

Microbial siderophores and their potential applications: a review

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Abstract Siderophores are small organic molecules produced by microorganisms under iron-limiting conditions which enhance the uptake of iron to the microorganisms. In environment, the ferric form of iron is insoluble and inaccessible at physiological pH (7.35–7.40). Under this condition, microorganisms synthesize siderophores which have high affinity for ferric iron. These ferric iron-siderophore complexes are then transported to cytosol. In cytosol, the ferric iron gets reduced into ferrous iron and becomes accessible to microorganism. In recent times, siderophores have drawn much attention due to its potential roles in different fields. Siderophores have application in microbial ecology to enhance the growth of several unculturable microorganisms and can alter the microbial communities. In the field of agriculture, different types of siderophores promote the growth of several plant species and increase their yield by enhancing the Fe uptake to plants. Siderophores acts as a potential biocontrol agent against harmful phyto-pathogens and holds the ability to substitute hazardous pesticides. Heavy-metal-contaminated samples can be detoxified by applying siderophores, which explicate its role in bioremediation. Siderophores can detect the iron content in different environments, exhibiting its role as a biosensor. In

the medical field, siderophore uses the “Trojan horse strategy” to form complexes with antibiotics and helps in the selective delivery of antibiotics to the antibiotic-resistant bacteria. Certain iron overload diseases for example sickle cell anemia can be treated with the help of siderophores. Other medical applications of siderophores include antimalarial activity, removal of transuranic elements from the body, and anticancer activity. The aim of this review is to discuss the important roles and applications of siderophores in different sectors including ecology, agriculture, bioremediation, biosensor, and medicine.

Keywords Iron · Siderophore · Microbial ecology · Bioremediation · Biosensor · Medicine

Introduction

Iron is the fourth most abundant element in Earth’s crust (Huber 2005; Gamit and Tank 2014). It is a transition metal that can exist in two oxidation states, Fe (III) and Fe (II). The variable valence of iron allows it to play a key role in the oxidation-reduction reactions (Taylor and Konhauser 2011). Iron is required in several metabolic processes including tricarboxylic acid cycle, electron transport chain, oxidative phosphorylation, and photosynthesis (Messenger and Barclay 1983; Fardeau et al. 2011). It also regulates the biosynthesis of porphyrins, vitamins, antibiotics, toxins, cytochromes, siderophores, pigments, and aromatic compounds, and nucleic acid synthesis (Messenger and Barclay 1983). Recently it has also been observed that iron plays an important role in the microbial biofilm formation as it regulates the surface motility of microorganism (Glick et al. 2010; Cai et al. 2010). At physiological pH (7.35–7.40), the ferrous form (Fe^{2+}) of iron is soluble, while the ferric form (Fe^{3+}) is insoluble (Bou-Abdallah 2010). At this condition, several reports showed

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the concentrations of dissolved ferrous iron to be around 10^{-10} to 10^{-9} M (Poole and McKay 2003; Kraemer 2004) while the required level of ferrous iron by living organisms is around 10^{-7} to 10^{-5} M (Poole and McKay 2003; Matsumoto et al. 2004). In order to survive under such iron-depleted environment, microorganisms produce certain organic compounds with low molecular masses called siderophores (Ahmed and Holmstrom 2014). Siderophores (Greek *sideros* meaning iron and *phores* meaning bearer) are the metal-chelating agents that primarily function to capture the insoluble ferric iron from different habitats (Nagoba and Vedpathak 2011). Existing literature showed that both gram-negative and gram-positive bacteria synthesized siderophore under iron-deprived condition (Tian et al. 2009; Saharan and Nehra 2011). Generally, most of the aerobic and facultative anaerobic bacteria were found to produce siderophore under iron stress condition (Neilands 1995). It has been reported that a facultative aerobic bacterium *Pseudomonas stutzeri* CCUG 36651 can produce siderophores in both aerobic and anaerobic conditions, but the siderophore produced in aerobic condition varies from siderophores produced in anaerobic condition (Essen et al. 2007). Under aerobic condition, *Pseudomonas stutzeri* CCUG 36651 was reported to produce four ferrioxamine siderophores. In contrast, none of these ferrioxamines siderophores were found under anaerobic conditions (Essen et al. 2007). Siderophore first binds with iron (Fe^{+3}) tightly and then the siderophore-iron complex moves into the cell through the cell membrane using the specific siderophore receptors. In case of gram-positive bacteria, siderophore-binding proteins, permeases, and ATPases are involved in the transport of siderophore iron (Fe^{+3}) complex in the cell membrane (Ahmed and Holmstrom 2014). The membrane network of gram-negative bacteria is markedly different from that of gram-positive bacteria. In case of gram-negative bacterial membranes, an outer membrane receptor, a periplasmic binding protein, and a cytoplasmic membrane protein belonging to ATP-binding cassette transporter (ABC-transporter) are involved in the transport of siderophore iron (Fe^{+3}) complex (Ahmed and Holmstrom 2014). Once siderophores bound to ferric iron moves to cytosol, the ferric iron gets reduced to ferrous form 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. A schematic diagram for siderophore-mediated iron uptake by microorganism is shown in Fig. 1. Although the primary function of siderophores is to supply the soluble iron to microorganism for their growth, they also have numerous applications in different fields like ecology, agriculture, bioremediation, biosensor, and medicine. More than 500 different siderophores were reported, of which 270 were well characterized (Boukhalfa et al. 2003), while the rest remain uncharacterized and their functions are yet to be determined (Ali and Vidhale 2013).

Types of siderophore

Depending on the oxygen ligands for Fe (III) coordination, siderophores can be classified into three main categories, namely, hydroxamates, catecholates, and carboxylates.

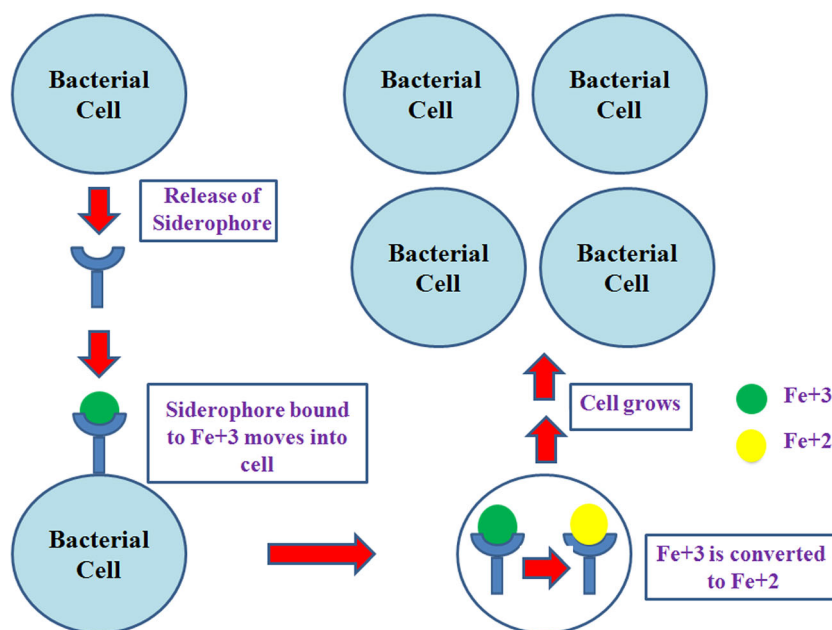
Hydroxamate siderophore

Hydroxamate type of siderophores comprises the most common group of siderophores found in nature. These siderophores are produced by microorganisms including bacteria and fungi (Table 1) (Hofte 1993; Winkelman and Drechsel 1997). For example, *Pseudomonas fluorescens* secretes a hydroxamate siderophore, ferribactin (Maurer and Keller-Schierlein 1968), whereas *Trichoderma* spp. and *Fusarium* spp. produce the hydroxamate siderophores coprogens (Zahner et al. 1963) and fusigen (Diekmann and Zahner 1967; Sayer and Emery 1968; Neilands 1973) respectively. Most of the hydroxamate groups consist of $\text{C}(=\text{O})\text{N}(\text{OH})\text{R}$, where R is either an amino acid or a derivative of it. Two oxygen molecules coming from each hydroxamate group form a bidentate ligand with iron. Thus, each siderophore is capable of forming a hexadentate octahedral complex with Fe^{3+} . The hydroxamates bind with ferric iron at binding constants in the range of 10^{22} to 10^{32} M^{-1} (Winkelmann 2007). This strong binding between ferric iron and siderophore protects the complexes against hydrolysis and enzymatic degradation in the environment (Winkelmann 2007). The hydroxamate type of siderophores can be detected by several methods. Neilands spectrophotometric assay was initially used for the detection of the hydroxamate type of siderophores (Neilands 1981). Electrospray ionization mass spectrometry (ESI-MS) has been widely used to detect the structure of hydroxamate siderophore (Gledhill 2001; McCormack et al. 2003). Modified overlaid chrome azurol S (O-CAS) assay can also be used for the detection of hydroxamate siderophore (Perez-Miranda et al. 2007). Another widely used assay includes Csaky's assay which can detect hydroxamate siderophores like aerobactin of *Escherichia coli* (Pal and Gokarn 2010).

Catecholate (phenolates) siderophore

Catecholate type of siderophores is mostly produced by certain bacteria (Dave et al. 2006) (Table 1). Each catecholate group supplies two oxygen atoms for chelation with iron in order to form a hexadentate octahedral complex. Certain bacteria like *Escherichia coli*, *Salmonella typhimurium*, and *Klebsiella pneumoniae* produce enterochelin (Dertz et al. 2006) which can bind to ferric ion (Fe^{3+}) very tightly ($K=10^{52} \text{ M}^{-1}$). This strong binding between enterochelin and iron can be exploited to estimate even very low concentration of iron in environmental sample. Certain bacteria can produce

Fig. 1 Under iron-limited conditions, bacterial cell releases siderophore. This siderophore forms complex with the insoluble ferric iron and binds to the surface of the bacterial cell. The Fe^{3+} -siderophore complex gets transported inside the cell and the insoluble ferric iron (Fe^{3+}) is converted into the soluble ferrous form (Fe^{2+}). The siderophore either gets degraded inside the cell or is released in free form outside the cell. Bacterial cell utilizes this ferrous form of iron for their growth and thereby increases in number



either catecholate siderophore alone or mixed siderophores where catecholate is one of the member. For example, bacteria *Erwinia carotovora* can produce only catecholate siderophore whereas some members of *Pseudomonas* produce a mixed siderophore consisting of both catecholates and hydroxamates (Leong and Neilands 1982). The catecholate siderophores can be detected by following several assays. One of the most reported assay for catecholate detection is the Neilands spectrophotometric assay (Neilands 1981), where the catecholate type of siderophore binds with FeCl_3 and forms a wine colored complex which showed the maximum absorbance at 495 nm (Neilands 1981). High-performance liquid chromatography (HPLC) analysis with diode array detection (DAD) and electrospray ionization mass spectrometry (ESI-MS) assay can be used to detect catecholate siderophore (Fiedler et al. 2001). O-CAS assay, can also be used for the detection of catechol siderophore (Alexander and Zuberer 1991; Perez-Miranda et al. 2007).

Carboxylate siderophore

Carboxylate type of siderophores is produced mostly by bacteria like *Rhizobium* and *Staphylococcus* and fungi like mucorales (Table 1). This type of siderophore binds to iron through carboxyl and hydroxyl groups (Dave and Dube 2000). Rhizobactin, produced by *Rhizobium meliloti* strain DM4 is the best characterized carboxylate siderophore having an amino poly carboxylic acid consisting of ethylene diamine dicarboxyl and hydroxyl carboxyl moieties that act as iron-chelating groups (Smith and Neilands 1984). Staphyloferrin A, a highly hydrophilic carboxylate-type siderophore was isolated from *Staphylococcus hyicus* DSM 20459 under reduced

iron conditions (Meiwees et al. 1990). This siderophore transports iron not only to the producer strain but also to other 37 different *Staphylococci* (Meiwees et al. 1990). 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 280 nm (Shenker et al. 1992). O-CAS assay, can be used for the detection of carboxylate siderophore (Alexander and Zuberer 1991; Perez-Miranda et al. 2007). Recently, it has been reported that with the aid of HPLC and MS, the structure of the carboxylate type of siderophore can be identified (Velasquez 2011).

Applications of siderophore

Siderophore, a small biological organic molecule produced by microorganisms, has profound applications in the following fields.

Microbial ecology

Microbial ecology is the study of relationship between microorganisms and their surrounding environments. In the current review article, we have discussed the role of siderophores in the following domains of microbial ecology.

Siderophore enhances the growth of unculturable microorganisms in artificial media

Microbial community represents the complex microbial association in a habitat. Habitat reveals the balanced interaction

Table 1 List of microorganisms which can produce different types of siderophores

Types of siderophore	Name of siderophore	Siderophore-producing microorganism	References
Hydroxamate	Ferribactin	<i>Pseudomonas fluorescens</i>	Maurer and Keller-Schierlein 1968
	Unknown	<i>Pseudomonas fluorescens</i>	Kannahi and Senbagam 2014
	Unknown	<i>Pseudomonas fluorescens</i>	Sayyed et al. 2005
	Dimerum acid, fusigen, coprogen, ferricrocin	<i>Trichoderma</i> spp.	Lehner et al. 2013
	<i>Fusarinine A</i> , <i>Fusarinine B</i>	<i>Fusarium roseum</i>	Sayer and Emery 1968
	Unknown	<i>Escherichia coli</i>	Kannahi and Senbagam 2014
	Unknown	<i>Pseudomonas putida</i>	Sayyed et al. 2005
	Unknown	<i>Aspergillus flavus</i>	Kannahi and Senbagam 2014
	Unknown	<i>Rhizopus</i> sp.	Kannahi and Senbagam 2014
	Unknown	<i>Micrococcus luteus</i>	Cabaj and Kosakowska 2009
	Unknown	<i>Bacillus silvestris</i>	Cabaj and Kosakowska 2009
	Unknown	<i>Vibrio harveyi</i>	Murugappan et al. 2011
	Unknown	<i>Aureobasidium pullulans</i>	Murugappan et al. 2012
	Unknown	<i>Vibrio vulnificus</i>	Simpson and Oliver 1983
	Unknown	<i>Histoplasma capsulatum</i>	Burt et al. 1981
	Unknown	<i>Absidia corymbifera</i>	Holzberg and Artis 1983
	Unknown	<i>Aspergillus niger</i>	Holzberg and Artis 1983
	Unknown	<i>Rhizopus arrhizus</i>	Holzberg and Artis 1983
	Unknown	<i>Rhizopus oryzae</i>	Holzberg and Artis 1983
	Unknown	<i>Blastomyces dermatitidis</i>	Holzberg and Artis 1983
	Unknown	<i>Sporothrix schenickii</i>	Holzberg and Artis 1983
	Unknown	<i>Candida albicans</i>	Holzberg and Artis 1983
	Unknown	<i>Trichophyton mentagrophytes</i>	Holzberg and Artis 1983
	Ferrirubin	<i>Paecilomyces variotii</i>	Renshaw et al. 2002
	Ferrirubin	<i>Paecilomyces variotii</i>	Holinsworth and Martin 2009
	Unknown	<i>Methylobacterium mesophilicum</i>	Lacava et al. 2008
	Unknown	<i>Methylobacterium extorquens</i>	Lacava et al. 2008
	Unknown	<i>Methylobacterium radiotolerans</i>	Lacava et al. 2008
	Unknown	<i>Methylobacterium zatmanii</i>	Lacava et al. 2008
	Unknown	<i>Methylobacterium fugisawaense</i>	Lacava et al. 2008
	Ferrichrome	<i>Ustilago sphaerogena</i>	Saharan and Nehra 2011
	Desferrioxamine B	<i>Streptomyces pilosus</i>	Saharan and Nehra 2011
	Desferrioxamine B, desferrioxamine E	<i>Streptomyces coelicolor</i>	Saharan and Nehra 2011
	Fusarinine C	<i>Fusarium roseum</i>	Saharan and Nehra 2011
	Ornibactin	<i>Burkholderia cepacia</i>	Saharan and Nehra 2011
	Unknown	<i>Gloephyllum trabeum</i>	Ahmed and Holmstrom 2014
	Desferrioxamine mesylate	<i>Streptomyces pilosus</i>	Vala et al. 2006
	Unknown	<i>Monilia</i> sp.	Vala et al. 2000
	Unknown	<i>Penicillium</i> sp.	Vala et al. 2000
	Unknown	<i>Penicillium chrysogenum</i>	Vala et al. 2000
	Unknown	<i>Penicillium citrinum</i>	Vala et al. 2000
	Unknown	<i>Penicillium funiculosum</i>	Vala et al. 2000
	Unknown	<i>Aspergillus</i> sp.	Vala et al. 2006
	Unknown	<i>Aspergillus nidulans</i>	Vala et al. 2006
	Unknown	<i>Aspergillus niger</i>	Vala et al. 2006
	Unknown	<i>Aspergillus ochraceus</i>	Vala et al. 2006
	Unknown	<i>Aspergillus versicolor</i>	Vala et al. 2006
	Unknown	<i>Aspergillus duricaulis</i>	Vala et al. 2006
	Unknown	<i>Aspergillus fumigatus</i>	Vala et al. 2006

Table 1 (continued)

Types of siderophore	Name of siderophore	Siderophore-producing microorganism	References
Catecholate	Enterobactin	<i>Escherichia coli</i>	Saharan and Nehra 2011
	Unknown	<i>Escherichia coli</i>	Kannahi and Senbagam 2014
	Pyoverdine	<i>Pseudomonas aeruginosa</i>	Peek et al. 2012
	Salmochelins	<i>Salmonella enterica</i>	Hantke et al. 2003
	Bacillibactin	<i>Bacillus anthracis</i>	Saharan and Nehra 2011
	Bacillibactin	<i>Bacillus subtilis</i>	Saharan and Nehra 2011; May et al. 2001
	Petrobactin, Bacillibactin	<i>Bacillus cereus</i> , <i>Bacillus anthracis</i>	Wilson et al. 2006
	Bacillibactin	<i>Bacillus thuringiensis</i>	Wilson et al. 2006
	Vibriobactin	<i>Vibrio cholerae</i>	Saharan and Nehra 2011; Griffiths et al. 1984
	Unknown	<i>Pseudomonas fluorescens</i>	Kannahi and Senbagam 2014
	Unknown	<i>Aspergillus flavus</i>	Kannahi and Senbagam 2014
	Unknown	<i>Rhizopus</i> sp.	Kannahi and Senbagam 2014
	Enterobactin	<i>Streptomyces</i> sp.	Fiedler et al. 2001
	Photobactin	<i>Photorhabdus luminescens</i>	Ciche et al. 2003
	Unknown	<i>Synechococcus</i> sp.	Barbeau et al. 2003
	Unknown	<i>Acinetobacter calcoaceticus</i>	Prashant et al. 2009
	Unknown	<i>Rhizobium</i> sp.	Joshi et al. 2009
	Unknown	<i>Mesorhizobium</i> sp.	Joshi et al. 2009
Carboxylate	Rhizobactin	<i>Rhizobium meloti</i>	Drechsel et al. 1995
	Staphyloferrin A	<i>Staphylococcus hyicus</i>	Meiwees et al. 1990
	Staphyloferrin A, Staphyloferrin B	<i>Staphylococcus aureus</i>	Beasley et al. 2011
	Unknown	<i>Halococcus saccharolyticus</i>	Dave et al. 2006
	Unknown	<i>Halorubrum saccharovororum</i>	Dave et al. 2006
	Unknown	<i>Haloterrigena turkmenica</i>	Dave et al. 2006
	Unknown	<i>Halogeometricum</i> sp.	Dave et al. 2006
	Unknown	<i>Natrialba</i> sp.	Dave et al. 2006
	Rhizoferrin	<i>Rhizopus microsporus</i>	Drechsel et al. 1995
	Rhizoferrin	<i>Mucor mucedo</i>	Thieken and Winkelmann 1992
	Rhizoferrin	<i>Phycomyces nitens</i>	Thieken and Winkelmann 1992
	Rhizoferrin	<i>Chaetostylum fresenii</i>	Thieken and Winkelmann 1992
	Rhizoferrin	<i>Cokeromyces recurvatus</i>	Thieken and Winkelmann 1992
	Rhizoferrin	<i>Cunninghamella elegans</i>	Thieken and Winkelmann 1992
	Rhizoferrin	<i>Mycotypha africana</i>	Thieken and Winkelmann 1992
	Rhizoferrin	<i>Mortierella vinacea</i>	Thieken and Winkelmann 1992
	Rhizoferrin	<i>Basidiobolus microsporus</i>	Thieken and Winkelmann 1992

between biotic and abiotic sources. Among the microbial community, only 0.1 to 1 % of the population can be cultivated in laboratory condition whereas most of the populations are uncultivable (Torsvik and Ovreas 2002). This is a major unsolved problem in microbiology which is referred to as “the great plate count anomaly” (Staley and Konopka 1985; Rappe and Giovannoni 2003; Keller and Zengler 2004). The reason behind this high number of unculturable microbial population is that microbiologists are unable to replicate some of the basic requirements including temperature, osmotic shock, nutrient

load, pH, and many more in their artificial growth environment (Vartoukian et al. 2010). Proper exploration of the physiology of these bacteria and their roles in ecology, remediation, host health, and natural compound production requires their comfortable cultivation in the artificial growth condition (Stewart 2012). In this context, several strategies were undertaken to gather more information regarding the cultivation of unculturable organisms in artificial growth media under laboratory conditions (Lewis et al. 2010). It was reported that bacteria isolated from the chambers created by Lewis and

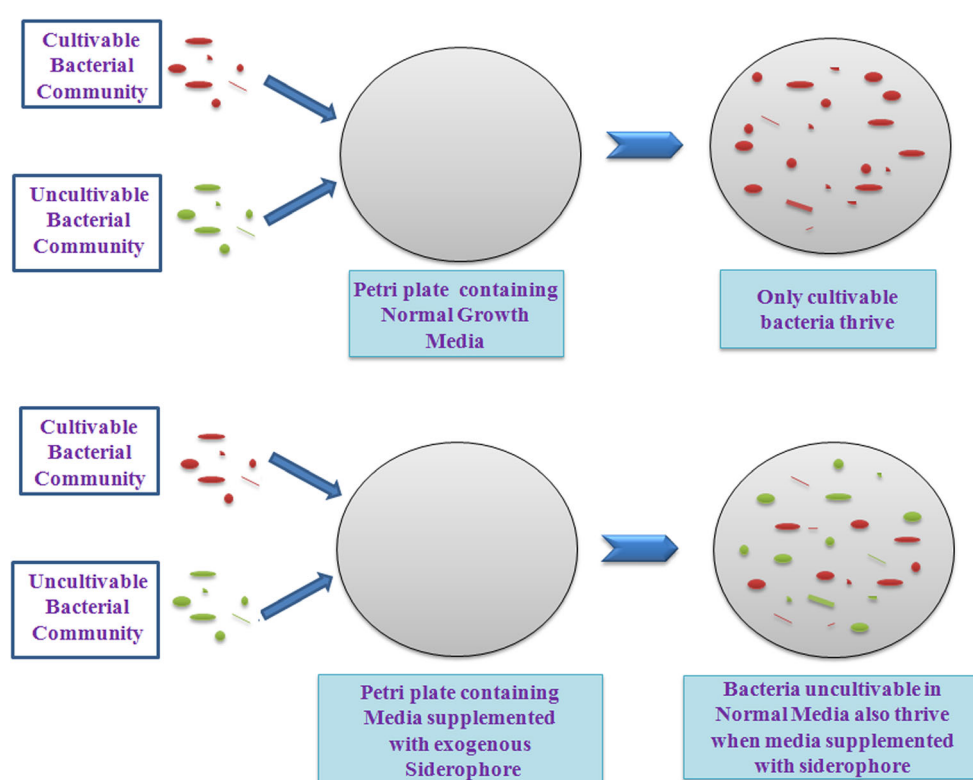
Epstein can only grow on a petri plate when they were growing close to the other bacteria isolated from the same environment (Stewart 2012). In an interesting report, Sung and co-workers identified several anaerobic thermophiles in the family *Clostridiaceae* only when these bacteria were grown in the presence of the extract from *Geobacillus toebii* (Kim et al. 2008, 2011). Toward this direction, Kaerberlein et al. (2002) showed that in the course of coculture of microorganisms, one type of microorganism produces siderophore which acts as a growth factor that promotes the growth of other unculturable microorganisms (Kaerberlein et al. 2002; Lewis et al. 2010). Later on, it was reported that one culturable organism, namely *Micrococcus luteus* KLE1011 synthesizes five new acyl-desferrioxamine siderophores wherein each of them promotes the growth of the unculturable organism *Maribacter polysiphoniae* KLE1104 considerably (D'Onofrio et al. 2010). In a separate study, it was found that the exogenous addition of siderophores enhances the growth of uncultivable marine bacterial species in laboratory growth medium (Guan and Kamino 2001). Uncultured bacteria growing on sand biofilm were cultivated by the exogenous siderophores released from neighboring microorganisms within the biofilm (Lewis et al. 2010). Thus, siderophore-based approach has markedly facilitated the growth and cultivation of unculturable microorganisms (Fig. 2). Although it was reported that many strains of unculturable organisms are not able to grow in the laboratory as they are unable to autonomously produce the siderophores, their chemical dependence on other neighboring

microorganisms helps in the regulation of community establishment in the environment (D'Onofrio et al. 2010). Therefore, with the aid of siderophore, many unculturable organisms can be cultivated and purified as pure culture. Once the pure culture of the unculturable organisms can be prepared, the potential applications of the organisms in different fields can be investigated extensively.

Siderophore alters microbial community

Several studies illustrated the fact that mineral addition to soil microcosms can result in substantial changes in bacterial community structure and these changes are dependent on the type of mineral added (Carson et al. 2007, 2009). Similarly, it was reported that the amount of iron can modulate the microbial community structure considerably (Eldridge et al. 2007; Jin et al. 2010, 2014). However, high iron demand and its low accessibility under aerobic condition pose a big threat for the growth and survival of the microorganisms in nature. Under such environmental constraints, many aerobic and facultative anaerobic microorganisms synthesize and secrete specific molecules known as siderophores that can effectively capture iron from the environment and make the iron available to the microorganisms (Schwyn and Neilands 1987; Chincholkar et al. 2007). Although iron is a trace metal for the microorganism, it regulates several vital cellular functions including energy production and enzyme stability (Sullivan et al. 2012). Therefore, the increase in iron availability to soil

Fig. 2 Siderophore enhances the growth of unculturable microbial community in laboratory condition. The bacterial population of natural sample containing both cultivable (red symbols) and uncultivable (green symbols) bacteria is allowed to grow on growth media lacking siderophore under laboratory conditions, only cultivable bacteria (red symbols) survive and grow efficiently (upper panel). Similarly, when the same sample containing both cultivable (red symbols) and uncultivable (green symbols) bacteria is allowed to grow on the same growth media containing siderophore, both cultivable (red symbols) and uncultivable (green symbols) bacteria survive and grow (lower panel)



microorganism might increase the proliferation of soil microbial population. To this end, it has been reported that the presence of siderophore markedly increases the bioavailability of iron to the microorganisms that resulted in the proliferation of microbial population, causing an alteration in soil microbial community (Sullivan et al. 2012).

Agriculture

Siderophores can be considered to be an eco-friendly alternative to hazardous chemical pesticide in the agricultural sector by the following ways.

Siderophore promotes plant growth

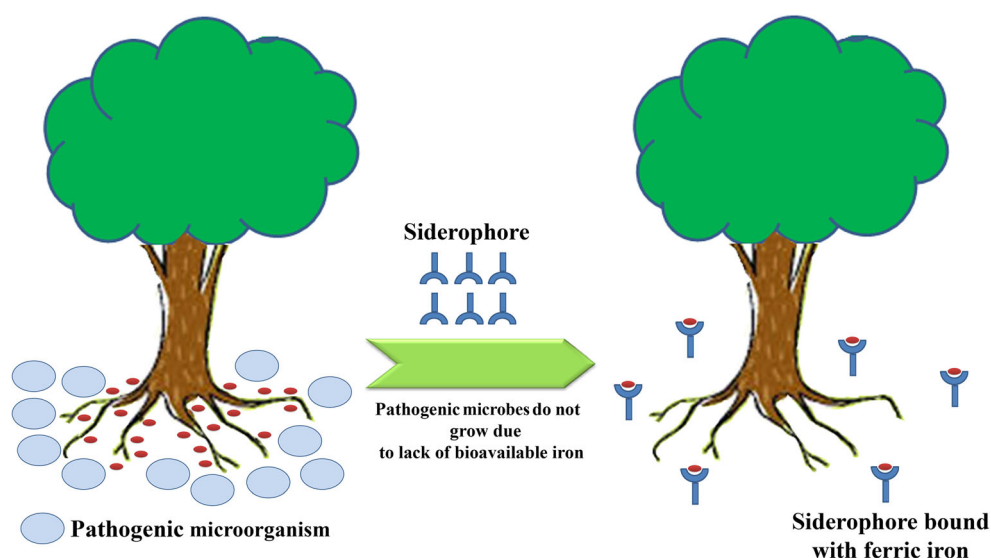
Although iron is a micronutrient, it is required for chlorophyll biosynthesis, redox reactions, and some important physiological activities in plants (Briat et al. 1995). Therefore, iron starvation significantly reduces the quantity and quality of crop production. This reduction in crop production also alters the natural food web of the ecosystem. The level of available iron required by plants at neutral pH is around 10^{-17} mol/L while the level of available iron required by microorganism is 10^{-6} mol/L under the similar condition (Omidvari et al. 2010). For several decades, it has been known that different *Pseudomonas* species can enhance plant growth by producing pyoverdine siderophores (Kloepper et al. 1980; Gamalero and Glick 2011). These types of bacteria are therefore considered as plant-growth-promoting bacteria (Kloepper et al. 1980; Gamalero and Glick 2011). To investigate the role of soil microbial activity in Fe uptake by plant, an experiment was carried out by Masalha et al. 2000, where plants were grown under both sterile and non-sterile conditions on a loess loam soil. After the incubation, it was observed that plants cultivated under non-sterile conditions grew well, exhibiting higher Fe concentrations in the roots. In contrast, plants grown in the sterile condition showed very little growth and suffered from severe iron deficiency. Through this experiment, Masalha et al. 2000 showed that the production of microbial siderophores was totally suppressed when the plants were grown under sterile conditions. Thus, they concluded that microbial siderophores might be considered as an efficient iron source for the plants (Masalha et al. 2000). In agreement with this observation, Crowley 2006 also showed that microbial siderophores are used as the major source of iron in plants (Crowley 2006). *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 considerably (Gangwar and Kaur 2009). Siderophore produced by an endophytic *Streptomyces* sp. isolated from the roots of a Thai jasmine rice plant induced plant growth and markedly elevated root and shoot biomass and lengths (Runгин et al. 2012). Recently, *Trichoderma*

asperellum was found to produce siderophore which had a potential role in enhancing cucumber growth by ameliorating salt stress (Qi and Zhao 2013). An investigation conducted on the plant-growth-promoting activities of fungi revealed that the siderophores produced by *Aspergillus niger*, *Penicillium citrinum*, and *Trichoderma harzianum* increases the shoot and root lengths of chickpeas (*Cicer arietinum*) (Yadav et al. 2011). Ecto-mycorrhiza is a type of symbiotic relationship that occurs between a fungal symbiont and the roots of various plant species. In this symbiotic relationship, it was reported that fungal symbiont depends on fungal siderophores in order to supply iron to the host roots of plants (Van Scholl et al. 2008). Sometimes, the plant also modifies the structure of root soil microbial community and favors the growth of more siderophore-secreting microbes by secreting phenolic exudates from their roots (Jin et al. 2010). This improves the solubility of insoluble iron and enhances plant uptake of iron via microbial siderophores (Jin et al. 2010). Besides microbial siderophores, plants can also synthesize phyto-siderophore which can chelate the iron directly (Masalha et al. 2000). In some plants, the sign of iron shortage decreased completely with the rapid consumption of phyto-siderophore (Marschner et al. 1986). Thus, the siderophores originated either from microbes or from plants are recognized as the potential source of iron for their survival and growth.

Siderophore as potential biocontrol agent

Siderophores play a significant role in the biological control mechanism against certain phyto-pathogens (Fig. 3). Siderophores bind with the iron tightly and reduce the bioavailable iron for the plant pathogens, thus facilitating the killing of phyto-pathogens (Beneduzi et al. 2012; Ahmed and Holmstrom 2014). Several studies have illustrated the role of siderophores as a biocontrol agent. Kloepper et al. for the first time illustrated the importance of siderophore production as a mechanism of biological control of *Erwinia carotovora* by several plant-growth-promoting *Pseudomonas fluorescens* strains A1, BK1, TL3B1, and B10 (Kloepper et al. 1980). Pyoverdine siderophores produced by Pseudomonads are involved in the control of wilt diseases of potato caused by *Fusarium oxysporum* (Schippers et al. 1987). Pyoverdine siderophore is also active against *Gaeumannomyces graminis* which is associated with a deficiency of wheat and barley growth (Voisard et al. 1989). Pyoverdines were also reported to suppress the plant pathogens in peanuts and maize (Pal et al. 2001). Besides Pseudomonads, siderophores produced by *Bacillus subtilis* also play a pivotal role in the biocontrol of *F. oxysporum*, which is responsible for the Fusarium wilt of pepper (Yu et al. 2011). Certain siderophores produced by *Azadirachta indica* chelates Fe (III) from soil with high affinity and thus suppresses the growth of several fungal pathogens (Verma et al. 2011). Consistent with the above information, it

Fig. 3 Siderophore enhances plant growth by killing pathogenic bacteria through iron sequestration. Phyto-pathogens associate with the root of the plant and causes pathogenesis. Siderophore binds with the iron that results in iron depletion to the phyto-pathogens, causing the death of the pathogens



was reported that siderophores can also inhibit the growth of certain phytopathogenic fungi, such as *Phytophthora parasitica*, *Pythium ultimum*, and *Sclerotinia sclerotiorum* (Seuk et al. 1988; Hamdan et al. 1991; McLoughlin et al. 1992). All the above reports established siderophore as a potential biocontrol agent against several phyto-pathogens.

Siderophore enhances bioremediation of heavy metals

Soils may become contaminated by the rapid accumulation of heavy metals and metalloids coming from the rapidly growing industry, mine tilling, improper disposal of metal wastes, indiscriminate application of chemical fertilizers, pesticides, wastewater irrigation, abnormal spillage of petrochemicals, and atmospheric deposition (Zhang et al. 2010; Wuana and Okieimen 2011). Although the principal role of siderophores is to chelate ferric iron, they can also play significant roles in detoxifying heavy-metal-contaminated samples by binding to wide array of toxic metals, e.g., Cr^{3+} , Al^{3+} , Cu^{2+} , Eu^{3+} , and Pb^{2+} (Nair et al. 2007; Rajkumar et al. 2010; O'Brien et al. 2014). Therefore, siderophores can become a useful eco-friendly agent for heavy metal remediation (Rajkumar et al. 2010). Most of the metals at low concentrations promote the growth of the bacteria while at higher concentrations they are toxic for the bacteria (Heldal et al. 1985). For example, low concentration of copper promotes bacterial growth by participating in electron transport chain and enzymatic functionality, but at high concentrations, it generates oxidative stress which can cause damage in DNA (Gaetke and Chow 2003; Valco et al. 2005). Siderophores bound to other heavy metals do not enter the cell efficiently whereas siderophore bound to iron moves into the cell adequately (Miethke and Marahiel 2007; Braud et al. 2009a; Noinaj et al. 2010). Siderophore produced by *Pseudomonas azotoformans* was associated with the removal of arsenic

from contaminated soil (Nair et al. 2007). It has been reported that certain *Rhizobacteria* can improve the plant growth by reducing the severity associated with nickel toxicity (Bollard 1983; Bingham et al. 1986; Yang et al. 1996; He and Yang 2007). Neubauer and colleagues (2000) reported that siderophores like desferrioxamine B can bind Co (III) better than Fe (III) in high pH conditions. Pyochelin, a siderophore produced by *Pseudomonas aeruginosa*, can chelate a variety of metals like Ag^+ , Al^{3+} , Cd^{2+} , Co^{2+} , Cr^{2+} , Cu^{2+} , Hg^{2+} , Mn^{2+} , Ni^{2+} , Pb^{2+} , and Zn^{2+} and prevents the entry of these metals into the bacteria (Braud et al. 2009b). Azotochelin and azotobactin, two siderophores produced from *Azotobacter vinelandii*, have the ability to pursue molybdenum (Mo) and vanadium (V) acquisition (Wichard et al. 2009). It was observed that siderophores play a crucial role in mobilizing metals from metal-contaminated soils (Ahmed and Holmstrom 2014). In a separate study, it was reported that the siderophores synthesized by *Agrobacterium radiobacter* removed approximately 54 % of the arsenic from a metal-contaminated soil (Wang et al. 2011). Siderophores also played vital roles in mobilizing metals from mine waste (Edberg et al. 2010). Several metals (Fe, Ni, and Co) were mobilized from waste material (acid-leached ore) of a uranium mine with the aid of siderophores produced by *Pseudomonas fluorescens* (Edberg et al. 2010). A siderophore-overproducing mutant of *Kluyvera ascorbate* SUD165 was found to reduce the heavy metal toxicity such as Ni, Pb, and Zn in soil samples collected from a metal-impacted wetland near Sudbury, Ontario (Burd et al. 2000). It was reported that pyoverdinin secretion by fluorescent *Pseudomonas* isolated from wastewater treatment plant and from compost can sequester zinc markedly and thus act as a potential zinc bioremediating agent (Ines et al. 2012). Considering all the above information, siderophore can be used as an efficient bioremediating agent for metals.

Siderophore as biosensor

Biosensor is a simple, integrated device capable of generating specific quantitative or semi-quantitative analytical information using a biological recognition element attached to a transducer (Thevenot et al. 1999; Gupta et al. 2008). A biosensor generally consists of a biorecognition component, biotransducer component, and electronic system containing a signal amplifier, processor, and display (Eggins 1996). The recognition component, often regarded as a bioreceptor, interacts with the specific analyte. The extent of binding is measured by the biotransducer which generates a signal directly correlating with the concentration of analyte in the sample. The ultimate objective of designing of any biosensor is to conveniently test the analyte at the point of concern where the sample was collected. Figure 4 depicts the schematic diagram of siderophore-based biosensor operations and functions. Pyoverdine produced from *Pseudomonas aeruginosa* are yellow-green water-soluble fluorescent siderophores, already been considered as a promising agent for the construction of biosensors (Pesce and Kaplan 1990). It was reported that a natural fluorescent pigment pyoverdine biosynthesized by *Pseudomonas* can act as a new biosensor for the monitoring and detection of iron (Barrero et al. 1993). This biosensor is very selective for iron (III). This biosensor can detect and analyze the sample either in solution (detection concentration=10 ng/mL) or in immobilized form (detection concentration=3 ng/mL). The biosensor possesses good stability and can be used over a period for at least 3 months or over 1000 determinations. The sensor was successfully applied to determine iron in various water samples (Barrero et al. 1993). However, this siderophore-mediated detection showed no significant difference with the inductively coupled plasma atomic emission spectroscopy (ICPAES) reference method (Barrero et al. 1993). N-Methylantranyl 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 waters (Palanche et al. 1999). The concentration of iron present in ocean has been quantified by using a siderophore named as parabactin secreted from *Paracoccus denitrificans* (Chung Chun Lam et al. 2006). Siderophores present in crude culture broth supernatant of *Pseudomonas fluorescens* have been characterized to function as a sensitive, robust, and specific Fe^{3+} biosensor (Gupta et al. 2008). This siderophore-based biosensor is cheap, user-friendly, and simple as it relies only on spectrophotometer (Gupta et al. 2008). Another study suggested the use of the fluorescent siderophore derivative MA-DFB to act as a photoactive sensor for the biologically available iron content in aquatic systems (Orcutt et al. 2010). Although some of the siderophores have been used as potential biosensors, most of them have not yet been characterized. Thus, it could be hypothesized that some of the uncharacterized siderophores may turn out to be novel and potential biosensors.

Siderophore as medicine

Siderophores have important applications in the medical field to fight against antibiotic-resistant bacteria and in the treatment of several human diseases which has been discussed below.

Trojan horse antibiotics

The ability of bacteria to gain resistance to antimicrobial agents poses major threats in the treatment of bacterial infections (Mollmann et al. 2009). One possible method to circumvent permeability-mediated drug resistance is the implementation of the “Trojan horse” strategy (Mollmann et al. 2009). Siderophore can mediate selective delivery of antibiotics to

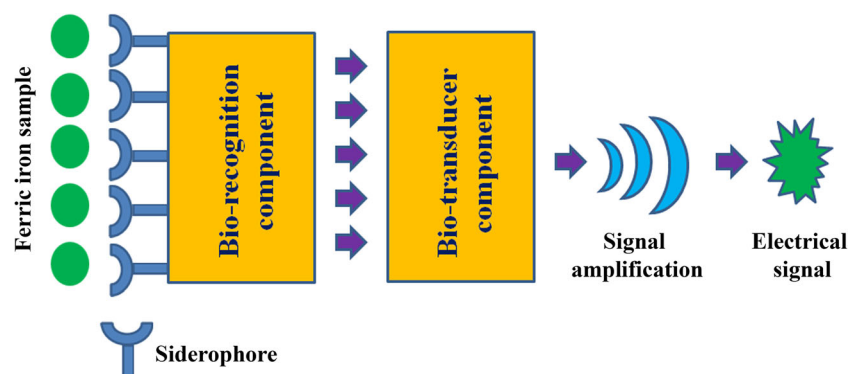


Fig. 4 Schematic diagram of a siderophore-based biosensor. Siderophore, a sensitive biorecognizing component, interacts (binds or recognizes) with the iron analyte under the experimental condition. The biotransducer part transforms the signal resulting from the interaction

between iron and siderophore into another signal which can be more easily measured and quantified through an amplifier and a sensitive detector

antibiotic-resistant bacteria by the Trojan horse strategy (Huang et al. 2013). This strategy exploits the iron transport abilities of siderophores to carry drugs into cells by preparation of conjugates between siderophores and antimicrobial agents (Huang et al. 2013). Figure 5 shows the diagram of the formation of Trojan horse complex. The siderophore-drug complex selectively interacts with the siderophore receptors on the bacterial cell surface and is then actively transported across the outer membrane (Gorska et al. 2014). In this case, antimicrobial agent bound siderophore can further bind to iron and the resulting complex (antimicrobial agent-siderophore-iron) moves into the cell (Huang et al. 2013). Albomycin, a naturally occurring antibiotic, belongs to the class of compounds made up of antibiotic moiety bound to siderophore known as sideromycins (Pramanik and Braun 2006). It has been reported that albomycin inhibits some of the members of both gram-negative and gram-positive bacteria (Pramanik and Braun 2006). In albomycin, the siderophore part which is very similar to ferrichrome is joined to toxic molecule by a serine spacer (Ali and Vidhale 2013). Albomycin enters into the microorganism using the ferrichrome uptake system, and thereafter, the toxic part of albomycin is released enzymatically inside the cell (Ali and Vidhale 2013). Similarly, salimycins, another naturally occurring sideromycins, use a dicarboxylic acid as a linker between the tri-hydroxamate siderophore and the aminoglycoside antibiotic (Ali and Vidhale 2013). It has been found that sideromycin transport across the bacterial membranes greatly increases the antibiotic diffusion in the bacterial cell (Braun et al. 2009). It was reported that the sideromycin-mediated antibiotic transport rate is very high compared to the antibiotic moiety alone without the siderophore (Braun et al. 2009). The antibiotic released from sideromycin showed at least 2 orders of magnitude lower minimal inhibitory concentration (MIC) than the MIC of the antibiotic alone (Braun et al. 2009). Although natural sideromycin showed better antimicrobial activity, in many cases, the sideromycin-mediated antibiotics suffered from poor solubility, chemical instability, inadequate absorption, and tissue penetration (Rautio et al. 2008). It was reported that in some cases, synthetic siderophore-drug complexes can turn out to be a promising solution for the treatment

of multidrug-resistant bacterial infections or other human diseases (Krewulak and Vogel 2008). Synthetic conjugates have drawn attention in circumventing common antibiotic resistance mechanisms including outer membrane permeability barriers, enzymatic malfunction, or blocked diffusion (Nagoba and Vedpathak 2011). Existing literature documented that conjugates of synthetic siderophores with beta-lactam antibiotics exhibited considerable antimicrobial activity. Once inside the cell, siderophore-beta-lactam antibiotic complex binds to penicillin-binding proteins present in the periplasm and inhibit the growth of gram-negative bacteria (Brochu et al. 1992). To date, mainly catecholate and hydroxamate types of siderophores are used as delivery vehicles for antimicrobials to overcome membrane-permeation-based drug access problems (Milner et al. 2013). However, carboxylate-type siderophores, such as staphyloferrin A, can be a good option for certain applications, as this type of siderophore showed better iron chelating property in acidic environments than catecholate and hydroxamate siderophores (Milner et al. 2013). The hydrophilicity nature of staphyloferrin A improves the water solubility of its conjugates and enhances the rate of transport of the drug to the cell (Milner et al. 2013). Since *Staphylococcus aureus* secretes staphyloferrin siderophores, Milner et al. synthesized a series of novel staphyloferrin based Trojan horse conjugates and tested the antimicrobial properties of those conjugates on *Staphylococcus aureus* (Milner et al. 2013). It was reported that one of the conjugate was found to exhibit antimicrobial property against *Staphylococcus aureus* (Milner et al. 2013). *Staphylococcus aureus* can colonize human skin and gut and associates with some problematic health-care-associated infections, including surgical site infections, bacteraemias, and lower respiratory tract infections (Milner et al. 2013). Chemically synthesized Trojan horse was found to be active against some of the members of the pathogenic microorganism. However, nanotechnology has emerged as a new field offering new possibilities in designing efficient therapeutic systems that enable more precise delivery of drugs to the appropriate site of action. The development of iron oxide nanoparticle based therapeutic systems can facilitate more precise delivery of drug to the appropriate location (Gorska et al. 2014).

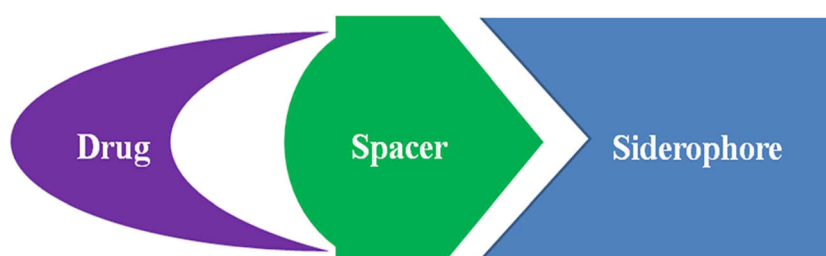


Fig. 5 Siderophore inhibits the growth of drug-resistant microorganisms through “Trojan Horse strategy.” In this case, siderophore binds to the drug through a spacer. The siderophore along with the drug enters into the

cell using the siderophore receptors on the membrane. Once the complex enters into the bacterial cells, the spacer gets hydrolyzed and the drug becomes free, causing the death of the cells

Iron overload therapy

Some siderophores have potential applications in the treatment of iron overload diseases. In the treatment of β -thalassemia and certain other anemia like sickle cell anemia, periodic whole blood transfusions are required (Hershko et al. 2002). As there are no specific physiological mechanisms for iron removal in humans, repeated transfusion therapy results in a steady buildup of iron. This excess iron as well as the primary iron overload should be minimized in the body by elimination of iron from the system especially the liver. Diseases associated with iron overload can be treated with the help of siderophore-based drug (Pietrangelo 2002). Desferal is the drug used for the treatment of thalassemia major (Propper et al. 1977; Summers et al. 1979; Robotham and Lietman 1980) and sickle cell anemia.

Antimalarial activity

It was reported that some siderophores possess antimalarial activity against *Plasmodium falciparum* (Tsafack et al. 1996). For example, the siderophore produced by *Klebsiella pneumoniae* (Gysin et al. 1991) and the siderophore desferrioxamine B, produced by *Streptomyces pilosus*, have antimalarial activity against *Plasmodium falciparum* (Nagoba and Vedpathak 2011). Desferrioxamine B enters inside the parasite and causes intracellular depletion of iron. This agent conjugates with methyl anthranilic acid and shows 10-fold greater in vitro activity against *Plasmodium falciparum*, which can be further enhanced by using nalidixic acid as a conjugate. This conjugate exhibits its action similar to the metal-catalyzed oxidative DNA damage (Gysin et al. 1991; Loyevsky et al. 1993, 1999).

Removal of transuranic elements

The process of electricity generation by nuclear energy has increased the chances of human exposure to transuranic elements such as aluminum and vanadium (Nagoba and Vedpathak 2011). Aluminum overload occurs in patients with dialysis encephalopathy (a major complication of long-term dialysis, which is caused by the accumulation of aluminum in the brain) and in dialysis patients having end-stage renal failure (ESRF). Siderophores such as desferol can be used to treat chronic aluminum overload (Nagoba and Vedpathak 2011). Desferol mobilizes and chelates aluminum bound to the tissues by forming an aluminosiderophore complex, which is freely soluble in water and is readily excreted through urine or feces. Desferal can also eliminate vanadium, another transuranic element 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 % (Nagoba and Vedpathak 2011). Desferal has also been shown to increase the urinary and fecal

excretion of vanadium (Ackrill et al. 1980; Arze et al. 1981; Poggiltsch et al. 1981; Hansen et al. 1982; Nagoba and Vedpathak 2011).

Cancer therapy

Iron acts as a carrier of oxygen inside the human body. However, excess iron can increase the risk for cancer through the production of reactive oxygen species. Iron reduction by phlebotomy has been reported to decrease the risk of cancer in a supposedly normal population with peripheral arterial disease (Zacharski et al. 2008; Toyokuni 2009). 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 peroxide levels (Toyokuni 2009). Iron in free form is reactive and can damage biomolecule (Gutteridge et al. 1982). Diseases such as hemochromatosis and endometriosis are associated with complications of iron overload that resulted in the induction of cancer (Toyokuni 2009). Patients with a long-standing history (>10 years) of ovarian endometriosis are at high risk of having ovarian cancer (Brinton et al. 1997; Toyokuni 2009). It was reported that a high level of catalytic iron is present in ovarian endometriotic cysts resulting in greater amount of oxidative DNA damage of the epithelia of those cysts (Yamaguchi et al. 2008). Iron was reported to induce cancer in several animal models also (Toyokuni 2009). Mice exposed to iron oxide dust caused pulmonary tumors whereas injection of iron dextran was associated with soft tissue sarcoma (Campbell 1940; Richmond 1959; Toyokuni 2009). Cancer cells have higher requirement of iron as compared with healthy cells because of their rapid cell division. Their iron uptake and storage rate is also higher (Elford et al. 1970; Vaughn et al. 1987). As iron plays an essential role in cellular proliferation, iron chelators like siderophores can be beneficial for cancer therapy (Wandersman and Delepelaire 2004). Desferrioxamines were reported to significantly decrease the growth of aggressive tumors in patients with neuroblastoma (NB) or leukemia (Buss et al. 2003; Lovejoy and Richardson 2003). Studies have demonstrated that a 4-h incubation of NB cells with desferrioxamine can inhibit DNA replication (Blatt et al. 1988) whereas a 72-h incubation can reduce the cell viability up to 80 % (Blatt and Stitely 1987). Desferrioxamine E produced by *Actinobacterium* was reported to reduce the viability of malignant melanoma cells significantly (Nakouti et al. 2013). Several other siderophores, namely, dexrazoxane, O-trensox, desferrioxochelins, desferrithiocin, and tachpyridine, are used as iron chelators in cancer therapy (Miethke and Marahiel 2007). Siderophores are also useful in the clearance of non-transferrin-bound iron in serum which is seen in cancer therapy as a result of exposure to some chemotherapy (Chua et al. 2003).

Conclusion

Iron is a vital element required by every living organism for numerous cellular processes. Under iron-deficient conditions, the growth of microorganisms become impaired. The microorganisms survive under such iron-limited conditions by secreting siderophores. The wide applications of siderophores reveal that it holds the promise to be implemented as a potential agent in different areas including ecology, agriculture, bioremediation, biosensor, and medicine. However, further investigation is indeed important to unveil its new functions. Therefore, the need of the hour is to identify and characterize more and more siderophores from different habitats for the benefit of living beings and the environment.

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Conflict of interest The authors declare that they have no conflict of interest.

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