



Siderophores: an alternative bioremediation strategy?

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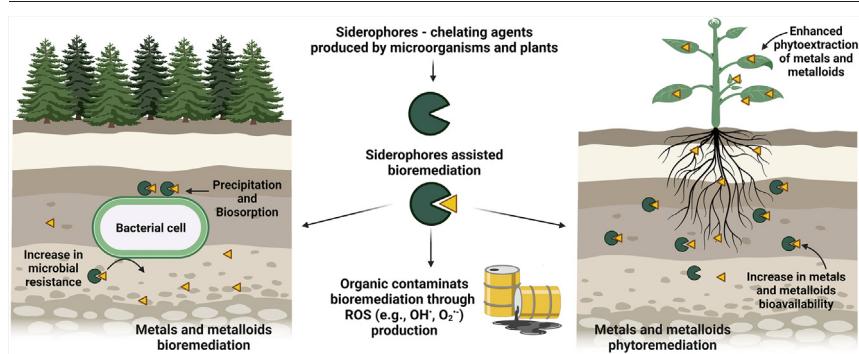


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HIGHLIGHTS

- Siderophores assisted bioremediation is promising remediation method.
- Siderophores increase bioavailability of heavy metals and metalloids.
- Siderophores enhance phytoremediation of heavy metals and metalloids.
- Siderophores can mediate formation of reactive oxygen species (ROS).
- Siderophores via ROS are involved in biodegradation of organic matrix.

GRAPHICAL ABSTRACT



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ABSTRACT

Siderophores are small molecular weight iron scavengers that are mainly produced by bacteria, fungi, and plants. Recently, they have attracted increasing attention because of their potential role in environmental bioremediation. Although siderophores are generally considered to exhibit high specificity for iron, they have also been reported to bind to various metal and metalloid ions. This unique ability allows siderophores to solubilise and mobilise heavy metals and metalloids from soil, thereby facilitating their bioremediation. In addition, because of their redox nature, they can mediate the production of reactive oxygen species (ROS), and thus promote the biodegradation of organic contaminants. The aim of this review is to summarise the existing knowledge on the developed strategies of siderophore-assisted bioremediation of metals, metalloids, and organic contaminants. Additionally, this review also includes the biosynthesis and classification of microbial and plant siderophores.

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1. Introduction

An increasingly industrialised economy over the past century has led to considerable environmental contamination. Wide range of contaminants include heavy metals and metalloids (Cd, Cu, Ni, Co, Zn, Pb, and As), petroleum hydrocarbons, halogenated hydrocarbons, pesticides, and solvents (Arihilam and Arihilam, 2019). Remediation of metals and metalloids remains challenging because of its environmental persistence (Ali et al., 2019). Conventional in situ physicochemical remediation techniques are generally exceedingly expensive and adversely affect the subsurface environment (Suthersan et al., 2016). In recent years, biological methods are being designed to effectively restore polluted environments in an eco-friendly approach and in a cost-effective manner (Azubuike et al., 2016).

Although metals such as Cu, Co, Zn, or Cr are essential nutrients that are required for various biochemical and physiological functions, they present varying degree of toxicity toward bacteria (Sterritt and Lester, 1980). However, certain metals such as Cd, Pd, and Hg are generally toxic. Considering the long-term exposure to metal contamination, microorganisms (MOs) have developed mechanisms to cope with metal toxicity, including metal reduction (Lovley, 1993), reduced cell permeability (Bruins et al., 2000), extracellular sequestration (metal precipitation) (Igiri et al., 2018), biosorption (Malik, 2004), and complexation. Siderophores, which are organic compounds produced by MOs and plants, have been shown to play an important role in metal detoxification processes. Although the primary role of siderophores is to increase Fe(III) bioavailability, these natural chelators exhibit a varying structure, which clearly demonstrates that they cannot be selective to just one metal ion (Hofmann et al., 2020). In fact, they form complexes with other metals and metalloids (e.g. Cu, Ni, and Zn) in the environment (Hu and Boyer, 1996). The affinity between siderophores and different metals depends on several factors, but is mainly controlled by the characteristics and the coordinative environment of the attached ligands, and the type of the central metal ion (e.g. ligand configuration or size and charge of the central metal ion). For example, the stability constants (K_{stab}) for pyoverdine (Pvd) with Zn(II), Cu(II), and Mn(II) are between 10^{17} and 10^{22} M^{-1} , whereas that with Fe(III) is 10^{32} M^{-1} (Chen et al., 1994). This unique property of forming complexes with various metals and metalloids makes siderophores precious molecules that help separate metals and metalloids from nutrient solutions, and promote microbial resistance (Sharma et al., 2018). Metals and metalloids enter bacterial cells mainly through diffusion (Braud et al., 2009a). Their binding to siderophores reduces the concentration of free metals and metalloids in the environment, and prevents their diffusion across the bacterial membrane (Schalk et al., 2011), thereby reducing metal and metalloid toxicity.

The detoxifying effect of siderophores (Cornu et al., 2019; Hazotte et al., 2018; Nair et al., 2008; Péron et al., 2019) or siderophores-producing MOs (Rajkumar et al., 2010) have been used for bioremediating metal and metalloid pollution (Ahmed and Holmström, 2014; Sayyed and Patel, 2011). After chelated by siderophores, metals and metalloids can be sequestered through different extracellular mechanisms, such as biosorption and bioaccumulation (Banerjee et al., 2019). Furthermore, siderophore-producing bacteria majorly contribute in the phytoremediation of heavy metal-contaminated soils (Lebeau et al., 2008; Sessitsch et al., 2013; Sharma et al., 2018). Through chelation, siderophores can enhance metal and metalloid accumulation in plants; therefore, they offer a natural alternative to

synthetic compounds (e.g. ethylene diamine tetraacetic acid (EDTA)) that are used for chelate-assisted phytoextraction (Wang et al., 2013a). Furthermore, siderophores serve as redox-cycling molecules, mediating the production of reactive oxygen species (ROS) and subsequently oxidising organic compounds, which indicates their potential role in bioremediation of organic contaminants (Gu et al., 2018). Over the past decades, numerous studies have been conducted to understand the role of siderophores in environmental remediation. Thus, the aim of this review is to summarise and identify the mechanisms involved in siderophore-assisted bioremediation. This review makes a novel contribution to the literature by providing an insight into the role of siderophores in environmental bioremediation.

2. Siderophores

Like most organisms, MOs and plants also require iron as an enzyme co-factor to catalyse redox reactions involved in fundamental cell processes. Although iron is one of the most abundant elements in the Earth's crust, its bioavailability is low. Iron in the soil parent materials is mainly in its oxidised (Fe(III)) state, and is insoluble at neutral and basic pH, which is typical for many natural environments. To obtain iron from the environment, MO and gramineous plants (grasses) have developed specific iron acquisition mechanisms, such as (i) direct ferrous iron (Fe(II)) uptake, (ii) direct ferric iron (Fe(III)) uptake, (iii) siderophore-mediated Fe(III) uptake, and (iv) uptake and degradation of haeme, which are transcriptionally up-regulated during iron limitation (Petrik et al., 2017). In general, MOs (Petrik et al., 2017) and plants (Grobelak and Hiller, 2017) mostly secrete siderophores to scavenge extracellular iron. Fe(III) threshold levels, which repress siderophore synthesis, depend on the organism, and range from 3 μM in *Aspergillus* sp. to 27 μM in *Pseudomonas* sp. (Dave and Dube, 2000).

Siderophores, also known as metallophores (Zhang et al., 2017), are naturally-occurring small molecules (up to 1 000 Da (Patel et al., 2018)) with high affinity to ferric iron (Schwyn and Neilands, 1987), which are produced mainly by bacteria, fungi (Varma and Chincholkar, 2007), and plants (Neilands, 1995) under iron deficiency (Bellenger et al., 2008). The role of siderophores is to primarily remove iron from different terrestrial and aquatic environments by forming soluble Fe(III) complexes that can be actively accumulated by MOs and plants (Arrieta and Grez, 1971; Neilands, 1981; Rathi and Nandabalan, 2017). The term "siderophore" (in Greek, pherin and sideros mean "iron carrier") includes a unique function that can be performed by different molecules that exhibit species-specific structural diversity. To date, more than 500 siderophores have been identified, and classified according to their iron-binding functional groups: catecholate, hydroxamate, phenolate, carboxylate, and mixed-type (containing more than one functional group).

Siderophores with various functional groups mainly utilise negatively charged deprotonated oxygen molecules to establish a donor-acceptor bond with Fe(III). However, their affinity to bond with Fe(III) varies; the higher the charge on oxygen, the tighter is the interaction (Hider and Kong, 2010). Most siderophores use six donor oxygen atoms to completely surround Fe(III), thereby forming an octahedral structure that produces a hexadentate centre. Depending on the siderophore, the octahedral field may be altered, wherein nitrogen or sulphur may sometimes be included as a donor atom. Such modifications reduce the affinity for Fe(III). Different bidentate functional groups with appropriate molecular design can be

incorporated into hexadentate structures (Singh et al., 2014); the three main bidentate groups incorporated include catechol, hydroxamate, and α -hydroxycarboxylate.

Although siderophores preferentially form hexadentate-octahedral complexes with Fe(III), they also bind to other metal ions. The affinity of metal ions for ligands depends on several factors, but is largely influenced by the nature and coordinative environment of the ligand, and the type of the central metal ion. For instance, the charge and size of the metals contributes substantially; the greater the charge-to-size ratio, the more stable is the complex. For example, desferrioxamine B (DFOB) exhibits the following order of complexing stability: Zn(II) < Pb(II) < Cu(II) < Bi(III) < Fe(III) (Butler and Theisen, 2010; Hernlem et al., 1996). A useful tool for predicting the thermodynamic stability of metal-ligand complexes is the “concept of hard and soft acids and bases (HSAB)”. According to the HSAB concept, oxygen, a hard Lewis base, exhibits increased affinity for hard Fe(III)-Lewis acid and other comparable trivalent metal cations, such as Al(III), Co(III), and Cr(III). In addition, siderophores that contain weaker bases such as sulphur or nitrogen, exhibit increased affinities to metals with softer characteristics such as Zn(II), Cu(II), Ni(II), and Mn(II). Siderophores structure and chelate conformation also play important roles in maintaining the stability of metal complexes (Hofmann et al., 2020). Cyclic siderophores, such as enterobactin, usually form more stable complexes compared to linear siderophores (e.g. fusigen) because cyclisation enhances the chemical stability, complex stability, and resistance to enzyme-mediated degradation (Winkelmann, 2002). K_{stab} plays an important role in accessing the affinity of a siderophore to a certain metal. The K_{stab} value (Table 1) determines the metal siderophore that is most likely to bind, which is important for remediation applications. In general, metal complexes that exhibit an extremely high K_{stab} in solution are known as stable complexes.

2.1. Types of siderophores based on the producing organism

MOs produce a wide range of siderophores. Certain bacterial siderophores are carboxylates (e.g. staphyloferrin A produced by *Staphylococcus* sp. (Pandey et al., 2014)), but most are catecholates, e.g. enterobactin produced by *Streptomyces* sp. (Fiedler et al., 2001) or *Escherichia coli* (Sussman, 1997)) (Schalk et al., 2011). However, certain bacterial siderophores contain at least two different iron-binding functional groups (Miethke and Marahiel, 2007). These mixed-type siderophores include pseudobactin and Pvd produced by *Pseudomonas* sp. (Bonneau et al., 2020; Trapet et al., 2016), which carry both hydroxamate and catecholate groups (Cornelis, 2010). Examples of bacterial siderophores are shown in Figure 1. Most fungi produce hydroxamate-type siderophores that can be further grouped into four structural families: rhodotorulic acid, fusarinines, coprogens, and ferrichromes (Schalk et al., 2011) (Figure 2). In addition, many fungal species simultaneously produce more than one type of siderophore (Schrett et al., 2004). The mugineic acid family, which are the only known siderophores produced by plants, contain α -hydroxycarboxylates (McFarlane and Lamb, 2020) (Figure 3). Both MOs and grasses have developed sophisticated mechanisms for siderophore synthesis, excretion, and import.

2.1.1. Bacterial siderophores

Most bacterial species produce siderophores; the production and secretion of siderophores is the most dominant mechanisms for iron scavenging in the microbial world (Hersman et al., 2000; Kramer et al., 2020). For example, a study of siderophore-producing bacteria in the tobacco rhizosphere demonstrated that 85% of the 354 isolates produced siderophores (Fang et al., 2009). Bacterial siderophores are typically peptide-like molecules that are synthesised non-ribosomally by large multidomain enzymes termed as non-ribosomal peptide synthases (NRPS) (Barry and Challis, 2009; Visca et al., 2007), with occasional contributions from polyketide synthases (PKS) (Årstøl and Hohmann-Marriott, 2019). Siderophores synthesised via NRPS/PKS include enterobactin (Figure 4a) produced by *E. coli* (McRose et al., 2018), yersiniabactin produced by *Yersinia pestis*

Table 1
Siderophores binding ability for various metals and metalloids

Siderophore	Element	Log K_{stab}	Source
Azotochelin	Mo(VI)	35	Duhme et al. (1998)
Amphibactin and synechobactin	Fe(II)	11.44–11.91	Moore et al. (2021)
DFOB	Zn(II)	9.55	Hernlem et al. (1996)
	Cu(II)	21.3	
	Pb(II)	16.29	
	Sn(II)	31.18	
	Mn(II)	8.8	Duckworth and Sposito (2005)
	Mn(III)	29.9	
	Pt(II)	16.2–17.2	Dahlheimer et al. (2007)
	Pd(II)	19.2–23.2	
	Co(III)	37.5	Duckworth et al. (2009)
	Fe(III)	32.02	
	Lu(III)	15.19	Christenson and Schijf (2011)
	Yb(III)	15.17	
	Y(III)	13.98	
	La(III)	10.09	
	Cr(III)	30.6	Duckworth et al. (2014)
	Ce(IV)	36	Kraemer et al. (2017)
	Ce(III)	11.5	
	Ga(III)	13.82–24.53	Jain et al. (2019)
	Zr(IV)	47.7	Toporivska and Gumienna-Kontecka (2019)
	Fe(III)	30.99–42.33	Février et al. (2021)
2,3-Dihydroxybenzoic acid	U(VI)	27.5–37.5	
	Pu(IV)	38.39–84.42	
Enterobactin	Fe(III)	25.32	Porwal et al. (2015)
	Al(III)	5.15	Loomis and Raymond (1991)
	Ga(III)	4.53	
	Fe(III)	4.95	
Methanobactin	Cu(II)	>18.8	Choi et al. (2006)
Protobactin	Mn(III)	41.6	Harrington et al. (2012a)
Pseudobactin	Cu(I)	20.83	El Ghazouani et al. (2011)
	Fe(III)	22.5	Chen et al. (1994)
	Zn(II)	16.9	
	Mn(II)	14.8	
Pvd	Fe(III)	30.8	Albrecht-Gary et al. (1994)
	Fe(II)	9.0	
	Cu(II)	20.1	Cornu et al. (2014)
	Cd(II)	8.2	
Pyochelin	Fe(III)	28.8	Brandel et al. (2012)
	Cu(II)	25.0	
	Zn(II)	26.0	
Rhizoferrin	Mn(III)	29.8	Harrington et al. (2012b)
	Cr(III)	29.2	Duckworth et al. (2014)
	Fe(III)	25.3	

(Gehring et al., 1998) and vibriobactin produced by *Vibrio cholera* (Keating et al., 2000). Furthermore, some siderophores are assembled from dicarboxylic acid subunits and dinucleophile linkers by the action of a conserved family of adenylation/condensation enzymes that are structurally distinct from NRPS and PKS (Barry and Challis, 2009; Crosa and Walsh, 2002; Khan et al., 2018). These NRPS-independent synthases (NIS) catalyse the biosynthesis of achromobactin (Figure 4b) produced by *Pseudomonas syringae* (Berti and Thomas, 2009; Schalk et al., 2020), or Staphyloferrin A and B produced by *Staphylococcus aureus* (Haag et al., 1994). The mechanisms involved in extracellular siderophore secretion are performed by exporters belonging to efflux pumps; (Figure 5c) of the major facilitator superfamily (MFS); the resistance, nodulation, and cell division (RND) superfamily; and the ATP-binding cassette (ABC) superfamily (Wilson et al., 2016). The import mechanism of iron-loaded siderophores varies between gram-negative (Figure 5 a, b, and c) and gram-positive bacteria (Figure 5d) (Miethke and Marahiel, 2007). At the outer membrane level, iron-loaded siderophore complexes are recognised by specific outer membrane transporters called TonB-dependent transporters (TBDTs) that mediate their translocation into the periplasmic space. Examples include FhuA, BtuB, FecA (outer membrane transporters of *E. coli*), and FpvA (outer membrane transporter of *Pseudomonas aeruginosa*) (Nader et al., 2011). The fate of

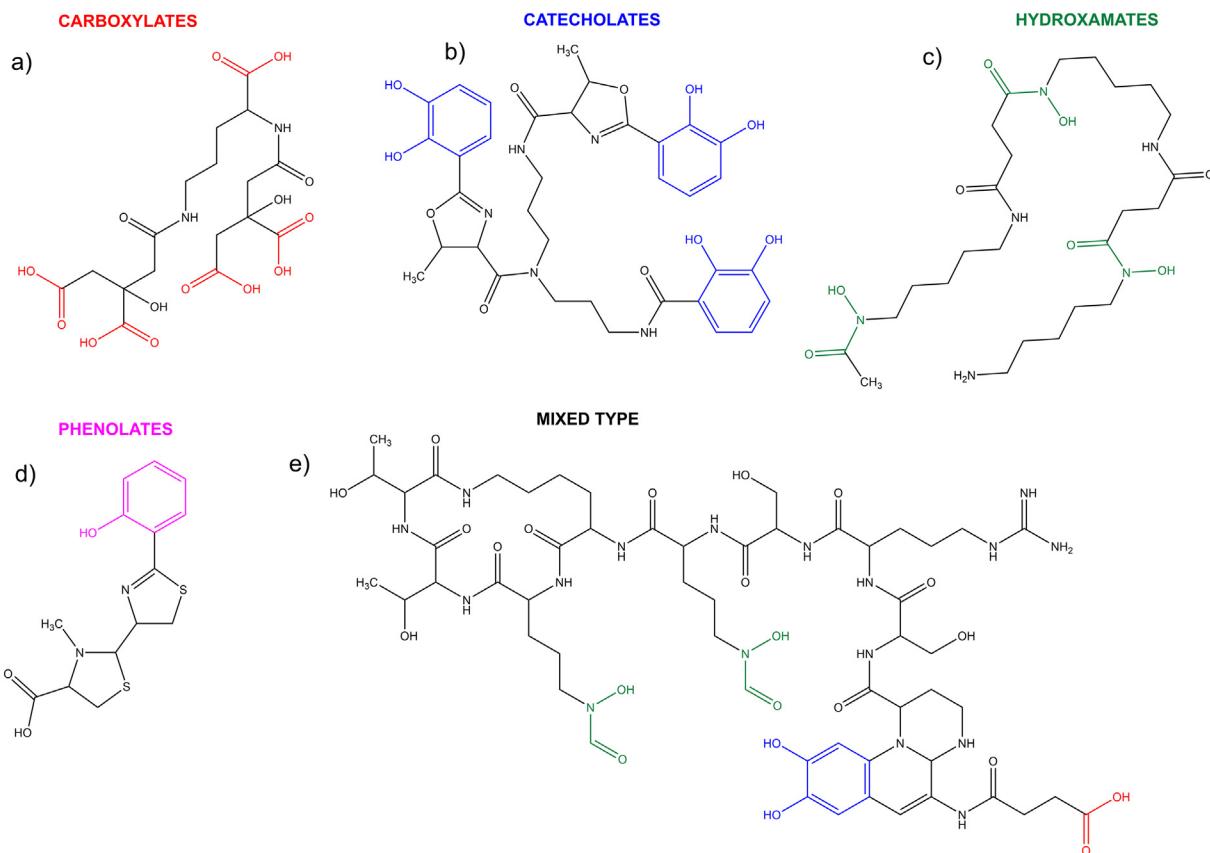


Fig. 1. Chemical structure of typical bacterial siderophores. Highlighted functional groups are responsible for metal interaction, which combines to form the metallophore complex.

siderophores after the release of iron ions is unclear. Siderophores can either be recycled through a specific recycling mechanism or may undergo hydrolysis (Schalk and Guillon, 2013).

2.1.2. Fungal siderophores

Fungi have developed various strategies that are often used in parallel, to sequester iron. These include the most commonly used reductive iron assimilation and siderophores-assisted iron mobilisation. Fungi mainly synthesise siderophores with three hydroxamate groups (except for rhizoferrin). The hydroxamate-type siderophores in fungi are derived from the non-proteinogenic amino acid ornithine (Figure 6). In contrast, little is known about the mechanism of fungal siderophore secretion (Haas et al., 2008). However, four mechanisms have been proposed for iron-loaded siderophore uptake in fungi (Helm and Winkelmann, 1994); among them, three depend on the specific recognition of various siderophores. In the shuttle mechanism (Emery, 1971) (e.g. ferrichrome in *Ustilago sphaerogena*), the entire iron-loaded siderophore is transported across the membrane, followed by the release of Fe(III) from the ligand inside the cell. The free siderophore is then secreted from the cells. The toxicab mechanism (Müller et al., 1985) observed in *Rhodotorula* species (rhodotorulic acid) involves Fe (III) transfer across the membrane from the extracellular siderophores to intracellular ligands, without the entry of siderophore in the cell. The hydrolytic mechanism (Helm and Winkelmann, 1994) used for Fe (III)-triacetyl fusarinine C uptake involves its transport into the cell, followed by simultaneous reductive and degradative steps. In a reductive mechanism, the iron-loaded siderophore (e.g. ferrichrome A in *U. sphaerogena*) is not transported into the cell; however, Fe(III) reduction occurs at the membrane and Fe(II) is then absorbed into the cell (Renshaw et al., 2002).

2.1.3. Plant siderophores

Plants have been classified into iron-efficient or iron-inefficient species based on their ability to reduce ferric chelates in response to iron deficiency. The inducible Fe(III) reduction, which has been identified in several studied species, was not observed in grasses (Tsai and Schmidt, 2017). Alternatively, grasses that include important staple crops such as rice, wheat, and barley, effectively solubilise and absorb iron from the environment by secreting siderophores (Römhild, 1991). Plant siderophores, also known as phytosiderophores (PS), are amino acids such as nicotianamine, mugineic acid, or avicbic acid that are synthesised by plants and secreted by roots into the rhizosphere (Prasad et al., 2014). Compared to microbial siderophores, PSs are chemically different and belong to the class of compounds called mugineic acids (MAs) (Crowley et al., 1991). Members of this family are hexadentate ligands with aminocarboxylate and hydroxycarboxylate functional groups that are synthesised by nicotianamine hydroxylation (Takahashi et al., 2003) (Figure 7). PS is secreted into the rhizosphere through the transporter of the MA family (TOM) (Nozoye et al., 2015). Fe(III)-PS complexes are loaded into root cells via Fe(III)-PS transporters called yellow stripe (YS) or yellow stripe-like (YSL) transporters without prior reduction (Inoue et al., 2009).

3. Role of siderophores in bioremediation of metals and metalloids

Metals and metalloids are ubiquitous components of the Earth's crust; however, human activities have resulted in their environmental dissemination, resulting in both point and non-point accumulation. The remediation of metals and metalloids-containing contaminated soils is challenging because of their environmental persistence and the adverse impacts on health. In recent years, investigating the potential of siderophores in metal bioremediation has been receiving increasing interest because of their strong

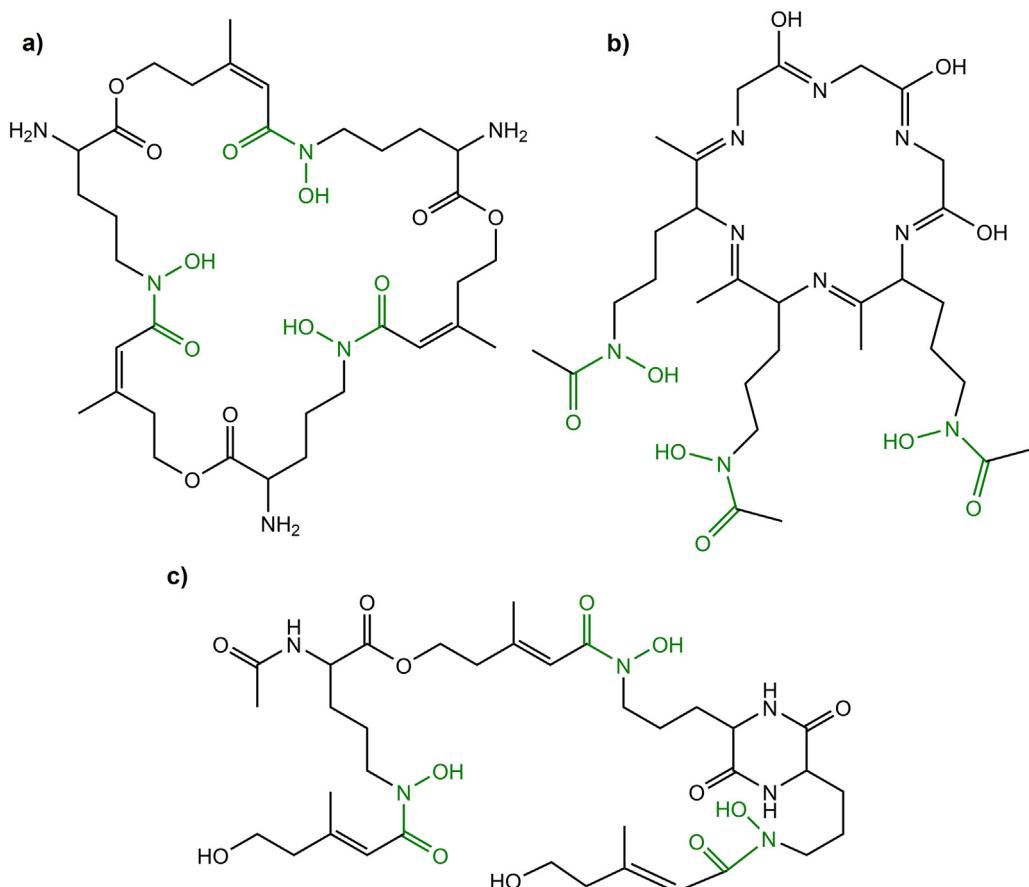


Fig. 2. Chemical structures of selected fungal siderophores: a) fusarinine C, b) ferrichrome A, and c) coprogen.

affinity for metals other than iron (Cornu et al., 2014; Ferret et al., 2015). Siderophores appear to be important players in mediating the mobility of metal and metalloid on the subsurface (Desouky et al., 2016; Dubbin and Ander, 2003), and the resistance of MOs and plants. Siderophores-mediated bioremediation can provide an economically and ecologically stable alternative to more hazardous chemical-dependent remediation methods (Rajkumar et al., 2010). Here, we discuss and summarise (Tables 2 and 3) different experiments investigating the effects of metals and metalloids on siderophore synthesis, and their role in the

biologically-mediated immobilisation and detoxification of metals and metalloids, and phytoremediation.

3.1. Effect of metals and metalloids on siderophores synthesis

Although iron is the key factor in siderophore production, other factors such as external pH, temperature, carbon source, and the presence of other metals are also important (Winkelmann, 2007). Metals other than iron have been reported to stimulate and repress (Table 2) bacterial siderophore production, even during high iron concentrations (Braud et al., 2010).

Höfte et al. (1992) suggested that Zn(II) and Ni(II) stimulate siderophores production in various pseudomonads, including *P. aeruginosa*. Duhme et al. (1998) reported that the amount and type of siderophores produced by *Azotobacter vinelandii* are modulated by the environmental Mo(VI) concentration and not by the Fe(III) level alone. In fact, Mo-azotochelin stability is sufficiently high to inactivate the azotecholin function of the iron scavenger and stimulates the production of a more efficient iron chelator, protochelin. Dao et al. (1999) found that Cd(II) stimulated Pvd production in *P. aeruginosa*; however, Zn(II) was ineffective. Teitzel et al. (2006) studied siderophores production in *P. aeruginosa*, which was exposed to two separate Cu(II) stress conditions. Although Cu-shocked cultures did not grow and produce siderophores under elevated Cu(II) levels, Cu-adapted cultures grew actively and secreted siderophores up to a concentration of 500 µM. The study showed different expression levels of the genes involved in the production of Pvd and pyochelin siderophores; Pvd biosynthetic genes were upregulated in Cu-adapted populations, whereas pyochelin genes were downregulated. Dimkpa et al. (2008a) reported that the presence of Al(III), Cd(II), Cu(II), and Ni(II) stimulated *Streptomyces* spp. strain to produce three hydroxamate siderophores: desferrioxamine E (DFOE), DFOB, and coelichelin (Cch). A similar trend of hydroxamate production in the presence of Cd(II) was also

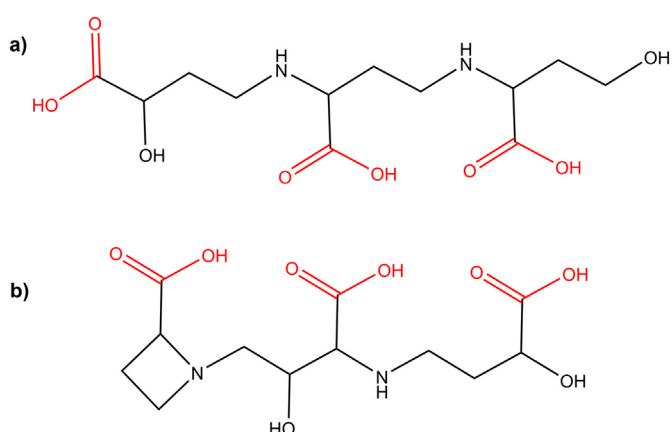


Fig. 3. Chemical structures of selected phytosiderophores: a) avenic acid and b) mugineic acid.

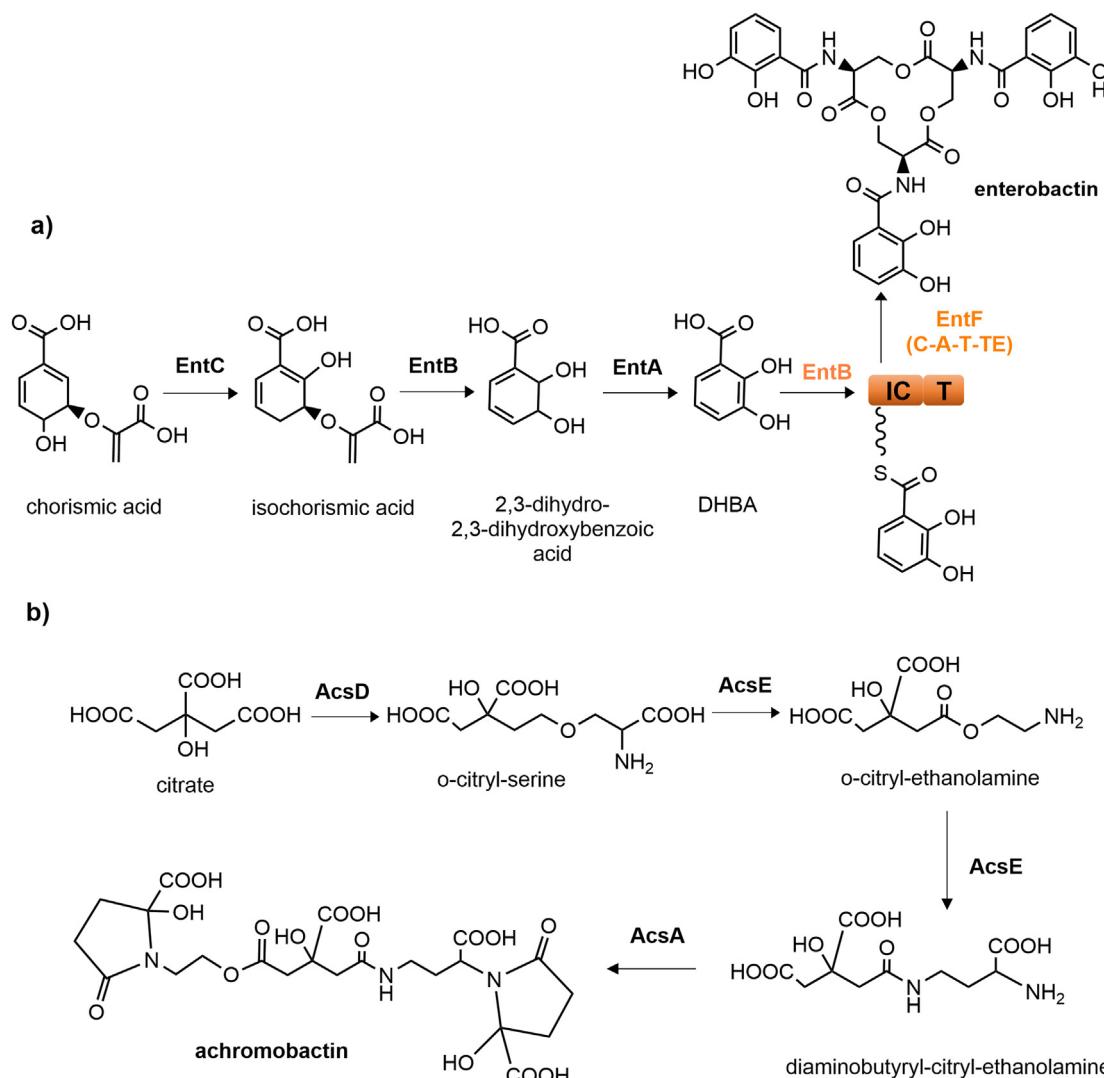


Fig. 4. Biosynthesis pathways for bacterial siderophores, a) enterobactin – 2,3-dihydroxy-benzoic acid (DHBA) synthesised from chorismic acid before incorporation into the NRPS assembly line, followed by assembly of enterobactin by NRPS EntF. IC – isochorismatase. A: adenylation domain; C: condensation domain; IC: isochorismatase; T: thiolation domain; TE: thioesterase domain; b) achromobactin – biosynthesis of achromobactin by the typeA NIS synthetases AcsD, AcsE, and AcsA.

observed in *Streptomyces tendae* F4 (Dimkpa et al., 2009). Similarly, Braud et al. (2009a) observed increased Pvd secretion in the presence of Al(III), Cu(II), Ga(III), Mn(II), and Ni(II) by *P. aeruginosa* (Braud et al., 2009a). In contrast, O'Brien et al. (2014) observed that Cu toxicity accelerated the evolution of non-siderophore-producing cheats in *P. aeruginosa* culture. Furthermore, Złoch et al. (2016) observed increased synthesis of different types of siderophores (hydroxamates, catecholates, and phenolates) by *Streptomyces* sp. strains after exposure to Cd(II). In addition, the study showed that the secretion is higher at slightly acidic pH (~5) than that at neutral pH. An increase in siderophore production was also observed in *Bacillus amyloliquefaciens* NAR38.1 in the presence of Zn and Mn (Gaonkar and Bhosle, 2013). Rashmi et al. (2013) observed that U(IV) increased siderophores production in the marine cyanobacterium *Synechococcus elongatus* BDU 130911. Giovanella et al. (2017) showed enhanced siderophore secretion in *Pseudomonas* sp. B50D in the presence of Hg(II), Ni (II), and Pb(II). Ghosh et al. (2018) observed an increased siderophore production in *Bacillus aryabhattai* AS6 in an As(V)-enriched environment, which was inhibited by As(III) (Ghosh et al., 2018). Although the capacity of several metals and metalloids to stimulate siderophore production has been described, its physiological role has not been fully clarified to date. One possible explanation for the increased siderophore secretion is that

metals and metalloids bind to free siderophores, preventing iron chelation, and thus activating additional siderophore secretion (Dimkpa et al., 2008a). Furthermore, increased siderophore secretion can be explained by the direct involvement of metals and metalloids in the siderophore biosynthesis pathway (Höfte et al., 1994). Several bacteria excrete siderophores to acquire essential metals such as Cu, Zn, or Mo from the environment (Hofmann et al., 2020). For example, siderophores containing S and N in metal-binding moieties reportedly bind to Zn(II) and Cu(II), and function as zincophores (Loboda and Rowińska-Żyrek, 2017) and chalkophores (Kenney and Rosenzweig, 2018). The secretion of Zn(II)-chelating compounds has been confirmed as a Zn(II) acquisition mechanism in several pathogenic organisms such as *Yersinia pestis* (Bobrov et al., 2014; Hood and Skaar, 2012). Methanotrophs produce methanobactin under Cu-limiting conditions that act as Cu(II)-chelating compounds and are a part of the copper uptake mechanism (Kim Hyung et al., 2004). In addition, some methanotrophs secrete methanobactin, which also forms strong complexes with Hg(II), enabling the degradation of methylmercury (Yin et al., 2020).

Metals and metalloids can partly or completely inhibit siderophore production, indicating that metal resistance is strain-dependent (Table 2). Abd-Alla (1998) observed that the *Bradyrhizobium* strain inhibited siderophore biosynthesis in the presence of Hg(II). Gaonkar and Bhosle (2013) observed

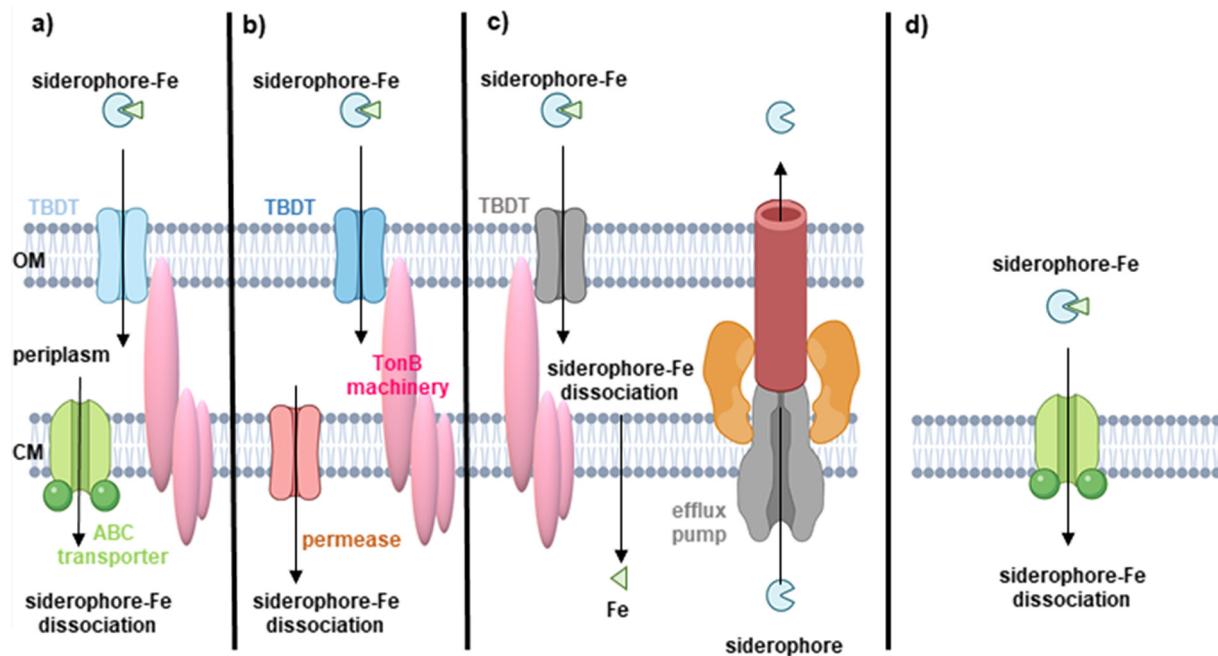


Fig. 5. Different mechanisms and strategies for siderophore pathways in Gram-negative (a, b, and c) and Gram-positive bacteria (d). Uptake across the outer membrane (OM) in Gram-negative bacteria (e.g. *Escherichia* sp. and *Pseudomonas* sp.) is powered by TonB-dependent complexes, which reside in the cytoplasmic membrane, but spans into the periplasm, delivering energy for import via the proton motive force. Each TBDT recognises and transports only a siderophore related to its chemical structure. Siderophores are subsequently transported across the periplasm and the cytoplasmic membrane (CM) into the cytosol, where iron reduction occurs mostly by periplasmic-binding proteins component of the ABC transporters (Faraldo-Gómez and Sansom, 2003). Iron-loaded siderophore transported across the CM exhibits less specificity than that transported across the OM. In addition to ABC transporters (panel a), permeases (panel b) are also involved in translocation into the cytosol (Cuiv et al., 2004). Iron can be released into the periplasm (panel c), followed by its transport into the cytosol through diffusion (Schalk et al., 2011). In contrast, gram-positive bacteria (e.g., *Bacillus* sp.) contain only a single membrane, and do not use the OM transporters to recognise and bind to iron-loaded siderophores (panel d). Instead, periplasmic-binding proteins anchored to the cell membrane bind to the extracellular iron-loaded siderophores, which is imported into the cytoplasm by the ABC transporters (Kramer et al., 2020).

a decrease in siderophore production in the presence of Cd(II) (0.01–0.1 mM) by *Bacillus amyloliquefaciens* NAR38.1, which also exhibited varied tolerances to multiple metals. Zn(II) and Mn(II) stimulated siderophore production, whereas the addition of Co(II), Mo(VI), As(V), Pb(II), and Al(III) decreased their secretion. Similarly, Giovanella et al. (2017) studied different tolerances of *Pseudomonas* sp. B50D to TMM, wherein Cd(II) inhibited siderophore production. The inhibition of siderophore production is concentration dependent and increases with increasing metal concentration (Gaonkar and Bhosle, 2013; Rizvi and Khan, 2017). Hussein and Joo (2017) studied the effect of Zn(II) concentration on 16 bacterial strains isolated from the rhizosphere of a ginseng plant. Zn(II) stimulated siderophore secretion up to a concentration of 100 µg·mL⁻¹ in all bacterial isolates, including *Pseudomonas putida* or *Bacillus subtilis*. A higher Zn(II) concentration inhibited siderophore secretion. Unfortunately, siderophore biosynthesis can also be inhibited by soluble iron, which may occur under certain environmental conditions (e.g. anoxic) (Braud et al., 2006b). Iron levels control bacterial transcription repressors in the family of ferric uptake regulator protein (Fur). Under iron-excess conditions, Fe(III) is complexed with Fur, repressing the genes responsible for siderophore biosynthesis (Prince et al., 1993). The negative effect of iron on siderophore biosynthesis can be offset by divalent cations that include metals and metalloids such as Cd(II), Hg(II), Pb(II), Mn(II), and Co(II), which can interact with Fur protein thiols (Braud et al., 2007; Coy and Neilands, 1991). The decreased siderophore biosynthesis in the presence of metals and metalloids can be explained by the inhibition of the ferric reductase enzyme, resulting in iron uptake blockage (Alcántara et al., 1994). In addition, the increasing impact of metals and metalloids on siderophore production with increasing concentrations indicates that a siderophore-based detoxification strategy does not entirely protect the organism against free metal diffusion into the cell at high concentrations (Gaonkar and Bhosle, 2013), which inhibits growth and siderophore production. Moreover, in case the

siderophore uptake receptor cannot distinguish between the iron-siderophore and metal-siderophore complex, it can result in intracellular metal accumulation, causing cell damage or death (Schalk et al., 2011).

The inhibitory effect of metals and metalloids on siderophore production during remediation can be avoided by the exogenous application of siderophores or bioaugmentation with siderophore-producing microbes. Kraemer et al. (2019) reported that the exogenously applied DFOB siderophore facilitates the mobilisation of Cr from igneous rock samples, and causes stable fractionation of Cr isotopes. Additionally, Desouky et al. (2016) reported that the *P. aeruginosa* siderophore enhanced Th(IV) and UO₂⁺ extraction from thorium-uranium concentrate. In contrast, the addition of siderophores is unlikely to be effective in the remediation of historically-contaminated sites, wherein siderophore production is stabilised by selection (Hesse et al., 2018). Moreover, using purified siderophores may be expensive and unsustainable for field applications. Additionally, inhibition of siderophore synthesis can also be minimised by immobilising the cell into a carrier (e.g. Na-alginate ($C_6H_7NaO_6$)_n or Ca-alginate ($C_{12}H_{14}CaO_{12}$)_n) (Braud et al., 2006a). Braud et al. (2007) reported the importance of carbon source, wherein an appropriate choice of substrate can enhance siderophore production in the presence of metals and metalloids.

3.2. Siderophores assisted bioremediation of metals and metalloids

Complexation with siderophores does not guarantee the entry of metal into the cell. Metal-siderophore complexes can be absorbed into the cell either using the same receptor/transporter systems as that of iron or independently, next to the iron acquisition function. For example, yersiniabactin, produced by *Y. pestis*, binds both Fe(III) and Zn(II), and acts as both siderophore and zincophore (Bobrov et al., 2014). However, metals and metalloids in microbial cells at concentrations above the threshold levels

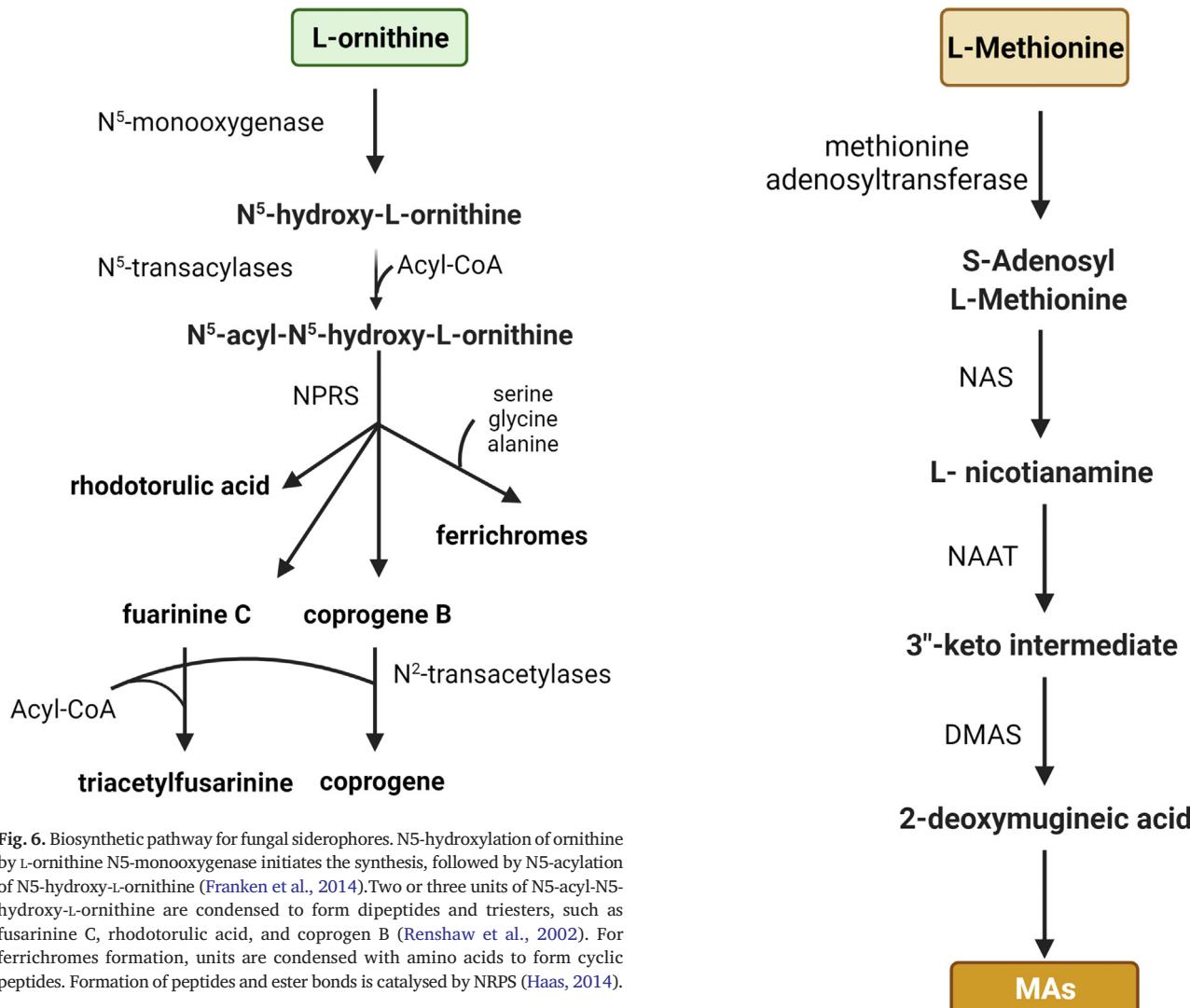


Fig. 6. Biosynthetic pathway for fungal siderophores. N5-hydroxylation of ornithine by L-ornithine N5-monooxygenase initiates the synthesis, followed by N5-acylation of N5-hydroxy-L-ornithine (Franken et al., 2014). Two or three units of N5-acyl-N5-hydroxy-L-ornithine are condensed to form dipeptides and triesters, such as fusarinine C, rhodotorulic acid, and coprogen B (Renshaw et al., 2002). For ferrichromes formation, units are condensed with amino acids to form cyclic peptides. Formation of peptides and ester bonds is catalysed by NRPS (Haas, 2014).

adversely affect the physiological functions of bacterial cells. However, bacteria have developed various mechanisms of resistance. FpvA on the surface of *P. aeruginosa* binds to Ag(II), Al(III), Cd(II), Co(II), Cu(II), Fe(III), Ga(III), Hg(II), Mn(II), Ni(II), and Zn(II), and complexes with Pvd; however, the TonB-dependent uptake was successful only for Cu(II), Ga(III), Mn(II), and Ni(II), indicating high selectivity for metals/metalloids-siderophore uptake (Braud et al., 2009a).

Because of this high selectivity, siderophores play an important role in increasing bacterial resistance to metals and metalloids, which potentially enhances bioremediation. When they do not enter the cell, metal/metalloid-siderophore complexes can be subsequently removed from the contaminated environment by extracellular bacterial polymers, such as proteins through precipitation and biosorption (Harrington et al., 2015; Ramasamy et al., 2007). In addition, complexation enhances the metal solubility and mobility in the environment (Neubauer et al., 2000), and its bioavailability in plants, thereby increasing the phytoremediation efficiency (Hrynkiewicz et al., 2018; Lebeau et al., 2008; Sessitsch et al., 2013). For example, Nair et al. (2008) studied different washing solutions to identify their capacity to extract metals and metalloids from contaminated sludge, and observed that Ni, Zn, Cr, and Pb were efficiently extracted using siderophores produced by *Pseudomonas azotoformans*. Although the removal capacity by the siderophores was lower than that of EDTA and citric acid, the results showed their ability to remove metals and metalloids from the environment. Giovannella et al. (2017) reported that the produced siderophores contributes to the resistance exhibited by *Pseudomonas* sp. B50D during Hg(II) removal. The industrial effluents containing Cd, Ni,

Fig. 7. Biosynthetic pathway for PS. Their synthesis is initiated by the hydroxylation of three molecules of L-methionine by methionine adenosyltransferase, followed by condensation of three molecules of S-adenosyl-L-methionine by nicotianamine synthases to produce one molecule of L-nicotianamine. Nicotianamineaminotransferase (NAS), a critical enzyme in the specific pathway, catalyses the transfer of an amino residue to L-nicotianamine (Aciksoz et al., 2011; Pujar, 2008). The amino group of L-nicotianamine is transferred by nicotianamineaminotransferase (NAAT), and the resultant 3'-keto intermediate is reduced to 2'-deoxymugineic acid (DMA) by deoxymugineic acid synthase (DMAS) (Bashir and Nishizawa, 2006). DMA is the precursor for all other MAs.

and Pb, which were artificially contaminated with Hg(II) were studied. The results indicated that the isolate removed Hg(II) through volatilisation; however, the concentrations of other metals and metalloids were not reduced. Banerjee et al. (2019) identified siderophore production together with biosorption and bioaccumulation as key mechanisms in Cr(VI) removal from contaminated soils using *Pseudomonas brenneri* MF957286. Khan et al. (2020) examined the role of hydroxamate siderophores produced by *Aspergillus nidulans* in Cd(II) bioaccumulation in *B. subtilis*, and observed an increased siderophores-mediated bioaccumulation of Cd(II) by *B. subtilis*. However, bioaccumulation was followed by a decrease in the microbial population, indicating the toxic effects caused by the uptake of siderophore-Cd complexes on *B. subtilis*. Liao et al. (2020) reported that *Pannonibacter phragmitetus* siderophore excretion facilitators, such as the RND efflux system (Li and Ma, 2017), were significantly upregulated in the single Pb(II) system, and the binary system of Cr(VI) and Pb(II).

Table 2

Summary of investigations focused on the effect of metals and metalloids on siderophores synthesis

Species/MOs	Siderophores	Element	Concentration	Effect on siderophores synthesis	Study
<i>Pseudomonas aeruginosa</i> PA103, PA103M and PA103MC	Pvd, pyochelin	Fe(II)	0–200 μM	0–6.25 μM ↑ >6.25 μM ↓	Prince et al. (1993)
<i>Pseudomonas aeruginosa</i> 7NSK2	Pvd	Zn(II)	1–5 mM	0–0.5 μM ↓ 2.5 mM ↑	Höfte et al. (1994)
<i>Bradyrhizobium</i> (lupin) stains USDA 3040, 3041, 3042	Hydroxamates	Fe(III)	0–20 μM	When precultured in medium with 20 μM of Fe and then cultured in 0–0.5 μM ↑ compared to bacteria preincubated in Fe-deficient medium. Conc. 4–20 μM ↓.	Abd-Alla (1998)
<i>Azotobacter vinelandii</i>	Azotochelin	Mo(IV)	0–100 μM	0–100 μM ↑, >100 μM ↓	Duhme et al. (1998)
<i>Pseudomonas aeruginosa</i> PAO1	Pvd	Cd(II)	0–200 μM 300–1000 μM	0 ↑	Dao et al. (1999)
		Zn(II)	0–1 mM	0	
<i>Pseudomonas aeruginosa</i> ATCC 9027 (PA), <i>Pseudomonas fluorescens</i> DSM 50090 (PF)	Pvd, pyochelin	Fe(III) Cr(III) Hg(II) Pb(II)	4 mg/L 5 mg/L 0.2 mg/L 13 mg/L	PA ↑↑; PF ↑ TMM mix: PA ↑; PF ↓	Braud et al. (2006a)
<i>Pseudomonas aeruginosa</i> PA01	Pvd, pyochelin	Cu(II)	0–500 μM	TMM + Fe: PA ↑↑; PF ↓ ↑	Teitzel et al. (2006)
<i>Pseudomonas aeruginosa</i> ATCC 9027, <i>Pseudomonas fluorescens</i> DSM 50090	Pvd, pyochelin	Cr(III) Hg(II) Pb(II) Fe(III)	5 mg/L 0.2 mg/L 13 mg/L 4 mg/L	TMM ↑; Fe ↓; Fe + TMM ↑↑.	Braud et al. (2007)
<i>Streptomyces</i> sp.	DFOE, DFOB, Cch	Fe(III) Al(III); Cd (II); Cu(II); Ni(II)	100 μM	↓↓ ↑	Dimkpa et al. (2008)
<i>Streptomyces tendae</i> F4	DFOE, DFOB, Cch	Cd(II)	100 μM	↑	Dimkpa et al. (2009)
<i>Bacillus amyloliquefaciens</i> NAR38.1	Cateholates	Fe(II) Fe(III) Mn(II), Zn (II), Mo(IV) Al(III), As (V), Cu(II), Co(II), Pb (II)	1–5 μM 5–50 μM 125–1000 μM 10–100 μM	>1 μM ↓ >30 μM ↓ 0–1000 μM Mn 0; Zn ↑, 0–125 μM Mo 0, >125 μM ↓ 0–20 μM Al ↓, 50–100 μM ↑ 0–100 μM As/Cd ↓; 0–10 μM Cu ↑; >10 μM ↓, 0–20 μM Co ↑, >20 μM ↓ 0–100 μM Pb ↓	Gaonkar and Bhosle (2013)
<i>Synechococcus elongatus</i> BDU 130911, <i>Oscillatoria boryana</i> BDU 141071, <i>Phormidium valderianum</i> BDU 140081, <i>Nostoc calcicola</i> BDU 40302	Hydroxamates and catecholates	U(IV)	1 mM	U ↑ in the strains BDU 130911 and BDU 141071 while for BDU 140081 and BDU 40302 ↓. U + Fe ↓ in all tested strains.	Rashmi et al. (2013)
<i>Pseudomonas aeruginosa</i> PAO1	Pvd, pyochelin	Cu(II)	0.624–6.17 mM	↓	O'Brien et al. (2014)
<i>Streptomyces</i> sp. SIIB-Zn-R8, SIB-Zn-R1, SIIB-Cd-R1, SIIB-Cd-R4, SIA-Zn-R4	Hydroxamates, catecholates, phenolates	Cd(II)	0.5–3 mM	2 mM of Cd ↑↑ for SIIB-Zn-R8, other concentration 0. 0.5 mM Cd ↑↑ for SIB-Zn-R1; other Cd conc. ↑. For SIIB-Cd-R1 and SIA-Zn-R4 0.5 and 3 mM of Cd ↓ whereas 1 and 2 mM Cd ↑.	Złoch et al. (2016)
<i>Pseudomonas</i> sp. B50D	NS	Hg(II) Cd(II) Ni(II); Pb(II)	10–50 μM 0.1–0.3 mM 0.25–1 mM	↑ 0 ↑	Giovanella et al. (2017)
<i>Pseudomonas</i> KNUK9	Pyoverdine	Zn(II)	50–250 μM	0–100 μM ↑, >100 μM ↓.	Hussein and Joo (2017)
<i>Pseudomonas aeruginosa</i> CPSB1	Pvd, pyochelin	Cu(II); Cd (II); Cr(VI)	0–400 μg/mL	↓	Prince et al. (1993)
<i>Pseudomonas aeruginosa</i> PA01	Pvd, pyochelin	Cu(II)	6.17 mM	In pre-cultured strain ↑	Höfte et al. (1994)

Explanations: 0 - no (significant) effect; ↑ - promotion; ↑↑- strong promotion; ↓- inhibition; ↓↓ - complete inhibition.

Moreover, the entry of Pb(II) in the cell was blocked by complexation with siderophores. *P. phragmitetus* effectively reduced Cr(VI) to Cr(III), and precipitated and absorbed Pb(II), which together with the detoxifying effect of siderophores may majorly contribute in the bioremediation of Cr(VI) and Pb(II). In contrast, soluble Cr(III) species (e.g. dissolved or ligand-complexed) can reoxidise to Cr(VI) under complex environmental conditions (Amacher and Baker, 1982), and siderophores may subsequently contribute to the environmental recontamination. In addition, siderophores may enhance Cr(III) solubility. For example, Saad et al. (2017) reported an increased Cr(III) dissolution from Cr(III)-Fe(III)-(oxy)hydroxide solid phases, which is the common reduction product of Cr(VI) abiotic remediation in the presence of DFOB siderophores. Cr(III) may reoxidise to Cr(VI), which indicate that siderophores may subsequently cause environmental recontamination.

3.3. Siderophores assisted phytoremediation of metals and metalloids

The idea of using plant hyperaccumulators that selectively remove metals from the environment was introduced in 1983 (Chaney, 1983). However, these hyperaccumulators exhibit limited potential because most have low biomass and slow growth rates, which limit the speed of metal and metalloid removal (Rascio and Navari-Izzo, 2011). Alternatively, high biomass producing non-hyperaccumulators can be used; however, they usually accumulate lower concentrations of metals and metalloids (Ebbs et al., 1997; Vamerali et al., 2010). To minimise these limitations and improve plant performance, research has been focused on using alternative methods of metal bioremediation (Gerhardt et al., 2009). Coupling phytoremediation and microbial bioremediation strategies has successfully improved metal remediation (Newman and Reynolds, 2005; Whiting et al.,

Table 3

Summary of investigations focused on siderophores assisted phytoremediation of metals and metalloids

Siderophores	MOs	Plants	Metals and metalloids (concentration)	Mechanism	Increase/decrease of TMM in biomass	Study
DFOB, DFOE, Cch	<i>Streptomyces acidiscabies</i> E13	<i>Vigna unguiculata</i> L.	Ni(II) (2 mM)	Reduction of toxic stress	Not significant	Dimkpa et al. (2008b)
NS ¹	<i>Pseudomonas aeruginosa</i> ATCC 9027, <i>Pseudomonas fluorescens</i> DSM 50090, and <i>Ralstonia metallidurans</i> CH34 ATCC 43123	<i>Zea mays</i> L.	Pb (382 mg·kg ⁻¹); Cr (488 mg·kg ⁻¹)	Increased bioaccumulation	2.6–4.4-fold ↑ of Cd in shoots and 1.2–3.5-fold ↑ of Pb in shoots, 1.8–2.9-fold ↓ of Cd in roots and 2.7–4.8-fold ↓ of Pb in roots	Braud et al. (2009b)
DFOB, DFOE, Cch	<i>Streptomyces tendae</i> F4	<i>Helianthus annuus</i> L.	Cd(II), Fe(III) (100 µM)	Increased bioavailability	1.5-Fold ↑ in bioaccumulation of Cd	Dimkpa et al. (2009)
NS	<i>Enterobacter aerogenes</i> LRE17, <i>Enterobacter</i> sp., LSE04, <i>Acinetobacter</i> sp., LSE06 and <i>Serratia nematodiphila</i> LRE07	<i>Solanum nigrum</i> L.	Cd(II) (pre-incubation in 0.5 mM then 0–40 mM of Cd)	Increased bioavailability	1.1–1.2 ↑ bioaccumulation in leaf, stem and root	Chen et al. (2010)
Catecholates and hydroxamates	<i>Pseudomonas</i> sp. SRI2 and <i>Psychrobacter</i> sp. SRS8 and <i>Bacillus</i> sp. SN9	<i>Brassica juncea</i> , <i>Brassica oxyrrhina</i>	Ni(II) (50 mg·L ⁻¹)	Increased bioavailability	Not significant	Ma et al. (2009)
NS	<i>Bacillus thuringiensis</i> GDB-1	<i>Alnus firma</i>	Pb(II) (80 mg·L ⁻¹), Zn(II) and As(III) (40 mg·L ⁻¹), Cd(II), Cu(II) and Ni(II) (10 mg·L ⁻¹)	Reduction of toxic stress	1.1–1.5 ↑ in bioaccumulation in roots and 1.1–1.75 in shoots in order As<Cu<Pb<Zn<Cd<Ni	Babu et al. (2013)
Pvd	<i>Pseudomonas aeruginosa</i> ATCC 15692	<i>Lycopersicon esculentum</i> , <i>Hordeum vulgare</i>	Cu(II) (400 mg·kg ⁻¹), Cd(II) (5 mg·kg ⁻¹)	Increase bioavailability and bioaccumulation	2-Fold ↑ of Cu in roots	Cornu et al. (2014)
NS	<i>Pseudomonas aeruginosa</i> ATCC 15692	<i>Pteris cretica</i> L.	3.0 g of As (V)-adsorbed ferrihydrite	Increased bioaccumulation	3-Fold ↑ of As in plant leaves	Jeong et al. (2014)
NS	<i>Arthrobacter</i> sp., <i>Pseudomonas putida</i> , <i>Delftia acidovorans</i> , <i>Brevundimonas</i> sp.	<i>Phragmites australis</i>	Cu (37.5 mg·L ⁻¹)	Increased bioavailability	NA ²	Huguenot et al. (2015)
Catecholates and DFOB	<i>Pseudomonas</i> sp. PG12	<i>Pteris vittata</i>	As(V) (10 mM)	Increased bioavailability and bioaccumulation	6-Fold ↑ of bioaccumulation of As in the roots and 4.5-fold ↑ in rhizome	Liu et al. (2015)
DFOB	NS	<i>Helianthus annuus</i> L. ES RICA and Kaplan	Cd (4.9 mg·kg ⁻¹ HF digestion), Cu (339), Ni (28), Pb (<7) and Zn (1120)	Reduction of toxic stress	Not significant	Cornu et al. (2017)
NS	<i>Enterobacter cloacae</i> -VITPASJ1	<i>Pennisetum purpureum</i>	Pb(II) (50–150 mg·kg ⁻¹)	Increased bioavailability, reduction of toxic stress	NA	Das et al. (2017)
DFOB, PG12 ³	NS	<i>Pteris vittata</i>	As(V)-adsorbed goethite 50 mg·L ⁻¹	Increased bioavailability	3-Fold ↑ of As concentration in fronds by DFOB and 7-fold ↑ by PG12 and 30-fold ↑ in roots by DFOB and 17-fold ↑ by PG12	Liu et al. (2017)
Pvd	<i>Pseudomonas fluorescens</i> ATCC 17400	<i>Trifolium pratense</i>	Cs(I)-spiked illite 0.1 g·L ⁻¹	Increased bioavailability	3-fold ↓ of Cs in plant parts	Hazotte et al. (2018)
NS	<i>Rhodopseudomonas palustris</i> C1 and <i>Rubrivivax benzoatilyticus</i> C31	<i>Oryza sativa</i> L.	As(III), As(V) (30mg·L ⁻¹)	Reduction of toxic stress	Slight ↓ of As content in seed and seedling	Nookongbut et al. (2018)
NS	<i>Cellulosimicrobium</i> sp.	<i>Medicago sativa</i>	Cr(VI) (5–2000 mg·L ⁻¹), Zn(II), Cu(II) (200–1000 mg·L ⁻¹)	Reduction of toxic stress, increased bioaccumulation	1.5-Fold ↑ of Cu and Cr in roots and 1.4-fold ↑ of Zn in roots. 3-fold ↑ roots > shoots	Tirry et al. (2018)
Pvd	<i>Pseudomonas fluorescens</i> ATCC 13525	NA	Cu (53–132 mg·kg ⁻¹)	Reduction of toxic stress, increased bioaccumulation	NA	Cornu et al. (2019)
Ferricrocin	<i>Aspergillus nidulans</i>	<i>Triticum aestivum</i>	As(V) (40 µM)	Reduction of toxic stress	3-Fold ↓ of As in roots and shoots	Kumari et al. (2019)
NS	<i>Microbacterium</i> sp. and <i>Klebsiella</i> sp	<i>Pelargonium hortorum</i> ,	Pb(II) (500–2000 mg·kg ⁻¹)	Increased bioavailability	1.3–1.9-Fold ↑	Manzoor et al. (2019)
Pyoverdine	<i>Pseudomonas fluorescens</i> ATCC 17400	<i>Trifolium pratense</i>	Cs(I) (0.1 mol Cs·kg ⁻¹ illite)	Increased bioavailability	6-Fold ↑ equal distribution of Cs to roots and shoots	Péron et al. (2019)
NS	<i>Bacillus mucilaginosus</i> , <i>Bacillus subtilis</i> , <i>Citrobacter</i> Werkman and Gillen, <i>Bacillus cereus</i> Frankland and <i>Bacillus thuringiensis</i>	<i>Lolium perenne</i> L., <i>Lolium multiflorum</i> Lam. and <i>Dactylis glomerata</i> L.	U(IV) (0–150 mg·kg ⁻¹)	Increased bioavailability	1.2–1.3-fold ↑ in <i>L. multiflorum</i> shoots and 1.2–1.5-fold ↑ in <i>L. perenne</i> shoots	Qi et al. (2019)
NS	<i>Bacillus subtilis</i> PAW3	<i>Vigna unguiculata</i>	Cr(VI) (0–500 mg·L ⁻¹)	Reduction of toxic stress	Slight ↓ of bioaccumulation of Cr (+ change of oxidation	Wani et al. (2019)

Table 3 (continued)

Siderophores	MOs	Plants	Metals and metalloids (concentration)	Mechanism	Increase/decrease of TMM in biomass	Study
DFOE, aerobactin	<i>Micromonospora</i> sp.	<i>Arabidopsis thaliana</i> L.	As(V), Cr(VI), Hg(II) (0.33–1 µM)	Reduction of toxic stress	state) NA	Ortúzar et al. (2020)
NS	<i>Bradyrhizobium japonicum</i> CB1809	<i>Glycine max, Helianthus annuus</i>	As(V) (5 µM)	reduction of toxic stress	1.3-Fold ↓ of As in soybean roots and 1.1-fold ↑ in shoots, 1.1-fold ↓ of As in sunflower roots and 1.3-fold ↑ in shoots	Seraj et al. (2020)
NS	<i>Pseudomonas vancouverensis</i> m318	<i>Pteris vittata, Pteris multifida</i>	As(III) (1 mM), As(V) (10 mM)	Increased bioavailability	NA	Yang et al. (2020)
NS	<i>Streptomyces</i> sp.	<i>Chlorophytum comosum</i>	Cd(II) (25–200 mg·L ⁻¹)	Increased bioavailability	1.1–1.3-Fold ↑ of Cd in roots and 1.2-fold ↑ in shoots	Junpradit et al. (2021)
NS	<i>Bacillus aerophilus</i> TR15c	<i>Helianthus annuus</i> L.	Cu (1754–3058 mg·kg ⁻¹)	Reduction of toxic stress	2- or 3-fold ↑ Cu in shoots	Kumar et al. (2021)
NS	<i>Pseudomonas</i> sp., <i>Bacillus</i> sp., <i>Achromobacter</i> sp.	<i>Medicago sativa</i>	Pb (142–317 mg·kg ⁻¹), Cd (30–227 mg·kg ⁻¹)	Reduction of toxic stress	NA	Tamariz-Angeles et al. (2021)

↑ - increase, ↓ - decrease.

¹ NS – not-specified.

² PG12 – PG12 siderophore.

³ NA – not-available.

2001). Siderophore-producing bacteria considerably contributes in enhancing plant survival and growth in contaminated soils, by reducing metal toxicity and providing nutrients (Benizri and Kidd, 2018; Salt et al., 1999). Additionally, these bacterial siderophores can enhance phytoremediation by increasing metal accumulation and inducing metal-tolerance in plants (Rajkumar et al., 2010).

Phytoremediation efficiency may be enhanced either by inoculating siderophore-producing microbes or by exogenous application of siderophores. For example, Braud et al. (2009b) observed a significant increase in Cr and Pb phytoextraction by maize when the contaminated soil was inoculated with *P. aeruginosa* or *Cupriavidus metallidurans* (former *Ralstonia metallidurans*), which are known for their siderophore-producing abilities. Enhanced potential of Pb(II) phytoextraction by *Mesembryanthemum criniflorrum* and *Pelargonium hortorum* in Pb-contaminated soil has also been reported for siderophore-producing bacteria *Klebsiella variicola* and *Microbacterium* sp. (Manzoor et al., 2019). Dimkpa et al. (2009) demonstrated that siderophores produced by *Streptomyces tendae* F4 significantly increased Cd(II) uptake by sunflower plant (*Helianthus annuus* L.). Similarly, Chen et al. (2010) demonstrated the ability of siderophore-producing bacteria, *Serratia nematodiphila* LRE07, *Enterobacter aerogenes* LRE17, *Enterobacter* sp. LSE04, and *Acinetobacter* sp. LSE06, which increased Cd(II) availability for *Solanum nigrum* L. Ma et al. (2009) reported an increase in Ni(II) concentration in the root and shoot tissues of *Brassica juncea* and *Brassica oxyrrhina* cultivated in soil bioaugmented with siderophore-producing strains, *Pseudomonas* sp. SRI2, *Psychrobacter* sp. SRS8, and *Bacillus* sp. SN9. Babu et al. (2013) identified siderophores as one of the factors that contributed to the enhanced metal bioaccumulation in *Alnus firma* inoculated with *Bacillus thuringiensis* GDB-1. Huguenot et al. (2015) reportedly enhanced Cu bioavailability in *Phragmites australis* when bioaugmented with siderophore-producing bacteria. Similarly, Cornu et al. (2019) demonstrated the ability of Pvd produced by *Pseudomonas fluorescens* ATCC 13525 in decreasing toxic stress and Cu(II) bioavailability in vineyard soils. Das et al. (2017) reported that *Pennisetum purpureum* bioaugmented with siderophore-producing bacteria *Enterobacter cloacae*-VITPASJ1 reduced Pb(II) toxicity and increased its bioavailability. Siderophores produced by the bacteria *Cellulosimicrobium* sp. NF2 enhances the growth and accumulation of metals in alfalfa (*Medicago sativa*) under Cr(VI), Zn(II), Cu(II), Ni(II), Pb(II), and Co(II) stress (Tirry et al., 2018). Similarly, alfalfa bioaugmented with siderophore-producing organisms enhanced seedling survival under toxic stress of Cd, Pb, and Al (Tamariz-Angeles et al., 2021). Additionally, U accumulated by *Lolium perenne* and *Lolium multiflorum* increased significantly after inoculating

siderophore-producing bacterial consortium (Qi et al., 2019). Tang et al. (2020) observed an increased Mn bioaccumulation in *Myriophyllum verticillatum* inoculated with *Bacillus cereus*. Yang et al. (2020) reported that the inoculation of *Pteris vittata* and *Pteris multifida* with siderophores produced by *Pseudomonas vancouverensis* m318 significantly increased As accumulation in ferns. Kumar et al. (2021) showed that the growth of a consortium containing an increased ACC deaminase-producing *Pseudomonas* sp. TR15a and siderophore-producing *Bacillus aerophilus* TR15c was enhanced, which consequently resulted in Cu uptake in sunflower plants. In addition, Junpradit et al. (2021) reported that inoculation of *Chlorophytum comosum* siderophore-producing bacteria in *Streptomyces rapamycinicus* and *Streptomyces cyaneus* enhanced Cd(II) phytoextraction.

Phytoextraction of metals and metalloids can also be enhanced by exogenous siderophores application into the rhizosphere. For example, Liu et al. (2015) observed increased FeAsO₄ dissolution, which resulted in As(V) and Fe(III) uptake by the plant *Pteris vittata* when treated with siderophores produced by the As-tolerant bacterium *Pseudomonas* sp. PG12, which was previously isolated from the rhizosphere of *Pteris vittata*. Furthermore, PG12 siderophores were more effective in treatment than that of DFOB produced by fungi. In addition, Liu et al. (2017) reported increased dissolution of As-goethite, and As(V) and Fe(III) uptake by *Pteris vittata* when treated with DFOB and PG12. Cornu et al. (2014) reported that Pvd treatment, produced by *P. aeruginosa*, improved Cu(II) phytoextraction; however, the fate of Cd(II) remained unaffected. Similarly, Pvd treatment increased Cs(I) phytoextraction in red clover (Hazotte et al., 2018; Péron et al., 2018).

Although research has indicated the enhanced phytoextraction by siderophores, in certain cases, siderophores inhibit plant-metal uptake and promote plant growth (Ortúzar et al., 2020). These contrasting effects indicate that siderophores can potentially help in containing metals within the rhizosphere and reduce off-site contamination. Dimkpa et al. (2008b) suggested that the hydroxymate siderophore produced by *Streptomyces acidiscabies* E13 reduces Ni(II) uptake by plants, thus increasing the plant biomass. Additionally, Dimkpa et al. (2008a) identified that the siderophore-metal complexes formed are responsible for the reduced inhibitory effect of TMM on auxin production. Nookongbut et al. (2018) demonstrated that inoculation of siderophore-producing bacteria *Rhodopseudomonas palustris* C1 and *Rubrivivax benzoatilyticus* C31 minimised As uptake in rice. Similarly, Kumari et al. (2019) observed the ability of a hydroxymate siderophore in preventing As(V) uptake. In addition, Seraj et al. (2020) identified that siderophore production was responsible for increased As tolerance in plants. Wani et al. (2019) suggested that siderophores produced by *B. subtilis* were involved in the complete reduction of Cr(VI) to Cr(III) in soil, and prevented the uptake

of Cr species in cowpea plants (*Vigna unguiculata*). Similarly, Ortúzar et al. (2020) documented the capacity of siderophores produced by *Micromonospora* strains in preventing the uptake of metals and metalloids by *Arabidopsis thaliana*, thereby promoting plant growth.

4. Role of siderophores in the degradation processes of organic contaminants

The microorganisms that produce siderophores are ubiquitously present in the environment, thereby focussing the research on the role of siderophores in organic compound remediation (Table 4). Siderophores facilitate the remediation of organic contaminants either directly by mediating ROS production (Gu et al., 2018) or indirectly by increasing the bioavailability of contaminants (Martinez and Butler, 2007), counteracting the contaminant toxicity (Khanolkar et al., 2015) or facilitating Fe acquisition by degrading microorganisms under Fe-limiting conditions (Barbeau et al., 2002).

Siderophores serve as redox-cycling molecules, acting as electron carriers (Rodríguez et al., 1999) for the biogenic Fenton-Haber-Weiss reactions (Eqs. (1)-(4)) (Cornish and Page, 1998; Gu et al., 2018).



These reactions produce ROS, such as hydroxyl radicals (OH^\bullet) and peroxy radical/superoxide radicals ($\text{HO}_2^\bullet / \text{O}_2^\bullet$), which subsequently attack or degrade organic compounds in the environment (Goodell et al., 1997). For example, Inoue et al. (2003) reported the ability of three Pvd substances produced by *Pseudomonas chlororaphis* to degrade the organotin compounds, triphenyltin and diphenyltin chlorides. However, triphenyltin degradation was significantly inhibited in the presence of Cu(II), Al(III), and Fe(III). Kim et al. (2009) reported the capacity of the Fe(II)-DFOB

complex to abiotically reduce nitroaromatic groundwater contaminants and suggested that siderophores are potent reductants that contribute to natural attenuation processes. Recently, Gu et al. (2018) identified siderophores that were involved in the production of ROS and mediated the biodegradation of Tetrabromobisphenol A by *Pseudomonas* sp. Similarly, Wang et al. (2021) and Wang et al. (2020) demonstrated that the siderophore-mediated extracellular biogenic Fenton-like reaction effectively biodegraded the carbon-based materials such as buckminsterfullerene. Furthermore, Wang et al. (2013b) suggested the capacity of Fe(III) siderophores in enhancing the abiotic oxidation of propanol.

In addition, Martinez et al. (2000) and Denaro et al. (2014) hypothesised that hydrocarbon-degrading bacteria secrete amphiphilic siderophores, such as amphibactin, to simultaneously increase the bioavailability of highly hydrophobic substrates, which is required for the growth of petroleum hydrocarbons. Similarly, Gauglitz et al. (2012) showed that marine *Vibrio* spp. isolated from the Gulf of Mexico after the 2010 Deepwater Horizon oil spill produced amphiphilic ochrobactins that were suggested to efficiently contribute in petroleum hydrocarbon biodegradation. Furthermore, Khanolkar et al. (2015) identified that siderophore production induces tolerance toward tributyltin chloride in *Klebsiella pneumoniae*, thereby facilitating its degradation. Furthermore, Kundu et al. (2016) observed the expression of Fe transport systems in 2,6-dinitrotoluene biodegradation and identified siderophores as a substantial source of Fe for the degradation process, where Fe acts as a cofactor for various enzymes involved in the degradation of various hydrocarbons. Similarly, Singha et al. (2018) identified siderophore production as crucial mechanism for pyrene biodegradation, which helps in sequestering Fe from the environment for microbial degradation.

5. Conclusion and direction for further research

The role of siderophores in remediation applications has been investigated over the last three decades and is summarised in this review. In addition, we identified different mechanisms involved in siderophores-assisted bioremediation (Fig. 8). The ability of siderophores to complex metals and metalloids enhances bioremediation by preventing their entry in the bacterial cell and promoting their subsequent use in biomass. In contrast,

Table 4

Summary of investigation focused on the role of siderophores in bioremediation of organic contamination.

Siderophore	Bacterium	Contaminant	Mechanism	Degradation efficiency (%)	Study
2,3-Dihydroxybenzoic acid, 3,4-dihydroxybenzoic acid (DHBAs) Pvd	Not used <i>Pseudomonas</i> sp.	2-Chlorophenol, 4-chlorophenol Triphenyltin, tributyltin chlorides	ROS production ROS production	60 10	Rodríguez et al. (1999) Inoue et al. (2003)
DFOB Ochrobactins	Not used <i>Vibrio</i> sp.	4-Cl-nitrobenzene Petroleum hydrocarbons	ROS production Increases bioavailability	100 NA ^b	Kim et al. (2009) Gauglitz et al. (2012)
NS ^a Amphibactins, pseudomonine	<i>Stenotrophomonas maltophilia</i> 15 <i>Alcanivorax borkumensis</i> SK2	Propanolol n-Tetradecane	ROS production Increases bioavailability	30–60 40–50	Wang et al. (2013b) Denaro et al. (2014)
NS	<i>Klebsiella pneumoniae</i> SD9	Tributyltin chloride	Induce microbial resistance	NA	Khanolkar et al. (2015)
NS	<i>Rhodococcus pyridinivorans</i> NT2	2,4-Dinitrotoluene	Fe mediation to enzymatic biodegradation	100	Kundu et al. (2016)
NS	<i>Pseudoalteromonas</i> sp. GCY	Tetrabromobisphenol A	ROS production	30–75	Gu et al. (2018)
NS	<i>Klebsiella pneumoniae</i> AWDS	Pyrene	Fe mediation to enzymatic biodegradation	60	Singha et al. (2018)
Catecholate-type siderophores	<i>Labrys</i> sp. WJW	Fullerene C60,	ROS production	65	Wang et al. (2021)
Catecholate-type siderophores	<i>Labrys</i> sp. WJW	Graphene oxide, carbon nanotubes (CNT), oxidized CNT	ROS production	NA	Wang et al. (2020)

^a NS – not-specified.

^b NA – not-available.

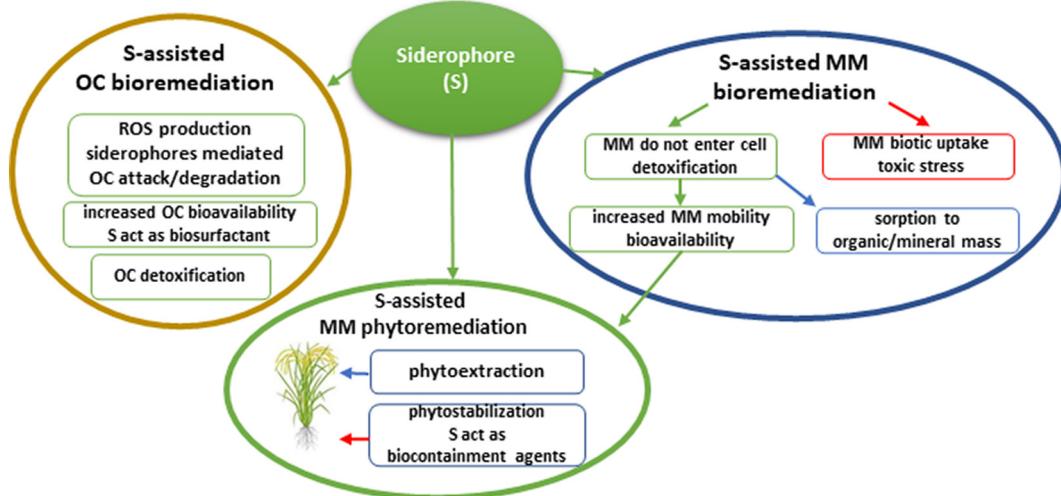


Fig. 8. Various mechanisms involved in siderophores-assisted bioremediation. Siderophores (S) secreted by MOs chelate metals and metalloids (MM). The S-MM complex enters a bacterial cell, wherein MM concentration above threshold levels affect the physiological function of bacterial cells. High selectivity for S-MM complexes prevents MM from entering the cell. The S-MM complex can be removed from the subsurface by sorption into the organic/mineral mass. Complexation increases MM mobility, which increases plant bioavailability. MM can be subsequently removed by phytoextraction. Siderophores can also prevent MM uptake in plants and play the role of biocontainment agents. Siderophores mediate ROS production such as hydroxyl radicals ($\bullet\text{OH}$), which subsequently oxidises organic contaminants (OC) in the environment. Amphiphilic siderophores act as biosurfactants and increase the bioavailability of highly hydrophobic OC. Siderophores can also induce microbial resistance to OC.

siderophore production is affected by numerous factors (e.g. metal and metalloid concentrations), and does not guarantee the enhancement of metal and metalloid bioremediation. Furthermore, siderophores can increase the bioavailability of metals and metalloids in plants, thereby naturally increasing the phytoremediation efficiency (Jeong et al., 2014). Phytoextraction of metals and metalloids is often limited by the low bioavailability of the contaminants. Extensive research has been conducted on process optimisation to improve the bioavailability of metals and metalloids using synthetic chelating agents such as EDTA, ethylene glycol tetraacetic acid (AGTA), and diethylene triamine pentaacetic acid (DTPA) (Yan et al., 2020). However, synthetic compound-assisted phytoextraction has received increasing criticism due to its environmental persistence and associated risks of leaching (Römkens et al., 2002). Although some studies have indicated higher efficiency of synthetic compounds (Cornu et al., 2017), the use of siderophores avoids the potential for secondary environmental damage. However, siderophores-mediated increase in the concentrations of metal and metalloid bioavailability differ, and in certain cases, do not promote phytoextraction. In addition, in the bioremediation of metals and metalloids, siderophores play a role in the organic contaminant bioremediation.

These findings show that siderophores are important players in biologically driven processes in the subsurface. Therefore, its presence in the environment and its contribution to natural attenuation processes should be considered when designing remedial action. Currently, reduction in the “footprint” of remediation activities and thus the potential for secondary environmental damage has been emphasised. Coupling abiotic and biotic remediation processes can reduce the demand placed on the environment during the application of chemical agents to the subsurface (Honetschlägerová et al., 2019). In contrast, MOs can negatively affect the efficiency of chemical-based remediation methods (McGachy et al., 2021). Understanding the interactions between siderophores-producing MOs and chemical-based remediation methods is of considerable importance and of special interest. Additionally, the removal behaviours of TMM in co-exposure patterns with organic contaminants are expected to differ with individual patterns; therefore, knowledge about the effect of co-contaminants on siderophore-assisted bioremediation would help to establish successful and effective remediation.

CRediT authorship contribution statement

Zuzana Roskova: Writing – original draft, Investigation. **Radek Skarohlid:** Writing – original draft. **Lenka McGachy:** Conceptualization, Supervision, Investigation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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