MINI REVIEW

Microbial siderophores as molecular shuttles for metal cations: sources, sinks and application perspectives

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Abstract

Iron is one of the highly abundant elements on the earth's crust, an essential micronutrient for a majority of life forms, and exists in two frequent oxidation states such as ferrous (Fe^{2+}) and ferric (Fe^{3+}). These two oxidation states are interconvertible by redox reactions and form complexes with a wide range of siderophores. At neutral pH in soil, Fe^{2+} is highly soluble upto 100 mM but have less biological value, whereas Fe^{3+} is less soluble upto 10^{-9} M. This reduced bioavailability of Fe^{3+} induces competition among microorganisms. As many microorganisms need at least 10^{-6} M of Fe^{3+} form of iron for their growth, siderophores from these microbes readily withdraw Fe^{3+} iron from a variety of habitats for their survival. In this review, we bring into light the several recent investigations related to diverse chemistry of microbial siderophores, mechanisms of siderophore uptake, biosynthetic gene clusters in microbial genomes, various sources of heavy metal cations in soil, siderophore-binding protein receptors and commercialisation perspectives of siderophores. Besides, this review unearths the recent advancements in the characterisation of novel siderophores and its heavy metal complexes alongside the interaction kinetics with receptors.

Keywords Microbial siderophores · Siderophore-binding proteins · Biosynthetic genes · Organometallics · Biosensors

Introduction

Siderophores are low molecular weight cation chelating compounds produced by living organisms under cation limitations in order to overcome mineral needs to the cells, circumvent abiotic stresses introduced by toxic heavy metals and lessen biotic stresses (caused by pathogens with metal-based virulence) in the hosts. The term *Siderophore* was originally coined by Lankford in 1973 (Lankford and Byers 1973), derived from the Greek words "*Sideros*" refers to "iron" and "*Phores*" refers to "carrier" and means "iron carrier" (D'Onofrio et al. 2010). More often, the term *Siderophore* is used to indicate iron-chelating molecules having immense roles in iron-based interaction kinetics of the rhizosphere, especially in the biocontrol mechanisms exerted by rhizobacteria.

Iron, as the fourth highly abundant element on the earth's crust and an essential macronutrient for a majority of life forms, exists in two frequent oxidation states such as ferrous (Fe^{2+}) and ferric (Fe^{3+}) forms. Rare oxidation states such as Fe^{1+}, Fe^{4+}, and Fe^{5+} have roles as intermediates of enzymatic biotransformation (Johnstone and Nolan 2015). These two frequent oxidation states are interconvertible by redox reaction and form the basis of its interaction with a wide range of coordination compounds such as haemoglobin and siderophores (Silva Lopes 2011). Under acidic conditions, the iron bioavailability is high (Sabatier et al. 2020). Unfortunately, the biological and environmental pH is near neutral. Fe^{2+} forms are highly soluble to a concentration of 100 mM at neutral pH but have less biological

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value (Timoshnikov et al. 2020). However, Fe^{3+} forms are soluble upto 10^{-9} M only and essential for the growth of several organisms. Hence, the ferric iron bioavailability is very much limited in nature. This reduced bioavailability of Fe^{3+} induces competition for iron among microorganisms (Lewin et al. 2005).

As many microorganisms (almost all bacteria and fungi) need at least 10^{-6} M of iron for their growth and multiplication (McMorran et al. 2001), siderophores produced by the microbiome readily withdraw insoluble ferric iron from a variety of habitats to sustain their survival (Nagoba and Vedpathak 2011). Siderophores are produced only under such cation limiting conditions to scavenge the iron from the environment. Mechanism behind the process is that the released siderophores bind with iron (Fe^{3+}) firmly to form the ferric–siderophore complex, and this complex migrates into the cell through the cell membrane via specific siderophore-binding protein receptors (Armstrong et al. 2004). Fortunately, the process also induces iron starvation for root colonising plant pathogens, leading to disease inhibitory effects and accounts for suppression of disease incidence (Gu et al. 2020). In line with bacteria, several reports describe the involvement of siderophores under iron starvation to satisfy iron needs in bacteria (Tian et al. 2009; Saharan and Nehra 2011). In an investigation by Essén et al. 2007, types of siderophore produced by *Pseudomonas stutzeri* in aerobic condition differ from the types of siderophore produced by the same bacteria in anaerobic conditions. It implies the robustness of siderophore biosynthetic genes for the changing environmental conditions and their peculiar genome adaptation.

In industrial sectors, siderophores find their application as antioxidants to scavenge free radicals in food preservation process (Todokoro et al. 2016). Siderophores are useful in the remediation of industrial wastes rich in heavy metals and the reprocessing of nuclear fuels because of their high affinity towards heavy metal cations (Renshaw et al. 2002). In the field of medicine, desferrioxamine, and desferrithiocin siderophores produced from actinobacteria *Streptomyces* spp. are used to treat iron and aluminium poisoning (Terra et al. 2021). Siderophores from pathogenic *Klebsiella pneumoniae* find applications as antimalarial agents (Gysin et al. 1991). Siderophores and their producer microorganisms are constantly been employed as bioinoculants to reduce disease incidence and to promote plant growth for more than four decades (Kloepper et al. 1980; Wang et al. 2022).

In this connection, one would observe handsome of translational research outcomes in the previous literatures describing multifarious potentials of siderophores from various biological sources, their targeted applications and commercialisation of the siderophore-based products to improve the health and safety of plants, animals, and environment. The published review manuscripts of the past decade are tremendous between 2010 and 2020 which brought into light separately the role, biosynthesis, characterisation and applications of siderophores in various sectors such as ecology, bioremediation, agriculture, medicine and biosensors (Saha et al. 2013, 2016; Ahmed and Holmström 2014; Pluháček et al. 2016; Ghosh et al. 2020). However, a holistic understanding about the different classes of microbial siderophores, updated biosynthetic microbial sources, metallic cation sources in soil, microbial uptake machinery, and multifaceted applications are still scanty due to lack of illustrative reviews so far which would guide the researchers promptly in attaining their futuristic goals on siderophore research. Hence, our review serves as a reservoir to provide information on the above topics of thirst and highlights the key components of siderophore research such as structural classification and molecular diversity, siderophore biosynthetic gene clusters in microbial genomes, role of siderophore-binding protein receptors on microbial membrane, sources and sinks of metal cations, and commercialisation of microbial siderophores in medicine, diagnostics, biosensors, agriculture and environmental protection with recent encroachments in siderophore research and critical comments to ignite the blossoming young minds.

Chemical classification of siderophores

Based on iron interacting functional groups, types of ligands, and structural features, siderophores are classified as Hydroxamates, Catecholates, Carboxylates, or Mixed forms (Fig. 1; Table 1) (Crowley 2006; Meneely and Lamb 2007). Both bacteria and fungi secrete hydroxamate types, Catecholates are secreted by bacteria, and Carboxylates are produced by only a few bacterial genera such as *Rhizobium* spp., and *Staphylococcus* spp., rather are exclusively synthesised by fungi representing the order Mucorales (Carroll et al. 2017). Fluorescent Pseudomonads mainly produce mixed type*s* (Ahmed and Holmström 2014). These siderophores are synthesised generally
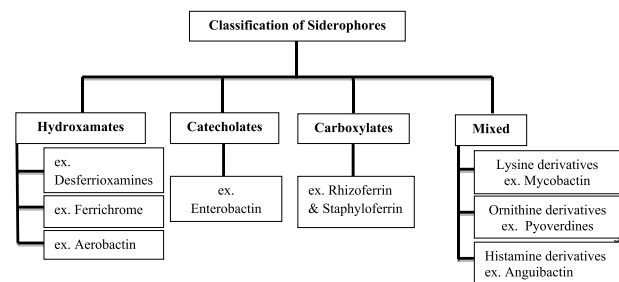

Fig. 1 Outline classification of microbial siderophores based on chemistry

Table 1 Different classes of siderophores with examples

S. no	Commercial names of some siderophores	Classes of siderophore based on metal cation interacting functional groups
1	Desferrioxamine B, desferrioxamine E, desferrioxamine G1, amphiphilic desferrioxamines, Rhodochelin, Erythrocelin, coeli-chelin, aerobactin, trichostatin A, vicibactin	Hydroxylamines or hydroxamate functional groups ($-CO-N\,(O^-)-)_n$
2	Enterobactin, L-parabactin, l-agrobactin, enterochelin, vibriobactin, bacillibactin	Phenol–catecholates functional groups (benzene-linked hydroxyl groups)
3	Rhizobactin, staphyloferrin A, rhizoferrin, vibrioferrin	Carboxylate functional groups (poly carboxylic acid groups)
4	Mycobactins, pyoverdines, anguibactins	Mixed forms containing hydroxamate, phenolate and carboxylate derivatives

through two different biosynthetic pathways and include (1) NRPS dependent and (2) NRPS independent.

Hydroxamate siderophores

Hydroxamate siderophores are of both fungal and bacterial origin. Most hydroxamates ($C(=O)N-(OH)R$) have R group as an amino acid or its derivative. These siderophores generally exhibit absorption maxima (Λ_{max}) lying between 420 and 450 nm, in its iron bound forms.

Studies have detailed several hydroxamates with their structural and functional information (Fig. 2). The iron chelation is afforded by a hydroxamate group ($-CO-N$ $(O^-)-$) donated by acetylated or formylated hydroxylamines that are usually derived from lysine or ornithine or histamine (Miethke and Marahiel 2007). Aerobactin (by *Aerobacter aerogenes*) and mycobactin (by *Mycobacterium* spp.) are the lysine derivatives of hydroxamates (Crosa and Walsh 2002). Pyoverdines (by *Pseudomonas aeruginosa*), ornibactin (by strains of *Pseudomonads*), exochelin (by saprophytic strains of *Mycobacterium* spp.), exomycobactin (by pathogenic strains of *Mycobacterium* spp.) (Chan 2009), fusarinine, ferrichrome, and coprogens (by a variety of plant pathogenic fungi) are the ornithine derivatives of hydroxamates (Renshaw et al. 2002). Anguibactin, (by *Vibrio anguillarum*, a fish pathogen) is the histamine derivatives of hydroxamates (Crosa and Walsh 2002).

Ferrichrome, the first siderophore to be isolated from the fungus *Ustilago sphaerogena*, was identified as a growth factor for its microbial neighbours (Messenger and Ratledge 1985). Ferribactin produced by *Pseudomonas fluorescens* was characterised as a hydroxamate (Philson and Llinas 1982). Nocobactin and Gonobactin produced in small quantities by *Neisseria meningitidis* and *N. gonorrhoea* are also found to be hydroxamates in chemistry, respectively. These hydroxamate siderophores were conventionally detected by Neilands' spectrophotometric assays.

Catecholate/phenolate siderophores

The second abundant class of siderophores, the phenol–catecholates, contains mono- or dihydroxybenzoic acid functional group to participate in iron chelation (Meneely and Lamb 2007). Catecholate siderophores have been reported only in bacteria (Fig. 3). According of Cox et al. 1988, this group is derived from dihydroxybenzoic acid or salicylate with varying iron-binding affinities ranging from a very tight as in case of enterobactin from *Escherichia coli* to a legitimately weak as in case of pyochelin from *P. aeruginosa*. *E. coli* and *Aerobacter aerogenes* synthesise the phenolate siderophore enterobactin (Yancey et al. 1979). Phenolate siderophores are produced by most enteric bacteria including *Salmonella typhimurium*, *Shigella sonnei*, and *K. pneumoniae* (Perry and San Clemente (1979). The presence of phenolate siderophores (derivatives of 2,3-dihydroxybenzoic acid (2,3-DHBA)) has been demonstrated in *A. aerogenes*, *E. coli* and certain species of *Salmonella* (Visca et al. 1991). Similarly, a threonine-conjugated 2,3-DHBA in cultures of *E. coli* and *Klebsiella oxytoca* (Nakouti 2008), a lysine conjugated diphenolic acid in *Azotobacter vinelandii* (Corbin and Bulen 1969), and also threonine- and glycine-conjugated 2,3-DHBA in N_2 fixing cowpea *Rhizobium* RA-1 have also been reported (Saxena et al. 1986). Enterochelin is the prototype of catecholate siderophores with cyclic trimester of 2,3-dihydroxybenzoylserine, produced by *E. coli*, *Salmonella typhimurium*, and *K. pneumoniae* (Ali and Vidhale (2013). Enterochelin results from a conformational change in the coordination chemistry of enterobactin under acidic environment (Rajendran and Marahiel 1999). *Carotovora* and *Erwinia* produce catecholates, whereas *Pseudomonas* produces a mixed catecholate–hydroxamate-type siderophores (Chakraborty et al. 2013). Bacillibactin and vibriobactin identified from *Bacillus subtilis* and *Vibrio cholerae*, respectively, are the other members of tricatecholate family of siderophores (Delepelaire 2019). Catecholate types with linear structures were also identified in certain species (Müller et al. 2009). It includes parabactin produced by *Paracoccus denitrificans* and agrobactin produced by
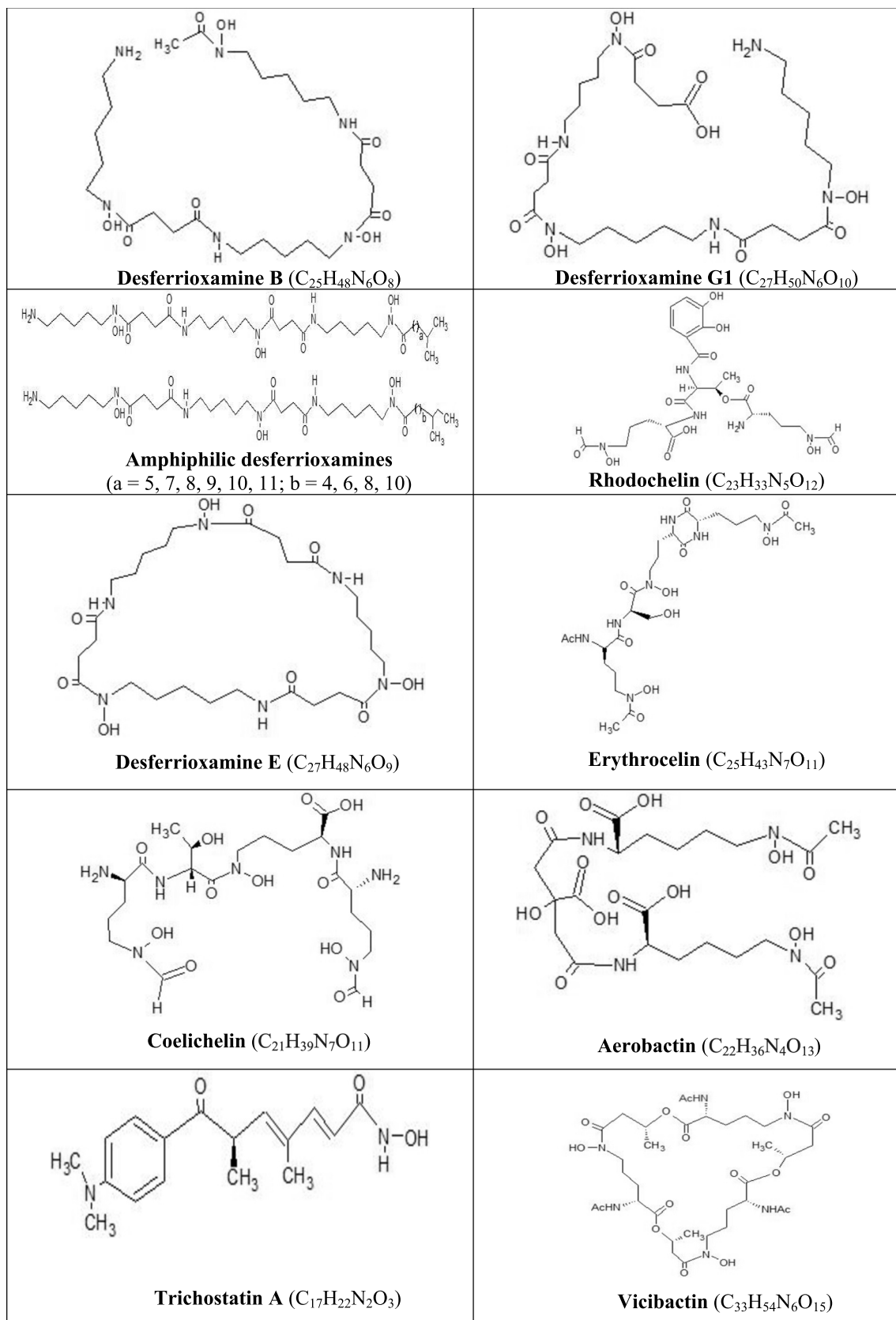
Fig. 2 Structures of various hydroxamate (–CO–N (O⁻)–) type siderophores produced by microorganisms. All the chemical structures were drawn using ChemDraw Ultra 12.0 software (PerkinElmer, Waltham, MA, USA)

Fig. 3 Structures of various catecholate/phenolate siderophores produced by microorganisms. All the chemical structures were drawn using ChemDraw Ultra 12.0 software (PerkinElmer, Waltham, MA, USA)
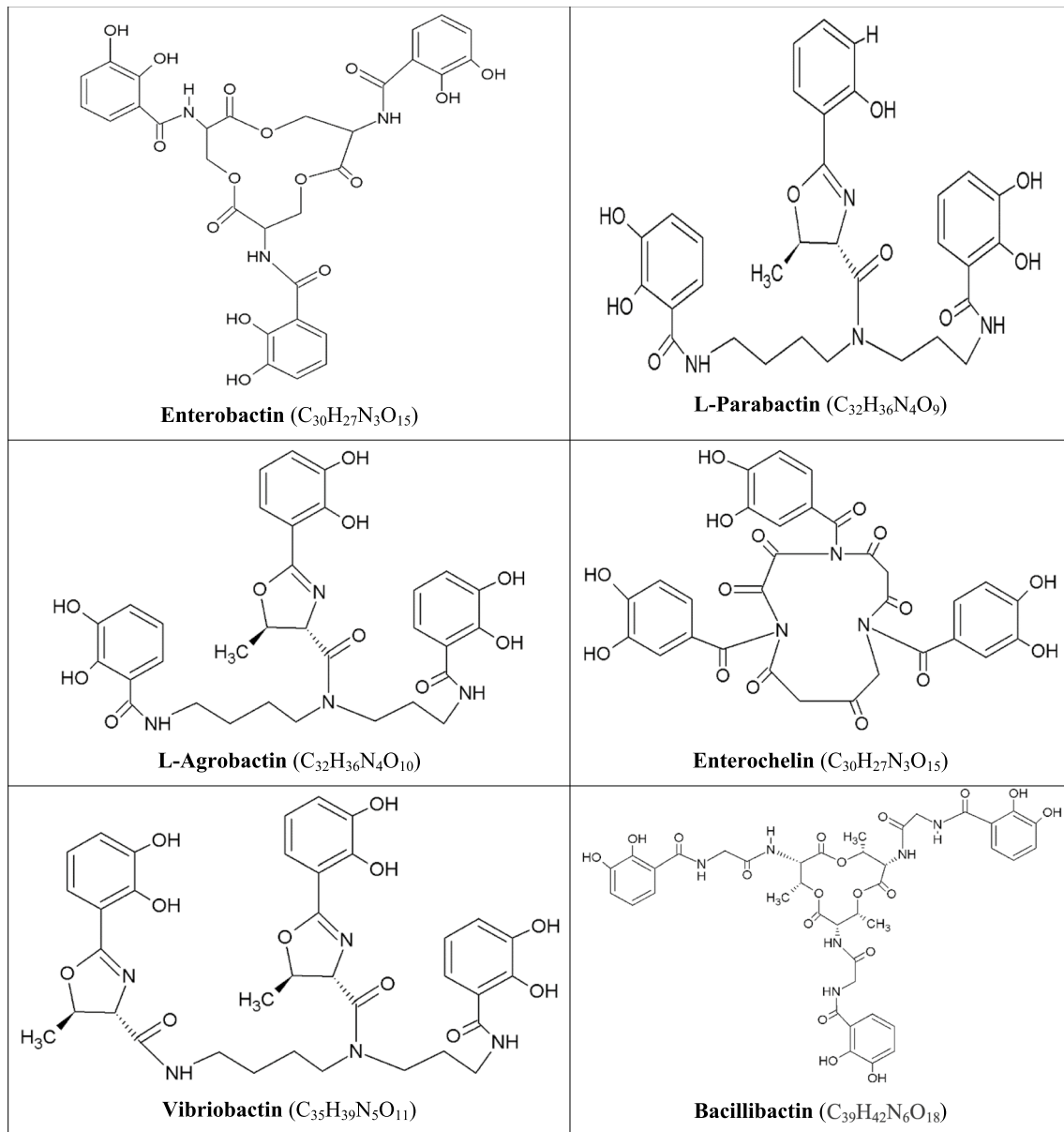
Agrobacterium tumefaciens. Each catecholate group delivers two of its oxygen atoms for coordination with iron resulting in a hexadentate octahedral complex which is much more like iron chelation by hydroxamate siderophores. Presence of catecholate is indicated by the formation of wine-coloured complex when in its iron bound form using Neilands' spectrophotometric assay and the absorption maxima ($λ_{max}$) is usually read at 495 nm.

Though catecholates are very rare from fungi, marine fungi like *Penicillium bilaii* produced pistillarin, a catecholate siderophore and thus making a sense that exception is always a rule in biology (Capon et al. 2007).

Carboxylate (complexone) siderophores

Bacterial carboxylates

The well-characterised and novel structured carboxylate-type siderophore is rhizobactin. Rhizobactin produced by *Rhizobium meliloti* is an amino poly carboxylic acid with hydroxyl carboxyl and ethylene diamine dicarboxyl moieties contributing iron chelation. Other carboxylate siderophores include Staphyloferrin from *Staphylococcus aureus*, and so on. Interestingly, both bacteria and fungi produce rhizoferrins. Fungi produce only R, R-rhizoferrin while a

few bacteria produce enantio-rhizoferrins (S, S-rhizoferrin) (Münzinger et al. 1999). *Staphylococcus hyicus* produced staphyloferrin A is a new member of complexone class. Staphyloferrin A consists of one D-ornithine and two citric acid residues connected by two amide bonds. Vibrioferrin is a tricarboxylic acid siderophore synthesised by virulent strains of *Vibrio alginolyticus* and *Vibrio parahaemolyticus*, which are aquaculture pathogens symbiotically associated with toxic blooms of dinoflagellates (Bellés-Garulera et al. 2016) (Fig. 4).

Fungal carboxylates

Members of the order *Mucorales* under *Zygomycotina* are the promising fungal producers of carboxylates (Dave and Dube 2000). Rhizoferrin is only known carboxylate siderophore produced by fungi, specially synthesised by members of the zygomycetes, mainly by *Rhizopus* spp. (Carroll et al. 2017). Polycarboxylate chemistry with two citric acid molecules forming the core structure connected by diaminobutane is seen in the siderophore, Rhizoferrin which is mainly synthesised by *Rhizopus microsporus* var. *rhizopodiformis* and *Cunninghamella elegans* (Vala et al. 2000).

Mixed forms of siderophores

Mixed forms of bacterial siderophores

Certain siderophores possess multiple functional groups to mediate iron chelation and are termed as mixed siderophores (Meneely and Lamb 2007). These siderophores have mixed ligands of lysine, ornithine, and histamine derivatives (Fig. 5).

Lysine derivatives

Mycobactins are 2-hydroxy phenyl oxazoline containing siderophore molecules for the acquisition of iron. Two chemical structures of siderophores were reported to be produced by *Mycobacterium tuberculosis*, one of the structures being more lipophilic in nature, and the other being more hydrophilic. Mycobactins produced by *Mycobacterium* spp., consisting of hydroxamate and phenol-catecholate classes which are highly lipid soluble. This class of siderophore is observed to span over the outer membrane of the producer bacteria of genus *Mycobacterium* and to work in connection with water-soluble chelating agents (exochelins) for iron sequestration (Ratledge 2004). Structural characterisation using X-ray crystallographic study have uncovered that the iron binding in mycobactin is favoured by two hydroxamate groups, one phenolate group, and an oxazoline nitrogen (Raymond et al. 1984). Generally, it is presumed that
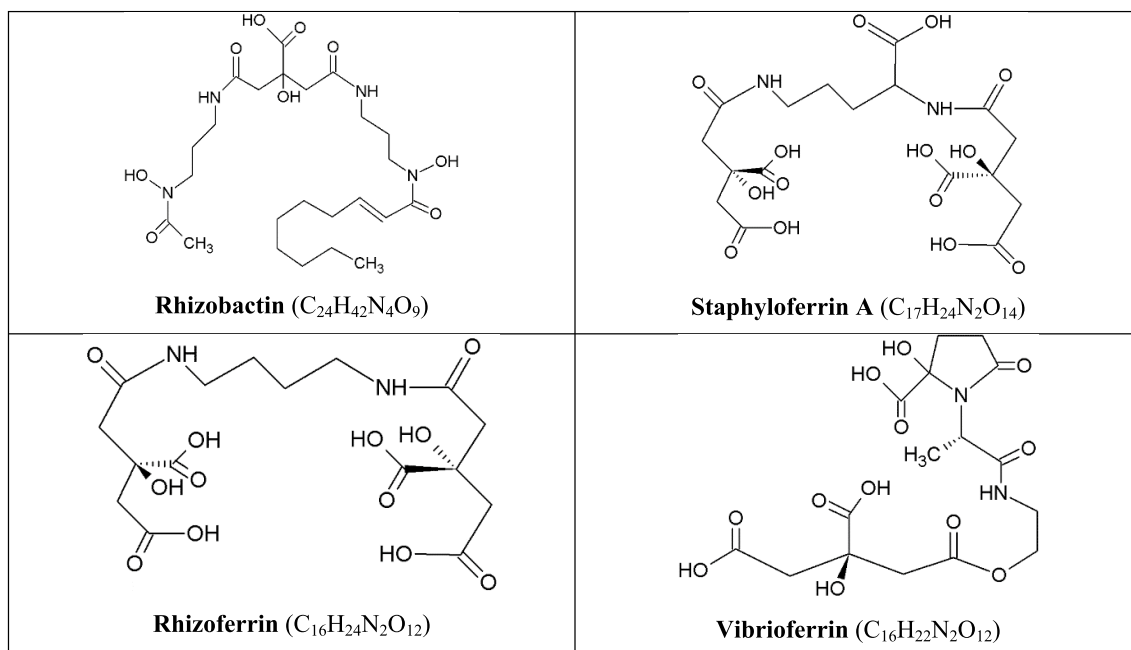

Fig. 4 Structures of carboxylate-type siderophores secreted by microorganisms. All the chemical structures were drawn using ChemDraw Ultra 12.0 software (PerkinElmer, Waltham, MA, USA)
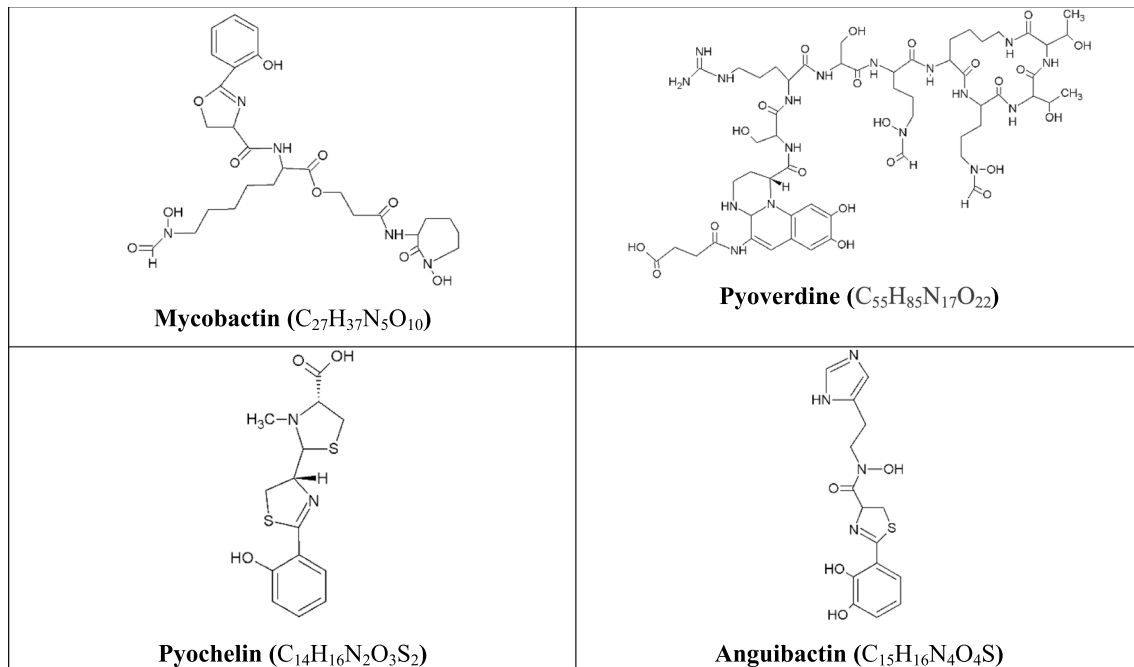
Structures shown: **Rhizobactin** ($C_{24}H_{42}N_4O_9$), **Staphyloferrin A** ($C_{17}H_{24}N_2O_{14}$), **Rhizoferrin** ($C_{16}H_{24}N_2O_{12}$), **Vibrioferrin** ($C_{16}H_{22}N_2O_{12}$)

Fig. 5 Structures of various mixed forms of siderophores secreted by bacteria. All the chemical structures were drawn using ChemDraw Ultra 12.0 software (PerkinElmer, Waltham, MA, USA)

oxazoline and thiazoline contained in donor-deficient sidero-phores, the imine-N will take part in ferric ion complexation.

Ornithine derivatives

Two important siderophore-mediated iron uptake systems have been found in Pseudomonads group of bacteria: one involving the fluorescent siderophore pseudobactin, is also known as pyoverdine; the other involving siderophore pyo-chelin (Mossialos et al. 2000; Meneely and Lamb 2007).

The fluorescent chromopeptide siderophore termed pseu-dobactin (or) pyoverdines are synthesised by *Pseudomonas* spp. It has importance both in agriculture and in medicine (Sah and Singh 2015). Pyoverdine is a water-soluble sidero-phores consisting of 6–12 amino acids, depending on the strains, with a dihydroxyquinoline fluorophore and a small dicarboxylic acid (Mossialos et al. 2000; Poole and Mcay 2003). Hence, it is mixed form of catecholate-carboxylates. Pyoverdine has exceptional affinity towards ferric iron with a dissociation constant of 10—30.8 M and has been dem-onstrated to scavenge iron from transferrin (Boukhalfa and Crumbliss 2002). Production of pyoverdine influences the virulence of pathogenic *P. aeruginosa* (Takase et al. 2000).

Pyoverdine can be classified into three main categories (Lamont et al. 2006):

Type I: Pyoverdines with two formyl-hydroxyornithines.

Type II: Pyoverdines with one formyl-hydroxyornithine and a terminal cyclised hydroxyornithine.

Type III: Pyoverdines with two formyl-hydroxyornith-ines in a different arrangement from type I.

Histamine derivatives

The chemical structure of anguibactin has been identi-fied as ω-N-hydroxy-ω-[[2′-(2″, 3″-dihydroxyphenyl) thiazolin-4′-yl]-carboxyl] histamine, isolated from marine *Vibrio anguillarum*, a potential aquaculture pathogen. It acts as an inhibitor for uptake of iron from aquatic verte-brate tissues, removes ferric iron from other siderophores, ferric hydroxides, and aqueous solutions like cell culture media (Jiménez 2021).

Mixed forms of fungal siderophores

Unlike bacteria, fungal siderophores with mixed chemis-try are very rare with an exception to include phenolate-catecholate mixed form produced by *Candida albicans* and wood degrading basidiomycetes fungi (Howard 1999). Hence, a grand scientific void needs to be filled with con-tinuous identification of novel mixed forms of fungal siderophores using present-day available characterisation technologies, as a result of which novel siderophores from fungi can be explored for mankind.

Various sources of heavy metal cations in soil

Natural sources

Heavy metals such as Cu, Fe, Mn, Mo, and Zn when present at optimum levels will support plants and animals as essential micronutrients. However, supra-optimum levels of these metals may induce toxic effects for both plants and animals. Natural processes such as breakdown of bedrocks, volcanic eruptions (Sidhu 2016), presence of organic and inorganic matter which mobilises heavy metals, soil ageing and soil edaphic factors contribute to the above normal level of heavy metals in the environment (Zwolak et al. 2019).

Manmade inputs

Advancements in industrialisation and agricultural practices have marked alarming levels of heavy metal implications in soil and increased the risk for ground water percolation, contamination of vegetables and other food stuffs. All these led to hyperaccumulation in biological systems which then mobilise heavy metals across varied food chains giving potential health threats to all the life forms. The following sources will increase such risks due to human activities in fertile soil.

Pesticides and fertilisers

Pesticides and insecticides that contribute increased levels of heavy metals in agricultural soil include organophosphorous (chlorpyrifos, methyl parathion, malathion, dimefox, etc.), organochlorine (DDT, heptaclor, eldrin, methoxychloro aldrin, endosulfan, etc.), ethyl mercuric phosphate, methyl mercuric chloride, sodium arsenate, calcium arsenate, lead arsenate, aluminium phosphide, zinc phosphide, and pentachlorophenols (Jayaraj et al. 2016). In addition, wastewater containing heavy metals are used for irrigation and the sewage sludge supplements are being used as an alternative to fertilisers but still contains heavy metal residues at subnormal levels (Sidhu 2016).

Untreated industrial effluents

In ore mining industries, metal tailings are directly discharged into nearby wetlands which increase the bioavailability of heavy metals and concerns for public health issues (DeVolder et al. 2003). Other industrial effluents from textiles, tanneries, petrochemical products and refineries, pesticide and pharmaceuticals possess varied concentrations of heavy metals such as Cr, Cu, Pb, Zn, and As and are released into soil as partially treated forms which can impose many serious environmental risks (Sumner 2000).

Microbial biosynthetic machineries sourcing siderophores

Biosynthesis of bacterial siderophores

A number actinobacteria were reported to produce various types of siderophores and to possess ferric–siderophore complex uptake systems on the cell membranes (Terra et al. 2021). In the array of siderophore secreting actinobacteria, *Streptomyces coelicolor* was well studied by Ronan et al. (2018), for the production of ferrioxamine E and B, with structural elucidation of its lipopeptide receptor using X-ray crystallography. In this study, the role of acyl transferase (DesD) in catalysing the N-acylation of N-hydroxycadaverine, one of the lead molecules in the assembly process of ferroxamines was explored. However, the derivates of ferrioxamines are decided by the kind of acylation of N-hydroxycadaverine with the groups such as acetyl, myristoyl and succinyl-CoA. Role of *des* gene cluster to biosynthesis of desferrioxamines in *S. coelicolor* and the same gene cluster along with *chh* cluster necessary for desferrioxamine and coelichelin synthesis respectively, in *Streptomyces ambofaciens* were well documented by Barona-Gomez et al. (2004, 2006). Besides the catechol types such as enterobactin and bacillibactin usually from *Streptomyces tendae* and *Bacillus subtilis*, respectively, Griseobactin, a novel candidate of catechol with 2,3-dihydroxybenzoate (2,3-DHBA) chemistry was observed to be secreted by *Streptomyces griseus* and its related strains (Patzer and Braun 2010). The candidate genes involved in griseobactin biosynthesis include gene for the enzyme isochorismatase (*DhbB gene*) and an aryl carrier protein (*DhbG gene*) which was identified by Patzer and Braun (2010).

Among the producer bacteria, *Pseudomonas aeruginosa* having pyoverdine biosynthetic system was well explored by Stintzi et al. (1999), with involvement of four of the open reading frames coding for pyoverdine chromophore (*pvc*) such as *pvcA*, *pvcB*, *pvcC*, and *pvcD*, and two regulatory genes such as *ptxR* and *pvdS* for the expression *pvcABCD* operon. In *P. aeruginosa*, the gene *pvdS* codes for alternate sigma factor of *pvc* expression and it is not entirely regulated by varying iron concentrations whereas an iron-mediated *ptxR* expression is essential for the *pvc* synthesis. In addition to these pyoverdine synthesising genes, some strains of *P. aeruginosa* contain genes for pyochelin synthesis, a catecholate-type siderophore. Biosynthesis of pyochelin involves expression of *pchDCBA* operon which is tightly regulated by available iron in the environment.

Paracoccus denitrificans was reported to produce L-parabactin, a catecholamide with efficient iron-binding ability which finds potential application in iron-overload syndromes and can replace the desferrioxamines in such treatments (Bergeron and Kline 1982). In *Paracoccus*, the candidate gene for parabactin is still unexplored. However, it is presumed that some family of modular enzymes such as non-ribosomal peptide synthetases (NRPS) and polyketide synthases (PKS) were probably involved in synthesising 2-hydroxypheny-5-methyloxazoline-acyl domain of parabactin (Wang et al. 2014). A similar family of NRPS gene designated as *VibF* is found in *Vibrio cholera*e and yields vibriobactin siderophores (Butterton et al. 2000). Enterobactin is a 2,3-DHB siderophore produced by *entCEBA* operon in *E. coli* (Brickman et al. 1990). The same enterobactin is detectable in *Aeromonas* spp. with an operon *aebCEBA* (Massad et al. 1994) and a mutation in *aebCEBA* genes render a second gene *amo* for amonabactin synthesis in few strains of *Aeromonas* (Barghouthi et al. 1991).

Symbiotic bacterium *Rhizobium leguminosarum* was marked to produce cyclic, trihydroxamate siderophore called vicibactin using an operon with eight genes for vicibactin biosynthesis (*vbs*) namely *vbsGSO*, *vbsADL*, *vbsC* and *vbsP* and is regulated by the expression of *rpol* gene which codes for the sigma factor of RNA polymerase under iron starvation (Viguier 2005). Though the operon is not directly linked to the symbiotic lifestyle of rhizobia, it indirectly supports the role of leghaemoglobin during N_2 fixation by iron homeostasis. A thioesterase like domain of vbsS facilitate trimerisation and cyclisation of subunits to form the entire vicibactin molecule (Carter et al. 2002). Overall understanding about the names of bacterial siderophores, producer bacteria, biosynthetic genes involved can be obtained from the following Table 2.

Biosynthesis of siderophores in actinobacteria

Heterobactin is catecholate siderophore proved to be produced by the actinobacterial genera such as *Rhodococcus*, *Streptomyces* and *Nocardia* (Lee et al. 2012). In the same study, the role of *entF* gene coding an essential NRPS in *Streptomyces* for enterobactin biosynthesis was confirmed by the PCR amplification of a 203 bp product.

Biosynthesis of fungal siderophores

A broad group of fungi secretes hydroxamate-type siderophores except the fungal class zygomycetes which principally secretes carboxylate-type siderophores, for example, rhizoferrin produced by the fungi of the order *Mucorales.* Majority of fungi possess ability to take up iron brought by xenosiderophores, also called heterologous siderophores (siderophores synthesised by other microbial communities). For example, *Aspergillus nidulans* exhibiting affinity for ferrirubin released from *Aspergillus ochraceus* (Oberegger et al. 2001) and for bacterially synthesised catechol, enterobactin (Fiedler et al. 2001). Hence, a chance for competition may persist between microorganisms for iron sequestration. Since the putative eukaryotic microbial model *Saccharomyces cerevisiae* does not produce siderophores and depend on siderophores of other species, the advancements in the genetics of fungal siderophore synthesis and storage is still lagging (Haas and Keel 2003). Four major chemically variant hydroxamate-type siderophores of fungal origin include fusarinines, ferrichromes, caprogens or rhodotorulic acid.

Table 2 Bacterial siderophores and their biosynthetic gene clusters

S. no	Name of the producer microorganism	Name of the siderophore	Gene cluster involved	Sources
1	*Streptomyces coelicolor*	Desferrioxamines	*des* gene	Barona-Gomez et al. (2004)
2	*S. ambofaciens*	Coelichelin	*chh* gene	Barona-Gomez et al. (2006)
3	*S. griseus*	Griseobactin	*DhbB* and *DhbG* genes	Patzer and Braun (2010)
4	*Pseudomonas aeruginosa*	Pyoverdine	*pvcABCD* genes	Stintzi et al. (1999)
5	*Pseudomonas aeruginosa*	Pyochelin	*pchDCBA* genes	Stintzi et al. (1999)
6	*Paracoccus denitrificans*	L-Parabactin	NRPS and PKS like genes but still unknown	Wang et al. (2014)
7	*Vibrio cholera*e	Vibriobactin	*VibF* genes	Butterton et al. (2000)
8	*Escherichia coli*	Enterobactin	*entCEBA* genes	Brickman et al. (1990)
9	*Aeromonas* spp.	Enterobactin	*aebCEBA* genes	Massad et al. (1994)
1	*Aeromonas* spp.	Amonabactin	*amo* genes	Barghouthi et al. (1991)
1	*Rhizobium leguminosarum*	Vicibactin	*vbsGSO*, *vbsADL*, *vbsC* and *vbsP*	Carter et al. (2002)
1	*Streptomyces* sp., *Nocardia* sp., *Rhodococcus* sp.	Heterobactin and enterobactin	*entF* gene	Lee et al. (2012)

Ferrichromes

The basidiomycetes fungus *Ustilago maydis* secretes iron-chelating siderophore ferrichrome A and other ferrichromes. Winterberg et al. (2010) demonstrated the role of an NRPS gene (*Fer3*), an enoylcoenzyme A (CoA)-hydratase gene (*Fer4*), a acylase gene (*Fer5*), and a hydroxymethyl glutaryl (HMG)-CoA synthase gene (*Hcs1*) with HMG-CoA as an essential precursor for the biosynthesis of ferrichrome A in *Ustilago maydis.* As the cytoplasmic acquisition of iron impose toxic effects, plant pathogenic fungi such as *Alternaria alternata*, *Magnaporthe grisea*, *Fusarium graminearum*, *F. pseudograminearum*, and *F. culmorum* do secrete intracellular ferrichromes like ferricrocin to get rid of iron-based cellular toxicity (Tobiasen et al. 2007). Hof et al. (2007) identified the role of L-ornithine N^5-monooxygenase (OMO1) encoded by NRPS family of genes and catalysing the principal step for ferricrocin biosynthesis, the N^5-hydroxylation of ornithine in *Magnaporthe grisea*, a rice blast disease agent. Ferrichrome biosynthesis requires an NRPS with three domains for the functions such as adenylation, thiolation and condensation which ultimately results in cyclic hexapeptides with three N^5-acyl-N^5-hydroxyornithines and three amino acids (i.e. glycine, serine, or alanine), so called ferrichromes (Jalal and Van der Helm 1991). The pivotal role of NRPS genes such as *nsp2* coding for intracellular ferricrocin, and *nsp6* coding for extracellular caprogens were well justified in *A. alternata* as the deletion mutants of them rendered reduced pathogenicity for tomato (Voß et al. 2020). There were speculations regarding the involvement of *SidA* gene coding L-ornithine N^5-monooxygenase for the biosynthesis of hydroxamates in *Aspergillus fumigatus* which was later confirmed with *sidA* deficient mutants of *A. fumigatus* lacking ability to counteract the iron-chelating role pyoverdines from *P. aeruginosa* (Sass et al. 2019). Blatzer et al. (2011) reported a new member of siderophore genetic cluster, *sidL* coding N^5-hydroxyornithine-acetylase for the biosynthesis of hydroxyferricrocin and ferricrocin which facilitates iron storage in the conidia and hypha, respectively, in the *A. fumigatus.*

Recently, a study on insect pathogenic dimorphic fungus *Nomuraea rileyi* has identified the *NrSidA* gene encoding L-ornithine-N^δ-monooxygenase, an essential enzyme responsible for biosynthesised siderophores with pivotal role such as offering complete virulence, conidia formation, dimorphic stage transition, antioxidant potential, microsclerotium formation and pigmentation (Li et al. 2016).

Fusarinines

Fusarinines are the extracellular siderophores secreted by countless *Fusarium* spp. Fusarinine C (FSC) and triacetyl fusarinine C (TAFC) contributes the virulence of *Fusarium* species complex. A *nps2* gene of NRPS family is essential for synthesis of fusarinine-like extracellular siderophores for iron uptake in *Fusarium graminearum* and its deficient mutants were unable to establish head blight disease in wheat, reduction in asexual spores, hypersensitivity to reactive oxygen species, and increased sensitivity to iron starvation (Oide et al. 2006). Watkins et al. (2018) have employed transcriptome analysis using microarray and RNA-sequencing to prove the participation of *sidIHFD* operon for the fusarinine C biosynthesis in various strains of pathogenic *Aspergillus fumigatus* followed by expression of *sidG* gene which mediates conversion of FSC into TAFC.

## Caprogens/rhodotorulic acid/dimerumic acid

Caprogens are diketopiperazine derivatives of dihydroxamates or trihydroxamates formed from condensation of two N^δ-hydroxyornithines and the resultant product is a dimerumic acid (Leong and Winkelmann 1998). Rhodotorulic acid is also a diketopiperazine dihydroxamic acid with strong iron-binding affinity which was primarily identified and characterised in the red yeast, *Rhodotorula pilimanae* by Atkin et al. (1970). Under iron demanding conditions, *Stemphylium botryosum* f. sp. *lycopersici*, a causal agent of leaf spot and leaf blight disease in tomato, secretes siderophores such as monohydroxamate A, caprogen B, and dimerumic acid. Clinically significant pathogenic fungal candidates such as *Blastomyces dermatitidis* and *Histoplasma capsulatum* were reported to produce dimerumic acid as a marker for their virulence (Howard 1999). The essential candidature of *Penicillium chrysogenum* in improving the hydroponic growth of cucumber and maize through the secreted caprogens and its hydrolysed dimerumic acid was evidenced by increased chlorophyll concentration comparable to ferrated EDTA supplements (Hördt et al. 2000). Involvement of putative NRPS genetic machinery (genes such as *Tex10*, *Tex20*, *Tex21*) for the siderophore biosynthesis was addressed in the genome of *Trichoderma virens* (Mukherjee et al. 2012)*.* Simplest understanding about the names of fungal siderophores and its producer fungi along with involved biosynthetic gene cluster can be obtained from Table 3.

Role of siderophore-binding protein receptors as sinks

Ferric iron post scavenged by siderophores gains entry into the cells to meet iron needs through surface-exposed binding proteins called siderophore-binding proteins. However, the mechanism with which the iron is transported into the host varies with the kinds of organisms acquiring it. For an instance, the mode of cation uptake differs between

Table 3 Fungal siderophores and their biosynthetic gene clusters

S. no	Name of the producer microorganism	Name of the siderophore	Gene cluster involved	Sources
1	*Ustilago maydis*	Ferrichrome A	*Fer3*, *Fer4*, *Fer5*, *Hcs1* genes	Winterberg et al. (2010)
2	*Magnaporthe grisea*	Ferricrocin	*NRPS* gene	Hof et al. (2007)
3	*Alternaria alternata*	Ferricrocin, caprogens	*nsp2*, *nsp6 gene*	Voß et al. (2020)
4	*Aspergillus fumigatus*	Hydroxyferricrocin and ferricrocin	*SidA*, *sidL* gene	Sass et al. (2019); Blatzer et al. (2011)
5	*Nomuraea rileyi*	Ferrichromes	*NrSidA* gene	Li et al. (2016)
6	*Fusarium* spp.	Fusarinine C (FSC) and triacetyl fusarinine C (TAFC)	*nps2* gene	Oide et al. (2006)
7	*Aspergillus fumigatus*	Fusarinine C (FSC) and triacetyl fusarinine C (TAFC)	*sidIHFD* genes; *sidG*	Watkins et al. (2018)
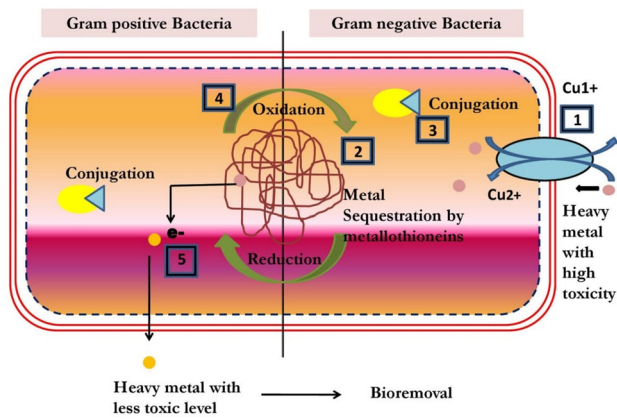
Fig. 6 Pictorial representation of diversified molecular mechanisms underlying the toxic heavy metal uptake process associated with Gram-positive and Gram-negative bacteria

Gram-positive and Gram-negative bacteria. The schematic representation in Fig. 6 shall define this process well in detail.

Figure 6 displays the heavy metal uptake mechanisms observed in both Gram-positive and Gram-negative bacteria and redox reactions occurring in the cytosol to reduce the toxicity of heavy metals, accumulation of toxic metals within cells through conjugation and metal sequestration process with the help of proteins like metallothioneins. The main difference lies on the surface distributed proteins between Gram-positive and Gram-negative bacteria. Bacterial cell walls with Gram-positive chemistry display siderophore-binding proteins (SBP) with ferrichelatase-like enzyme kinetics where ferric–siderophore complex behaves as a non-covalent cofactor (Endicott et al. 2020). This catalytic SBP resumes after the replacement of the cofactor with a new ferrated cofactor. Hence, an appropriate new terminology called "siderophore-dependent ferrichelatase" has been recently coined to define the catalytic Gram-positive surface-exposed SBPs.

On the contrary, Gram-negative bacteria possess outer membrane associated siderophore-binding protein receptors. Binding of ferric siderophores to these protein receptors form a complex which interacts with a membrane permease for internalisation of the ferric–siderophore into cytosol and the process is powered by ATP hydrolysis. However, membrane stress experienced due to the interaction between membrane bound SBP and membrane permeases play a vital role in the internalisation of ferric forms into microbial cell factories. Numerical simulation studies on such membrane stress during the siderophore interaction may guide us in the selection of suitable metal ligands and identification of the involved siderophore scavenging microorganisms (Lim et al. 2022a). It is also evident at molecular level from the studies of Peuckert et al. (2011) on *Bacillus subtilis*, which justifies the salt bridge formation between glutamate residues such as E90 and E221 on the siderophore-binding protein FeuA and the arginine residues of the transmembrane permease, FeuBC. This interaction is essential for the triscatecholate siderophores such as bacillibactin, vibriobactin, and enterobactin as well as the precursor catecholate like 2,3-Dihydroxybenzoic acid, transport across the membrane of the Gram-negative bacteria, in general. In the recent days, much of attention has been paid towards the interaction chemistry of metal-based drug ligands and membrane protein receptors to neglect anti-chemoresistance in cancer therapy. As chemoresistance is quite common for platinum-based drugs like cisplatin, researchers are developing CuZn-based combinations to replace cisplatin which then binds to chelators and form complexes with copper uptake high-affinity membrane protein receptors (CTR-1) for internalisation and efficient delivery (Lim et al. 2023). Hence, it is obvious that ligand–chelator complexation and receptor interaction is very much needed for the delivery of any metal-based pharmacophore to exert its biological function within a system. At this juncture, one can be ignited with an ideology to use microbial siderophores as an efficient CuZn-bound drug carrier framework to reduce toxic effects, neglect chemoresistance in cancer treatments.

Commercialisation of microbial siderophores

Siderophores in agriculture

In the past 4 decades, siderophores produced by several *Pseudomonas* spp. were well known for their effective biocontrol potentials through the release of siderophores in field conditions. Siderophores from *Pseudomonas* and *Bacillus* are demonstrated to be involved in the biocontrol of wilt pathogen *Fusarium oxysporum* in many crops such as potato, wheat, barley, and tomatoes (Karuppiah et al. 2022). Many mycorrhizal fungi are noted for their role in iron uptake in plants through released siderophores. Ectomycorrhizal fungi such as *Aspergillus niger*, *Penicillium citrinum* and *Trichoderma harzianum* are observed to produce siderophores to help in iron uptake by associated plants like chick pea. Hence, microbial siderophores will be suitable alternatives to hazardous pesticides in the market as they are more ecofriendly and non-hazardous (Schenk et al. 2012).

Siderophores in medicine and diagnosis

Sideromycins are nothing but the siderophore and antibiotic conjugates which follows Trojan horse concept forming active scaffold and exploits the iron need of multidrug-resistant pathogens in controlling infections (Pandey and Boros (2021). Siderophores are widely employed as drug carriers for their selectivity in delivering the bioactive pharmacophores within a complex system. These conjugates utilise the iron transport system on the microbial membranes to transpass through iron receptors such as a Trojan horse and exert antibiosis. Siderophores after releasing the antibiotics into cells engages itself in minimising the iron acquisition within pathogenic cells thereby reduces the virulence of the pathogens. Few examples from natural sources include ferrimycins, salmycins, microcins, danomycins, and albomycins. Some synthetic scaffolds include conjugates with carbapenems, sulphonamides, vancomycins, norfloxacins, spiramycin, and nalidixic acid (Górska et al. 2014). However, effective uptake and siderophores cross talk can be expected in pathogens that synthesises siderophores of its own kind to acquire iron from human host. Hence, further usage and approval is critical which require a long run expedition in the application perspectives.

Siderophores are also helpful in treating iron intoxication and related diseases. Desferrioxamines (Desferal) find its application as they can be converted into water-soluble ferrioxamines which are readily removed from our body through urine and faecal matter (Crisponi et al. 2019). Hyper-iron load diseases include haemochromatosis, haemosiderosis, and apparent iron overloads (serum ferritin level) during severe blood transfusions in sickle cell anaemia and thalassemia patients. In addition, siderophores are used in cancer therapy (example, desferriexochelins) and in removal of aluminium overload in dialysis patients (Nagoba and Vedpathak 2011).

In molecular imaging and diagnosis of infection using positron emission tomography (PET), radionuclide-labelled siderophores stand as inevitable chelators. Interesting examples include Gallium-68 labelled Triactylfusarinine C that helps in prognosis of fungal infection, and the Gallium-68 and Zirconium-89 labelled bifunctional desferrioxamine used in immuno-PET (Petrik et al. 2017). In the context biosensor applications, the fluorescent siderophore Azotobactin from soil bacterium *Azotobacter vinelandii* could accurately senses ferric iron levels in the body fluids like human serum. It acts as an optical biosensor even when encapsulated in sol–gel matrices without any loss in fluorescent signals as demonstrated in a study by Sharma and Gohil (2010). Lim et al. (2022b) have recently reviewed the failures in systemic therapeutic approaches for rheumatoid arthritis and osteoarthritis using intra-articular and surgical treatments due to drug clearance, lack of efficacy, infiltration, and target delocalisation. Hence, a novel drug delivery system in the form of biosensor would help in targeted systemic drug delivery to treat the disease neglecting the above list demerits. In our view, siderophores due to low molecular weight may support targeted delivery of drugs into bones by sensing the elemental levels in future treatment of arthritis. However, research study on this perspective is still rare and deserves investigation. Another study by Lim et al. (2022c), on the development of nanochip electrical biosensor using CuZn that bind with bioactive pharmaceutical ingredients for the non-enzymatic glucose sensing capabilities was highly attractive and one can even think of replacing the bioactives with Cu and Zn binding siderophores forming microbial siderophore-metal framework to electrically trigger and sense the systemic glucose levels which shall attribute to a novel point of care sensing technology.

Siderophores in environmental protection

Microbial siderophores have extended its applications in soil mineral weathering as it forms stable complexes with metal cations (stability constant ranges from 10^{29} to 10^{52}) and hence synergistically act along with low molecular mass organic acids in natural mineral weathering of soil (Reichard et al. 2007). In addition, it helps in the biogeochemical cycling of iron in the ocean. In the surface waters of Atlantic ocean, siderophores from marine bacteria increase the bioavailability of iron for phytoplanktons (Amin et al. 2012).

Examples include marinobactins, aerobactin, and aquachelins (Hider and Kong 2010). Under ferric iron limitations, biofilm formation is limited in bacteria due to the lack of motility and decreased hydrophobicity related to destabilisation of polysaccharide matrix (Chhibber et al. 2013). Biofilm forming communities in waste treatment plants overcome the Fe limitations in the environment through the synthesis of its own siderophores (Ahmed and Holmström 2014). Siderophores are helpful in controlling diseases in aquaculture systems especially in biocontrol of fish pathogens. Fish pathogens attack their host through the release of hydrolytic enzymes to evade fish immunity and secrete transferrin to compete for Fe in the host. Siderophore-producing bacteria are used as probiotics in aquaculture farms to improve the health of fishes and their gut microbiome to resist infection by aquaculture pathogens such as *Vibrio anguillarum*, *V. ordalii*, *Aeromonas hydrophila*, and *A. salmonicida* (Dimitroglou et al. 2011). During the bleaching process in paper and pulp industries, siderophores are used as biobleaching agents to depolymerise the cellulose, lignocellulose and hemicellulose in wood pulp. Siderophores from fungi such as *Gloeophyllum trabeum*, *Tinea versicolor* and *Coriolus versicolor* were used for this purpose (Wang et al. 2008).

Gauglitz et al. (2012) demonstrated role of amphiphilic siderophores, ochrobactins from the Mexican isolates of *Vibrio* spp. for their ability to degrade petroleum hydrocarbons in the oil spill over deep sea. Petrobactin sulfonate, siderophores isolated from oil-degrading *Marinobacter hydrocarbonoclasticus* helps in clean-up of oil sludges and spills over sea surface waters. Siderophores such as desferrioxamine B and pyoverdine forms a stable complex with actinides and aid in dissolution and removal of leftover nuclear fuel through the Purex process (Marshall et al. 2010) for its repurposing applications. Hence, microbial siderophores play a vital role in the environmental bioremediation processes. Siderophores such as azotobactin produced by *Azotobacter vinelandii* and parabactin produced by *Paracoccus denitrificans* are useful optical biosensors when encapsulated in sol–gel matrices for both environmental metal-sensing applications and iron sensing in biological fluids (Sharma and Gohil 2010).

Recent encroachments in siderophore research

Ferric siderophores characterisation research begins from simple detection assays using modified CAS reagent to high-throughput screening and characterisation from direct environmental samples. Marques et al. (2012) have performed high-throughput microtitre plate screening system to detect siderophore-producing environmental bacteria and scaled-up the process in a 5L stirred tank reactor through optimisation. Murakami et al. (2021) have developed microplate CAS shuttle assay for the detection of siderophores produced from

Pseudomonads, *Burkholderia* spp., and *Ottowia* sp. in the diluted broth media. Hofmann et al. (2021) have adapted C_{18} columns functionalised with bacterial siderophores for the recovery of rare-earth metal ions Gallium (III), Vanadium (III), and Indium (III) from the mixed metal solutions. Lewis et al. (2019) have performed a high-throughput screening of environmental samples such as rhizosphere soil and different plant tissues for the production of siderophores from the intact microbiome in the diluted M9 medium using a microplate CAS-Fe agar assay. Karuppiah et al. (2022) have explored the ability of rhizobacterial siderophores to mitigate iron and copper induced toxic effects in tomato plants through soil-free vermiculite pot cultures and supplied with increasing concentrations of copper–EDTA and iron–EDTA complexes separately after treating the root zone with siderophore-producing rhizobacterial consortium. In a study by Lim et al. (2022d), low brass filler biomaterial made up of copper and zinc showed potentials to be used as an articular cartilage scaffold design for osteoarthritic patients. It involved metallic filler polymer-reinforced method using polyester urethane to design the cartilage scaffold followed by characterisation using FESEM and XRD analyses (Lim et al. 2022e). However, the presence of chemical polymers in the metallic fillers to hold the crystal lattice of CuZn low brass would contribute incompatibility or mild side effects upon prolonged use in humans. Hence, one would think of employing the natural metal chelators like microbial siderophores which would not disturb the ordered-disordered transitional states to provide additional strength without any harm for the welfare of osteoarthritic patients. However, a long run expedition may bring exciting breakthroughs in translational therapeutics through siderophore research.

Conclusion

As siderophores behave like molecular shuttles and oscillated between metal rich environment and biological systems, propaganda of their importance with several scientific arguments in this review may attract the academic, industrial and scientific communities to further explore them for valuable applications. Hence, this review discusses the chemical diversity of microbial siderophores, vital roles of microbially synthesised siderophores in biotic and abiotic environmental niches, uptake and recycling mechanisms within microbial cell factories, different sources of heavy metal cations in the environment, biosynthetic gene clusters for siderophores linked in the producer microbial genomes, siderophore-binding protein receptors as sinks on microbial membranes, and commercialisation perspectives of microbial siderophores and recent scientific advancements in siderophore research to extend its novel applications for the future needy.

Data availability All datasets analysed in this study are included in the manuscript.

Declarations

Conflicts of interest All the authors declare that no competing interest exist.

Ethics of human and animal experimentation Not applicable.

Informed consent Not applicable.

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