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CHEMICAL AND BIOLOGICAL STUDIES OF MICROBIAL SIDEROPHORES

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ABSTRACT

Iron is an essential for the growth of almost all living micro organisms because it acts as Catalyst in enzymatic processes, oxygen metabolism, electron transfer and DNA and RNA syntheses. Siderophores are organic compounds with low molecular masses that are produced by micro organisms and plants growing under low Iron conditions. The primary function of these compounds is to chelate the ferric Iron [FeIII] from different terrestrial and aquatic habitas and thereby make it available for microbial and plant cells. Siderophores have received much attention in recent years because of their potential roles and applications in various fields like environmental, Agriculture, Biosensors, medical field etc. Their significance in these applications is because Siderophores have the ability to bind a variety of metals in addition to Iron and they have a wide range of chemical structures of specific properties.

KEYWORDS: Iron Chelation, Siderophores, Agriculture, Medicine, Biosensor.

1. INTRODUCTION

Iron is essential for almost all living organisms as it is involved in a wide variety of important metabolic processes. However, Iron is not always readily available; therefore, micro organisms use various Iron uptake systems to secure sufficient supplies from their surroundings. Iron is the fourth most abundant element in Earth's crust.[1]

It is a transition metal which exist in two oxidation states, Fe(III) and Fe(II). Variable valence of Iron allows it to play a key role in the oxidation-reduction reactions.[2,3] Iron is essential for various metabolic processes like tri-carboxylic acid cycle, electron Transport Chain, oxidative phosphorylation and photosynthesis. Recently it has also been noted that Iron plays an important role in the microbial bioflim formation as it regulates the biosynthesis of porphyrins, vitamins, antibiotics, toxins, cytochromes, Siderophores, pigments and aromatic compounds, and Nucleic acid synthesis.[4] At physiological pH (7.35-7.40), The ferrous form (Fe^{2+}) of Iron is soluble, while the ferric from (Fe^{3+}) is insoluble.[5]

At this stage several report suggested by different scientists in which the concentration of dissolved ferrous Iron to be around 10^{-10} – 10^{-9} M[6] while the required level of ferrous Iron by living organisms is around 10^{-7} to 10^{-5} M. Micro organisms produce certain organic compounds with low molecular masses to survive under such Iron-depleted environment called siderphores. Siderophores (Greek sideros meaning Iron and Phores meaning bearer) are small high affinity Iron chelating compounds secreted by micro organisms such as bacteria, Fungi, and also grasses. Siderphores are amonst the strongest soluble Fe^{3+} binding agents known. Siderophores first binds with iron (Fe^{3+}) tightly and then the Siderophores Iron complex moves into the cell through the cell membrane using the specific siderophore receptors.Once Siderophores bound to ferric Iron moves to cytosol, the Fe(III) ion gets reduced to Fe(II) ion and the ferrous form of Iron becomes free from the Siderophores. After release of Iron, Siderophores either get degraded or recycled by excretion through efflux pump system. Bacterial cell utilizes Fe(II)state and numbers of growing bacterial cells increases. as shown in Fig.1.

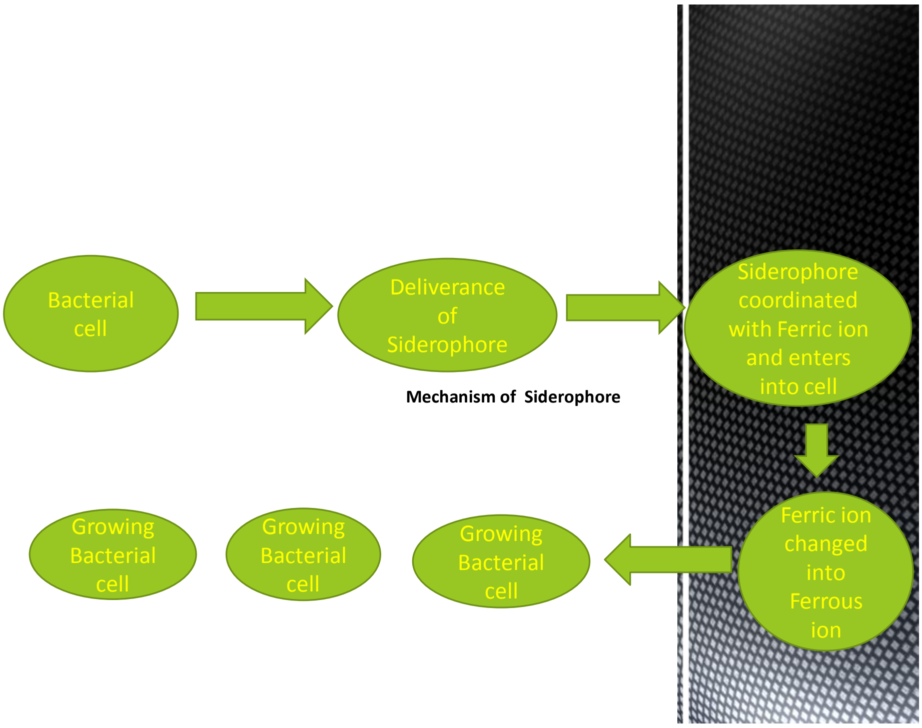


Fig. 1: Siderophore-mechanism.

Siderophores usually form a stable hexadentate octahedral complex Preferentially with Fe^{3+} compared to other naturally occurring abundant metal ions, although if there are fewer than six donor atoms water can also coordinate.

Siderophores have numerous applications in different fields like ecology, medical field, Agriculture, Biosensor and bioremediation.

At present more than 500 Siderophores were reported, of which 270 were well characterized[7] while the rest remain uncharacterized and their functions are yet to be determined.[8]

2. Classification of Siderophores on the basis of chemical and structural features.

Depending on the oxygen ligands for Fe(III) coordination, chemical properties and structural features siderophores have been classified into three main categories, namely Hydroxamates, Catecholates and Carboxylates as shown in Table-1 and Fig.-2.

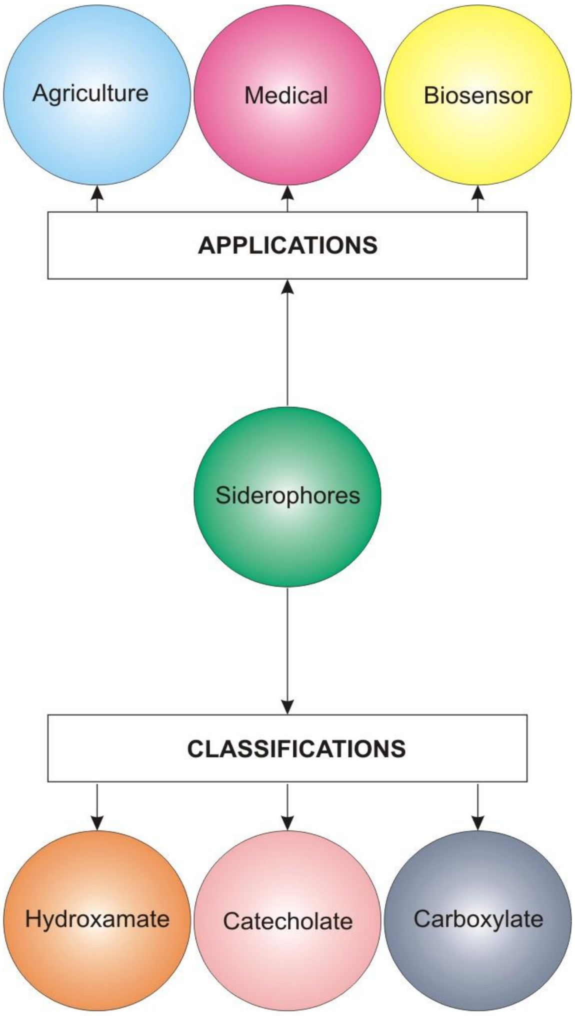
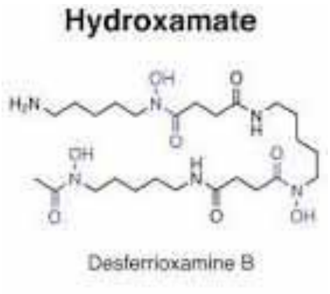


Fig.-2 Classification and applications of Siderophores

2.1 Hydroxamate Siderophores

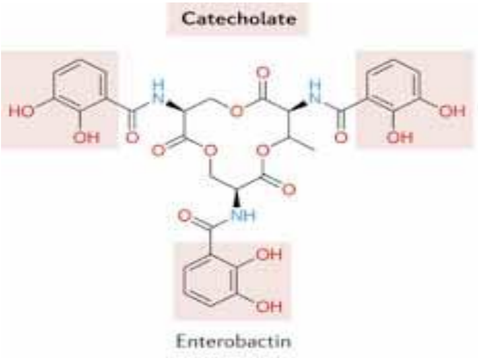
Hydroxamate Siderophores are produced by Bacteria and Fungi. Most hydroxamate groups, C(=O) N- (OH) R, where R is an amino acid or a derivative. Each hydroxamate group provides two oxygen molecules, which form a bidentate ligand with Iron, Each hydroxamate is capable of forming a hexadentate octahedral complex with ferric ion with a binding constant in the range of 10^{22} to 10^{32} M^{-1}.[9-10] This strong binding between ferric Iron and Siderophores protects the complexes against hydrolysis and Enzymatic degradation in the environment. The hydroxamate type of Siderophores can be detected by different methods like Neilands spectrophotometric assay.[11] Electrospray ionization mass spectrometry, (Saky's assay and modified overlaid chrome azurol S (O-CAS) assay.[12,13]



2.2 Catecholate (Phenolates) Siderophores

Such type of siderophore is found only in bacteria.[14] Each Catecholate group provides two oxygen atoms for Chelation with Iron so that a hexadentate octahedral complex is formed as in the case of the hydroxamate siderophore.[15] Certain Bacteria can produce either catecholate siderophore alone or mixed siderophores where Catecholate is one of the member. For example Erwinia Carotovora bacteria can produce only Catecholate siderophore whereas some members of Pseudo-monas produce a mixed siderophore consisting of both Catecholates and hydroxamates.[16]

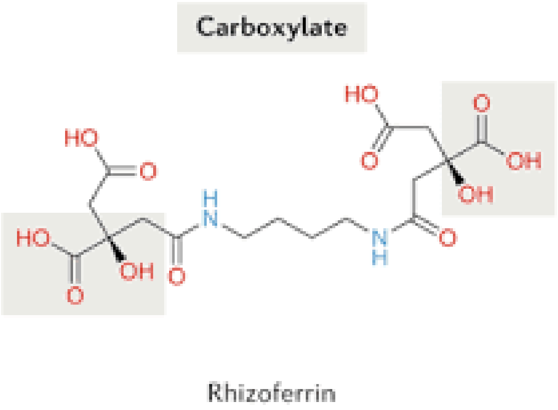
The several methods for the detection of Catecholate siderophores are Neilands spectrophotometric assay in which Catecholate siderophore binds with $FeCl_3$ and forms a wine colored complex which showed maximum absorbance at 495 nm, HPLC (High-performance liquid Chromatography, Electro spray ionization mass spectrometry (ESI-MS) and O-CAS assay.[17-19]



2.3 Carboxylate (Complexones) Siderophores

Carboxylate type of siderophores is produced by micro organisms including Bacteria and Fungi. Carboxylate siderophore binds to Iron through carboxyl and hydroxyl groups.[20,21] It consists of Citric acid or β–hydroxyaspartic acid that binds with Iron such as in staphyloferrin A, excreted by Staphylococcus aureus that consists of one D-Ornithine and two citric acid residues linked by two amide bond.

Carboxylate siderophores can be detected by a spectrophotometric test in which the siderophore copper complex is formed which is scanned for absorption maximum between 190 and 280nm[22] other methods for the detection of Carboxylate siderophore are O-CAS assay, High-Performance liquid Chromatography and Mass Spectrometry.[23]



3. Applications of Siderophores

Siderophore is biological molecule produced by micro organisms having wide applications which are discussed as follows:

3.1 Agriculture: In the field of Agriculture different types of siderophores promote the growth of several plant speices and increase their yield by enhancing the Iron uptake to plants[24] Most soil micro organisms can promote mineral weathering by the production of siderophores. Siderophores provide an efficient Fe-acquisition system because of its high affinity for Fe(III) complexation by means of mineral dissolution Inoculation of soil with Pseudobactin produced by Pseudomonas Putida increases growth and yield of various plants[25,26] Powell etal (1980)[27] stated that hydroxamate siderophores are present in various soils and they are also produced in aquatic environments. Further excessive accumulation of heavy metals in toxic to most plants and Contaminates the soil which result decreased soil microbial activity and soil fertility, and yield losses.[28] To remove this problem hydroxamate type siderophore present in soil play an important role to immobilize the metals. Pseudomonas species can enhance plant growth by producing Pyoverdine siderophores. Escherichia Coli from endo-rhizosphere of sugarcane (Saccharum Sp.) and rye grass (Lolium

Perenne) is associated with maximum siderophore production and thus enhances plant growth.[29] It has been reported that siderophores produced by Aspergillus niger, Penicillium Citrinum and Trichoderma harzianum increases the shoot and root lengths of chick peas (Cicer arietinum) Besides microbial siderophores, plants can also synthesize phyto-siderophore which can chelate the Iron directly.[30] Some Siderophores which are produced by Azadirachat indica Chelates Fe(III) from soil with high affinity and thus suppresses the growth of several Pathogens.[31]

Soils may become Contaminated by the rapid accumulation of heavy metals and metalloids. siderophores play an important role in detoxifying heavy metal Contaminated samples by binding to wide array of toxic metals e.g. Cr^{3+}, Al^{3+}, Cu^{++}, Eu^{3+}, Pb^{++} etc.[32] Molybdenum has been found to regulate production of azotobactin and Catecholate siderophore in Azobacter Vinelandil[33] Pyochelin, a siderophore produced by Pseudomonas aeruginosa can Chelate a variety of metals like Ag^{+}, Al^{3+}, Cd^{++}, Co^{++}, Cu^{++}, Hg^{2+}, Mn^{2+}, Ni^{2+} and Zn^{++} and prevents the entry of these metals into the bacteria.

3.2 Medical Field: Siderophores have important applications in the medical field to fight against antibiotic-resistant bacteria and in the treatment of several human diseases and infections. These are as follows:

Selective drug delivery-Trojan horse strategy.[34,35] (Siderophore-antibiotic Conjugates-sideromycins) is the potentially powerful application that uses the Iron transport abilities of siderophores to carry durgs into cells by preparation of conjugates between siderophores and antimicrobial agents. It uses siderophores as mediators to facilitate the cellular uptake of antibiotics. This interaction of antibiotic with siderophore results in a formation of siderophore antibiotic Conjugates known as sideromycins. Nature has provided examples for siderophore-antibiotics such as Albomycins, ferrimycins, danomycins, salmycins (isolated from Strephtomyces and Actinomyces) microcins (isolated from enteric bacteria).

Albomycins blocks protein synthesis by inhibiting t-RNA synthetase in E.coli Danomycins and Salmycins-inhibit protein synthesis in Gram Positive bacteria.

Ferrimycins inhibit Gram positive bacteria by altering protein biosynthesis Microcins- inhibit E.coli and Klebsiella SPP.[36, 37] Some siderophores have been used in the treatment of Iron overload diseases. In acute Iron intoxication and Chronic Iron overload diseases siderophores are used as chelating agents which are able to bind with Iron to produce complexes that lead to formation of ferrioxamine. The ferrioxamine is soluble in water and readily excreted through the kidneys it binds with Iron in the blood and enhances its elimination via urine and faeces. Thus it can be used to decrease the iron overload in the body. In the treatment of β-Thalassemia and certain other anemia like sickle cell anemia, Periodic whole blood transfusions are required. As there are no specific physiological mechanisms for Iron removal in humans repeated transfusion therapy results in a steady build up of Iron. Desferal is the drug used for the treatment of Thalassemia major and sicle cell anemia.[38-41]

Some siderophores have been found to be useful in the treatment of malaria caused by Plasmodium falciparum.[42] for example, The siderophore produced by Klebsiella Pneumoniae[43] and the siderophore desferrioxamine B, produced by streptomyces pilosus, have anti malarial activity against plasmodium falciparum[44] Desferrioxamine B enters inside the Prasite and causes intracellular depletion of Iron. This agent conjugates with methyl anthranilic acid and shows 10 fold greater invitro activity against P.Falciparum, which could be increased further by using nalidixic acid as a Conjuagte against multi-drug resistant P.Falciparum. This Conjugate exhibits its action similar to the metal-catlyzed oxidative DNA damage.[45,46]

Siderophore potential used as Iron Chelators in the treatemtn of cancers. Iron acts as a carrier of oxygen inside the human body. Iron found in hemoglobin, in Iron-Sulfur clusters or in other proteins plays a vital role in a variety of physiological and cellular functions like transport of oxygen, electron transport, energy metabolism and change in hydrogen per oxide levels.[47] Due to rapid proliferation cancer cells requires higher Iron concentration than normal cells for their growth and development. Recently use of certain Iron Chelators such as siderophores has been reported to decrease the growth of cancerous cells. For example desferrioxamines have been reported to significantly decrease the progression of aggressive tumors in patients with neuroblastoma or leukemia. Desferioxamine E produced by Actinobacterium was reported to reduce the viability of malignant melanoma cells significantly several other siderophores namely dexrazoxame, O-trensox, desferriexochelins, desferrithiocin and tachpyridine are used as Iron Chelators in Cancer therapy.[48-51]

Siderophores are used for the removal of transuranic elements such as Aluminium and Vanadium. The development of electricity generation by Nuclear energy has led to increase human exposure to transuranic elemtns. Aluminium overload occurs in patients with dialysis encephalopathy (a major complication of long term dialysis which is caused by the accumulation in the brain). Siderophores such as desferol can be used to treat chronic aluminum overload desferol mobilizes and Chelates aluminium bound to the tissues by forming an aluminoxamine comples, which is freely soluble in water and is readily excreted through urine or feces. Desferol can also eliminate vanadium from the body. It was reported that in rats, desferal reduced the vanadium content in kidney by 20% in lungs by 25% and in liver by 26%.[52-54]

Siderophore from Klebsiella Pneumoniae has been used in cosmetics as deodorant.

3.3 Biosensor: A biosensor is a molecule coupled to an electrical device such as a Transducer, amplifier or noise filter in order to increase the signal to noise ratio that allows detection of various types of responses through specifically engineered system. Pyoverdines are yellow green water soluble fluorescent siderophores characterized by the following properties (a) They form a strong complex with Fe(III) and have a weak negligible affinity for Fe(II) (b) The Fe(III) complexes have very high stability constants (approximately $k=10^{32}$) These characteristics make Pyoverdine a promising agent for the construction of optical biosensors using the siderophores with an exceptional Fe(III)- binding constant would be an ideal choice for the molecular recognition element of the sensor that could be applied in the determination of Fe bioavailability in oceanic water or soils. The concentration of Iron present in the ocean has been determined by using a siderophores as biosensor Azobactin produced by A. Vinelandii has been used as an optical biosensor for Fe(III) in a modified design that depends on the encapsulation of the azobactins in soil gel matrices without significant loss of its fluorescence signal. N-Methylanthranyl desferrioxamine (MA-DFB), a chemical derivative of desferrioxamine B(DFB) siderophore has been investigated to have a potential role as an environmental chemosensor in natural water. Thus, it could be hypothesized that some of the uncharacterized siderophores may turn out to be novel and potential biosensor.[55-59]

4. Concluding remarks and future

Iron is an element for the growth of almost all living microorganisms because it acts as a catalyst in enzymatic processes, oxygen metabolism, electron transfer and DNA and RNA synthesis. It has become clear that siderophores represent cental organic compounds in Fe uptake in many microorganisms and plants.

Understanding the chemical structures of different siderophores and the membrane receptors involved in Fe uptake has opened new areas for research. The wide applications of siderophores reveals that it holds the promise to be implemented as a potential agent in different areas including Agriculture, bioremediation, biosensor and medical science.

The relationship between siderophores and microbial structure in environment with low Fe bioavailability i.e. oceans and some soil conditions are still unknown combining metagenomics with detailed chemical analysis will reveal important information that could be used to improve the current applications and develop new applications for siderophores.

Table 1: List of Micro organism which which can produce different types of siderophores.

Classification of Siderophores	Name of Siderophores	Siderophores producing micro organism
Hydroxamate	Ferribactin Ferrichrome Desferrioxamine Fusasinine Omibactin	Pseudomonas fluorescens Ustilago Sphaerogena Streptomyces Pilosus Fusarium roseum Burkholderia Cepacia
Catecholate	Enterobactin Salnochelins Vibriobactin Enterobactin Bacillibactin	Escherichia Coli Salmonella enterica Vibrio Cholerae Streptomyces Sp. Bacillus Subtilis
Carboxyl ate	Rhizobactin Staphyloferrin A and B Rhizoferrin Rhizoferrin Rhizoferrin	Rhizobium Meloti Staphylococcus aureus Rhizopus microsporus Mucor Mucedo Phycomyes niteus

Conflict of interest

The author declare that there is no conflict of interest.

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