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A Review of Important Bacterial Siderophores and their Potential Applications

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Abstract

Many environment have limited bioavailable iron, which leads to a variety of response strategies aimed at maintaining iron homeostasis Microorganisms, in particular, have specialized iron uptake system and frequently coordinate the synthesis and up take of iron with other cellular function like motility and biofilm formation. Microorganism produce and release low – molecular – weight compounds called siderophores in to the extracellular medium. these chelators have a high affinity and selectivity for Fe(III), making them a crucial component of an iron acquisition strategy. Sidrophores are often characterized as low – molecular – mass substances that chelate iron. Siderophores are more attracted to ferric iron than the majority of proteins. Through their role as iron-complexing ligands, they scavenge available iron and create a very stable ferric ion complex. This complex is know as Fe-siderophores complex or siderophores –iron ion complex.even if the precursor iron is present below the solubility limit, these siderophores –iron complex can stay in solution because they more soluble. Bacteria siderophres will be classified according to their chemical structure, including hydroxycarboxylates, hydroxamic acids, mixed ligands/hydroxamic acids, catecholates/metabolites, and keto acids/chelated metabolites, as well as their source, including surface-associated chelators on the bacterial envelope and released chelators. Example of siderophores Enterobactin it synthesized by Enterobacteriaceae and Pyoverdine produced by Pseudomonas species. bacteria siderophores have many application in several field, they have important role in bioremediation by removing heavy metal from environment and detection dissolving deleterious drugs and contaminants and in medical care, it help to killing or inhibiting pathogenic bacteria through strategies that limit iron acquisition within the host also as in agriculture it support plant growth via availability of iron that help of development and nutrition it.

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1. Introduction

In bacteria, iron is an essential nutrient because of its physiological roles and involvement in oxidative stress prevention. Many environments have limited bioavailable iron, leading to a variety of response strategies aimed at maintaining iron homeostasis. In particular, microorganisms have specialized iron uptake systems and often coordinate the synthesis and uptake of iron with other cellular functions such as motility and biofilm formation (Seyoum *et al*., 2021) [86] (Bosma *et al*.2021) [3]. Siderophores are low-molecular weight compounds produced and released into the extracellular medium by microorganisms. These chelators have high affinity and selectivity for Fe(III) and are therefore an essential part of an iron acquisition strategy (Khasheii *et al*., 2021) [32]. For this reason, the siderophore structure is often tightly coordinated in its biochemical properties with the regulatory, conformational, and extracellular export systems that these organisms use to govern the traffic of these compounds into the cell. Bacteria produce an impressive range of siderophores, many of which exhibit complex structures and have garnered attention from a biotechnological perspective (Khasheii *et al*., 2021) [32] (Timofeeva *et al*., 2022) [97]. This review aims to provide an overview of those siderophores that are most significant in nature and describes relevant applications where available. In this detailed review, we highlighted the most important produced or discovered siderophores in bacteria; we have discussed their structure and other functionalities when available, and mechanisms of action (Khasheii *et al*., 2021) [32] (Prabhakar, 2020) [70]. The review is organized to start by discussing the most used and best studied catechols followed by hydroxamic acids, salicylic acids, siderophore hijackers, and finally the other siderophores arranged in alphabetical order (Al *et al*. 2020).

1.1. Overview of Siderophores

As essential elements of bacterial metabolism, iron cations are required for the growth of bacteria. In many natural ecosystems, free iron concentration is one-third less than the concentration achieved for normal biological growth, thus resulting in "iron starvation." Consequently, the absorption of iron through bacterial cell membranes would be dramatically hampered, leading to reduced concentrations of iron within the cell cytoplasm (Dulay *et al*., 2020) [17] (Vinuesa & McConnell, 2021) [102]. In order to obtain the iron required for surviving in low iron environments, bacteria have developed a rapid and efficient technique known as the "siderophore-dependent iron absorption system." (Pu *et al*., 2023) [71] (Carsten, 2023) [7]

Siderophores are a group of highly effective iron-chelating compounds that are typically released into extracellular space by bacteria, where they scavenge ferric iron and are synthesized as a plastic backbone (which encompasses active functional groups such as hydroxyl, α-hydroxycarboxylates, catechol, and salicylate residues) (Drechsel and Winkelmann 2022) [16] (Khasheii *et al*., 2021) [32]. It is these functional groups that determine the affinity and selectivity to iron and incorporate a coordination center for iron transport to the bacterial cells. Through either a specified or nonspecified energy-dependent mechanism, iron-loaded siderophores are brought into the cell cytoplasm (Kirby *et al*. 2020) [35] (Hofmann *et al*. 2021) [26]. Siderophores are a chemically diverse group of compounds and are typically classified into four categories based on their structural features: hydroxamates, carboxylates, catecholates, and nickel-complexing group proteins (Timofeeva *et al*., 2022) [97] (Khasheii *et al*., 2021) [32]. The maximum number of natural siderophores and their related derivatives are ligands produced by amino acids to synthesize a ring-based structure. Because these compounds are of paramount and profound significance, several valuable and efficient bacterial siderophores have been commercialized or industrialized (Danyal *et al*. 2023) [14] (Kapoor *et al*. 2024) [29]. The biological environment is predominantly aqueous solutions with a neutral to acidic pH, resulting in the loss of the siderophoric ability due to the formation of insoluble hydroxides and microscopic ferric hydroxide colloid dispersal. Furthermore, the fine solubility of the ferric-siderophore will also be increased to allow intake into the bacterial cells via alternative pathways (Rajapaksha *et al*.2022) [75] (Lei *et al*. 2023) [48]. Active structures have been classified through a thermodynamic and kinetic system with bacterial siderophores. Siderophore production in bacteria leads to pleiotropic benefits, making wild-type strains produce and suitable for their own colonization on long-term biological substrates (Qin *et al*. 2020) [72]. Because of this, their competitive effect enhances the ecological and evolutionary value of bacterial siderophores (Kramer *et al*., 2020) [43] (Butaitė *et al*.2021) [4].

Siderophores are an extremely diverse group of compounds that perform a function that is chemically and mechanistically impressive (Singh *et al*. 2022) [90]. Until recently, there had been nearly 120 entries available for siderophores alone, with a large number of proteins that have the ability to utilize siderophores for their iron-binding functions (Drechsel and Winkelmann 2022) [16] (Klebba *et al*. 2021). These emphasize the importance of siderophores and have revealed numerous compounds or analogues that have potential applications. Enhancing our understanding of the structural and functional relationships of siderophores highlights numerous areas that should be considered important for future research (Fan & Fang, 2021) [19] (Soares, 2022) [92]. This is particularly relevant since to date, reviews in which various siderophore chemical classes and their medical application potential have been discussed in detail have only minimally mentioned the structural and/or specific electronic properties that are important for biological activity (Timofeeva *et al*., 2022) [97] (Khasheii *et al*., 2021) [32]. Understanding iron competition and structure-activity relationships is necessary to discover potent synthetic or natural chelators (Kontoghiorghes, 2024) [41].

1.2. Importance of Bacterial Siderophores

The presence of siderophores can bestow on their producing bacteria an impressive selective advantage against rival indigenous microbial populations and, hence, play a pivotal role in biocontrol and biofertilization applications. In fact, there is increasing potential for using the siderophores of non-pathogenic strains in so-called "microbe-microbe" biocontrol to replace or supplement chemical control agents (Lozano-González *et al*. 2023) [50] (Swarnalatha *et al*. 2022) [96]. Moreover, siderophores can be used in agriculture for the formulation of iron chelate fertilizers and in industry for the decontamination of metal-polluted environments (Sundaram *et al*. 2021) [95]. It is imperative to understand the environment in which these compounds operate, their roles in microbial life and competition, and inorganic chemistry, and additionally to develop new methods of application in the personal and commercial sectors (Schalk, 2024) [83]. It is apparent that bacterial growth is significantly affected by the lower availability of essential micronutrients. Among the essential micronutrients, iron has been the most carefully studied. Due to insolubility in its oxidized forms, the concentration of labile iron in various environments is often quite low, leading to iron shortage for microorganisms (Piskin *et al*. 2022) [68] (Meyer *et al*.2024) [55]. When natural habitats are microbially reduced or deoxygenated, the precipitation of iron as insoluble iron oxyhydroxides occurs. Thus, the strategies that these microorganisms have evolved to obtain iron are universally important for both ecological niche colonization and clinical relevance (Zhou *et al.*2022) [115] (Rose *et al.* 2024) [78]. The concentration of iron that is free to move or react in a neutral aqueous milieu is 10^−10 M. Because of iron's low solubility and, often, unavailability, bacteria have developed ways of scavenging iron from both inorganic and organic iron sources (Rocky *et al.* 2023) [77] (Kim & Kim, 2021) [33]. Catecholate- and hydroxamate-type siderophores, which have suitably low formation constants under biological conditions, are two kinds of the siderophores used by bacteria to access iron under almost anoxic and anoxic conditions (Timofeeva *et al.*, 2022) [97] (Soares, 2022) [92].

2. Biochemical Properties of Siderophores

Siderophores are widely conserved Fe3+-binding agents that are specifically and efficiently synthesized by microorganisms to scavenge ferrometabolites from their natural environments. According to the chemical functional groups coordinating with Fe3+, these molecules are classified as hydroxamates, catecholate, phenolates, or mixed ligands, including the tris catecholamine group (Klahn *et al.*, 2022) [38] (Schwabe, 2022) [84]. The structure of these molecules is important to achieve specific and strict Fe3+ recognition, as only ferric iron is required for all forms of life, and free (unferrated) siderophores are generally non-toxic (Kircheva & Dudev, 2020) [36] (Wang *et al.* 2021) [66]. Because it cannot be oxidized or reduced in solutions under standard redox conditions, the ferric ion is stable. Fe3+ transfers exactly one electron to the coordination sphere and remains unable to take part in Fenton or Haber-Weiss reaction chemistry (Huang *et al.* 2021) [27] (Wang *et al.* 2024) [105]. This crypticity of the ferric ion seems necessary to limit iron redox-cycling toxicity, and it is a relatively solvated and kinetically labile Fe3+ that siderophore molecules use as a complexing entity. Irrespective of their particular characteristics, all siderophores inspire researchers because they are versatile molecules (Pita-Grisanti *et al.* 2022) [69] (Manko, 2022) [52]. Many are stable at a broad range of pH, and some may exist in the presence of atmospheric O2 or with very high free metal status. Most of them express a containment ability to intercept ferric iron and are impervious to traditional chelator-mediated complex decomposition (Drechsel and Winkelmann 2022) [16] (Butler *et al.*2021) [5]. The microorganisms have evolved to produce siderophores with bi- and multifunctional activities according to the diverse niches they need to colonize. Some siderophores are more suitable for a soluble extracellular environment, while others are more advantageous in a regime with a tendency to flocculate or form volcanogenic deposits because of their lower solubility (Schalk, 2024) [83] (Kour *et al.* 2023) [42].

2.1. Chemical Structure

Siderophores, which were traditionally known as low-molecular-weight iron-chelating compounds, have various chemical structures depending on species, sequence type, and environmental factors (Timofeeva *et al.*, 2022) [97]. These molecular building blocks help siderophores protect iron from redox cycling, prevent the formation of insoluble iron hydroxides, and transport iron back to the closest cells (Venkataramani, 2021) [100] (Kermeur *et al.*, 2023) [31]. The structural information includes molecular weight, molecular formula, and a schematic structure with surrounding functional side chains (Yao *et al.*, 2023) [111] (Feng *et al.* 2021) [20]. The functional groups on some specific positions of the main matrix can have a significant impact on structure–function relationships, metal complex formation, or allocation specificities and possibilities (Ertl *et al.*, 2020) [18] (Qiu *et al.*, 2023) [72]. The siderophores are grouped into hydroxamates, catecholates, and mixons of different resulting states that originate from combinations of functional groups (Timofeeva *et al.*, 2022) [97]. Additionally, structural diversity is shown at sites that do not directly alter the iron-chelating functional groups on the moiety(s) (Jiang *et al.*, 2020) [114] (Zhang *et al.* 2023) [114].

The general impact of useful structural features, such as unique siderophore structures with high iron affinities or production-specific strains, is described (Timofeeva *et al.*, 2022) [97] (Schalk, 2024) [83]. The impact of products designed with a degree of structural tolerance is also described in some instances. In addition, there are probably a great number of siderophore derivatives with distinctive structure–function attributes designed in academia or recognized as side effects in biotechnology approaches that are not represented in this progress report (Timofeeva *et al.*, 2022) [97] (Drechsel and Winkelmann 2022) [16]. The degree of siderophore structure flexibility in relevant business areas like heavyweight industrial chemicals, non-nutritional iron supplementation for humans, and iron delivery in plants and environmental applications such as in situ groundwater remediation and soil doping is strongly dependent on the presence of surface ligands and on biocompatibility with dissimilar biological hosts, both macro- and microbiological, in terms of safety and policy conditions (Shankar and Akhter 2024) [87] (Laisney *et al.* 2022) [44].

2.2. Mechanism of Iron Acquisition

Siderophores are molecules of primary importance to bacteria, given that they function in the accretion of iron, which is required for many fundamental biological processes. Ferric ion is a cation that has low solubility in aerobic environments and neutral pH; hence, its relative unavailability for microorganisms. There are mainly three different ways bacteria have evolved to obtain iron: siderophore-mediated uptake systems, haem uptake systems, and siderophore-independent methods. Among these, the siderophore-mediated uptake systems are the most well-studied. (Ghssein & Ezzeddine, 2022) [23] (Wade *et al.* 2021) [104]

Siderophores, in general, can be defined as low-molecular-mass, iron-chelating compounds. Siderophores have a higher affinity for ferric iron than most proteins. They scavenge available iron via a process in which they function as iron-complexing ligands and form a very stable ferric ion complex (Rai *et al.*, 2020) [74] (Vijay *et al.*2023) [101]. This complex is referred to as a siderophore–iron complex or Fe–siderophore complex. These siderophore–iron complexes are more soluble, allowing them to remain in solution even if their precursor iron is present below the solubility limit (Drechsel and Winkelmann 2022) [16] (Schalk, 2024) [83]. Bacteria may then take up siderophore-bound ferric iron via specific receptor-mediated transport systems in a process known as iron piracy and utilize it for their own benefits (Weakland, 2020) [107] (Roth-Walter, 2022) [80]. The active uptake of siderophore-iron by bacteria in various environmental conditions, such as pH, is discussed in detail. The significance of understanding uptake is for the development of siderophore-based novel strategies to kill resistant bacteria. Pathogens are known to produce their own siderophores and even exploit the host iron sources through these siderophores (Khasheii *et al*., 2021) [32] (Kramer *et al*., 2020) [43].

3. Types of Bacterial Siderophores

Siderophores are low-molecular-weight chelators produced by virtually all organisms to increase iron uptake in order to maintain normal cell growth. Siderophores produced by bacteria are categorized into distinct chemical classes: phenolates, catecholates, mixed ligands/ammoniacals, carboxylates, hydroxamates, and keto acid-type siderophores. However, in this review, the classification of bacterial siderophores will be based on their chemical structures, such as mixed ligands/hydroxamic acids, hydroxycarboxylates, hydroxamic acids, hydroxycarboxylates, catecholates/metabolites, and keto acids/chelated metabolites, and by their source, such as released chelators and surface-associated chelators on the bacterial envelope (Timofeeva *et al*., 2022) [97] (Khasheii *et al*., 2021) [32]. The primary criteria for bacterial siderophore classification are the functional groups and the hydrophilic or hydrophobic properties of siderophores (Singh *et al*.2020) [91] (Mular *et al*.2024) [59].

Hydroxamates are classically considered fungal-origin siderophores, but bacteria also produce hydroxamic acid siderophores. Enterochelin is the best known among the mixed ligands siderophores. Catecholates/metabolites contain a metal ion either in the ortho or para configuration, i.e., the carboxyl side of the hydroxyl group is either cis or trans positioned around the aromatic hydroxyl group (Al *et al*.2020) (Timofeeva *et al*., 2022) [97]. Amphiphilic keto-siderophores are commonly called chelated metabolites, syndromes, chlamydial, cupriachelin, kestonbachelin, and aerobactin. The structural diversity of these keto acid-type siderophores is due to the disaccharide chain, and the fatty acid moiety can be esterified or amide-linked to the sugar ring(s) or the siderophore moiety. Bacteria also produce α-keto-siderophores, such as complexes with Fe, Mg, and Co, which are cytotoxic. The best known is aurichrysin. These iron-chelating siderophores can form various stable complexes. The high affinities pursued by the catechol and hydroxamate siderophores reflect the high iron solubility, the bioavailability of $Fe3+$ and $Fe2+$ in equilibrium expressed by the association constant in water (Kircheva *et al*., 2022) [37] (Munjal *et al*.2024) [61] (Pall *et al*.2024) [64]. These high stability fields of the siderophore/iron complexes indicate the siderophores' high potential for the sequestration of soluble iron in the environment in the cutaneous layer, biofilm, or extracellular bacterial colonies (Roskova *et al*., 2022) [79].

3.1. Enterobactin

Enterobactin is one of the most studied but not the easiest siderophores (Nodwell & Britton, 2020) [63]. It is the most potent siderophore synthesized by enterobacteriaceae, with a formation constant for iron(III) enterobactin around 1052 and very low dissociation kinetics, with values near $10{-}53\ M\ s{-}1$ (Yang, 2022) [110] (Drechsel and Winkelmann 2022) [16]. The structure of enterobactin starts with a hexamolecule formed by 3 molecules of L-2, 3-diaminopolypropionic acid, coupled with 1,2-diamino-3-hydroxycyclohexane, a derivative of serine, and closed with two salicylic acid moieties. The triple bonds of DAP or serine and hydroxyl groups are the main ligands for Fe(III) chelation. This complex is named α-enterobactin, due to a backbone cycle constituted by the diaminopropionic acid units (Martin, 2024) [53] (Ul-Ain *et al*., 2024) [99]. Enterobactin is a catecholate siderophore, as its salicylic moieties act as chelating ligands (Dhuldhaj & Pandya, 2021) [15]. The nature of the ligands and the enterobactin chelation cycle result in one of the lowest dissociation constants when reacted with free cells at very low iron levels. Subsequently, iron (III) or ferric-α-enterobactin is coordinated by Zur or Mur, which accumulates in the cytoplasm, starting an oxidative process that eliminates the ligands that are metabolized (Chen, 2020) [113] (Saha *et al*. 2020) [81].

The synthesis of enterobactin is triggered by very low iron media, and the repressor, the ferric uptake regulator, is inactivated, allowing sigma factors to promote the enterobactin genes. The genes of the biosynthesis of unity are organized into an operon named ent or fep for ferri-enterobactin of entero- (Casanova-Hampton *et al*. 2021) [8] (Mohite *et al*.2022) [58]. The bacteria that have the fep operon annotations do not show any difference from the others, and the former could miss any other operons. The synthesis includes about 20 proteins that mainly take a portion of DAP, L-serine, adenosine triphosphate, or 6-phospho-L-serine biosynthesized in the organism to take the first metabolite. It is assimilated by the synthesized 2,3-dihydro-2,3-dihydroxybenzoate (Chatterjee *et al*., 2021) [9] (Apostolos *et al*. 2020) [2].

3.2. Pyoverdine

Pyoverdine is one of the most well-known siderophores produced by the majority of Pseudomonas species. Structurally, pyoverdine belongs to the chromophoric pyoverdine system and consists of a trimeric acidic peptide synthesized by non-ribosomal peptide synthetases to which a special dihydroxyquinoline chromophore is covalently linked at the C-terminus (Ghssein & Ezzeddine, 2022) [23] (Liu *et al*. 2021) [49]. The chromophore confers the typical greenish fluorescence to aqueous pyoverdine solutions, which has been exploited to visualize the secretion and recapture of the siderophore in situ. The two hydroxyl groups of the pyoverdine chromophore are rather acidic, hence promoting a very efficient complexation of ferric iron with unmatched high siderophore affinity constants. Indeed, pyoverdine is the siderophore with the highest affinity for Fe(III) ever measured (Lear *et al*., 2022) [47] (Cunrath *et al*. 2020) [13]. Furthermore, the high redox potential of the chromophore-bound ferric iron enables the efficient reduction of Fe(III) to Fe(II) already in the outer membrane, which allows direct transport across the cytoplasmic membrane into the periplasm by pyoverdine recycling for further rounds of iron acquisition (Lueder *et al*.2020) [51] (Cui *et al*.2024) [12].

Pyoverdines are highly ecologically relevant since they not only serve to support bacterial populations under iron-limiting conditions frequently encountered in the environment, but also shape the composition and structure of soil and water bacterial communities due to their specific interaction with other environmental microorganisms (Tostado-Islas *et al*. 2021) [98] (Lozano-González *et al*. 2023) [50]. For example, due to iron competition in the rhizosphere, pyoverdine overproducers can promote the accumulation of particular Pseudomonas species, which can facilitate plant growth. Of note, several additional, structurally diverse pyoverdines may be produced by different isolates of P. fluorescens and P. aureofaciens, which may allow these strains to adapt to and colonize distinct ecological niches more effectively (Figueiredo *et al*., 2021) [21] (Figueiredo *et al*., 2021) [22]. In addition, pyoverdine-secreting Pseudomonas species may also produce and secrete additional iron-scavenging molecules, such as small amphiphilic siderophores. The clinical relevance of pyoverdine has been recently further underscored by studies that showed its ability also to modulate iron homeostasis during infections (Ghssein & Ezzeddine, 2022) [23] (Schalk & Perraud, 2023) [82].

4. Applications of Bacterial Siderophores

Bacterial siderophores find applications in diverse fields. They play very important roles in bioremediation, bringing about the degradation of xenobiotics. In biotechnology, they find applications in detecting and dissolving deleterious drugs and contaminants (Soares, 2022) [92] (Roskova *et al*., 2022) [79]. In medical care, they aid in attempting to fight infections caused by pathogenic bacteria. In agriculture, they also play a crucial role, as the availability of iron is essential for proper plant development and nutrition (Chinemerem *et al*.2022) (Yu *et al*.2020). Combining a fundamental understanding of siderophore function with the diverse applications will certainly lead to innovative insights and developments targeting important environmental and health issues (Xie *et al*., 2024) (Schalk, 2024) [83].

Perhaps of importance is the application of siderophores in bioremediation. Siderophores aid in removing elements like heavy metals that could potentially be harmful to animals that live in and rely on soils used for agricultural purposes or groundwater that provides drinking water (Roskova *et al*., 2022) [79] (Sundaram *et al*.2021) [95]. Siderophores have led to the development of biotechnology that can utilize siderophores for imaging (Soares, 2022) [92]. Naturally occurring siderophores conjugated to imaging agents can provide high-resolution images of processes in soil and systems. Researchers are developing genetically modified plants that are resistant to aluminum toxicity, which is the result of the accumulation of iron compounds (Lakshminarayanan *et al*. 2024) [45] (Peukert *et al*. 2021) [67].

4.1. Bioremediation

Although the role of bacterial siderophores in promoting environmental benefits is not as frequently addressed as that utilized in agriculture, there exists an interest in biomolecules from understudied species for other aims, particularly bioremediation. In this case, bacterial siderophores can aid in the mobilization of heavy metals or metal contaminants, initiating detoxification processes (Roskova *et al*., 2022) [79] (Mitra *et al*.2021) [57]. As will be discussed, the functioning of siderophores makes their use in environmental cleanup an alluring prospect (Vijay *et al*.2023) [101]. Their behavior in natural systems may also shed light on how best to use siderophores when designing bioremediation strategies (Patil *et al*. 2024) [65]. This section introduces the general principles and screening techniques associated with bioremediation (King *et al*., 2023) [34] (Ławniczak *et al*. 2020) [46]. Next, the role siderophores play in metal detoxification will be discussed, explaining the sequestration, facilitated transport, and microbial growth mechanisms employed (Pecoraro *et al*. 2021) [66]. Examples will be given highlighting the potential for siderophore assimilation in bioremediation, reflecting the success of biological remediation efforts utilizing siderophores (Sevak *et al*., 2021) [85] (Newsome & Falagán, 2021) [62]. The use of negibacteriales is associated primarily with the external application of siderophores, though bacterial isolates from other classes can be separately targeted for bioaugmentation based on their pollutant degradation potential or siderophore production. This section will also address a couple of case studies involving cleanup using identified siderophores and raises the question of what is considered an environmentally appropriate result in a number of these studies (Roskova *et al*., 2022) [79] (Gomes *et al*. 2024) [25] (Calderón *et al*.2023). Shifting towards more ecologically engineered applications, the implementation of siderophores in situ will be introduced, particularly with a discussion of the potential for siderophore degradation and/or inhibition to coincide with cleaner discharges of toxic compounds in ecosystems, these predictably beneficial results being a con of using siderophores as well as a reason ethically warranted under the "do no (further) harm" echelon (Yi *et al*.2024) (Hofmann *et al*.2021) [26]. A brief discussion on whether or not there is incentive to use or mix with other treatments will then be included, considering questions of synthetic efficiency (Koch *et al*., 2022) [40] (Kaul *et al*.2022) [30]. For example, while other operable options are discussed, Siderophore-Assisted Phytoremediation (SAP), one of this study's primary construction scenarios, is underscored for its fundamental natural benefit: it is truly bioethical and natural, subordinated to the nature of plant photosynthesis. The role of siderophores in terms of remediation does not directly follow the prior section concerning metal bioavailability (Roskova *et al*., 2022) [79] (Gomes *et al*. 2024) [25]. Rather, contextually, this gives the reader an entirely different perspective: the promotion of bacterial populations which can aid in and enhance the complete detoxification of metals and other pollutants (Mathivanan *et al*. 2021) [54].

4.2. Medical Applications

The discovery of the potential application of bacterial siderophores as a novel or ancillary therapy in medicine, especially for treating infectious diseases, has emerged in recent years (Miller & Liu, 2021) [49]. These siderophores are considered therapeutic agents; to be useful, they must be effective at inhibiting bacterial growth, inhibiting biofilm or the mobility of bacteria, or inhibiting the formation of toxins or other virulence factors (Khasheii *et al*., 2021) [32] (Ribeiro *et al*., 2022) [76]. Siderophores show these properties by targeting pathogenic bacteria through strategies that limit iron acquisition within the host (Khasheii *et al*., 2021) [32] (Kramer *et al*., 2020) [43]. They sequester iron from human or mammalian iron-binding proteins such as transferrin, lactoferrin, and ferritin, among others, and offer an alternative route of acquiring iron over human glycoproteins such as albumin, which represents 70% of the iron-binding capacity of mammalian plasma (Vogt *et al*.2021) [103] (Silva *et al*. 2021) [89].

A variety of drugs targeting bacterial proteins in the siderophore compensational system have been developed and demonstrated *in vitro* and in preclinical models to be potent iron acquisition inhibitors, anti-virulence agents, and/or antibacterials by enhancing the activity of antibiotics (Stelitano *et al*.2023) (Ribeiro *et al*., 2022) [76]. Not only synthetic but also several natural compounds based on hydroxamate or catecholate scaffolds effectively inhibit Gram-positive and Gram-negative pathogens (Al *et al*.2020) (Weng *et al*.2023). These siderophore-based compounds demonstrate the efficiency of diagnosis and treatment in several *in vitro* assays and preclinical disease models

(Khasheii *et al*., 2021) [32] (Mular *et al*.2024) [59]. Although most of these drugs are still in their early stages of development, they are regarded as potential alternatives to traditional antibiotics. The most extensively researched bacterium with regard to the development of siderophore-based drugs is A. baumannii. Currently, advanced and detailed reviews are describing promising A. baumannii siderophore exploitation in detail (Sheldon & Skaar, 2020) [88] (Song & Kim, 2020) [93].

5. Conclusion

The aim of this review was to offer an in-depth description of the most interesting and important types of bacterial siderophores currently being studied and to emphasize their importance in various scientific fields. The structural outline of this review has guided us through the standard biochemical properties of siderophores, their ecological significance, their relationships to good and bad bacteria, and their potential applications in regard to biotechnology and medicine. The presented work was supplemented by the results of studies, which allow this review to document the current state of knowledge and demonstrate the areas requiring further experiments. Despite the extensive achievements in siderophore research, it is becoming increasingly clear that a much more comprehensive adoption of interdisciplinary approaches could lead to the discovery that these compounds may be used for the benefit of humanity in a variety of other fields that were previously not under consideration. In conclusion, bacterial siderophores are extremely important substances not only from the point of view of iron acquisition but also in the context of interactions with other bacteria. Siderophores, thanks to their ability to form stable complexes with toxic metal ions, can also be useful in the bioremediation of heavy metal contaminated areas. Therefore, the establishment of research based on this hypothesis should lead to the discovery of additional siderophores using good bacterial strains.

References

1. Al Shaer D, Al Musaimi O, de la Torre BG, Albericio F. Hydroxamate siderophores: Natural occurrence, chemical synthesis, iron binding affinity and use as Trojan horses against pathogens. European Journal of Medicinal Chemistry. 2020;208:112791. Available from: csic.es
2. Apostolos AJ, Nelson JM, Silva JRA, Lameira J, Achimovich AM, Gahlmann A, *et al*. Facile synthesis and metabolic incorporation of m-DAP bioisosteres into cell walls of live bacteria. ACS Chemical Biology. 2020;15(11):2966-2975. Available from: nih.gov
3. Bosma EF, Rau MH, van Gijtenbeek LA, Siedler S. Regulation and distinct physiological roles of manganese in bacteria. FEMS Microbiology Reviews. 2021;45(6):fuab028. Available from: oup.com
4. Butaitė E, Kramer J, Kümmerli R. Local adaptation, geographical distance and phylogenetic relatedness: Assessing the drivers of siderophore-mediated social interactions in natural bacterial communities. Journal of Evolutionary Biology. 2021;34(8):1266-1278. Available from: oup.com
5. Butler A, Harder T, Ostrowski AD, Carrano CJ. Photoactive siderophores: structure, function and biology. Journal of Inorganic Biochemistry. 2021;221:111457. Available from: sciencedirect.com
6. Calderón Celis F, González-Álvarez I, Fabjanowicz M, Godin S, Ouerdane L, Lauga B, *et al*. Unveiling the Pool of Metallophores in Native Environments and Correlation with Their Potential Producers. Environmental Science & Technology. 2023;57(45):17302-17311. Available from: hal.science
7. Carsten A. Super-resolved and live visualization of Yersinia type three secretion system components. Frontiers in Microbiology. 2023. Available from: uni-hamburg.de
8. Casanova-Hampton K, Carey A, Kassam S, Garner A, Donati GL, Thangamani S, *et al*. A genome-wide screen reveals the involvement of enterobactin-mediated iron acquisition in Escherichia coli survival during copper stress. Metallomics. 2021;13(9):mfab052. Available from: oup.com
9. Chatterjee B, Mondal D, Bera S. Diaminopimelic acid and its analogues: Synthesis and biological perspective. Tetrahedron. 2021. [HTML]
10. Chen X. The Investigation of the Binding Affinity of Enterobactin Toward Metal Ions Via Density Functional Theory (DFT) Calculations. Journal of Molecular Modeling. 2020. [HTML]
11. Chinemerem Nwobodo D, Ugwu MC, Oliseloke Anie C, Al-Ouqaili MT, Chinedu Ikem J, Victor Chigozie U, *et al*. Antibiotic resistance: The challenges and some emerging strategies for tackling a global menace. Journal of Clinical Laboratory Analysis. 2022;36(9):e24655. Available from: wiley.com
12. Cui D, He H, Xie W, Yang S, Guo Z, Liao Z, *et al*. Occurrence and cycle of dissolved iron mediated by humic acids resulting in continuous natural photodegradation of 17α-ethinylestradiol. Journal of Hazardous Materials. 2024;465:133155. [HTML]
13. Cunrath O, Graulier G, Carballido-Lopez A, Pérard J, Forster A, Geoffroy VA, *et al*. The pathogen Pseudomonas aeruginosa optimizes the production of the siderophore pyochelin upon environmental challenges. Metallomics. 2020;12(12):2108-2120. Available from: hal.science
14. Danyal Y, Mahmood K, Ullah S, Rahim A, Raheem G, Khan AH, *et al*. Phytoremediation of industrial effluents assisted by plant growth promoting bacteria. Environmental Science and Pollution Research. 2023;30(3):5296-5311. [HTML]
15. Dhuldhaj U, Pandya U. Diversity, function, and application of fungal iron chelators (Siderophores) for integrated disease management. In: Role of Microbial Communities for Sustainability. 2021. [HTML]
16. Drechsel H, Winkelmann G. Iron chelation and siderophores. In: Transition Metals in Microbial Metabolism. CRC Press; 2022. p.1-49. [HTML]
17. Dulay H, Tabares M, Kashefi K, Reguera G. Cobalt Resistance via Detoxification and Mineralization in the Iron-Reducing Bacterium Geobacter sulfurreducens. Frontiers in Microbiology. 2020. Available from: frontiersin.org
18. Ertl P, Altmann E, McKenna JM. The most common functional groups in bioactive molecules and how their popularity has evolved over time. Journal of Medicinal Chemistry. 2020. [HTML]
19. Fan D, Fang Q. Siderophores for medical applications: imaging, sensors, and therapeutics. International Journal of Pharmaceutics. 2021. [HTML]

20. Feng F, Guo D, Shao Y, Yan X, Yue K, Pan Z, *et al*. Thickness control of 2D nanosheets assembled from precise side-chain giant molecules. Chemical Science. 2021;12(14):5216-5223. Available from: rsc.org.
21. Figueiredo ART, Wagner A, Kümmerli R. Ecology drives the evolution of diverse social strategies in Pseudomonas aeruginosa. Molecular Ecology. 2021. Available from: wiley.com
22. Figueiredo ART, Wagner A, Kümmerli R. Ecology drives the evolution of diverse siderophore-production strategies in the opportunistic human pathogen Pseudomonas aeruginosa. bioRxiv. 2021. Available from: biorxiv.org
23. Ghssein G, Ezzeddine Z. A review of Pseudomonas aeruginosa metallophores: Pyoverdine, pyochelin and pseudopaline. Biology. 2022. Available from: mdpi.com
24. Ghssein G, Ezzeddine Z. The key element role of metallophores in the pathogenicity and virulence of Staphylococcus aureus: A review. Biology. 2022. Available from: mdpi.com
25. Gomes AF, Almeida MC, Sousa E, Resende DI. Siderophores and metallophores: Metal complexation weapons to fight environmental pollution. Science of The Total Environment. 2024;173044. [HTML]
26. Hofmann M, Heine T, Malik L, Hofmann S, Joffroy K, Senges CHR, Tischler D. Screening for microbial metal-chelating siderophores for the removal of metal ions from solutions. Microorganisms. 2021;9(1):111. Available from: mdpi.com
27. Huang J, Jones A, Waite TD, Chen Y, Huang X, Rosso KM, Zhang H. Fe (II) redox chemistry in the environment. Chemical Reviews. 2021;121(13):8161-8233. Available from: nsf.gov
28. Jiang X, Zhou T, Bai R, Xie Y. Hydroxypyridinone-based iron chelators with broad-ranging biological activities. Journal of Medicinal Chemistry. 2020. [HTML]
29. Kapoor D, Sharma P, Sharma MMM, Yadav S, Husen A. Exploring soil microbiota and their role in plant growth, stress tolerance, disease control and nutrient immobilizer. Biocatalysis and Agricultural Biotechnology. 2024;103358. [HTML]
30. Kaul A, Klößner S, Pfeifer G, Schieler M. Standard synthetic control methods: The case of using all preintervention outcomes together with covariates. Journal of Business & Economic Statistics. 2022;40(3):1362-1376. [HTML]
31. Kermeur N, Pédrot M, Cabello-Hurtado F. Iron availability and homeostasis in plants: A review of responses, adaptive mechanisms, and signaling. Plant Abiotic Stress Signaling. 2023. [HTML]
32. Khasheii B, Mahmoodi P, Mohammadzadeh A. Siderophores: Importance in bacterial pathogenesis and applications in medicine and industry. Microbiological Research. 2021. Available from: sciencedirect.com
33. Kim YE, Kim J. ROS-scavenging therapeutic hydrogels for modulation of the inflammatory response. ACS Applied Materials & Interfaces. 2021. [HTML]
34. King RB, Sheldon JK, Long GM. Practical environmental bioremediation: The field guide. 2023. [HTML]
35. Kirby ME, Sonnenberg JL, Simperler A, Weiss DJ. Stability series for the complexation of six key siderophore functional groups with uranyl using density functional theory. The Journal of Physical Chemistry A. 2020;124(12):2460-2472. Available from: academia.edu
36. Kircheva N, Dudev T. Gallium as an antibacterial agent: A DFT/SMD study of the Ga3+/Fe3+ competition for binding bacterial siderophores. Inorganic Chemistry. 2020. [HTML]
37. Kircheva N, Toshev N, Dudev T. Holo-chromodulin: Competition between the native Cr3+ and other biogenic cations (Fe3+, Fe2+, Mg2+, and Zn2+) for the binding sites. Metallomics. 2022. [HTML]
38. Klahn P, Zscherp R, Jimidar CC. Advances in the synthesis of enterobactin, artificial analogues, and enterobactin-derived antimicrobial drug conjugates and imaging tools for infection diagnosis. Synthesis. 2022. [HTML]
39. lebba PE, Newton SM, Six DA, Kumar A, Yang T, Nairn BL, *et al*. Iron acquisition systems of gram-negative bacterial pathogens define TonB-dependent pathways to novel antibiotics. Chemical Reviews. 2021;121(9):5193-5239. [nih.gov]
40. Koch N, Naumann L, Pretis F, Ritter N, Schwarz M. Attributing agnostically detected large reductions in road CO2 emissions to policy mixes. Nature Energy. 2022. [ssrn.com]
41. Kontoghiorghes GJ. The importance and essentiality of natural and synthetic chelators in medicine: Increased prospects for the effective treatment of iron overload and iron deficiency. International Journal of Molecular Sciences. 2024. [mdpi.com]
42. Kour D, Kour H, Khan SS, Khan RT, Bhardwaj M, Kailoo S, *et al*. Biodiversity and functional attributes of rhizospheric microbiomes: potential tools for sustainable agriculture. Current Microbiology. 2023;80(6):192. [HTML]
43. Kramer J, Özkaya Ö, Kümmerli R. Bacterial siderophores in community and host interactions. Nature Reviews Microbiology. 2020. [nih.gov]
44. Laisney J, Chevallet M, Fauquant C, Sageot C, Moreau Y, Predoi D, *et al*. Ligand-promoted surface solubilization of TiO2 nanoparticles by the enterobactin siderophore in biological medium. Biomolecules. 2022;12(10):1516. [mdpi.com]
45. Lakshminarayanan K, Murugan D, Venkatesan J, Vasanthakumari Thirumalaiswamy H, Gadais C, Rangasamy L. Siderophore-conjugated antifungals: A strategy to potentially cure fungal infections. ACS Infectious Diseases. 2024;10(8):2448-2466. [HTML]
46. Ławniczak Ł, Woźniak-Karczewska M, Loibner AP, Heipieper HJ, Chrzanowski Ł. Microbial degradation of hydrocarbons—basic principles for bioremediation: A review. Molecules. 2020;25(4):856. [mdpi.com]
47. Lear L, Hesse E, Buckling A, Vos M. Copper selects for siderophore-mediated virulence in Pseudomonas aeruginosa. BMC Microbiology. 2022. [springer.com]
48. Lei X, Lian Q, Zhang X, Karsili TK, Holmes W, Chen Y, *et al*. A review of PFAS adsorption from aqueous solutions: Current approaches, engineering applications, challenges, and opportunities. Environmental Pollution. 2023;321:121138. [sciencedirect.com]
49. Liu Y, Dai C, Zhou Y, Qiao J, Tang B, Yu W, *et al*. Pyoverdines are essential for the antibacterial activity of Pseudomonas chlororaphis YL-1 under low-iron conditions. Applied and Environmental Microbiology. 2021;87(7):e02840-20. [asm.org]

50. Lozano-González JM, Valverde S, Montoya M, Martín M, Rivilla R, Lucena JJ, *et al*. Evaluation of siderophores generated by Pseudomonas bacteria and their possible application as Fe biofertilizers. Plants. 2023;12(23):4054. [mdpi.com]
51. Lueder U, Jørgensen BB, Kappler A, Schmidt C. Photochemistry of iron in aquatic environments. Environmental Science: Processes & Impacts. 2020;22(1):12-24. [au.dk]
52. Manko H. Spatio-temporal organization and regulation of enzymes involved in siderophore biosynthesis in Pseudomonas. HAL Science. 2022.
53. Martin RB. Complexes of α-amino acids with chelatable side chain donor atoms. Metal Ions in Biological Systems. 2024. [HTML]
54. Mathivanan K, Chandirika JU, Vinothkanna A, Yin H, Liu X, Meng D. Bacterial adaptive strategies to cope with metal toxicity in the contaminated environment–A review. Ecotoxicology and Environmental Safety. 2021;226:112863. [sciencedirect.com]
55. Meyer JS, Davison W, Sundby B, Oris JT, Laurén DJ, Förstner U, *et al*. Synopsis of discussion session: The effects of variable redox potentials, pH, and light on bioavailability in dynamic water-sediment environments. Bioavailability. 2024;155-170. [CRC Press]
56. Miller MJ, Liu R. Design and syntheses of new antibiotics inspired by nature's quest for iron in an oxidative climate. Accounts of Chemical Research. 2021. [nih.gov]
57. Mitra A, Chatterjee S, Kataki S, Rastogi RP, Gupta DK. Bacterial tolerance strategies against lead toxicity and their relevance in bioremediation application. Environmental Science and Pollution Research. 2021;28:14271-14284. [HTML]
58. Mohite OS, Lloyd CJ, Monk JM, Weber T, Palsson BO. Pangenome analysis of Enterobacteria reveals richness of secondary metabolite gene clusters and their associated gene sets. Synthetic and Systems Biotechnology. 2022;7(3):900-910. [sciencedirect.com]
59. Mular A, Hubmann I, Petrik M, Bendova K, Neuzilova B, Aguiar M, *et al*. Biomimetic analogues of the Desferrioxamine E siderophore for PET imaging of invasive aspergillosis: Targeting properties and species specificity. Journal of Medicinal Chemistry. 2024. [acs.org]
60. Mular A, Piasta K, Jedyńczuk A, Kamińska K, Olshvang E, Nolte NM, *et al*. The diversity and utility of arylthiazoline and aryloxazoline siderophores: Challenges of coordination chemistry, biological activity and selected applications. Coordination Chemistry Reviews. 2024;501:215551. [sciencedirect.com]
61. Munjal R, Kyarikwal R, Sarkar S, Nag P, Vennapusa SR, Mukhopadhyay S. A siderophore mimicking gelation component for capturing and self-separation of Fe (III) from an aqueous solution of mixture of metal ions. Inorganic Chemistry. 2024;63(15):7089-7103. Available from: [HTML].
62. Newsome L, Falagán C. The microbiology of metal mine waste: bioremediation applications and implications for planetary health. GeoHealth. 2021. Available from: wiley.com.
63. Nodwell MB, Britton R. Enterobactin on a bead: parallel, solid phase siderophore synthesis reveals structure–activity relationships for iron uptake in bacteria. ACS Infectious Diseases. 2020. Available from: [HTML].
64. Pall AE, Bond S, Bailey DK, Stoj CS, Deschamps I, Huggins P, *et al*. ATH434, a promising iron-targeting compound for treating iron regulation disorders. Metallomics. 2024;16(10):mfae044. Available from: [HTML].
65. Patil A, Chakraborty S, Yadav Y, Sharma B, Singh S, Arya M. Bioremediation strategies and mechanisms of bacteria for resistance against heavy metals: a review. Bioremediation Journal. 2024:1-33. Available from: [HTML].
66. Pecoraro L, Wang X, Shah D, Song X, Kumar V, Shakoor A, *et al*. Biosynthesis pathways, transport mechanisms and biotechnological applications of fungal siderophores. Journal of Fungi. 2021;8(1):21. Available from: mdpi.com.
67. Peukert C, Langer LN, Wegener SM, Tutov A, Bankstahl JP, Karge B, *et al*. Optimization of artificial siderophores as 68Ga-complexed PET tracers for *in vivo* imaging of bacterial infections. Journal of Medicinal Chemistry. 2021;64(16):12359-12378. Available from: acs.org.
68. Piskin E, Cianciosi D, Gulec S, Tomas M, Capanoglu E. Iron absorption: factors, limitations, and improvement methods. ACS Omega. 2022;7(24):20441-20456. Available from: acs.org.
69. Pita-Grisanti V, Chasser K, Sobol T, Cruz-Monserrate Z. Understanding the potential and risk of bacterial siderophores in cancer. Frontiers in Oncology. 2022;12:867271. Available from: frontiersin.org.
70. Prabhakar PK. Bacterial siderophores and their potential applications: a review. Current Molecular Pharmacology. 2020. Available from: [HTML].
71. Pu D, Zhao J, Chang K, Zhuo X, Cao B. “Superbugs” with hypervirulence and carbapenem resistance in Klebsiella pneumoniae: the rise of such emerging nosocomial pathogens in China. Science Bulletin. 2023. Available from: sciencedirect.com.
72. Qin H, Liu Y, Cao X, Jiang J, Lian W, Qiao D, *et al*. RpoS is a pleiotropic regulator of motility, biofilm formation, exoenzymes, siderophore and prodigiosin production, and trade-off during prolonged stationary phase in Serratia marcescens. PLoS One. 2020;15(6):e0232549. Available from: plos.org.
73. Qiu C, Jiang L, Gao Y, Sheng L. Effects of oxygen-containing functional groups on carbon materials in supercapacitors: A review. Materials & Design. 2023. Available from: sciencedirect.com.
74. Rai V, Fisher N, Duckworth OW, Baars O. Extraction and detection of structurally diverse siderophores in soil. Frontiers in Microbiology. 2020. Available from: frontiersin.org.
75. Rajapaksha AU, Selvasembian R, Ashiq A, Gunarathne V, Ekanayake A, Perera VO, *et al*. A systematic review on adsorptive removal of hexavalent chromium from aqueous solutions: Recent advances. Science of the Total Environment. 2022;809:152055. Available from: [HTML].
76. Ribeiro M, Sousa CA, Simões M. Harnessing microbial iron chelators to develop innovative therapeutic agents. Journal of Advanced Research. 2022. Available from: sciencedirect.com.
77. Rocky MMH, Rahman IM, Biswas FB, Rahman S, Endo

M, Wong KH, *et al*. Cellulose-based materials for scavenging toxic and precious metals from water and wastewater: A review. Chemical Engineering Journal. 2023;472:144677. Available from: [HTML].

78. Rose KC, Ferrer EM, Carpenter SR, Crowe SA, Donelan SC, Garçon VC, *et al*. Aquatic deoxygenation as a planetary boundary and key regulator of Earth system stability. Nature Ecology & Evolution. 2024;8(8):1400-1406. Available from: [HTML].
79. Roskova Z, Skarohlid R, McGachy L. Siderophores: an alternative bioremediation strategy?. Science of the Total Environment. 2022. Available from: [HTML].
80. Roth-Walter F. Iron-deficiency in atopic diseases: innate immune priming by allergens and siderophores. Frontiers in Allergy. 2022. Available from: frontiersin.org.
81. Saha P, Yeoh BS, Xiao X, Golonka RM, Abokor AA, Wenceslau CF, *et al*. Enterobactin induces the chemokine, interleukin-8, from intestinal epithelia by chelating intracellular iron. Gut Microbes. 2020;12(1):1841548. Available from: tandfonline.com
82. Schalk IJ, Perraud Q. Pseudomonas aeruginosa and its multiple strategies to access iron. Environ Microbiol. 2023. Available from: wiley.com
83. Schalk IJ. Bacterial siderophores: diversity, uptake pathways and applications. Nat Rev Microbiol. 2024. Available from: hal.science
84. Schwabe R. Metallophores from selected actinobacteria for metal extraction and phytomining of strategic elements. QuCosa.de. 2022. Available from: qucosa.de
85. Sevak PI, Pushkar BK, Kapadne PN. Lead pollution and bacterial bioremediation: a review. Environ Chem Lett. 2021. Available from: [HTML]
86. Seyoum Y, Baye K, Humblot C. Iron homeostasis in host and gut bacteria–a complex interrelationship. Gut Microbes. 2021. Available from: tandfonline.com
87. Shankar G, Akhter Y. Molecular insights into ferric-siderophore transport by the putative TonB-dependent transporter in Mycobacterium tuberculosis. J Biomol Struct Dyn. 2024;1-18. Available from: [HTML]
88. Sheldon JR, Skaar EP. Acinetobacter baumannii can use multiple siderophores for iron acquisition, but only acinetobactin is required for virulence. PLoS Pathog. 2020. Available from: plos.org
89. Silva AM, Moniz T, de Castro B, Rangel M. Human transferrin: An inorganic biochemistry perspective. Coord Chem Rev. 2021;449:214186. Available from: sciencedirect.com
90. Singh P, Chauhan PK, Upadhyay SK, Singh RK, Dwivedi P, Wang J, *et al*. Mechanistic insights and potential use of siderophores producing microbes in rhizosphere for mitigation of stress in plants grown in degraded land. Front Microbiol. 2022;13:898979. Available from: frontiersin.org
91. Singh P, Khan A, Kumar R, Kumar R, Singh VK, Srivastava A. Recent developments in siderotyping: procedure and application. World J Microbiol Biotechnol. 2020;36:1-15. Available from: researchgate.net
92. Soares EV. Perspective on the biotechnological production of bacterial siderophores and their use. Appl Microbiol Biotechnol. 2022. Available from: [HTML]
93. Song WY, Kim HJ. Biochemical understanding regarding the metabolism of acinetobactin, the major siderophore of the human pathogen Acinetobacter baumannii, and outlook for its applications. Nat Prod Rep. 2020. Available from: [HTML]
94. Stelitano G, Cocorullo M, Mori M, Villa S, Meneghetti F, Chiarelli LR. Iron acquisition and metabolism as a promising target for antimicrobials (bottlenecks and opportunities): where do we stand? Int J Mol Sci. 2023;24(7):6181. Available from: mdpi.com
95. Sundaram L, Rajendran S, Subramanian N. Metal stress impacting plant growth in contaminated soil is alleviated by microbial siderophores. In: Role of Microbial Communities for Sustainability. 2021. p. 317-332. Available from: [HTML]
96. Swarnalatha GV, Goudar V, Reddy ECRG, Al Tawaha ARM, Sayyed RZ. Siderophores and their applications in sustainable management of plant diseases. In: Secondary metabolites and volatiles of PGPR in plant-growth promotion. 2022. p. 289-302. Available from: [HTML]
97. Timofeeva AM, Galyamova MR, Sedykh SE. Bacterial siderophores: Classification, biosynthesis, perspectives of use in agriculture. Plants. 2022. Available from: mdpi.com
98. Tostado-Islas O, Mendoza-Ortiz A, Ramírez-García G, Cabrera-Takane ID, Loarca D, Pérez-González C, *et al*. Iron limitation by transferrin promotes simultaneous cheating of pyoverdine and exoprotease in Pseudomonas aeruginosa. The ISME J. 2021;15(8):2379-2389. Available from: nih.gov
99. Ul-Ain Q, Das S, Nguyen N, Poduska B, McAuliffe M, Franks M, *et al*. A library of copper-peptide/peptidomimetic complexes to explore the effect of ligand framework modification on electrocatalytic water oxidation. ChemRxiv. 2024. Available from: chemrxiv.org
100. Venkataramani V. Iron homeostasis and metabolism: two sides of a coin. In: Ferroptosis: Mechanism and Diseases. 2021. Available from: [HTML]
101. Vijay K, Shibasini M, Sivasakthivelan P, Kavitha T. Microbial siderophores as molecular shuttles for metal cations: sources, sinks and application perspectives. Arch Microbiol. 2023;205(9):322. Available from: google.com
102. Vinuesa V, McConnell MJ. Recent advances in iron chelation and gallium-based therapies for antibiotic resistant bacterial infections. Int J Mol Sci. 2021. Available from: mdpi.com
103. Vogt ACS, Arsiwala T, Mohsen M, Vogel M, Manolova V, Bachmann MF. On iron metabolism and its regulation. Int J Mol Sci. 2021;22(9):4591. Available from: mdpi.com
104. Wade J, Byrne DJ, Ballentine CJ, Drakesmith H. Temporal variation of planetary iron as a driver of evolution. Proc Natl Acad Sci USA. 2021;118(51):e2109865118. Available from: pnas.org
105. Wang H, Liu Y, Li Y, Xu X, Liu X, Yao Y, *et al*. Tactics for boosting the desalination stability of capacitive deionization. Chem Eng J. 2024;153808. Available from: [HTML]
106. Wang Z, Wang H, Cheng X, Geng J, Wang L, Dong Q, *et al*. Aptamer-superparamagnetic nanoparticles capture coupling siderophore-Fe3+ scavenging actuated with carbon dots to confer an “off-on” mechanism for the ultrasensitive detection of Helicobacter pylori. Biosens

Bioelectron. 2021;193:113551. Available from: [HTML]
107. Weakland D. Investigating the Contribution of Iron Acquisition to Serratia marcescens Pathogenesis during Bloodstream Infection. Univ Mich. 2020. Available from: umich.edu
108. Weng C, Tan YLK, Koh WG, Ang WH. Harnessing transition metal scaffolds for targeted antibacterial therapy. Angew Chem Int Ed. 2023;62(50):e202310040. Available from: wiley.com
109. Xie B, Wei X, Wan C, Zhao W, Song R, Xin S, Song K. Exploring the Biological Pathways of Siderophores and Their Multidisciplinary Applications: A Comprehensive Review. Molecules. 2024. Available from: mdpi.com
110. Yang T. Characterization of iron acquisition catalyzed by Fiu. 2022. Available from: [HTML]
111. Yao ZF, Wang JY, Pei J. Controlling morphology and microstructure of conjugated polymers via solution-state aggregation. Prog Polym Sci. 2023. Available from: [HTML]
112. Yi S, Wei M, Li F, Liu X, Fan Q, Lu H, Zhang M. In-situ enrichment of ARGs and their carriers in soil by hydroxamate siderophore: A promising biocontrol approach for source reduction. Environ Int. 2024;190:108915. Available from: sciencedirect.com
113. Yu T, Jiang G, Gao R, Chen G, Ren Y, Liu J, *et al*. Circumventing antimicrobial-resistance and preventing its development in novel, bacterial infection-control strategies. Expert Opin Drug Deliv. 2020;17(8):1151-1164. Available from: tandfonline.com
114. Zhang L, Guan Q, Jiang J, Khan MS. Tannin complexation with metal ions and its implication on human health, environment and industry: An overview. Int J Biol Macromol. 2023;253:127485. Available from: [HTML]
115. Zhou N, Kupper RJ, Catalano JG, Thompson A, Chan CS. Biological oxidation of Fe(II)-bearing Smectite by microaerophilic iron oxidizer Sideroxydans lithotrophicus using dual Mto and Cyc2 iron oxidation pathways. Environ Sci Technol. 2022;56(23):17443-17453. Available from: acs.org