Microbial Siderophores and their potential applications

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Abstract

Siderophores are naturally occurring iron chelating agent secreted by bacteria, fungi, and plants. Iron is considered to be the fourth most abundant element in the earth's crust from soil, however, many plants struggle to absorb iron due to its insoluble form, which severely limits the bioavailability of this metal. Therefore, there is a problem with the absorption of iron. Siderophores are responsible for enhancing the absorption of iron from the surrounding environment to carry out vital metabolic processes. This paper is an attempt to review the importance of siderophore in increasing the iron utilization strategy of plants, the mode of transport of accessory cells with iron across membranes, and depending on differences in chemical structure, functional form, and source of isolation, four different groups of siderophores (hydroxamates, catecholates, carboxylates, and mixed ligand siderophores) identified. Siderophores function as bio-controllers, biosensors, and bioremediation and chelating agents, in addition to their important roles in altering soil minerals and improving soil and plant growth.

Keywords: Siderophores, microorganisms, iron transport, bioremediation.

1. INTRODUCTION

Iron (Fe) a catalyst for all enzymatic processes plays a vital role in the formation of oxygen metabolism, and electron transfer, also for the biofilm formation to regulate the stability of polysaccharide matrix (Weinberg, 2004; Chhibber et al., 2013) and for the synthesis of DNA and RNA (Aguado- Santacruz et al., 2012) in all the living organism for its various cellular activities (Litwin and Calderwood, 1993). Iron is an important micronutrient present in nature, but it is not acquired by microorganisms (Saha et al., 2013) when it undergoes oxidation from Fe^{2+} to Fe^{3+} which is an insoluble form.

Therefore, microorganisms such as *Pseudomonas*, *Azotobacter*, *Bacillus*, *Rhizobium*, and *Serratia* (Glick et al., 1999; Looper et al., 1999) secretes to overcome the iron-deficient conditions (Neilands, 1981), fungi such as *Aspergillus*, *Penicillium*, *Trichoderma*, *Rhizopus*, *Fusarium*. Phytoplanktons and cyanobacteria are also known to produce these chelating compounds (Trick et al., 1983; Armstrong and Van Baalen, 1979) which are low molecular weight having a high affinity towards iron, known as ‘scavengers’(Jenifeer and Sharmili, 2015; Krewulak and Vogel, 2008).

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Siderophores not only scavenge Fe but also form complexes with other essential elements in the environment such as Mo, Mn, Co, and Ni and provide to the microbial cells (Bellenger et al., 2008; Braud et al., 2009).

In Gram-negative and Gram-positive bacteria, uptake of iron is regulated by several repressor proteins (Visca and Imperi, 2018), Siderophore binding proteins (SBPs) or outer membrane proteins (OMPs), on the bacterial cell membrane (Schalk et al., 2009 and Fukushima et al., 2014). Siderophore forms complex with the molecules and are transported inside the cells by membrane receptors by an operon, regulated by five genes (Lewin, 1984) transported in the intracellular periplasmic space.

Metal acquisition using siderophores by other microorganisms increased their applications in a wide range of fields such as bioremediation, agriculture, medicine, cell communication, virulence, and oxidative stress (Johnstone et al., 2015). In this review, microbial siderophores will be discussed with their role and potential applications in different fields.

2. MICROBIAL SIDEROPHORES

There are wide ranges of siderophores produced by microorganisms (Fig.1). Most common siderophores produced by bacteria are hydroxamate (i.e. ferrioxamine B), catecholates (i.e. Enterobactin), and few are carboxylates (i.e.rhizobactin), another is nixed types (i.e. pyoverdine) (Cornelis, 2010). Hydroxamates are most commonly produced by fungi belonging to the ferrichrome family. (Renshaw et al., 2002; Winkelmann, 2007) produced by *Aspergillus ochraceous*, *Ustilago sphaerogena* (Jalal and Vander Helm, 1991; Ali et al., 2011; Neilands, 1981).

Gram-positive and Gram-negative bacteria possess different transport mechanisms for iron acquisition. It is a multi-component system both receptors and an energy-dependent process (Sigel and Sigel, 1998).

These systems include Ton B- dependent outer membrane protein complex in Gram-negative bacteria e.g. *Escherichia coli* which identifies the complexes (Krewulak and Vogel, 2008; Wandersman and Delepelaire, 2004) and binds to the outer membrane receptor, it crosses the membrane through the energy-dependent system consisting of outer membrane proteins bound with periplasmic binding proteins and inner membrane proteins (Fec CDE-Fep CDE proteins) (Matzanke, 1991) and accompanied towards the cytoplasmic membrane via ATP- binding cassette (ABC) transport system, reaches the cytoplasm and releases in form of Fe(II)(Fig. 1).

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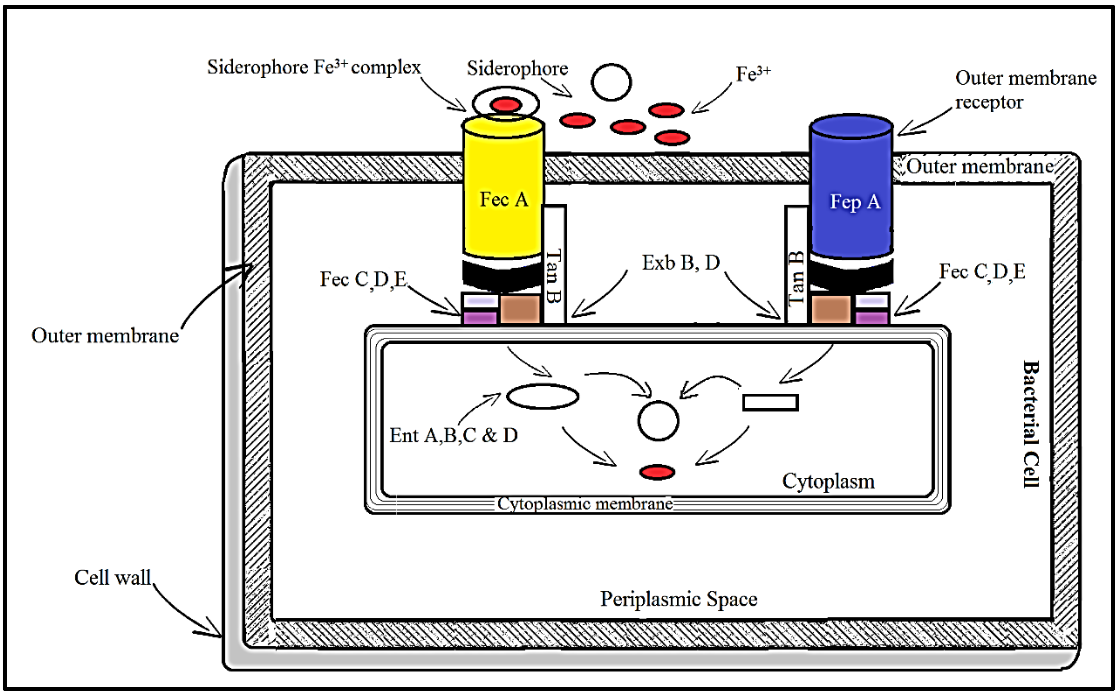
Fig.1: Iron transport system.



In contrast, Gram positive bacteria e.g. *Bacillus* sp. Lacks Outer membrane therefore Fe(III)- siderophore complexes bound by the periplasmic binding proteins that are attached to the cell membrane due to the absence of the periplasmic space (Fukushima et al., 2013) are then transported to cytoplasm via ATP-dependent (ABC) transporters (Braun and Hantke, 2011).

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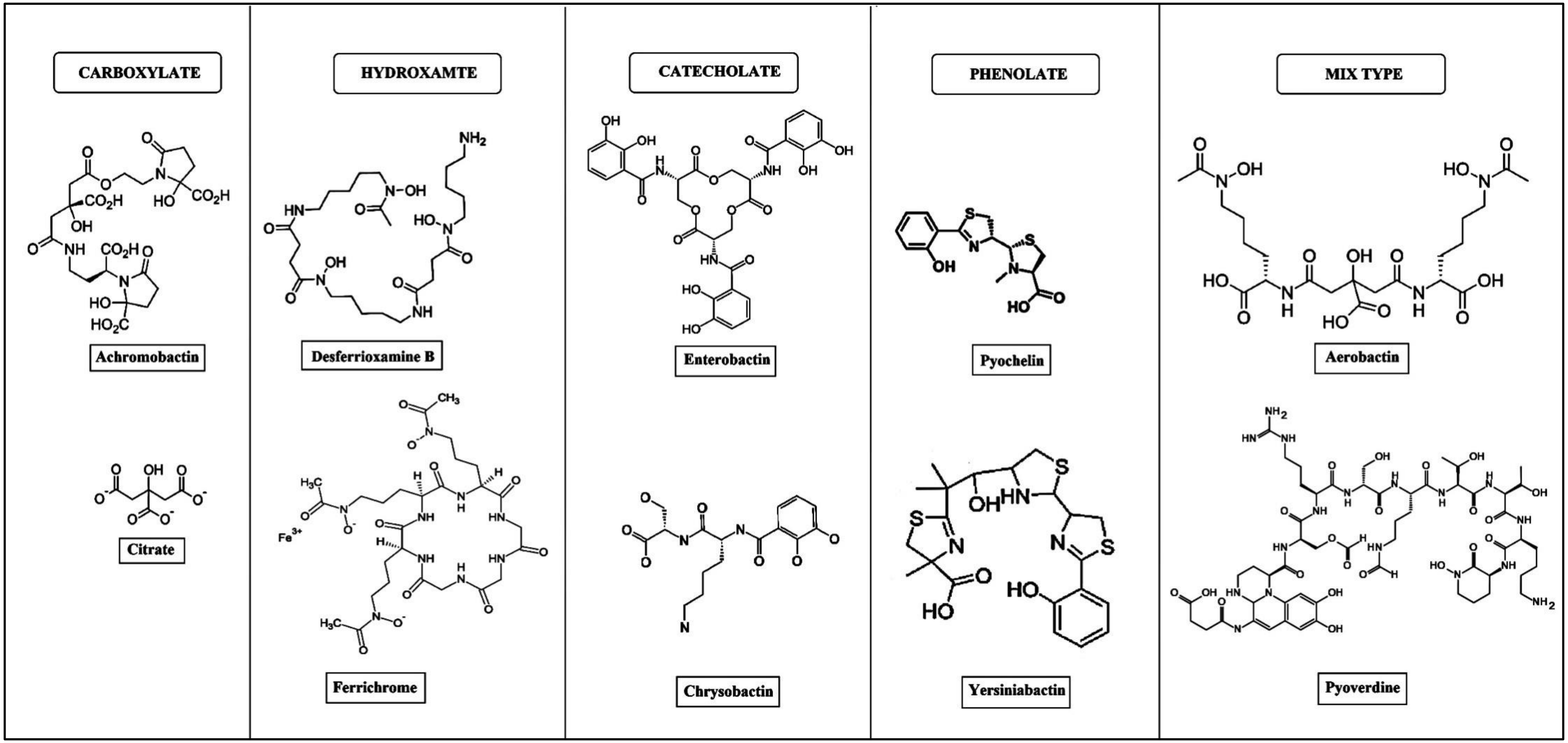
Fig.2: Molecular structures of Siderophores



There are four different Fe transport systems in fungi (Vander Helm and Winkelmann, 1994):

(i) In Shuttle mechanisms, reductive enzymes breakdown the ligand between the Fe (III) - siderophore complex when it is transported across the cell membrane and free siderophore is released and recycled (Ardon et al., 1998).
(ii) In the taxicab mechanisms, is used by Rhodotorula sp. Where the Fe (III) complex is transferred to intracellular ligands (Winkelman and Huschka, 1987).
(iii) In the Hydrolytic mechanism, the whole Fe (III)-siderophore complex undergoes several degradative and reductive processes to release and reduce Fe (III) →Fe (II) inside the cell (Adjimani and Emery, 1988).
(iv) In the reductive mechanism, Fe (III) - siderophore complexes are not transported, reduction of Fe (III) → Fe (II), and Fe is taken up by the cell (Eckery and Emery, 1983).

3. APPLICATIONS OF SIDEROPHORE

Agricultural application

Production of siderophores by soil microorganisms can help promote mineral weathering, as it plays a significant role in the iron dissolution. The introduction of *Pseudomonas putida* in soil produces pseudobactin which increases the yield and growth of plants (Kloepper et al., 1980). Hydroxamate type siderophore plays a vital role in the immobilization of metals in soil (Barton et al., 1954), they are known to reduce the heavy metals deposition as it reduces the soil fertility. They are known to provide Fe as a micronutrient to enhance growth. Siderophores are also known as an eco-friendly alternative to pesticides (Schenk et al., 2012) for protecting them from phytopathogens e.g. production of Pyoverdine by *Pseudomonas* species. Recent investigation on plant growth activities and siderophores produced by *Aspergillus niger*, *Penicillium citrinum* and *Trichoderma harzinum* were found to increase the length and are also responsible for growth in the shoot and root of chickpeas (Yadav et al., 2011). Siderophores produced by bacterial species are also known to inhibit the growth of phytopathogens such as Pyoverdine in peanuts and maize (Pal et al., 2001) and siderophores secreted by *Bacillus subtilis* showed an important role in the biocontrol of *Fusarium oxysporum* causing wilting of the pepper plant (Yu et al., 2011).

Optical biosensor

A biosensor is a biomolecule bound to an electrical device. Devices such as converters, amplifiers, and noise filters. To increase the signal-to-noise ratio that allows different types of responses to be recognized by the engineered system (Gupta et al., 2008). Pyoverdine is a yellow-green water-soluble fluorescent dye. Siderophores are characterized by the following characteristics (Barrero et al., 1993): (a) They form

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strong Fe(III) complexes with weak or negligible affinity for Fe (II), (b) Fe (III) complex has very high stability constant (Approximately K = 1032) (Kurtz and Crouch, 1991). This Property makes pyoverdine a promising remedy for the construction of optical biosensors (Pesce and Kaplan, 1990). Uses of siderophore with anomalous Fe (III) coupling constants are an ideal choice for applicable sensor molecular recognition elements. In determining the bioavailability of Fe in seawater or soil (Chung Chun Lam et al., 2006) concentration. The amount of Fe present in the ocean was determined by using Siderophore as a biosensor (Chung Chun Lam et al., 2006). In this study, they used parabactin produced by *Paracoccus denitrificans* as a biosensor, encapsulation into a sol-gel thin film on a quartz substrate. Seawater samples were analyzed by a Flow cell that was placed in a fluorescent sample split spectrometer. Siderophore also provides an excellent sensitive and selective detection system that mimics the biological uptake process (Ellerby et al., 1992). For example, azotobactin was produced by *A. vinelandii* .Fe (III) (Sharma and Gohil,) redesigned based on encapsulating azotobactin in a sol-gel matrix without significant loss of fluorescent signal.

Bioremediation of Persistent pollutants in the environment

Siderophores have a strong binding affinity towards Fe but are also effective in solubilizing other wide range of metals such as Co, Cd, Ni, Cu, Pb, Zn, Th(IV), U(IV), and Pu (IV) (Schalk et al., 2011). Therefore, it becomes a vital tool in bioremediation which increases due to the manufacturing industries, sludge applications, mining, and nuclear power stations, which led to metal deposition and cause pollution (Wasi et al., 2013). It is an economic and eco-friendly method (Rajkumar et al., 2010).

Hong and colleagues (2010) recorded in vitro solubilizing of Cu and Zn by siderophores produced by Fusarium solani. Wang et al., (2011) reported the removal of As from metal-contaminated soil by siderophores produced by *Agrobacterium radiobacter*. Phytosiderophores are also reported for the efficient metal mobilization in soil (Rajkumar et al., 2009) compared to that synthetic chelators and microbial siderophores (Awad and Romheld, 2000; Singh et al., 2008).

Petroleum hydrocarbons

Petroleum hydrocarbons in marine ecosystems are one of the major environmental threats which can be overcome by using microorganisms, in their remediation activity from the marine environment. Under Fe- limiting conditions, microbial and through indirect method siderophores participate in the biodegradation activity of petroleum hydrocarbons. *Marinobacter hydrocarbonoclasticus* was the first reported marine bacterium responsible for oil-degrading and its siderophore was structurally characterized (Barbeau et al., 2002).

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Reprocessing of Nuclear fuel

The Purex technique has been used commercially to reprocess irradiated nuclear gas with the aid of using solvent extraction and U and Pu separation strategies for reuse from fission merchandise, including Ti and Np (Taylor and May 1999). During this technique, U and Pu circulate the solvent and turn out to be infected with Np. Siderophores had been proven to permit the selective elimination of Np from the solvent phase (Taylor et al., 1998), and thus siderophores might be used inside the Purex technique to simplify the doing away with the actinides (Renshaw et al., 2002). Desferrioxamine B bureaucracy is a strong complex with U (VI), in which its hydroxamate purposeful institution is comparable to acetohydroxamic acid, a ligand that has been proposed for actinide complexion (Mullen et al., 2007). Marshall et al. (2010) found that low siderophore levels were high enough to affect the dissolution of usage of natural gas and good for the use of artificial desferrioxamine B and pyoverdine produced with the help of *P.fluorescens*.Based on research, siderophores have been proposed for the restoration of radioactive waste and the reprocessing of nuclear gas.

Siderophore and MRI

To improve contrast enhancement, for example, in Magnetic resonance imaging, different paramagnetic ions such as Mn^{2+}, $Fe^{3+,}$ and Gd^{3+} was used. Gd^{3+} is especially suitable as a contrast agent in diagnostic medical MRI because of its high magnetic moment and cheap electronics. The mitigation rate, Gd^{3+} is high, toxic at the concentration required for MRI. Therefore, this requires a chelating agent Prevents release of free cations in vivo. Again, siderophore and synthetic analogs Serves as the main model for such things Chelating agent.

Iron chelators in cancer therapy

Siderophores are potentially used as chelating agents in the treatment of cancer, such as Dexrazoxane, O-trensox, Desferriexochelin, Desferrithiocin, Tachpyridine has been found in cancer therapy (Miethke and Marahiel, 2007). Also used for siderophore clearance non-transferrin-bound serum iron occurs as a result of cancer treatment Several Chemotherapy (Chua et al., 2003).

Antimalarial activity of iron chelators

Some siderophores had been determined to be beneficial withinside the remedy of malaria caused via way of means of *Plasmodium falciparum*. Siderophore produced via way of means of *Klebsiella pneumoniae* act as an antimalarial agent (Gysin et al., 1991). Desferrioxamine B produced via way of means of *Streptomyces pilosus* (Now produced via way of means of chemical synthesis also) is lively against *P. falciparum* in vitro in addition to in vivo. Siderophore enters internal *P. falciparum* molecular and reasons intracellular iron depletion. The identical siderophore changed into proven to

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inhibit boom of *Trypanosoma brucei*, some other protozoic parasite inflicting Trypanosomiasis in human bloodstream (Breidbach et al., 2002).

Trojan horse antibiotics (Siderophore- antibiotics conjugates)

Siderophore can be used for selective use Delivery of antibiotics in antibiotics resistant bacteria. It's possible powerful application using iron carry siderophore transport capacity to carry intracellular drug by conjugating siderophore with an antibacterial agent (Trojan horse strategy). Nature provided an example for siderophore-antibiotics such as Albomycin (Benz et al., 1982). Ferrimycin (Bickel et al., 1966) or Salimycin (Vertesy et al., 1995). Albomycin uses part of the ferrichrome Structure of Fe3 + chelation connected via a Serine spacer to toxic molecules. Several Microorganisms introduce albomycin via the Ferrichrome system for cells with toxic parts which showed harmful effects on cells are enzymatically released. Similarly, ferrimycin has attached with a unit containing antibiotics activity of amides to ferrioxamine B. Salimycins is a dicarboxylic acid Spacer between trihydroxamate siderophore and aminoglycosides antibiotics. Nature outbreak Siderophore-antibiotics paved the way create a synthetic Trojan.

4. CONCLUSION

Currently, there are some references to the microbial siderophore and its agricultural, health and environmental benefits. Therefore, it is necessary to investigate and study the details of siderophore ecosystems, from mesophilic to extremophiles, and to harness those advances for life and environmental well-being.

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