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Role and Applications of Microbial Siderophores in the Environment

Shivangani Sharma[1], Ajay Kumar[1]*, Monika Chauhan[1], Diwakar Chauhan[2] and Vanya Garg[1]

[1]*Division of Life Sciences, School of Basic and Applied Science, Galgotias University, Greater Noida, UP, India*
[2]*Division of Chemistry, School of Basic and Applied Science, Galgotias University, Greater Noida, UP, India*

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ABSTRACT

Siderophores are the low-molecular weight secondary metabolites which have a strong preference for ferric iron and are generated by bacteria when they are exposed to iron stress. Iron is a vital nutrient which is required for the various cellular processes such as electron transport but due to aerobic conditions most of the iron becomes unavailable as surface iron get oxidized into oxyhydroxide polymers and free iron get reduced. Siderophores have clinical, environmental as well as agricultural applications. Clinical applications involve anticancer activity, anti-malarial activity and also help to remove transuranic elements and in agriculture, various types of siderophores help in the promoting the growth of some plant and enhance the uptake of Fe which leads to increase the plant yield and also protect plants from pathogens. Environmental applications involve the binding of the toxic metals such as Pb^{2+}, Cd^{2+}, Hg^{2+}etc, with siderophores which helps in heavy metal bioremediation. The purpose of this review is to explore about siderophores, their varieties, and their uses.

Key words: *Metabolites, Microorganisms, Chletaing agent and Siderophores etc.*

Introduction

In terms of abundance on earth, iron is the fourth most common element (Huber *et al.*, 2005; Gamit *et al.*, 2014) but most of it is unavailable. Due to aerobic conditions and physiological pH, ferrous iron gets oxidized into its ferric form which further gets hydroxylates into soluble $Fe(OH)_3$ polymer , which makes iron unavailable for the plants and the other organisms. Fe^{3+} and Fe^{2+} are the two oxidation states in which it can exist. Iron can play a significant role in oxidation-reduction reactions due to its variable valence (Taylor *et al.*, 2011). As iron is the vital nutrient it is required for the electron transport, synthesis of DNA and other metabolic processes. That's why under iron limiting conditions few bacteria, fungi and some plants produce iron chelating molecule known as siderophores. These siderophores produce ferric iron which is transported to the cytosol where these ferric irons get reduced into ferrous iron. When iron become accessible then the ferrous iron is dissociated from the siderophores and the siderophore is recycled by the efflux pump system (Saha *et al.*, 2015). Siderophores is a low- molecular weight (<10KD) secondary metabolite which has high affinity to chelate iron (Fe). They are produced by many bacteria viz. *Pseudomonas*, *Azotobacter*, *Bacillus*, *Enterobacter*, *Serratia*, *Azospirillum* and *Rhizobium* (Glick *et al.*, 1999; Ali *et al.*, 2013). Siderophores are small peptide molecule with side chain and functional group that have high-affinity ligand that binds with the ferric ions and transport them through the cell membrane with the help of siderophore receptors (Niehus *et al.,* 2017; Raymond *et al.,* 2015). Both Gram positive and Gram-negative bacteria can produce these. The proteins that bind to siderophores, permeases, and ATPases help Gram positive bacteria deliver the iron siderophore complex to the cell membrane, whereas in Gram negative bacteria, the transport of the iron siderophore complex is mediated by the cytoplasmic membrane protein, outer membrane receptor and periplasmic binding proteins (Ahmed *et al.,* 2014). Siderophores are also produced by aerobic and facultative aerobic bacteria under iron stressed conditions (Saha *et al.,* 2015). Aerobic microorganisms require iron for various functions such as for heme formation, DNA ribotide precursor reduction, reduction of oxygen for ATP synthesis and for other essential purposes. For survival and growth of bacteria in the competitive environment of the soil, it is important for the bacteria to synthesize siderophores as it is an important component of the bacterial machinery for sufficiency of iron (Khan *et al.,* 2006). *Pseudomonas stutzeri*CCUG 36651, a facultative aerobic bacterium, has been found to synthesize siderophores under each aerobic as well as anaerobic conditions, although the siderophores generate in aerobic circumstances are different from those synthesize under anaerobic conditions (Essén *et al.,* 2007). Detection of siderophore can be done by variety of techniques such as mass spectrometry (Dimkpa *et al.,* 2008a; Dimkpa *et al.,* 2008b) and by production of siderophore on Chrome Azurol S assay (CAS) (Carrillo-Castañeda *et al.,* 2005). This technique depends on the competition for iron between the bacterially produced siderophore and the ferric complex of the indicator dye (Carrillo-Castañeda *et al.,* 2005). Siderophore forms an 'orange halo' surrounding the bacterial colonies. Orange halo indicates the production of Fe- binding compounds. It should be noted that not all microbes need or require iron for their growth for example: Lactic acid bacteria do not stimulate growth in the existence of the Fe. Siderophores typically scavenge Fe from the environment, but they also create complexes with other vital substances (such as Ni, Co, Mo, and Mn) and create them viable for various microorganisms (Braud *et al.,* 2009a; Braud *et al.,* 2009b). Some bacteria are able to produce more than one siderophores. These bacteria help to fulfil the requirement of other microorganisms. This property of siderophores leads to the increase in applications of siderophores. Primary purpose of siderophore is to provide soluble Fe to the microbes for their development. They are also used in a variety of other disciplines, including agriculture, biosensors, heavy metal bioremediation, ecology, and medicine. At present nearly 500 siderophores are identified out of which 270 are well characterised (Boukhalfa *et al.,* 2003).

Classification/Types of Siderophore

On the basis of chemical structure and co-ordination sites of iron siderophores are characterised as: Catecholate, hydroxymate and carboxylate.

Catecholate (Phenolates)

These are only found in bacteria viz. *Enterobactin, Bacilibactin* and *Vibriobactin* (Hider *et al.,* 2010). These bacteria can bind tightly with ferric ions (Fe^{3+}). Each group of catecholate can form hexadentate octahedral complex, by the supply of two oxygen atom which chelates with iron (Saha *et al.,* 2016). Some species can also form linear catecholate siderophore (Ali *et al.* 2013). Several methods are used to detect catecholate type of siderophore such as High Performance Liquid Chromatography (HPLC) with diode array detection (DAD) (Fiedler et al. 2001), O-CAS assay (Pérez-Miranda *et al.,* 2007), Neiland's spectrophotometric assay (Neilands *et al.* 1981).

Hydroxymate

These siderophores are manufactured by both bacteria and fungi. Such as, ferribactin produced by *Pseudomonas fluorescens* (Maurer *et al.,* 1968), coprogens (Zahner *et al.,* 1963) and fusigen (Neilands *et al.,* 1973) produced by *Trichoderma spp.* and *Fusarium spp.* respectively (Saha *et al.,* 2015). With ferric iron, hydroxymate exhibits significant binding over a wide range (10^{22} to 10^{32} M^{-1}). These siderophores are generated by acylated and hydroxylated alkylamines in bacteria, and by hydroxylated ornithine in fungi (Baakza *et al.,* 2004). This strong binding helps to prevent enzymatic and hydrolytic breakdown in the environment (Winkelmann *et al.,* 2007). It has a secondary C (=O) N-(OH) R group for chelating iron, where R is an amino acid or one of its derivatives. Each siderophore forms a bidentate ligand with iron (Fe^{3+}), forming a hexadentate octahedral complex, with the help of two oxygen molecules from the hydroxamate group. Several methods are used to detect hydroxymate type of siderophores such as Neiland's spectrophotometeric assay (Neilands *et al.,* 1981), Csaky's assay (Pal *et al.,* 2010), Modified overlaid Chrome azurol S (O-CAS) assay (Pérez-Miranda *et al.,* 2007).

Carboxylate

In addition to bacteria, fungi also produce these siderophores. The greatest example of this type of siderophore is *Rhizobium*, which resembles rhizobactin in structure. Iron chelator of this type of siderophore is hydroxycarboxyland ethylenediamine D-carboxylic acid structures. Carboxylate siderophores are most beneficial for the microbes surviving in the acidic environment because these siderophores are more successful at acidic pH as compared to catecholate and hydroxylate type (Miethke *et al.,* 2007). These siderophores have carboxyl and hydroxyl group for Fe binding (Dave *et al.,* 2000). Several methods are used to detect carboxylate type of siderophore such as Spectrometer; O-CAS assay (Alexander *et al.,* 1991).

Applications

Agricultural applications

Siderophores in crop improvement

Iron is required for various important activities in plants such as redox reaction, synthesis of chlorophyll and physiological activities (Briat *et al.,* 1995; Saha *et al.,* 2015). That's why lack of iron leads to the reduction in the quality and quantity of crop production. Plant might get Fe from microbial siderophore via two different mechanisms, according to the study: (i) High redox microbial siderophore provide Fe^{2+} to the plant's transport system.This technique explains how siderophore reduction may occur when microbial Fe^{3+} -siderophores are transferred to the apoplast of plant roots (Ahmed *et al.,* 2014). As a result, Fe^{2+} is thereby trapped in the apoplast, raising Fe levels in the root (Ahmed *et al.,* 2014). (ii) Microbial siderophores have the ability to chelate Fe from soils and subsequently exchange ligands with phytosiderophores (Masalha *et al.,* 2000; Ahmed *et al.,* 2014). Important factors in this system include the pH of root atmosphere, redox levels of the root atmosphere, the amounts of microbial and phytosiderophores, and their stability constants (Crowley *et al.,* 2006).Various siderophores helps in the enhancing the plant growth by providing Fe, synthesis of phytohormones and production of organic acids (Souza *et al.,* 2015). They have been proposed as a non-hazardous pesticide alternative (Schenk *et al.,* 2012). Siderophores produced by microorganisms prevents the proliferation of the other microbes by releasing antibiotics. Hydroxamate siderophores are mainly present in soil (Ghosh *et al.,* 2020). They promote a crucial role in the immobilization of the metals. Excessive toxic heavy metals are present in the soil which affects the fertility of the soil and decreases the microbial activity. There are several bacteria that promote plant growth and improve plants growth by generating siderophores such as pyoverdine siderophores produced by *Pseudomonas* sp. (Saha *et al.,* 2015). Some bacteria, produce ferrioxamines, such as *Azadirachta indica*, may help plants obtain the iron they need and promote the growth of their roots and shoots (Verma *et al.,* 2011).

Siderophores as biocontrol agents

The biological control mechanism against certain phytopathogens relies heavily on siderophores. Siderophore facilitates the killing of phyto-pathogen by binding the iron which lowers the amount of bioavailable iron, making it easier to destroy them (Ahmed *et al.,* 2014). Pyoverdine siderophores produced by *Pseudomonads* help to prevent potato wilt brought on by *Fusarium oxysporum* (Schippers *et al.,* 1987). *Gaeumannomyces graminis* is also susceptible to the pyroverdine siderophore. It has been linked to a wheat and barley deficiency expansion (Voisard *et al.,* 1989). Pyoverdines have also been discovered in peanuts and maize to decrease plant diseases (Pal *et al.,* 2001). As biocontrol agents, microorganisms other than *Pseudomonas* are also a potential. In the case of *Fusarium oxysporum*, the causative agent of Fusarium wilt of pepper, *Bacillus subtilis* siderophores were essential in its biocontrol (Yu *et al.,* 2011).

Environmental applications

Siderophore as biosensor

A biosensor is an analytical tool that uses specially designed systems to detect various types of reactions. This system can be a single biomolecule or a collection of biomolecules that are connected to an electrical device (Gupta *et al.,* 2008). Three parts make up a biosensor: a biotransducer, a biorecognition component, and an electrical system comprising a processor, signal amplifierand display (Eggins *et al.,* 1996). The bioreceptor-like recognition element communicates with the target analyte. The biotransducer gauges the degree of binding by producing a signal directly proportional to the analyte concentration in the sample. Any biosensor design should aim to make it simple to analyse the analyte where the sample was taken, at the point of concern (Saha *et al.,* 2015). Pyoverdin, a naturally occurring fluorescent pigment generated by *Pseudomonas*, has been suggested to be a potential new biosensor for iron monitoring and detection (Barrero *et al.,* 1993). The characteristics of pyroverdines, which are fluorescent siderophores that are yellow-green and soluble in water, are as follows (Barrero *et al.,* 1993): (a) They have a strong affinity for Fe^{3+} and a minimal or non-existent affinity for Fe^{2+}. (b) The stability constants of Fe^{3+}combinations are extremely high (about $K= 10^{32}$) (Kurtz *et al.,* 1991). Pyoverdine is a potential compound for the development of optical biosensors due to these features (Ahmed *et al.,* 2014). This biosensor is extremely iron-selective (III). The sample can be detected and analysed in solution either in immobilised form (detection concentration=3 ng/ml) or at (detectable concentrations of 10 ng/ml) using this biosensor. The sensor was successfully used to assess the presence of iron in a variety of water samples (Barrero *et al.,* 1993). *Pseudomonas fluorescens* is a $Fe3^{+}$ biosensor that is reliable, sensitive, and selective. The biosensor is low-cost and simple to use, depending solely on spectrophotometry. The low-cost biosensor can be used for a variety of purposes, including (a) medical applications such as determining $Fe3^{+}$ concentrations in biological samples and medication interactions with $Fe3^{+}$, (b) environmental applications such as $Fe3^{+}$ concentrations in water samples can be determined and (c) commercial applications such as Fe3+ concentrations in reactors can be determined (Gupta *et al.,* 2008). Although some siderophores have been investigated as possible biosensors, the majority have yet to be fully described. There is a chance that some of the uncharacterized siderophores will end up being a novel biosensor as a result.

Bioremediation of heavy metals

The contamination of the soil was caused by the build-up of metalloids and heavy metals. Due to the rapid expanding firms, incorrect metal waste ejection, waste water irrigation, mine tilling, and atmospheric deposition, heavy metals and metalloids are accumulating (Wuana *et al.,* 2011). Some heavy metals are used as micronutrients by plants. The most common contaminated heavy metals are Pb, Ni, cd, Cu, Cr and Hg (Ali *et al.,* 2013). Siderophores can be used for heavy metal bioremediation. Bioremediation is the removal of contaminants from the contaminated sites like water, soil, oceans etc. The removal of contaminants varies due to siderophores concentration, bioavailability of metal, solubility and environmental conditions such as electron potential, ionic strength and pH (Gadd *et al.* 1996). Siderophores can bind with wide array of toxic metals (eg: Cr^{3+}, Pb^{2+}, Al^{3+}, Eu^{3+} and Cu^{2+}) which leads to the detoxification of heavy-metal-contaminants (Rajkumar *et al.,* 2010; O'Brien *et al.* 2014). Iron-bound siderophores efficiently enter cells while those bound to heavy metals do not (Noinaj *et al.,* 2010). *Pseudomonas aeruginosa* produced the siderophore pyochelin, are capable of chelating a wide variety of metals, including Ag^{+}, Pb^{2+}, Sn^{2+}, Tb^{3+}, Tl^{+}, Cd^{2+}, Al^{3+}, Co^{2+}, Eu^{3+}, Ga^{3+}, Cr^{2+}, Hg^{2+}, Cu^{2+}, Cu^{2+}, Ni^{2+}, Zn^{2+} and Cu^{2+}; however, no metal other than Fe^{3+} appeared to be taken up by the absorption process (Braud *et al.,* 2009a) and stop these metals from entering the bacteria (Braud *et al.,* 2009b). *Azotobacter vinelandii* developed siderophores like azotobactin and azotochelin, which it used to acquire both Mo and V (Wichard *et al.,* 2009). Siderophores have been found to be important in the mobilization of metals from metal-contaminated soils (Ahmed *et al.,* 2014). They had a considerable impact on the mobilization of metals from mine waste or metal-contaminated soil. In the presence of *P. fluorescens*-produced siderophores, a large number of metals (Ni, Co and Fe) were mobilized from waste material (acid-leached ore) from a former uranium mine (Edberg *et al.,* 2010).

Medical applications

Iron overload therapy

Treatment for β-thalassemia and some other anemias involves regular whole blood transfusions (Hershko *et al.,* 2002). Continuous transfusion of whole blood leads to the steady accumulation of iron which causes excess of iron in human body. These excessive iron causes iron overload diseases such as accidental iron poisoning, hemochromatosis and hemosiderosis.In order to reduce both excess iron and the initial iron overload, the body needs to eliminate iron from the system, especially from the liver. In humans, there is no specific physiological mechanism for iron excretion that's why siderophore mediated drugs was used to remove excessive iron from the body (Pietrangelo *et al.,* 2002). The medicine Desferal is used to treat thalassemia major (Robotham *et al.,* 1980) and sickle cell anaemia.

Removal of transuranic element

The risk of human exposure to transuranic elements like vanadium and aluminium has increased as a result of the usage of nuclear energy to produce electricity (Nagoba *et al.,* 2011). End-stage renal failure (ESRF) and dialysis encephalopathy individuals on dialysis are at risk from aluminium overload (a serious side effect of prolonged dialysis caused by aluminium aggregation in the brain). Siderophores can be used to expel these substances from the body. The ability of siderophores to eliminate such elements from the body has been investigated (Ali *et al.,* 2013). Chronic aluminium overload can be treated with siderophores like Desferol, which also remove vanadium, another transuranic metal (Nagoba *et al.,* 2011).

Torjan horse antibiotics

Antibiotics can be delivered selectively to antibiotic-resistant bacteria using siderophores (Ali *et al.,* 2013). The Trojan horse approach can use siderophores to deliver drugs selectively to antibiotic-resistant bacteria. By producing conjugates between siderophores and antimicrobial medicines, this technique takes advantage of siderophores' iron transport abilities to transfer medications into cells (Huang *et al.,* 2013). Using the Fe-siderophore harvesting technique, the antibiotic molecule binds the siderophore as a "Trojan horse" transporter and enters the microbial cell. A linker connects the drug to the siderophore to give regulated chemical or enzymatic release of the drug into the targeted bacterial cell. The pharmaceutical and siderophore combination kills the cell by either releasing the drug, acting as a full antibacterial agent, or preventing further iron uptake once inside the cell (Nagoba *et al.,* 2011). There are two forms of siderophore-antibiotic conjugates: synthetic and natural. Natural siderophore-antibiotic conjugates are ferrimycin, salmycin, albomycin (derived by *Actinomyces* as well as *Streptomyces*), and microcin (extracted from gut of bacteria). A member of the sideromycins class of substances, albomycin is a naturally occurring antibiotic that consists of an antibiotic moiety joined to a siderophore. It has been demonstrated that various types of gram-positive and gram-negative bacteria are inhibited by albomycin (Pramanik *et al.,* 2006). Albomycin inhibits protein synthesis in *E. coli* via blocking t-RNA synthetases (Khasheii *et al.,* 2021). In synthetic siderophore-antibiotic conjugates, siderophores can bind antibiotics like beta-lactams (carbacephalosporins), nalidixic acid, erythromycin, vancomycin, sulfonamides, norfloxacin, and others. The results demonstrate that these conjugates are more effective and that siderophore-mediated drug transport is very important. As siderophore is recognized by microbes as an iron transporter, the conjugated molecule is absorbed and terminates the bacteria (Ding *et al.,* 2008). Antimicrobials are now delivered using mostly hydroxamate and catecholate types of siderophores to circumvent membrane-permeation-based drug access issues (Milner *et al.,* 2013). For some applications, therefore, carboxylate-type siderophores, like staphyloferrin A, may be a better choice since they have more potent iron chelating activities under acidic circumstances than catecholate and hydroxamate siderophores (Milner *et al.,* 2013). Staphyloferrin A's hydrophilic characteristic promotes medication transmission to bacterial cells by enhancing its water solubility (Khasheii *et al.,* 2021; Milner *et al.,* 2013).

Conclusion

Every living entity needs iron for growth and development. But inorganic iron is particularly insoluble under aerated circumstances at neutral to alkaline pH, and its concentration is less than ideal for bacterial development. To obtain that ideal concentration of iron some microorganisms generate siderophores during iron deficient conditions and scavenge iron. The application of microbial siderophores for human, animal, and plant sustainability has immense potential. Siderophores' diverse applications show that they have the potential to be used as a potential agent in a variety of fields, including ecology, agriculture, bioremediation, biosensors, and medicine. However, siderophore research has yet to be implemented in numerous fields of Microbiology. As a result, more and more siderophores from various habitats must be identified and characterized from both normal and extremophiles conditions for the welfare of environment and living things.

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