

REVIEW ARTICLE

Molecular signaling involved in microbial siderophore-producing bacteria assisted improvement of micronutrient availability and crop productivity in saline/alkaline soils

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ABSTRACT

Iron is an essential plant nutrient that is not replaceable with any other macro or micronutrient. In alkaline and saline soil plant growth is limited due to poor nutrient availability as iron is also present in its insoluble Fe³⁺ oxidation state. Certain microorganisms produce small metal (iron) chelating agents called siderophores that bind iron/other metals, thereby enhancing their availability. Considering the need for enhancing the bioavailability of immobilized nutrients in stressed soil with the help of siderophore and other plant growth-promoting mechanisms shown by microorganisms. Hence, the aim of this review article is mainly focused on the general information related to siderophore, and its types (catecholate, hydroxamate, carboxylate, and mixed ligand siderophore) and their structural differences, mechanism of transport of iron across the membrane by siderophores, molecular signaling, and genes involved in biosynthesis and their application for humans to making a better world.

Keywords: Alkaline/ saline soil; iron chelation, siderophore; molecular mechanism.

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INTRODUCTION

Soil salinization and alkalization are the most serious global environmental problems and arising threats to crop productivity. The cultivated land, which is affected by salt may cause an adverse effect and oxidative damage to the soil as a result growth, nutrient uptake by plants, and their metabolic & photosynthetic activities are reduced. Agriculture is the largest private enterprise in India but the present population growth rate together with diversions of fertile land for non-agriculture uses exerts tremendous pressure on agriculture. Due to continual agricultural operations and incorrect waste disposal (chemical wastes, industrial wastes, nuclear wastes, etc.), undesirable changes occur in soil, generating soil pollution and resulting in salinization/alkalization of soil, which is the second most important factor of soil degradation. Out of the total geographical area (329 Mha) of land in the world, 175 Mha area is considered a salt-affected area in which alkaline and saline soils account for 3.6Mha and 5.5 Mha respectively. It is estimated that 1.5 billion land worldwide is salt-affected [1]. Salt-affected areas are one of the most important degraded areas where soil productivity is reduced due to either salinization (EC > 4dS/m) or sodicity i.e. exchangeable sodium percentage (ESP > 50) or both.

When the pH of the soil exceeds 7.0, the availability of micronutrients such as manganese, iron, copper, boron, and zinc decreases due to the formation of low solubility compounds, increased retention by soil colloids (clay and organic matter), and the conversion of soluble forms into fixed (insoluble) forms that plants cannot absorb [2]. Thus, nutrient availability becomes the main limiting factor for plant growth in such stressed soils. To overcome nutrient deficiency and increase agricultural productivity, large amount of chemical fertilizer are added to the soil, but nearly 70% of it becomes fixed and unavailable to plants

[3]. As a result, it is critical to shift toward the employment of halo-alkalo-tolerant soil microorganisms with plant growth-boosting properties for reclamation and enhancing nutrient bioavailability in place of/as an alternative to chemical fertilizers. Several rhizosphere-competent bacteria are known to stimulate plant growth by creating various growth-promoting properties such as micro- and macronutrient solubilization, siderophore production, ACC deaminase production, nitrogen fixation, and so on [4]. Iron is a key micronutrient that modulates bacteria's surface motility and also plays a vital role in biofilm formation. Despite being one of the most abundant elements in the earth's crust, it has a low bioavailability. Alkaline and calcareous soils are thought to be the primary causes of iron deficiency in plants; despite the high iron content of the soil, the accessible Fe concentration is below the recommended level for plant growth, i.e. 10^{-9} to 10^{-4} M [5]. Metal chelating agents, such as siderophores, are being studied as a remedy for reclaiming alkaline and calcareous soils.

Saline/Alkaline soil: Existing scenario and nutrient status

Distribution of saline/ alkaline soil in India

India has 2.4 % area of the total world's area which supports about 16.7 % of the total world's population and only 49.2 % (162Mha) area is arable. In India, alkaline/salt-affected soils are mainly found in the states of Madhya Pradesh, Andhra Pradesh, Karnataka, Rajasthan, West Bengal, Tamil Nadu, and Gujarat, which cover about 6.74 million ha of land (Fig 1). According to a report, the salinization of agricultural land will damage roughly 30% of cultivable land within the next 25 years (up to 50% of land degradation), and the problem will worsen by 2050 [6]. Because of the implementation of irrigation in new regions, salinized areas in India continue to grow yearly and the annual speed of increment is around 10%.

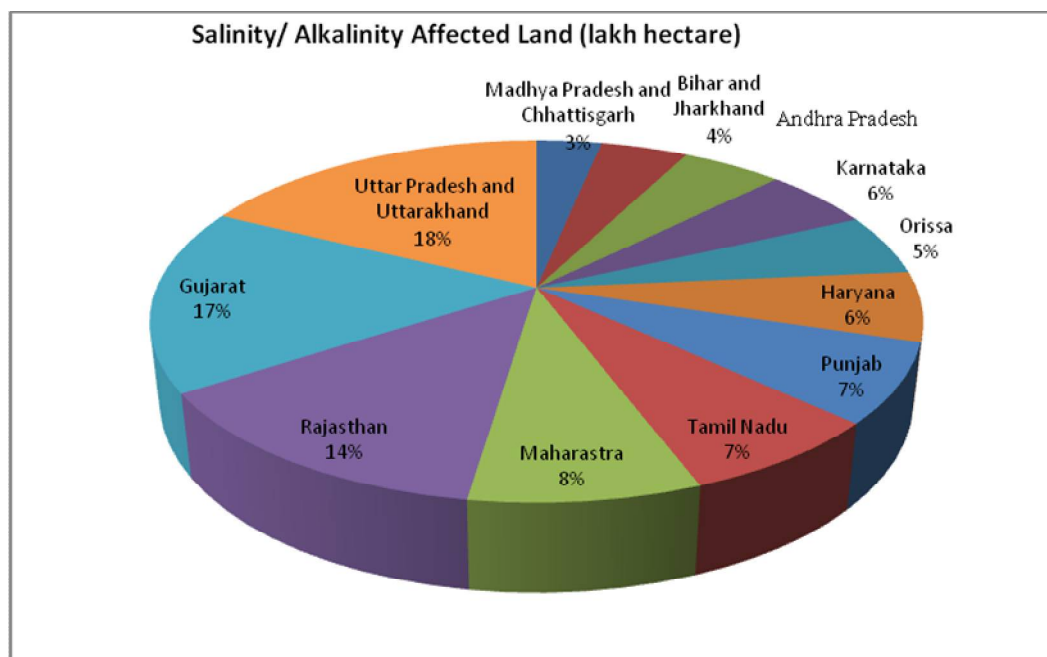


Fig 1 Graphical representation of saline/alkaline affected land in India.

General classification of salt-affected soil

In saline soil, the concentration of soluble salt is in excess due to the presence of sulphates, chlorides and carbonates of sodium, calcium and magnesium while alkaline soils are rich in sodium carbonate [7]. Salt-affected soils are classified into three types: (i) saline soil, which contains a huge concentration of soluble salts like calcium, magnesium, potassium etc. (ii) sodic soil in which sodium is the dominating species and (iii) sodic-saline soil in which there is high salt concentration as well as high sodium content. In general, there are two types of salt-affected soils: (i) saline soils that show high electrical conductivity (>4 dS m^{-1}) but low sodium content, and (ii) sodic soils that have high electrical conductivity (>4 dS m^{-1}) and high sodium content [8].

Nutrient status saline/alkaline soil

The high concentration of certain ions such as calcium, chloride, magnesium, sodium, sulphate etc. causes the soil salinity thereby degrading the soil structure also. Salinity affects the arid or semi-arid regions and its deposition around the rooting zone decreased productivity, nutrient uptake [9] and affects plant water intake due to high osmotic pressure [10]. Effect of soil alkalinity is more fatal, it reduces uptake of calcium ions, breakdown the soil structure etc. The excess salinity in soil water results in plant available water

and plant stress [11]. More than 6% of total world agricultural lands are on the edge of disappearing because of salt stress [10]. In alkaline soil, as calcium (Ca^{2+}) ions are abundant, tri-calcium phosphate (TCP) is the most common fixed form of phosphorus, likewise in acidic soil, ferric phosphate (FePO_4) and aluminum phosphate (AlPO_4) are the more profuse inorganic phosphorus forms. As a result, the concentration of soluble P in the soil is minimum and thus, unavailable to plants.

Iron is an important plant nutrient

Iron is the fourth most abundant vital element in Earth's crust required for all the living life forms and it plays an important role in host-bacteria interactions [12]. Iron is known to be a central component of the chain of electrons as well as a co-factor of several enzymes. It is important for various metabolic activities, acting as the major element in respiratory (TCA), photosynthesis (ETS), co-factor for enzymes (e.g. nitrogenase, catalase, etc.), synthesis of chlorophyll and other pigments. It is also important for the formation of biofilm as it regulates surface motility and stabilizes the polysaccharide matrix [13]. In plants, iron deficiency caused iron chlorosis (interveinal chlorosis) [14]. Iron chlorosis is very common all over the world, especially in semi-arid and arid regions, although there is an abundant amount of iron present in the soil but is not available for many plant species because of the existence of calcium carbonate, phosphate and other factors in soil that fix and limits its availability. The soluble oxidation state of iron i.e. (Fe^{2+}) is not stable under aerobic conditions and at physiological pH (7.0), so it is converted into Fe^{3+} oxidation state and forms insoluble hydroxide and oxyhydroxide precipitates [15] and reduces its availability. Iron hydroxide and oxides are responsible for the reddish and yellowish color of soil [16]. In acidic soil, if microbial activities are adequate to decrease the oxygen supply, transform some ferric ions into soluble ferrous forms. While in alkaline or calcareous soil, rapid microbial respiration leads to high carbon dioxide concentration in soil that may react with water, which forms bicarbonate ions. Plants absorb these ions, which immobilize iron within the plants resulting in a deficiency. Alkaline and calcareous soils are considered the main inducers of iron deficiency in plants; the available iron concentration is below the optimum level for the plant [17]. Once inside, iron forms complex with chelators and distributed to sink tissues where it is used predominantly in the production of enzyme cofactors or components of electron transport chain [18]. The distribution of species of plant in natural ecosystems limits the yield and nutritional quality of crops indicating the availability of iron in soil.

Microbially induced nutrient alleviation

Soil reclamation using beneficial microbes.

Different strategies have been developed to overcome this sodic/alkaline stress, such as the development of salt-tolerant crop plants, but the use of microorganisms to withstand this unhealthy environment is a more reliable measure to be taken [19]. Plant nutrient uptake is influenced by the architecture of the root, proton efflux from the roots release phytometallophore which increase the solubility of nutrients i.e. (Ca, Mg, Fe, Co, Zn and Mn) for plant. These phytometallophores are stable chelates so they extract the ions from calcareous soil (deficiency of these metals is common in calcareous and non-calcareous soil [20]). Many moderate salt tolerant rhizobia (e.g., *Sinorhizobium arboris*) have been isolated from Acacia, which can withstand 2%-3% NaCl concentration. Many bacterial strains such as *Chryseobacterium balustinum*, have been reported to enhance plant growth in saline stress conditions- by enhancing the nitrogen- fixation rate, root surface area and germination rate. Reclamation is a common practice to reduce runoff and erosion in sodic soils. Recovery of sodic soils includes the replacement of exchangeable Na with Ca ions [21].

Microbial ionophores and plant growth promotion

Plant growth-promoting rhizobacteria (PGPR) have gained widespread acceptability and relevance in agriculture over the last several decades due to the use of various modes of action that allow for increased crop output [22]. The term PGPR was firstly used by Kloepper, (1970) [23]. Plant growth-promoting rhizobacteria (PGPR) are the rhizosphere bacteria that enhance plant growth by a variety of mechanisms like phosphate solubilization, siderophore production, biological nitrogen fixation, rhizosphere engineering, production of 1-Aminocyclopropane-1-carboxylate deaminase (ACC), quorum sensing (QS) signal interference and inhibition of biofilm formation, production of phytohormone, exhibiting antifungal activity, production of volatile organic compounds (VOCs), induction of systemic resistance, promotion of beneficial plant-microbe symbioses, interference with pathogen toxin production etc [24]. There are many alkalo-halo tolerant plant growth promontory microorganisms such as *Pseudomonas*, *Trichoderma*, *Rhizobium*, *Bacillus*, and *Thiobacillus* which can increase plant growth under saline/alkaline stress conditions [25]. Plant growth promoting microbes (PGPM) are sustainable plant growth enhancers and have the potential to aid with the variety of stresses in their environment. Considering the long-term evolutionary relationships between plants and microbes, it is probably that much remains unknown about the potential benefits of microbes that could be harnessed from PGPM

[26]. The use of PGPR in agribusiness began in the 1950s and is utilized commercially in form of biofertilizers and biopesticides [27]. Salt tolerant endophytic bacteria are reported to promote plant growth indirectly or directly by the production of phytohormone, biocontrol of host plant disease and by improving its nutritional status. Endophytic bacteria can improve the health of the plant by targeting pests and pathogens with antibiotics, hydrolytic enzymes, nutrient limitation, as well as by priming plant defenses [28]. Some halotolerant bacteria possess the capacity to solubilize phosphates [29]. *Bacillus* species significantly increase the stomatal conduction in *Glomus* species under saline conditions [30]. Zhao *et al.*, [31] reported the growth-promoting potential of *Trichoderma* sp. under saline stress, by providing ferrous ion availability to cucumber via siderophore production. *Trichoderma* sp. also shows contradictory activity against *Sclerotium rolfii* under saline stress [32]. Various genera of salt-tolerant plant growth-promoting rhizobacteria (STPGPR) have been isolated from highly alkaline, saline and acidic soils. Many of them are also known to alleviate various biotic and abiotic stresses in plants [33]. Due to increasing soil acidity and salinity, increasing metal toxicity in soil, abiotic stress, drought, heat, and soil deterioration affect plant growth and severely limit crop production. Several studies point to the useful microbes, especially plant growth-promoting rhizobacteria (PGPR), which play a significant role in helping the plants in overcoming stresses and retain their productivity [34].

Synthesis of microbial ionophores (siderophore) in response to iron stress

There are different ways to produce siderophores by bacteria, fungi and plants. The aerated atmosphere of the earth results in the surface iron becoming converted to oxyhydroxide polymers that are very sparingly soluble. The concentration of free ferric ions at neutral pH is dependent on the solubility product constant of ferric hydroxide. Microorganisms growing under aerobic conditions need iron for a variety of functions like in reduction of oxygen to produce ATP, the reduction of ribonucleotide precursors of DNA, the formation of heme, and other vital purposes. However, in reference to micronutrient uptake by PGPM, most of the research has been carried out on two elements: Fe and zinc (Zn). Almost one-third soil of the earth can be considered Fe deficient [35].

Concerned by the pathways of microbial siderophores biosynthesis, they are primarily contingent on non-ribosomal peptide synthetase [36]. In Fe-starved conditions, siderophores produced by rhizospheric microbes play an important role in plant health management [37]. Along with growth promotion in crop plants siderophore also helps in controlling phytopathogens and diminishing the toxic effects of heavy metals in soil [38]. *Pseudomonads* [39], *Bacillus* spp. [40], *Azotobacter* spp. [41], *Acinetobacter* spp., and *Rhizobium* spp. are known as siderophore-producing plant growth promoting rhizobacteria efficiently. According to Rawat *et al.*, [42], a siderophore produced by *Trichoderma* sp. combats the detrimental effects of abiotic stress on the plant. Prabhavati and Mallaiah, (2008) [43] reported that the production of siderophore in *Rhizobium* strains increases with an increase in the salt concentration with respect to control (without salt), and the maximum production of siderophore was shown by strains HGR5 and HGR8 (90 µg/mL) at 600mM salt concentration.

Deshwal and Kumar, [44] reported that the *Pseudomonas* strain shows optimum siderophore production at 1% NaCl concentration and with an increase in the NaCl concentration siderophore production is delayed. *Pseudomonas fluorescence* NT1 strain showed maximum siderophore production at 6% NaCl concentration after 72h of incubation i.e. (1000 µg/mL) [45]. The biosynthesis of siderophore by *Streptomyces* isolates are increased in the presence of NaCl and the highest production of siderophore was observed in 300 Mm NaCl. The effect of pH on siderophore production was observed on *A.oryzae* [46]. The maximum siderophore production was observed at pH 7.0 followed by pH 8.0, i.e., 54.47% gradual decrease was observed below pH 7.0 and above pH 7.0. For all isolates, production of siderophores occurred when the value of pH exceeds 7.5, it was also determined that siderophores produced by the isolate were capable of binding with Fe³⁺, Ga³⁺ and Al³⁺ ions [47]. McMillan *et al.*, [48] reported an alkaliphilic *Bacillus* sp. having optimum pH greater than 9.0 for growth and siderophore production. The alkaliphilic siderophores contain hydroxamate and catecholate moieties and its synthesis was suppressed with the addition of FeCl₃ and stimulated by manganese (II) addition. Figueroa [49] checked siderophore production in *Halomonas* sp. SL01 under alkaline pH ranging from (8-11), the *Halomonas* sp. SL01 showed siderophore production upto pH 11 and maximum siderophore production (40 µM) was shown at pH 9. *Azotobacter vinelandii*, *B. megaterium* and *B. subtilis* are known to be the bacterium with the simplest performance since the individual medium filtrate had the flexibility to advance iron expeditiously at hydrogen ion concentration 9.0 with the best iron complexation capability [50].

Role of siderophores in nutrient acquisition.

The first reported siderophore was isolated from *Ustilago sphaerogena* [51]. These are iron-chelating low molecular weight compounds (<10 KD) [52]. It chelates free iron and forms a complex which is transported into the cell via membrane receptor protein molecules. These protein molecules are encoded

by five genes in the operon and turned off when an adequate amount of iron has been taken into the cell [53, 54]. In Gram-positive bacteria, transport of siderophore iron complex is by the involvement of siderophore irrevocable proteins, ATPases and permeases, while in Gram-negative bacteria siderophore iron complex is transferred through a periplasmic binding protein and cytoplasmic membrane protein corresponding to ATP binding cassette transfer. Siderophore-producing organisms act as a biocontrol agent by depriving phytopathogens of iron nutrition [55]. Chincholkar et al., [56] studied an iron-binding pigment produced by *Pseudomonas fluorescense* NCIM 5096 and found its utilization not only in plant growth promotion but in disease control. Some siderophore producing microorganisms are shown in **Fig 2**. There are some bacteria which produce one or more than one siderophore which can be utilized by other microorganisms for iron and other metal acquisition [54]. As compared to microbial siderophores, the affinity of phytosiderophores is less. Till now, 500 types of siderophores are reported from selected microorganisms [57], and significant variations are observed in the structure of siderophores from different species [54].



a. Control

b. *Pseudomonas aeruginosa* c. *Trichoderma harzianum*

Fig 2. Siderophore produced by microbial cultures (a) control (b) *Pseudomonas aeruginosa* (c) *Trichoderma harzianum* on CAS agar plate

Biology and Chemistry of siderophores

Hydroxamate, catecholate and carboxylate are three different kinds of siderophores [52]. Hydroxamate, which is found in both plants and fungi, provides two oxygen molecules and forms a bidentate ligand with iron due to which each siderophore forms a hexadentate octahedral complex with ferric ion. Ferribactin produced by *Pseudomonas* is a hydroxamate siderophore, and gonobactin produced by *Neisseria gonorrhoeae* is also a hydroxamate siderophore [58]. Ferrichrome a hydroxamate siderophore have a special ecological interest because it is produced by many soil fungi [59]. Certain ferrichrome derivatives show antibiotic activity and are called ferrimycine [60]. Catecholates that are produced only by bacteria provide two oxygen atoms for chelation with Fe which forms a hexadentate octahedral complex same as in the hydroxamate siderophore. Enterobactin was the first tricatecholate type of siderophore isolated from *E.coli*. Enterobactin is the strongest siderophore, these siderophores chelates iron present in very low iron concentration in the environment [58]. Both fungi as well as bacteria also produce Carboxylate siderophore, it is a novel class of siderophore. The member of this class neither possess hydroxamate nor phenolate ligands, iron binds with hydroxyl carboxylate and carboxylate groups [51]. Ferrichrome, produced by the fungus *Ustilagosphaerogena*, was the first siderophore to be isolated and has shown to be a growth factor for other microbes [51]. Fungi and bacteria both produce rhizoferin, but fungi produce only R- rhizoferin. Bacteria produce S-rhizoferin both are enantiomers [61]. Apart from these siderophores, some siderophores have mixed ligand, like pyoverdines/ pseudobactins which contains di-hydroxyl quinoline derivative. The chromophore di-hydroxyquinoline is linked to a peptide chain having two hydroxamate groups or one hydroxamate or one hydro-carboxylate group [51]. Different types of fluorescent chromopeptides, termed pseudobactin or pyoverdines, are synthesized by *Pseudomonas sp.* [62].

Siderophore-mediated iron transport

Microorganisms secrete iron trapping molecules i.e. siderophores under iron-deficient conditions into their external environment and form complexes with iron molecules (Fig3). After receiving this complex by cell surface receptors, many other transport complexes work in a sequence manner and finally released the siderophore iron complex into the cytoplasm. Mostly Gram-negative bacteria are reported, that produce iron scavenging molecules and transport the iron by using a siderophore. As microbes consist of various types of secretion systems including and all are ATP cassette transporters that transport molecules from the cell surface into the cytoplasm at the expense of ATP hydrolysis. Firstly, cell

surface receptors bind these complexes with high fidelity as this binding is very specific and strong and transports this complex into the periplasm. During this transport, microbes change the structural confirmation into the receptor so that it can easily release the iron-siderophore complex inside the periplasm and for this various protein complexes are involved, e.g. Ton B. This complex converts one form of energy into another using proton motive force to bring the structural changes into the receptors for efficient transportation into the periplasm. After the complex reaches the periplasm, various siderophore-specific binding molecules are present including fhv A, fep B, and fec B, which bind to the siderophore and release iron into free form (Fig 3). Now, this free iron molecule is bounded by a periplasmic protein which translocates this iron into the cytoplasm by using cytoplasmic-associated transporters [51]. Pyoverdine (pvd) siderophores are produced by pseudomonads that are noticed to promote iron nutrition in different plant species (Arabidopsis, clover and grasses) [63].

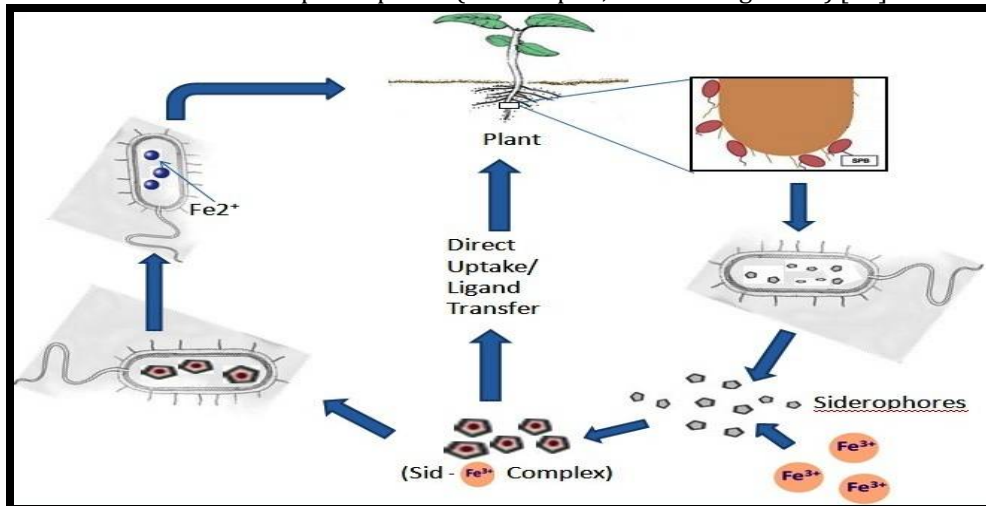


Fig 3 Mechanism of iron solubilization by siderophore produced by microorganisms.

Siderophore biosynthesis genes and its uptake regulations

Hohnadel and Mayer, [64] reported that there is an extensive homology present between the DNA of different species showing that the different siderophore synthesis genes evolved from the same ancestor. Various siderophore biosynthesis genes are illustrated in Table 1.

Table 2 Genes involved in siderophore biosynthesis

| Genes | ORF | Functions |
|----------------------------|---------------|--|
| pvdA | PA2386 | Ornithine hydroxylase |
| fpvR | PA2388 | Anti-sigma factor for PvdS and Fpv1 |
| fpvI | PA2387 | ECF sigma factor required for the expression of fpvA |
| pvdF | PA2396 | N5-Hydroxyornithine transformylase |
| pvdE | PA2397 | ABC transporter (secretion) |
| fpvA | PA2398 | Ferripyoverdine receptor protein |
| pvdD | PA2399 | Pyoverdine peptide synthetase |
| pvdJ | PA2400/1 | Pyoverdine peptide synthetase |
| pvdI | PA2402 | Pyoverdine peptide synthetase |
| pvdS ECF iron sigma factor | PA2426 | ECF iron sigma factor |
| pvcABCD | PA2254-PA2257 | Synthesis of Pyoverdine chromophore |

In Gram-negative bacteria, Fur (ferric uptake regulator) family including transcriptional repressors are responsible for the transcriptional regulation of these genes. Fur is a DNA-binding protein that requires a divalent heavy-metal ion as an activator. The gene product of the Fur gene also acts as a classical repressor and requires Fe^{2+} as an activator. When iron concentration is high, Fur forms a complex with Fe^{2+} in the promoter region which prevents transcriptions of these genes. In the case of iron-deficient conditions, Fe^{2+} is removed from Fur and fur-dependent genes are transcribed (Fig 4). Thus, Fur regulates iron metabolism [65]. Two other iron-regulated genes, *fhuA* and *fepA*, also reported which code for the ferrichrome and ferric enterobactin receptors, respectively. A palindromic "iron box," 5'-GATAATGATAATCATATC-3', was suggested as the sequence recognized by the ferrous Fur complex

[66]. Although Fur is an essential gene family for iron-controlled gene regulation, its mutation can have led to adverse effects. The *P. aeruginosa* fur gene transcription is regulated by tandemly arranged promoters. Out of all one promoter lies in the adversely oriented *omlA* gene. The downstream promoter has a consensus sequence for RpoD-dependent RNA polymerase (RNAP), the upstream promoter does not contain any specific sequence, but there is a possibility of the requirement of additional regulatory proteins for transcription arising from this promoter [67].

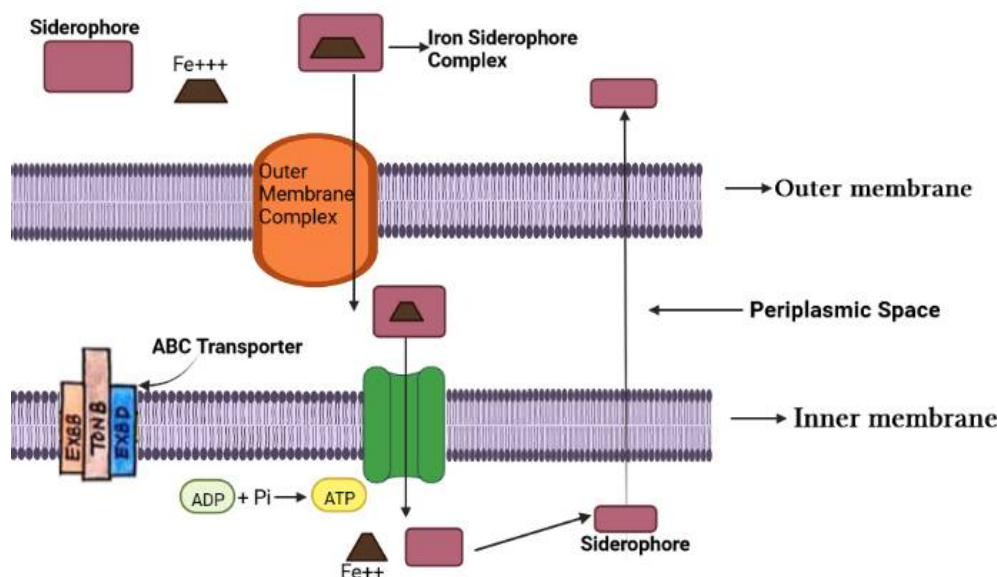


Fig 4 Transport of iron across the outer and inner membrane.

Another class of siderophores biosynthetic gene family is Pyoverdines (pseudobactin in soil pseudomonads), which are chromophores having the fluorescent ability and are produced by the rRNA homology group I pseudomonads and some newly reported species. Like, most siderophores composed of three domains, Pyoverdines are likely to have the same, out of which peptidic domain specifically aids great strain-dependent diversity that reflects in the regulation of uptake specificity. It contains both usual and unusual amino acids, the latter include acylated or cyclic forms of N8-hydroxyornithine, diamino butyrate, 13-hydroxyaspartate, 13-hydroxyhistidine, and D-amino acids [68]. All pyoverdines have a high affinity ($K_f = 1032 \text{ M}^{-1}$) towards binding with Fe(III) that results in the formation of a hexadentate complex which includes the hydroxyl residues of the chromophore along with hydroxamate, hydroxyl, and carbonyl group of the peptidic moiety. The biosynthesis of pyoverdines is a complex process. The biosynthesis of the peptide moiety and the chromophore of pyoverdines are preceded by non-ribosomal peptide synthetase activity [69]. These modular enzymes are large and regulate the multi-step reaction according to the carrier thio-template mechanism that results in outer membrane-bound proteins acting as receptors for the ferric diversity of pyoverdines. Moreover, a variety of enzymes are involved in pyoverdine biosynthesis and regulation. Also, another gene *FpvA* (ferric pyoverdine) encodes an iron-regulated pyoverdine, ferric pyoverdine 116. CD spectroscopy analysis reported that *FpvA* is composed of 57% β structure, 3% α helix structure, and 40% random coils showing similarity with porins and other receptors of siderophore [70]. The ferric pyoverdine transport through the receptor *FpvA* is an active process i.e. energy-dependent process that proceeds with the help of three TonB homologues gene (*tonB 1*, *tonB 2* and *PA0695*) that are identified in the genome of *P. aeruginosa*. The *tonB1* is one of the important genes for the siderophore-mediated uptake of iron. This gene is Fur repressible and regulated by iron. Fur is repressible, and essential for siderophore-mediated iron uptake. The N terminal extension of *FpvA* shows a vital role in the activity of *TonB1* and also prevents its degradation. Some reports also suggested that N terminal extensions are generally involved in signaling and the rest of the protein involved in pyoverdine transport. Indeed, a truncated *FpvA* fails to restore pyoverdine biosynthesis but can transport siderophores [71].

Binding of ferri-pyoverdines to *FpvA* generates a signaling pathway comprising cytoplasmic membrane spanning anti-sigma factor *FpvR*, ECF sigma factor *PvdS* shown in Fig 5. Interaction of *FpvA* with the periplasmic domain of *FpvR* results in the transduction of signal through the cytoplasmic membrane to the cytoplasmic domain of *FpvR*. *FpvR* generally regulates the ECF sigma factor *PvdS* activity [72].

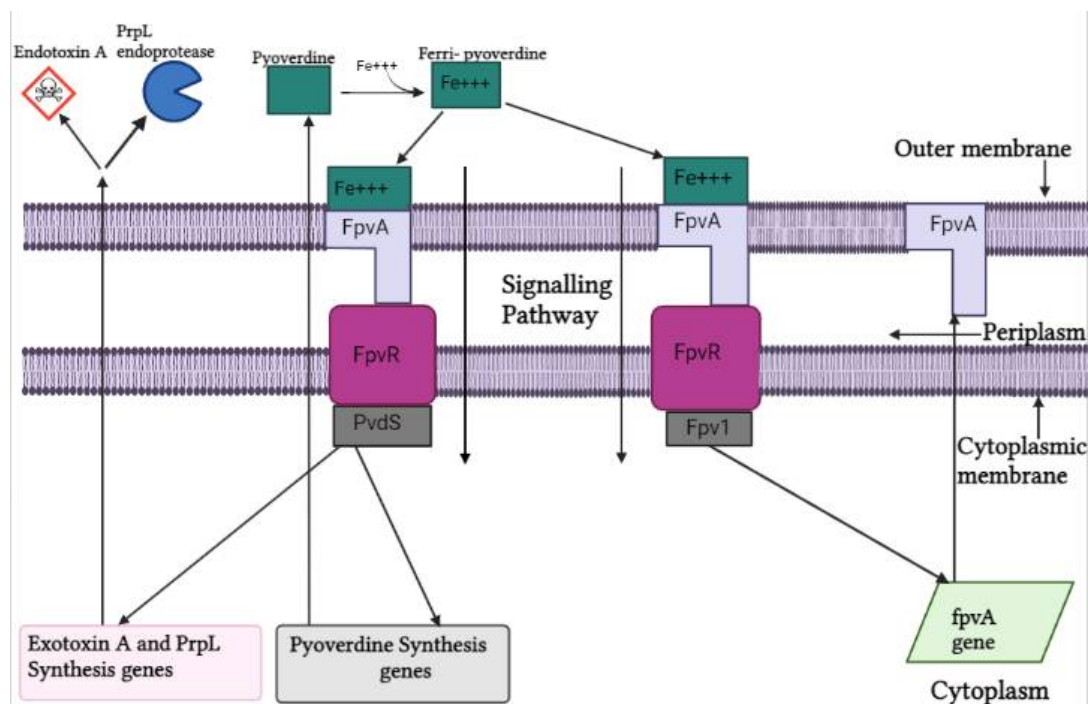


Fig 5 Schematic representation of Fpv signaling system

Signal transmission results in the release of FpvI and PvdS from inhibition by FpvR. Some reports suggested that a helix-turn-helix (HTH) DNA binding motif is present in the FpvI sequence. FpvR gene is located adjacent to the FpvI or PvdS and it regulates the activity of both the genes. PvdS then bind to the RNA polymerase and initiate transcription of the genes that direct the expression of pyoverdines, secreted proteins exotoxin A and Prp Lendo protease; whereas FpvI initiates the expression of FpvA. The intergenic sequence between *fpvI* and *fpvR* contains overlapping divergent sigma 70(σ 70) recognition sites (-35 and-10) for both *fpvI* and *fpvR* that were highly similar to those of the σ 70 consensus sequence. The binding site of iron-responsive Fur repressor protein is located in the DNA of the intergenic region between FpvI and FpvR [73]. The intergenic region contains two Fur repressor recognition sites that overlap the σ 70-dependent promoters. Analysis of some data it is reported that the expression of FpvI and FpvR is regulated by the Fur family. The presence of iron in the growth medium results in the decreased production of FpvI and this is likely to repress the expression of *fpvA*. After these regulatory signals, pyoverdines are exported into the extracellular medium via a twinarginine translocation (TAT)-dependent mechanism. After excretion into the medium, the iron-pyoverdine complex is disrupted and it delivers iron to the cells following the receptor-mediated uptake mechanism. After that, pyoverdines are recycled back and thus, proceed through several rounds of iron transport by the same molecule [71].

Applications of siderophores

Siderophores are the biological molecules produced by different types of microorganisms having a wide range of applications in various fields like agriculture, environmental applications, biocontrol, bioremediation and medicinal application [74]. In agriculture, inoculation of soil with *Pseudomonas* sp. produces pseudobactin which increases the growth of many plants [75]. It works as a biosensor as it can detect the content of iron in different environments [76]. Excessive accumulation of heavy metals in the soil becomes toxic to various plants; in this concern, hydroxamate siderophore present in soil plays an important role to immobilize metals [77]. Under metal stress, soil microorganisms including plant growth promoting bacteria (PGPB) have developed several strategies to evade the toxicity generated by the various heavy metals plant growth promoting bacteria (PGPB) have developed various strategies. Such metal-resistant PGPB, when utilized as bioinoculant or biofertilizers, significantly increased the growth of plants in heavy metal contaminated/stressed soils [78]. Research has concentrated on microbial-mediated redox transformations that can change the redox chemistry of actinides through direct and indirect mechanisms that affect their environmental solubility as well as mobility [78]. Siderophores themselves also act as growth inhibitors for many pathogenic fungi such as *Pythium ultimum*, and *Fusarium oxysporum* [79]. Kloepper et al. [75] were the first to report the importance of siderophore in controlling *Erwinia carotovora*. In the medical field, certain diseases like hemochromatosis,

hemosiderosis and accidental iron poisoning require iron removal from the body, mainly the liver. Such diseases can be treated with siderophore-based drugs.

CONCLUSION AND FUTURE PROSPECTS

Under aerated conditions in saline /alkaline soil, iron is found in extremely insoluble and fixed form, so its concentration becomes limited for optimal plant growth. Currently, several applications of siderophores are reported in various fields such as medicine, agriculture, biocontrol of phytopathogens, and environmental applications. It can also be applied for combating both biotic and abiotic stresses. It also has the potential for the treatment of diseases caused by pathogenic microorganisms by exploiting their antimicrobial property. There is a close relationship between siderophore utilization and virulence. The strategy of iron-dependent pathogen control is a promising field for future investigations and offers a wide array of possible therapeutic applications. However, research in the microbiological aspects of siderophore is still very limited. Combining metagenomics with detailed chemical analysis will disclose important information that could be used to improve its current applications and develop new applications for siderophores.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent to participate

All authors participant agree to publish this work

Consent to publish

Yes, all authors have given their consent

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