore biosynthesis system, some of which are widely distributed in the family (e.g., aerobactin and vibrioferrin), while others (e.g., bisucaberin and vibriobactin) are found in one lineage.

The *Vibrio sp*. DS40M4 produced a new triscatechol amide siderophore, trivanchrobactin (1), a related new biscatecholamide compound, divanchrobactin (2), and previously reported siderophores, vanchrobactin (3) and anguibactin (4). Vanchrobactin is consist of L-serine, D-arginine- and 2, 3-dihydroxybenzoic acid, while trivanchrobactin is a linear trimer of vanchrobactin joined by two serine ester linkages. The cyclic trivanchrobactin product was not detected. In addition to siderophore production, extracts of Vibrio sp. DS40M4 were screened for biologically active molecules; anguibactin was found to be cytotoxic against the P388 Murine leukemia cell line (IC50 < 15 µM.

Vibrio campbellii BAA-1116 (formerly *Vibrio harveyi*) is a model organism for quorum sensing producing anguibactin and amphi-enterobactin siderophore. This study examined the mechanisms and specificity of siderophore uptake in *V. campbellii* and *V. harveyi*, and examined the diversity of *V. campbellii* and *V. harveyi* strains in siderophore.

Electrospray ionization mass spectrometry and bioassay revealed that different *V. campbellii* and *V. harveyi* strains produce a series of amphi-enterobactins with different fatty acid appendages, including several novel amphi-enterobactins.

6. Genetic basis of siderophore production by *V. campbellii*

Vibrio campbellii BAA-1116 Amphi enterobactin gene cluster harbors a gene called fapA, which is a counterpart that encodes Fe (III)-siderophore-specific outer membrane receptors. Also carrying this cluster including fapA is another strain, *V. campbellii* HY01, a pathogenic strain to shrimp.HY01-derived indicator strains show that the FapA protein located in *V. campbellii* HY01 outer membrane fraction is essential for the uptake of both Fe (III)-Amphi-enterobactin and enterobactin from E. coli, but not *V. anguillarum* RV22 vanchrobactin while *V. anguillarum* may use Fe (III)-Amphi-enterobactin.*V. campbellii* HY01 may absorb Amphi-enterobactin via FapA, indicating that Amphi-enterobactin production is a common phenotype among *V. campbellii* and *V. harveyi*, whereas earlier work, reported here in, showed that *V. campbellii* strains are produced only by an anguibactin. In both anguibactin and Amphi- enterobactin biosynthesis, the 2, 3-dihydroxybenzoic acid gene, aebA, located in the Amphi-enterobactin gene cluster, suggest the possibility that Amphi-enterobactin may is a native siderophore of *V. campbellii* and *V. harveyi*, while V. campbellii acquired the anguibactin system during evolution.

Genomic analysis revealed that *V. campbelli* DS40M4 harbors genes related to the transport of iron, virulence and environmental fitness, such as proteins encoding anguibactin and vanchrobactin. Secretion system for protein, types II, III, IV and VI and proteorhodopsin were also present[51].

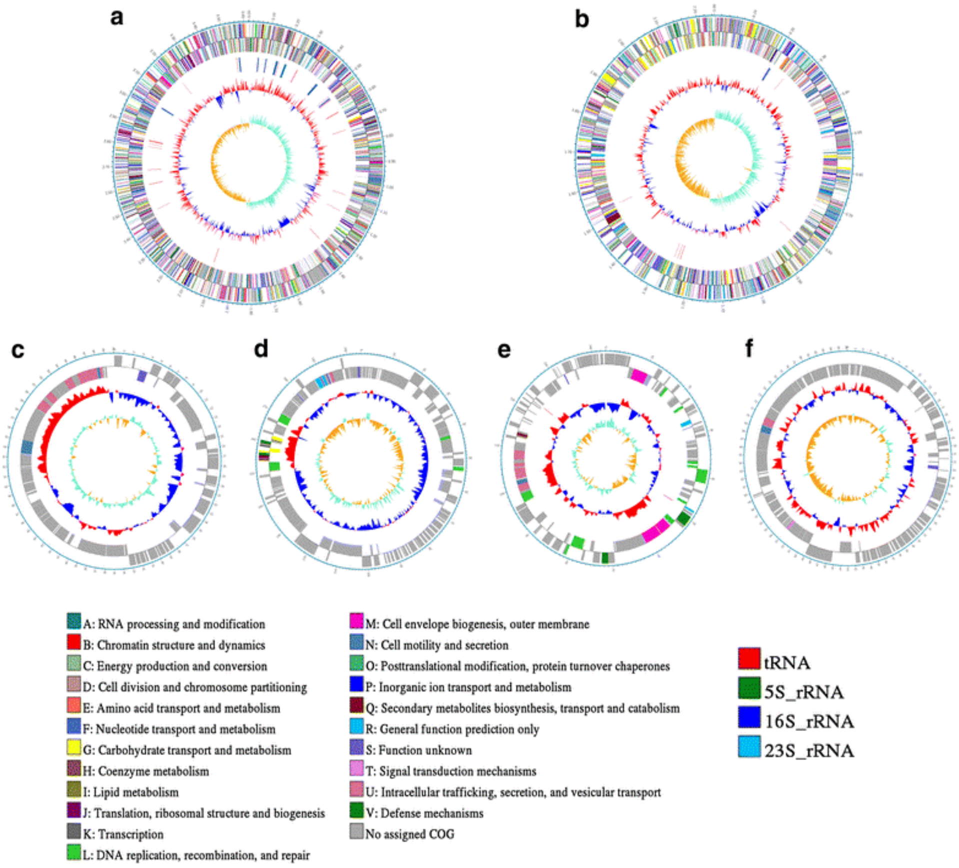

Fig. 2: Complete genomic studies of Vibrio campbellii[51]

CONCLUSION

Siderophores, the iron-chelating compounds, are usually produced to hydrolyze and metabolize iron by bacteria, fungi and plants**.** The siderophore production has mostly been linked to virulence and hence, most of the marine pathogenic bacteria secrete siderophore molecules. Among these, Vibrionaceae are the focus of current research owing to their relevance in aquaculture activities. Many of the *Vibrio* sp. have been widely explored for siderophore production, however, emerging aquaculture pathogens like *V. campbellii* are still largely unexplored. Detailed research on siderophore production potential of *Vibrio* sp. would be highly beneficial to the aquaculture fraternity.

Acknowledgements

The authors are grateful to The Director, National Institute of Ocean Technology (NIOT), Chennai for providing the necessary facilities for carrying out this research and Madras University for granting Ph.D. registration to the first author. The authors also gratefully acknowledge the contributions of Mrs. Siva Gayathri Kola to this research work, who was instrumental in initiating this work, but unfortunately she is not with us today to witness the fruition of her efforts and has found solace in the divine self.

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