Microbiological Research 250 (2021) 126790

Contents lists available at ScienceDirect

Microbiological Research

journal homepage: www.elsevier.com/locate/micres

Siderophores: Importance in bacterial pathogenesis and applications in medicine and industry

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ARTICLE INFO

Keywords:
Siderophore
Trojan horse
Iron
Pathogenesis
Cancer
Medicine
Industry

ABSTRACT

Iron is an essential element for all microorganisms. Siderophores are low-weight, high-affinity iron chelating molecules produced in response to iron deficiency by Gram-positive and Gram-negative bacteria which also known as essential virulence factors of bacteria. Several studies have indicated that defective production and/or function of these molecules as well as iron acquisition systems in pathogens are associated with a reduction in pathogenicity of bacteria. Because of their potential role in various biological pathways, siderophores have been received special attention as secondary metabolites. Siderophores can detect iron levels in a variety of environments with a biosensor function. In medicine, siderophores are used to deliver antibiotics (Trojan horse strategy) to resistant bacteria and to treat diseases such as cancer and malaria. In this review, we discuss the iron acquisition pathways in Gram-positive and -negative bacteria, importance of siderophore production in pathogenesis of bacteria, classification of siderophores, and main applications of siderophores in medicine and industry.

1. Introduction

Iron is an essential element that plays a vital role in the cellular reactions. This element is involved in the biological processes such as tricarboxylic acid cycle (TCA cycle), electron transfer chain, oxidative phosphorylation, nitrogen fixation, and biosynthesis of aromatic compounds. It also participates in the generation of metabolic products including porphyrins, toxins, antibiotics, cytochrome, pigments and siderophores, and the production of the mentioned substances is therefore, influenced by increasing or decreasing iron levels (Fardeau et al., 2011). Peroxidase, catalase, and certain forms of superoxide dismutase enzymes that contribute to the cell maintenance by eliminating harmful radicals also contain iron. Besides, the iron cations act as cofactors for several other enzymes which in turn affect cell composition. In case of iron deficiency, DNA and/or RNA synthesis is reduced and bacterial growth and sporogenesis are also inhibited leading to morphological changes in bacteria. For example, iron in *Escherichia coli* is required for the activity of B2 ribonucleotide phosphate reductase subunit which is responsible for the synthesis of deoxyribonucleotides and DNA synthesis. During iron deficiency, DNA and RNA synthesis is decreased in *Mycobacterium smegmatis*, and under severe iron deficiency, DNA synthesis is arrested causing structural changes of tRNA molecule in *Bacillus subtilis* (Messenger and Barclay, 1983). Iron has been shown to be involved in the virulence of pathogenic bacteria by the fact that several virulence factors are regulated by the iron level. Shiga toxin (*Shigella*), Shiga-like toxin (*Enterohemorrhagic E. coli*), Diphtheria toxin (*C. diphtheriae*) and exotoxin A (*Pseudomonas aeruginosa*) are directly regulated by iron concentration or through iron response regulators (Litwin and Calderwood, 1993). Bacteria show various phenotypical and genotypical changes in biofilm structure and thereby the concentration range of growth factors requirement, including iron, is different for growth in planktonic and biofilm states. In fact, they need less iron in the biofilm state than in the planktonic state both *in vitro* and *in vivo* (Weinberg, 2004).

Furthermore, some studies have shown that iron is essential for the formation of bacterial biofilms, because it controls surface activities and

Abbreviations: PMA, phorbol myristate acetate; NETs, Neutrophil extracellular traps; ROS, Reactive oxygen species; TfR, transferrin receptor; DMT-1, divalent metal transporter 1; FPN, ferroportin; HIF-1α, Hypoxia-inducible factor 1-alpha; TOMM20, Translocase of Outer Mitochondrial Membrane 20; TIMM23, Mitochondrial Import Inner Membrane Translocase Subunit Tim23; LC3, Microtubule-associated protein 1A/1B-light chain 3; p62, Nucleoporin p62; PINK1/Parkin, PTEN-induced kinase 1; BNIP3, BCL2 interacting protein 3; UPEC, Uropathogenic Escherichia coli; UTI, urinary tract infection; OM, outer mmembrane; GTP, Guanosine-5′-triphosphate; ATP, Adenosine triphosphate; Fur, ferric uptake regulator.

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https://doi.org/10.1016/j.micres.2021.126790
Received 22 February 2021; Received in revised form 14 May 2021; Accepted 24 May 2021
Available online 27 May 2021

stabilizes the polysaccharide matrix (Chhibber et al., 2013). Under iron deficiency conditions, the hydrophobicity of microbial surface decreases and the composition of surface proteins changes leading to a restriction in the formation of biofilms (Simões et al., 2007). In an experiment performed by Massonet et al. (2006), the effect of iron on the expression of iron-related genes (sirR, sitABC operon), involved in the formation of biofilm structures in the planktonic and sessile conditions was studied on *Staphylococcus epidermidis* both *in vitro* and *in vivo,* and the results showed that in the planktonic form, the bacterium produces siderophores in medium with limited iron and grows more slowly in this environment than in iron-rich environment. But at high concentrations of iron (25 μM $FeCl_3$), sirR expression was increased in the early stages of bacterial incubation and the expression of sirR in the planktonic state was not different *in vitro* in the medium without Fe or with 1 μM $FeCl_3$ iron concentration. However, in the sessile form, *in vitro* sirR expression was high and not dependent on the iron concentration (Massonet et al., 2006). *In vitro* studies have also shown that the expression of genes from sitABC operon in planktonic bacteria is affected by iron and manganese concentrations (Hill et al., 1998). In 2012, Lin et al. showed that PGG (1, 2,3,4,6-Penta-O-galloyl-b-D-glucopyranose) could chelate iron and after the addition of iron to the medium containing PGG, the expression of iron-regulated genes was increased in *S. aureus* SA113 cells grown in the medium and they were able to form biofilm. These results indicated that iron is needed for the formation of biofilms by *S. aureus* SA113 (Lin et al., 2012). Bacteria require nearly 10^{-6} mol/L concentration of iron for their growth. In other words, 1μM or higher concentrations of iron are needed to support bacterial growth and reproduction (Raymond et al., 2003). The level of cytosolic free iron is adjusted to about 10 μM to be sufficient for cellular processes, since higher concentration is toxic to the cell (Keyer and Imlay, 1996). When bacteria uptake sufficient iron from the extracellular environment, they can have stored iron in intracellular iron-storage proteins (*e.g.* bacterioferritins, ferritins, and Dps proteins), and use it when they are in iron deficiency (Tosha et al., 2010). One of the major pathways for iron uptake and bacterial survival under iron-restricted conditions is the production of low-weight iron chelating molecules for iron absorption, which are called siderophores, as well as the expression of receptors with high affinity for uptake of iron or siderophore-iron complexes (Lankford and Byers, 1973). In bacterial cells, iron acquisition is regulated by Fur box (for ferric uptake regulation) in iron concentration-dependent process (Crosa et al., 2004). At high concentrations of iron, siderophore synthesis is ceased due to the binding of Fur protein to the promoter of siderophore-producing genes (Sandy and Butler, 2009). Whereas, at low concentrations of iron, Fur proteins are separated from the Fur box, and transcription and translation processes are performed from genes involved in siderophore synthesis (De Serrano, 2017). Siderophores are low molecular weight molecules (600−1000 Da) with high affinity for ferric ions (Fe^{3+}) but low affinity for ferrous ions (Fe^{2+}), which are produced by bacteria in response to iron deficiency and their production is suppressed in the presence of iron. Siderophores are produced extracellularly and turn iron into a soluble and absorbable form (Messenger and Barclay, 1983). Although the primary task of siderophores is to explore iron, but they can also complex with other essential elements such as Mo, Mn, Co, and Ni to make these metals available to microbes (Ahmed and Holmström, 2014). Iron uptake by siderophores is even essential during infections caused by many pathogenic agents since the erosion of this system significantly reduces the ability of pathogens to colonize the host (Holden and Bachman, 2015). Siderophores not only contribute to iron uptake from insoluble hydroxide forms but also acquire iron from ferric citrate, ferric phosphate, ferric transferrin, iron bound to plant flavonoid pigments, sugars and glycosides (Winkelmann, 2002). Several reports have indicated a strong effect of Fe^{3+} concentration on the production of siderophores by Gram-positive bacteria such as *Micrococcus luteus* and *Bacillus silvestris* (Cabaj and Kosakowska, 2009). Microorganisms like *Escherichia coli* not only use their own siderophores but also take the advantage of the siderophores secreted by other microorganism *e.g.* fungi. Siderophores are involved in ligand exchange reaction, as reported in the case of *Aeromonas hydrophila*, in which iron is swapped from a ferric-siderophore to a receptor bound iron free siderophore. This mechanism of ligand exchange occurs at cell surface by siderophores (Stintzi et al., 2000). Different types of siderophores have been discovered in Gram-positive *Actinobacteria*. *Streptomyces* species as Gram-positive members of *Streptomycetaceae* produce Desferrioxamine G, B, and E, and *Mycobacterium tuberculosis* synthesizes extracellular siderophores such as carboxymycobacterin and exochelin (Winkelmann, 2002). It should be noted that in addition to microorganisms, other organisms such as phytoplanktons and cyanobacteria have the ability to generate siderophores (Ahmed and Holmström, 2014).

2. Iron acquisition systems in Gram-positive and Gram-negative pathogenic bacteria

Both Gram-positive and Gram-negative bacteria produce siderophores under the iron deficiency conditions (Chu et al., 2010). Gram-negative bacteria have outer membrane protein receptors that detect specific Fe^{3+}-siderophore complexes on the cell surface. Ferric-siderophore complexes are actively transported through the cell membrane, which is an energy-dependent system consisting of outer membrane siderophore protein receptors, periplasmic binding proteins, and inner membrane transport proteins (Winkelmann, 2002). As shown in Fig. 1, a common mechanism involves the recognition of iron-containing siderophores by β-barrel receptors on the outer membrane in Gram-negative bacteria. After ligand binding, the receptors undergo structural changes and the iron-bearing siderophore is transported to the periplasmic space, a process supported by TonB complex which consists of TonB, ExbB, and ExbD proteins and supplies energy through proton motive force (PMF). The transfer of iron-containing siderophore to the cytosol, where iron reduction occurs, is typically mediated by ATP-binding cassette (ABC) transporters within the inner membrane (Faraldo-Gómez and Sansom, 2003; Krewulak and Vogel, 2008; Schalk and Guillon, 2013). Although the TonB, ExbB, and ExbD proteins are found in many Gram-negative bacteria, they are best known in *E. coli* cells. In this bacterium, the energy transfer process requires direct contact between TonB and OM (outer membrane) receptors (Krewulak and Vogel, 2008; Garcia-Herrero et al., 2007). TonB has three domains. Residues 1–33 form the amino terminal domain and anchor to the inner membrane to act as an interaction site with ExbB-ExbD proteins. Residues 34–154 with Pro-Glu and Pro- Lys repeats form the central domain in the periplasm space, and residues 155–239 make the D-carboxyterminal domain located in the periplasm. Residues 155–239 interact with the N-terminal region of ferric siderophore receptors on the outer membrane (Chakraborty et al., 2007). The expression level of TonB protein increases under the iron-restricted conditions (Wiener, 2005). ExbB is a 26-KDa cytoplasmic membrane protein containing three transmembrane domains and its structure is not yet fully understood. ExbD is a 17-kDa protein that has topological similarity to TonB protein and has a transmembrane domain as well as a periplasmic domain with 90 amino acids (Krewulak and Vogel, 2008; Garcia-Herrero et al., 2007). Although *E. coli* has only one TonB-ExbB-ExbD system, some bacteria have more than one system. For example, *Vibrio cholerae* contains two TonB proteins: TonB1 and TonB2, which appear to show specificity for different OM receptors (Mey and Payne, 2001). It seems that outer membrane receptors enhance ferric-siderophore uptake, enabling bacteria to effectively search for ferric-siderophore in the surrounding environment (Braun et al., 1998; Furrer et al., 2002). The siderophore receptors on the outer membrane are generally expressed by iron starvation and are not typically present under the iron deficiency conditions. An important reason for this phenomenon may be the targeting of OM receptors as s gateway into bacterial cells by bacteriophages, colicins and antibiotics. *E. coli* K-12 has at least six OM receptors that allow access to eight iron chelation complexes, from which four (coprogen, ferrichrome, ferrioxamine, and rhodotorulic acid) are

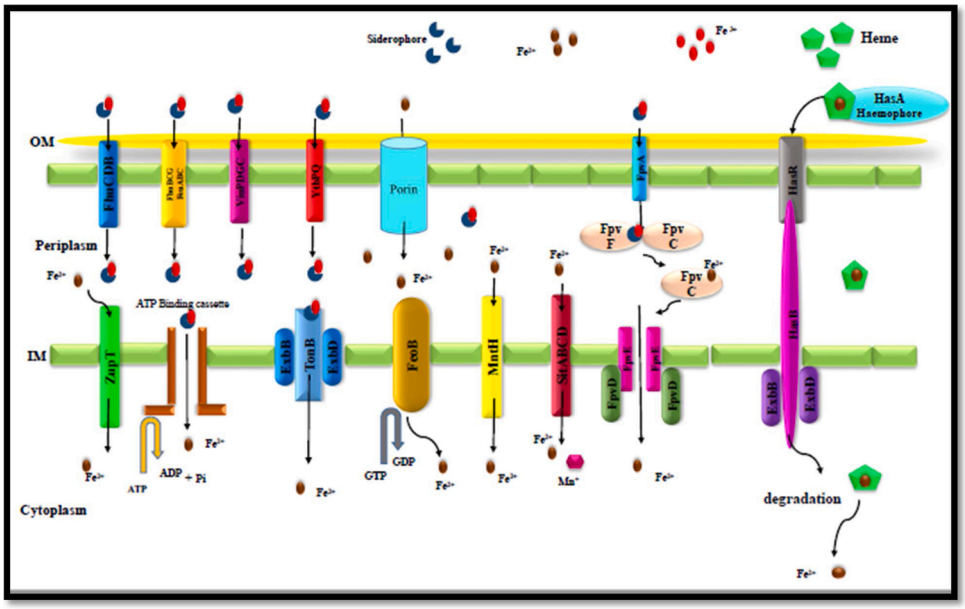

Fig. 1. Iron acquisition systems with or without siderophore mediation in Gram-negative bacteria. Transfer of ferric-siderophores through fhuCDB / ViuPDGC / YtbPQ / fhuBCG-feuABC in *Escherichia coli* (FeoABC, SitABCD, MntH, EfeUOB, and ZupT are capable of importing ferrous iron), *Serratia marcescens* (heme transfer through HasA / HasR / HasB), and *Pseudomonas aeruginosa* (iron uptake is mediated by FpvR, FpvA, and PvdS proteins).

produced externally, *i.e.* by other organisms (Andrews et al., 2003). FeABC and fhuBCG belong to ABC superfamily transmit hydroxymate siderophores of Gram-negative bacteria (Chakraborty, 2013; Locher and Rosenbusch, 1997; Wyckoff et al., 2015). Diffusion of ferri-siderophore complex through periplasm and cytoplasmic membrane requires a specific binding protein that acts as a shuttle. These binding proteins (including FhuD) collect the ferri-siderophore released from the outer membrane receptors and deliver it to a permease such as ABC permease in the inner membrane; two mechanisms have been described for the release of iron from ferric-siderophore complex in Gram-negative bacteria. The first mechanism involves hydrolysis of the complex in *E. coli* so that with the introduction of ferri-siderophore complex, the ester bond in this complex is hydrolyzed by *fes* gene, releasing iron and producing dihydroxybenzoyl serine that acts as a weak siderophore (Stintzi et al., 2000; Köster, 2001). The second mechanism includes the reduction of ferric iron to ferrous, which has lower affinity for the siderophore (Matzanke et al., 2004). At least five transporters in *E. coli*, namely FeoABC, SitABCD, MntH, EfeUOB, and ZupT are capable of importing ferrous iron (Snyder et al., 2004; Hantke, 2003; Kammler et al., 1993; Cao et al., 2007; Makui et al., 2000), among which the SitABCD system is specifically associated with UPEC (Uropathogenic *Escherichia coli*) virulence. Sit is present in two widely used model strains of UPEC (UTI89 and CFT073), and its expression increases during bladder infection in experimental models (Snyder et al., 2004). The Sit system is encoded by the genes present in *Salmonella* Pathogenicity Island 1 (SPI-1) and is required to infect mice (Kehres et al., 2002). In the absence of oxygen there is iron in soluble form (Fe^{2+}), which can be removed directly by the bacteria (Beauchene et al., 2017). When oxygen is present, iron is oxidized to an insoluble form (Fe^{3+}) and the uptake of ferric iron requires the synthesis and secretion of chelator molecules such as siderophores. In fact, due to the effect of oxygen on the oxidation state of iron, Fur controls the expression of ferrous and ferric iron uptake pathways and the expression of Fur regulon is dependent on the input oxygen and is felt physiologically (Andrews et al., 2013; Beauchene et al., 2017). High concentrations of metals disrupt cellular functions, damage DNA and cell membrane, and alter enzymatic properties (Bruins et al., 2000). Genes encoding metal transporters must be highly regulated in bacteria *via* Fur box, because metals such as iron are toxic to bacteria at high concentration. The suppression of iron transport systems in environments with high concentrations of iron, is a good way to reduce the toxicity of this metal (Porcheron et al., 2013). The general changes in the expression of Fur regulon under anaerobic conditions with sufficient iron concentration, switch the expression of iron transport systems from Fe^{3+} to Fe^{2+} and allow *E. coli* to use the most appropriate physiological form of iron. Transfer of ferrous iron to bacteria is associated with its growth under anaerobic, microaerophilic and low pH conditions (Beauchene et al., 2017). In Gram-negative bacteria, ferrous iron passes freely through the outer membrane purines. Therefore, ferrous iron can enter the periplasm and thus cytoplasm through various transport systems (Ge and Sun, 2012). Also, Fe^{2+} can be transmitted by inner membrane ATP-Binding Cassette (ABC) transporters (Klein and Lewinson, 2011). Accordingly, in the absence of siderophore, Fe^{2+} can be transported by ATP-Binding Cassette (ABC) transporters or outer membrane purines (please see the Fig. 1). Different systems are required to transfer ferrous iron, however, ferrous iron transfer systems are less well known than ferric iron (Lau et al., 2016). The FeoABC system was first discovered in *E. Coli* K-12 living in anaerobic conditions (Hantke, 1987). In a number of Gram-positive bacteria such as *Bacillus anthracis*, *Staphylococcus aureus*, and *Listeria monocytogenes*, homology to the FeoAB system (Fe^{2+} uptake) has been identified. But the function of this system in Gram-positive bacteria is less known (Ledala et al., 2010, 2014). The enterobacterial ferrous iron transport system consists of three FeoABC genes. *feo*A is a small soluble cytoplasmic protein with SH2 domain in the cytosol. The *feo*B cytoplasmic membrane protein contains G protein domain in the N-terminal part as well as C-terminal domain in the inner membrane and consists of two Gate motifs responsible for transferring ferrous iron across the cytoplasmic membrane *via* active ATP/GTP transportation and indeed has a similar function to Fe^{2+} permease. *feo*C is a small protein that almost acts as an iron-dependent transcription repressor (Cartron et al., 2006). In microaerophilic *H. pylori* bacteria, *feo*B appears to provide the major route of iron uptake that is required for the colonization of *H. pylori* in gastric mucosa of mice as well as for normal growth and iron absorption under iron-limited conditions (Velayudhan et al., 2000). *feo*B is also required for the intracellular growth of *Legionella pneumophila* (Robey and Cianciotto, 2002). In *Pseudomonas*, iron uptake is mediated by FpvR, FpvA, and PvdS proteins (Lamont et al., 2002). After forming a ferri-pyoverdine complex, there is interaction with the cell surface

receptor of FpvA, part of which in turn interacts with the FpvR in the periplasm. In this way, PvdS triggers a signaling cascade and activates RNA polymerase. Transcription begins with pyoverdine, which again binds ferric iron. The activity of *pvdS* gene is controlled by Fur, an iron sensitive suppressor protein enabling *pvdS* transcription only in conditions of iron starvation (Cunliffe et al., 1995). Furthermore, bacteria can acquire heme iron from different media and transfer it to specific receptors on outer membrane through the expression of outer membrane receptors and specific transport proteins for heme and/or the secretion of hemophores (specific bacterial proteins) (Tong and Guo, 2009). Recently, it has been reported that the crystalline structures of HasA hemophore from *Serratia marcescens* bind HasR protein receptors on the outer membrane (Krieg et al., 2009). Gram-negative bacteria, particularly *Haemophilus influenzae*, *Neisseria meningitides*, and *Actinobacillus* (*Haemophilus*) *pleuropneumoniae*, are able to receive iron directly from iron-bearing proteins of their hosts *via* expressing outer membrane protein receptors for lactoferrin and transferrin (Cornelissen, 2003; Ekins et al., 2004).

Iron is taken from these proteins through direct contact between the bacterial surface and proteins binding the host iron. The binding of transferrin and lactoferrin is species-specific. For example, only human forms of these proteins are identified and used as a source of iron by *Neisseria* species (Gray-Owen and Schyvers, 1996). *Yersinia pestis*, on the other hand, obtains iron from hemoglobin and inorganic transporters using siderophores (Perry et al., 1999). In Gram-positive bacteria (Fig. 2), ferric-siderophore complexes are also detected by specific membrane protein receptors and transported to the cytoplasm by ABC transporter proteins (Brown and Holden, 2002). ViuPDGC and FhuCDB, from ABC transporter superfamily, transfer hydroxymate siderophores to Gram-positive bacteria (Miethke et al., 2006). YbtPQ and IrtAB transporter proteins from ABC transporter superfamily transfer carboxylate siderophores to Gram-negative and Gram-positive bacteria, respectively (van der Heide and Poolman, 2002). Chemical tests have shown that *Staphylococcus* species produce siderophores, especially under limited iron conditions. These siderophores include staphyloferrin A and B, and *Staphylococcus aureus* also produces a siderophore known as aurochelin (Courcol et al., 1997; Haag et al., 1994). Transferrin can be the main substrate of these siderophores during infection because staphyloferrin A removes iron from transferrin (Kuroda et al., 2001). In addition to producing siderophores, *Staphylococcus aureus* can use human transferrin as an iron source (Lindsay et al., 1995), and *Neisseria* species, *Staphylococcus aureus* and *Staphylococcus epidermidis* can directly bind transferrin to their cell walls (Modun et al., 1998). SstABCD, an ABC iron transporter in *Staphylococcus aureus*, is similar to ABC transporters for siderophore uptake in Gram-negative bacteria (Morrissey et al., 2000). A research has shown that Pia and Piu transport systems are needed for iron uptake by *Streptococcus pneumoniae*, indicating that they have a redundant function because the loss of one of them can be compensated by the other; however, the loss of both significantly affects the growth and virulence of bacteria (Brown et al., 2001).

Corynebacterium diphtheriae has at least three different iron uptake systems: a siderophore, an inorganic iron and a hemoglobin/hemin uptake mechanism. The use of transferrin by *C. diphtheriae* seems to be dependent upon the siderophore, whereas it is not reliant on the use of hemin and hemoglobin (Schmitt, 1997). In *Listeria monocytogenes*, direct binding to transferrin and ferric citrate as well as ferrous iron uptake have been reported (Adams et al., 1990; Hartford et al., 1993). A ferric reductase enzyme, reducing ferric iron to ferrous iron either outside the cell or at the bacterial surface, has been described in this bacterium (Cunliffe et al., 1995). This enzyme seems to be involved in the second step in acquiring iron from catecholamines, transferrin or other iron sources (Coulanges et al., 1997). *Listeria monocytogenes* can use catecholamines as a source of iron, an unusual ability that can explain the tropism of this pathogen for the central nervous system (Schmitt, 1997). The fate of siderophores after iron release is not well understood. In some cases, siderophores can be recovered through special recycling mechanisms (Imperi et al., 2009; Jones et al., 2014).

3. The importance of siderophore production in the pathogenesis of bacteria

Pathogenic factors encompass a wide range of substances such as bacterial toxins, adhesion factors, protective capsules, and siderophores that contribute to the colonization of pathogens in the host and increase the severity of disease (Soares and Weiss, 2015). Microbes have developed strategies for obtaining Fe from their host (Weinberg, 2009; Cassat and Skaar, 2013), which involve the expression of siderophores taking Fe from proteins bound to the host Fe (Diaz-Ochoa et al., 2014; Contreras et al., 2014). Deletion of genes regulating siderophore expression or other Fe harvesting systems is often associated with reduced virulence of pathogens, including infectious bacteria such as *Salmonella* and

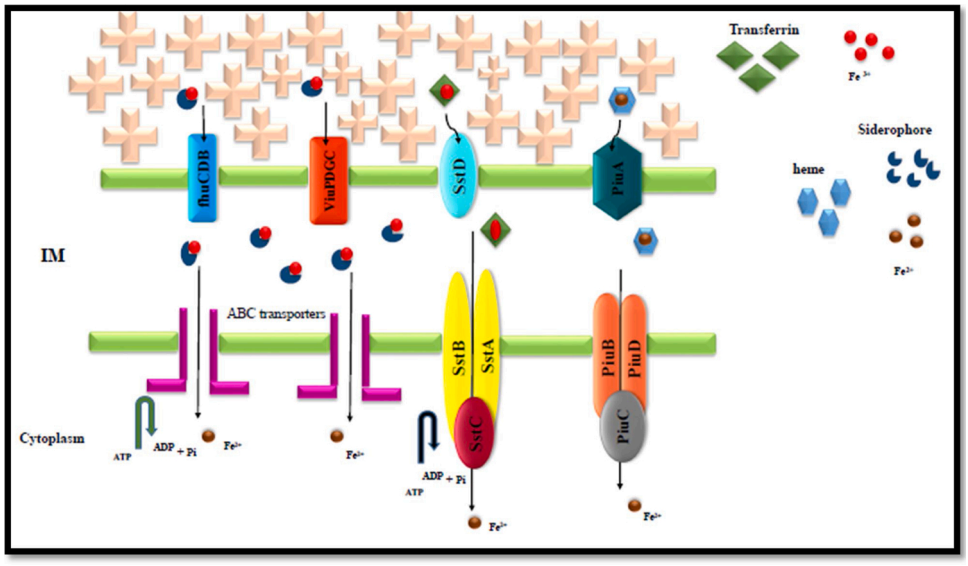

Fig. 2. Iron acquisition systems with or without siderophore mediation in Gram-positive bacteria. Transfer of ferric-siderophores through FhuCDB / ViuPDGC in *Streptococcus pneumoniae* (heme uptake is mediated by PiuA, PiuB-D, and PiuC proteins), and *Staphylococcus aureus* (transferrin transfer through SstD, A, B, and C proteins).

Staphylococcus (Cassat and Skaar, 2013; Andrews-Polymenis et al., 2010). In fact, strains that can produce more siderophores are highly virulent (Russo et al., 2011), and those unable to synthesize and secrete siderophore are less capable of virulence and colonization during infection (Codoner et al., 2006; Caza et al., 2011). Both Gram-positive and Gram-negative bacteria produce siderophores under iron deficiency (Chu et al., 2010; Khan et al., 2018). Bacterial siderophores can have potent cellular effects on the host by disrupting the iron homeostasis of organelles, activating transcription pathways and influencing cellular behavior. Recently, it has been shown that iron chelation directs cells toward mitophagy, namely controlled mitochondrial autophagy (Allen et al., 2013). In addition to causing mitophagy, bacterial siderophores can induce a hypoxic reaction in host cells even under normoxic conditions *via* stabilizing HIF-1α in the hos (Hartmann et al., 2008). HIF-1α upregulates many genes including molecules affecting the immune system such as antimicrobial peptides and inflammatory cytokines, and is a major regulator of cellular responses to hypoxic conditions as well (Semenza, 2011; Palazon et al., 2014).

Siderophores can act as a toxin and modulator of the immune system, but it is not known whether the activation of host pathways such as HIF-1α-regulated gene expression is eventually beneficial to the host or bacterium (Jin et al., 2018). In a 2020 study by Wang et al. concerning the effect of siderophores produced by *Klebsiella pneumonia* (enterobactin, yersiniabactin, salmochelin, and aerobactin) on mitophagy-associated proteins (p62, LC3, TIMM23, and TOMM20), signaling proteins (BNIP3 and PINK1/Parkin) and apoptotic protein (caspase3) and ROS levels, the results showed that all four siderophores produced at 10μM concentration enhanced the expression of LC3-II, induced the expression of mitochondrial membrane proteins TOMM20 and TIMM23 and increased ROS and caspase3 levels in platelets. Meanwhile, enterobactin siderophore has a significant effect on the increase of LC3-II and also activates mitophagy pathways in platelets (Wang et al., 2020). The production of siderophores can affect the anatomical site and infection pattern. In mouse models of pneumonia, the infection of wild-type mice with Ybt^{+} strains of *Klebsiella pneumoniae* (yersiniabactin) caused bronchopneumonia with moderate bacterial density in the lungs and spleen (Bachman et al., 2012). In bacteria such as *Acinetobacter baumannii*, siderophore is an essential compound for binding to surfaces and synthesis of extracellular polysaccharides for the formation of biofilms as well as microbial communities with sufficient iron mutualism (Harrison and Buckling, 2009; Gaddy et al., 2012). *Pseudomonas aeruginosa* produces two siderophores: pyoverdine and pyochelin. Pyochelin production is associated with biofilm formation, a feature of *P. aeruginosa* leading to chronic lung infections in patients with cystic fibrosis (Mossialos and Amoutzias, 2009). Pyoverdine, a *Pseudomonas* siderophore, is toxic to the mitochondria of *Caenorhabditis elegans* (a free-living transparent nematode), leading to mitochondrial fragmentation and loss of mitochondrial membrane potential, which causes cell and organ death (Kirienko et al., 2013). Siderophores can have protective effects against reactive oxygen species (ROS) caused by UV rays or antibiotic stresses (Gaddy et al., 2012). For example, pyoverdine produced by *Pseudomonas* bacteria absorbs extracellular UV radiation, thereby reducing ROS generation (Burke et al., 1990). UPEC strains produce four different types of siderophores, including enterobactin catecholate and salmochelin, aerobactin hydroxamate, and yersiniabactin (Henderson et al., 2009). The ability of *E. coli* to produce urinary tract infection (UTI) is significantly affected by siderophore. Competitive infection models in mice have revealed that non-catecholate siderophore receptors play an important role in the formation of bacterial colonies in progressive UT infections (Garcia et al., 2011). In UPEC, the salmochelin receptor IroN is involved in colonization of the urinary tract (Feldmann et al., 2007). and can be a factor invading urethral cells (Russo et al., 2002). Negre et al. (2004) showed that IroN is a key factor in the pathogenicity of *Escherichia coli* strains responsible for neonatal meningitis (Nègre et al., 2004). The production of salmochelin siderophore is mostly associated with urinary isolates and can be an important factor in the development of infection recurrence or resistance in urinary tract (Henderson et al., 2009). The production of aerobactin is a specific epidemiological indicator among UPEC strains, and studies have shown that the presence of aerobactin siderophore increases the progression of *E.coli* growth under limited iron conditions in serum and urine. Human UPEC strains causing symptomatic UTIs express higher aerobactin levels (49 %≤) than peripheral and fecal isolates (Johnson, 1991). In the study conducted by Khasheii et al. (2016) on iron uptake of UPEC strains in M9 medium, the results showed that the UPEC strains, which had the siderophore-encoding genes for yersiniabactin (*irp2*) and aerobactin (*iucA*), were more capable of absorbing iron in the minimum medium and had a higher growth rate in that environment (Khasheii et al., 2016). Saha et al. in 2017 reported that enterobactin (Ent), the catecholate siderophore expressed by *Escherichia coli*, inhibited the PMA (phorbol myristate acetate) produced by reactive oxygen species (ROS) as well as neutrophil extracellular traps (NETs) in mouse and human neutrophils. Ent also reduces the degranulation of primary granules, and inhibits phagocytosis and antibacterial activity of neutrophils without affecting their migration and chemotaxis (Saha et al., 2017). In another study performed by Saha et al. in 2019, it was shown that enterobactin (Ent) chelator is an advantage for the survival of *Salmonella*, which can chelate LIP (labile iron pool) inside the cell, disturbing the effective iron-dependent mechanisms in macrophages (Saha et al., 2019b). Yersinia species such as *Yersinia pestis*, the causative agent of bubonic plague, produce yersiniabactin siderophore (Chambers and Sokol, 1994). The yersiniabactin gene cluster is regulated by YbtA (a member of the AraC family of transcriptional regulators) and Fur repressor (ferric uptake regulator) (Rakin et al., 2012; Anisimov et al., 2005). In an infectious model of pneumonic plague, the absence of Ybt reduced the virulence of intranasal infection by *Yersinia pestis* (Fetherston et al., 2010).). Deletion of both genes (*psn* or *irp2*) involved in yersiniabactin biosynthesis leads to the disappearance of *Y. pestis* virulence in mice, highlighting the role of siderophore in pathogenicity of this bacillus (Haag et al., 1993). Bacterial iron homeostasis is highly regulated to achieve sufficient iron levels and accordingly, the expression of iron absorption systems is limited to environments in which there is no iron storage (Sheldon and Heinrichs, 2015; Andrews et al., 2003). In the gastrointestinal tract, the main source of iron comes from the diet (Stein et al., 2010), there is a gradient of iron in the gastrointestinal tract and the maximum concentration of iron is found in the intestinal lumen that decreases towards the mucosa. In the large intestine, total iron concentrations have been reported to be 4–5 times lower than the lumen contents (Li et al., 2015). Only 15 % (2 mg) of dietary iron is absorbed in the duodenum, and the remainder is delivered to the large intestine, despite the high concentration of iron (~ 25 mmol/L) in the large intestine, only a small part (~ 0.4 mmol) of it can be used by bacteria due to the limited solubility of inorganic iron in a non-acidic environment (Lund et al., 1998; Dev and Babitt, 2017). The presence of lactoferrin, transferrin, and defense proteins in the large intestine limits iron in this site. Therefore, bacteria have to synthesize siderophores and express membrane receptors to obtain iron from these proteins (Xiao et al., 2017).

The amount of iron required for *Vibrio* varies depending on the cell physiology and metabolism. Concentrations between 0.1 and 0.5 μM of iron are sufficient for *Vibrio* growth *in vitro* (Ju et al., 2006). To obtain iron, *Vibrio cholerae* uses vibriobactin siderophore and transmits Vibriobactin *via* the outer membrane receptors ViuA (Butterton et al., 1992; Henderson and Payne, 1994), or through direct heme uptake because of haemolysin production which lyses intestinal epithelial cells (Henderson and Payne, 1994). *V. cholera* has three heme receptors designated as HutA, HutR, and HasR (Mey and Payne, 2001).

3.1. Classification of siderophores based on chemical structure

More than 500 siderophores have been identified since the discovery of the first three siderophores, namely mycobactin, ferrichrome and

coprogen from 1949 to 1952 (Hider and Kong, 2010). Bacterial siderophores are divided into three major families based on the chemical groups involved in iron binding (Fig. 3): catecholates, hydroxamates, and carboxylates (Crumbliss and Harrington, 2009), and siderophores with mixed ligands that are classified into four groups of catecholate hydroxymate, phenolate hydroxymate, citrate catecholate and citrate hydroxymate. All families use negatively charged oxygen atoms to bind ferric iron, but each family has different properties that affect its affinity for iron (Miethke and Marahiel, 2007).

3.1.1. Catecholate type siderophores

This type of siderophore is only found in bacteria (Paul and Dubey, 2014). The main catecholate siderophores include enterobactin, bacillibactin, and vibriobactin (Hider and Kong, 2010). Enterobactin is a cyclic trimer of 2,3-dihydroxybenzoyl-L-serine isolated from various intestinal and pathogenic bacteria like *E. coli* (Raymond et al., 2003). Salmochelin is the glycosylated form of enterobactin containing two glucose-bearing catecholes in C-5 position that is isolated from uropathogenic *Escherichia coli* and *Salmonella enterica* (Raymond et al., 2003; Bister et al., 2004). The catecholate group of siderophores also forms an hexadentate octahedral complex by taking two oxygen atoms to chelate iron (Saha et al., 2016). Bacillibactin, which is isolated from *Bacillus subtilis* and other *Bacillus* species, has a tri-ester ring with an L-threonine scaffold, each threonine amine is added to the glycine bound to 2,3-dihydroxybenzoic acid (Dertz et al., 2006).

3.1.2. Hydroxymate type siderophores

This type of siderophore is mostly produced by fungi as well as by a number of filamentous Gram-positive bacteria such as *Streptomyces*. It has secondary C (= O) N- (OH) R groups, where R is an amino acid or its derivative that is responsible for chelating iron. Each hydroxymate group provides two oxygen atoms forming a two-way ligand with iron. The first group of these siderophores is ferrichrome produced by the fungus *Ustilago sphaerogena* (Messenger and Barclay, 1983). Other hydroxamate siderophores are hydroxamate, desferrioxamine B, E, and G (Dhungana et al., 2001), aerobactin (actually bearing citrate and hydroxymate groups), ferribactin released by *Pseudomonas fluorescens*, as well as gonobactin and nocobactin generated by *Neisseria gonorrhea* and *Neisseria meningiditis*. Desferrioxamine B (DFOB) is a desferrioxamine administered to treat iron overload diseases like beta-thalassemia major (Neilands, 1981).

3.1.3. Carboxylate type siderophores

These siderophores are a new class that is neither hydroxamate nor catecholate type, instead they have carboxylic structure and are produced by both bacteria and fungi. The best example of this type of siderophores is the structure of rhizobactin, which is generated by *rhizobium*. It has ethylenediamine D-carboxylic acid and hydroxycarboxyl structure as an iron chelator. Staphyloferrin A is released by *Staphylococcus hyicus* and is a member of this family having D-ornithine and two citric acids connected by two amide bonds (Henderson and Payne, 1994; Schwyn and Neilands, 1987). At acidic pH, carboxylate siderophores are more successful at chelating ferric iron relative to catecholate and hydroxylate types; therefore, carboxylate siderophore is useful for microorganisms living in acidic environments. However, it is predicted that carboxylate siderophores are inhibited in competition with catecholate siderophores in exploration of iron in human blood and serum (Miethke and Marahiel, 2007).

3.1.4. Mixed type siderophores

Among the mixed siderophores having carboxylate-hydroxymate groups, aerobactin has been reported in pathogenic strains of *E. coli*, *Shigella flexneri*, and *Klebsiella pneumoniae*. Yersiniabactin has moderate affinity for iron and includes phenolate, thiazole, oxazoline, and carboxylate groups for binding to iron (Crumbliss and Harrington, 2009). Parabactin and carboxymycobactin are mixed siderophores that contain oxazoline rings (Ratledge and Dover, 2000).

4. Application of siderophores

4.1. Use of siderophores in drug delivery

Resistance to antibiotics is a global health concern and a threat to modern medicine and society (Cornelis and Andrews, 2010). The growing problem of bacterial antibiotic resistance necessitates discovery and production of new antibiotics (Schalk et al., 2012). Microorganisms

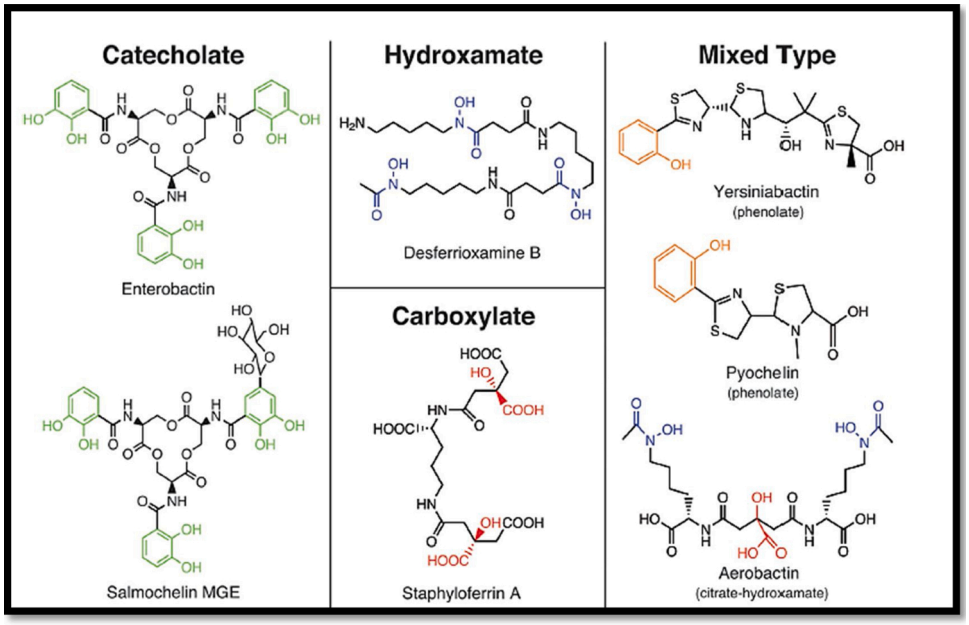

Fig. 3. Structure of siderophores produced by Gram-positive and Gram-negative bacteria. Siderophores are divided into three main structural families: catecholate, hydroxamate and carboxylate. Binding groups in green (catechol), blue (hydroxymate), red (carboxylate), and orange (phenolate) in mixed siderophores (Crumbliss and Harrington, 2009).

such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecium*, *Staphylococcus aureus*, *Acinetobacter baumannii*, and *Enterobacteriaceae* species are a serious threat to the health system (Pendleton et al., 2013). This group consists of Gram-positive and Gram-negative pathogenic bacteria that can cause antibiotic-resistant and potentially fatal infections (Tommasi et al., 2015). The cell wall of Gram-negative bacteria contains an additional outer membrane significantly preventing permeability and efficacy of many antibiotics (Zgurskaya et al., 2015). One approach to counteracting such resistance is to use iron transport systems of these bacteria (Anderson et al., 2012). Siderophores are particularly valuable for bypassing membrane-associated drug resistance using the iron transport capacity to deliver drugs into cells *via* siderophore-conjugated antibacterial agents with Trojan horse approach (Miller et al., 2009; Mollmann et al., 2009).

As depicted in Fig. 4, the antibiotic molecule engages siderophore as a "Trojan horse" transporter and enters into microbial cell using the Fe-siderophore harvesting system. Conjugated drugs usually contain a linker to bind the drug to siderophore, which allows for controlled chemical or enzymatic release of the drug into the target bacterial cell. Once inside the cell, the drug-siderophore conjugate kills the cell by releasing the drug, acting as a complete antibacterial agent, or preventing further iron uptake (Nagoba and Vedpathak, 2011).

The siderophore-antibiotic conjugate is of two types: natural and synthetic. Natural siderophore-antibiotic compounds are albomycin, ferrimycin, salmycin (isolated from *Streptomyces* and *Actinomyces*), and microcin (isolated from intestinal bacteria). For example, albomycin blocks protein synthesis *via* inhibiting t-RNA synthetases in *E. coli*. Synthetic siderophore-antibiotic compounds take advantage of antibiotic with better cell permeability and weaken the resistance mechanisms. In the synthetic model, siderophores can bind potent antibiotics such as beta-lactam antibiotics (carbacephalosporins), erythromycin, sulfonamides, vancomycin, nalidixic acid, norfloxacin and so on. The findings show that these conjugates give better results and that the siderophore-mediated drug transfer is highly significant. Microbes identify siderophore as the transporter of iron, so the conjugated compound is absorbed, killing the bacterium because the conjugated compound is lethal to the microbe (Miethke and Marahiel, 2007; Ding et al., 2008; Kinzel et al., 1998). Catecholate and hydroxymate siderophores are commonly used to deliver antibacterial drugs; however, carboxylate siderophores such as staphyloferrin can be a good choice for treatment regimens (Saha et al., 2016). The hydrophilic property of staphyloferrin A improves the rate of drug delivery to bacterial cells by increasing the water solubility (Milner et al., 2013). Recently, several siderophores conjugated to β-lactam antibiotics have been investigated in the pre-clinical and clinical stages, including MC-1 (monocarbam), BAL30072 (monosulfactam) (Coates et al., 2011), S-649,266 (cephalosporin) (Ito et al., 2016), and GSK3342830 (cephalosporin), which target multidrug-resistant Gram-negative bacteria including *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Santajit and Indrawattana, 2016).

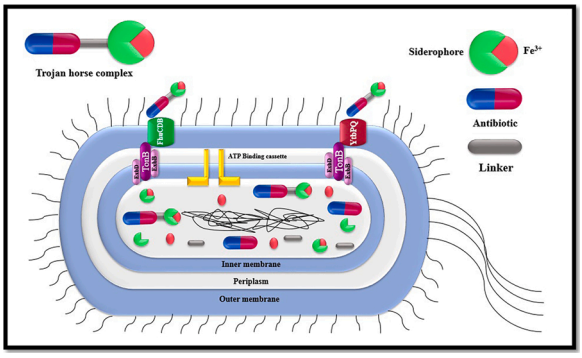

Fig. 4. Trojan horse strategy for drug (antibiotic) delivery into the antibiotic-resistant bacterial cells. In this process, siderophore is linked to the drug by a linker and siderophore-drug conjugate enters the cell through membrane receptors. After entering the cell, the linker is hydrolyzed and the drug is released into the cytoplasm and exerts its effects.

Cefiderocol (S-649,266) is a cephalosporin-catechol conjugate that is currently in phase III clinical trial, which uses active iron-mediated transport and has been more potent against multi-drug resistant (MDRs) Gram-negative pathogens (Negash et al., 2019). In 2014, Zheng et al. showed that the synthesized enterobactin-beta-lactam antibiotics (ampicillin, amoxicillin) have 1000-fold higher antibacterial property against bacteria such as *E. coli* strain CFT073 (Zheng and Nolan, 2014). Ghosh et al. in 2017 indicated that the conjugate of fimsbactin siderophore of *Acinetobacter baumannii* with daptomycin antibiotic has strong activity against drug-resistant *Acinetobacter baumannii* both *in vivo* and *in vitro* (Ghosh et al., 2017). In 2018, Liu et al. synthesized a siderophore-antibiotic conjugate with cephalosporin (as a linker) and oxazolidinone (as a toxic antibiotic), a conjugate compound that has been highly effective on clinical strains of beta-lactamase-producing *Acinetobacter baumannii*. In this compound, siderophore acts as a drug transporter across the membrane and bacterial beta-lactamase causes rapid hydrolysis of cephalosporin in the compound and efficient release of oxazolidinone in the bacterial cells. Furthermore, the results of this study showed that Gram-positive oxazolidinone can affect Gram-negative bacteria through beta-lactamase action (Liu et al., 2018). In 2011, Miller et al. reported that the synthesized mycobactin-artemisinin conjugate had potent effects against *Mycobacterium tuberculosis* (TB) as well as antimalarial activity (Miller et al., 2011).

4.2. Use of siderophores in the treatment of cancer

Compared to normal cells, cancer cells need more micronutrients because of continuous and rapid proliferation. Iron is one of the most essential nutrients for diverse cellular metabolic pathways, including oxygen transport, DNA synthesis, and ATP production (Richardson and Ponka, 1997; Lieu et al., 2001). Iron acts as an oxygen carrier in human body; nevertheless, excess iron can increase the risk of cancer by producing reactive oxygen species (Zacharski et al., 2008). Increased Fe requirement of tumor cells leads to higher expression of transferrin 1 receptor (TfR1) for endocytotic uptake of Fe^{3+} (Corcé et al., 2016). Numerous studies have revealed that cancer cells express higher levels of TfR1 than normal cells (Prutki et al., 2006). Brookes et al. reported that the progression of colorectal cancer was associated with increasing expression of Fe-importing proteins such as DMT1 and TfR1 as well as decreasing expression of Fe-exporting protein (Fpn1), which leads to elevated labile iron pool (LIP) (Sutherland et al., 1981). Pinnix and colleagues showed that the frequency of Fpn1 is reduced in some invasive lines of breast cancer cells compared to healthy cells (Pinnix et al., 2010). Therefore, given the essential role of iron in cell proliferation, iron chelators such as siderophores can be useful in the treatment of cancer (Wandersman and Delepelaire, 2004). Currently, several iron chelators such as Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) (Gojo et al., 2007), Desferrioxamine, and Deferasirox are tested in pre-clinical and clinical studies as anticancer agents (Yamasaki et al., 2011; Lui et al., 2013). Desferrioxamine (DFO) is a hexadentate siderophore isolated from *Streptomyces pilosus* that is used as an iron chelator in clinical treatment of iron overload in patients with beta thalassemia major (Aouad et al., 2002) and is the first iron chelator tested as an anti-cancer agent (Kontoghiorghes, 2006). Previous clinical studies and trials have shown that invasive tumors, including Neuroblastoma (NB) and leukemia, are susceptible to treatment with DFO iron chelator (Buss et al., 2003). DFO reduces oxidative stress in cells with iron overload and mitigates the symptoms associated with iron overload diseases (Olivieri and Brittenham, 1997). Deferasirox has been reported to completely cure a patient with chemotherapy-resistant acute monocytic leukemia, suggesting that this iron chelator may have effective

anti-leukemic effects (Fukushima et al., 2011). BE-32,030 and Amamistatins A–B, isolated from *Nocardia* spp. and *Actinomycete*, respectively, have been characterized as the first iron chelators with anticancer activity. Also, *M. tuberculosis* produces carboxymycobactins which inhibit growth of T47D-YB breast cancer (Dhusia et al., 2018). Ba et al. in 2011 found that iron deprivation by thiosemicarbazone-24 (TSC24) chelator suppresses liver cancer tumor growth by impairing iron homeostasis, reducing available iron and arresting the cell cycle and apoptosis without causing toxicity to the host (Ba et al., 2011). Nakouti et al. in 2013 reported that Desferrioxamine E generated by *Actinobacterium* significantly reduced the survival of malignant melanoma cells (Nakouti et al., 2013). In 2017, Gokarn et al. examined the effect of three siderophores, namely exochelin-MS, mycobactin S, and desferrioxamine B on mammalian malignant and non-malignant cell lines, and their results showed that these siderophores significantly reduced the survival of malignant cells without remarkable effect on non-malignant cells (Gokarn et al., 2017). Saha et al. in 2019, showed that enterobactin as a bacterial iron chelator can stop proliferation of cancer cells in RAW264.7 and J774A.1 monocyte cell lines and cause apoptosis in these cells by two mechanisms: disrupting intracellular iron homeostasis and inhibiting ROS production in mitochondria (Saha et al., 2019a). Siderophores are also useful in clearing serum non-transferrin-binding iron during cancer treatment with chemotherapy (Chua et al., 2003).

4.3. Other applications of siderophores (treatment of malaria)

Malaria is one of the most important parasitic diseases in the world, against which various treatment strategies have been employed, including antioxidant therapy, chemical drugs, and vaccine production (Dhusia et al., 2016; Isah and Ibrahim, 2014). The siderophore released by *Streptomyces pilosus* (Desferrioxamine B) and the siderophore produced by *Klebsiella pneumoniae* (aerobactin) have been shown to possess anti-malarial activity against *Plasmodium falciparum* (Gysin et al., 1993; Nagoba and Vedpathak, 2011). Desferrioxamine B has also been demonstrated to inhibit the growth of *Trypanosoma brucei*, a protozoan parasite causing African trypanosomiasis in humans (Breidbach et al., 2002). FBS0701, a newly identified industrial iron chelator, which inhibits the early gametocyte stage in *Plasmodium falciparum*, has a potentially negative effect on the reproduction of *Plasmodium falciparum* gametocytes and acts as a blocking drug against the transmission of malaria (Slavic et al., 2016).

4.4. Use of siderophores as biosensors

A biosensor is a simple and integrated device capable of generating specific quantitative or semi-quantitative analytical information using a biological identifier element attached to a transducer (Gupta et al., 2008). In recent years, scientists have used a variety of siderophore-based biosensors and nanosensors to detect a wide range of metal ion compounds (Gupta et al., 2008; Doorneweerd et al., 2010), antibiotics (Pawar et al., 2016), and pesticides to detect microorganisms (Doorneweerd et al., 2010) (Fig. 5). Siderophores can be used as potentially sensitive and selective detection systems mimicking biological processes (CCR de Carvalho et al., 2011). Among several siderophore-based methods for estimating metal ions, especially iron, fluorescent probes along with siderophores (or analogs) or fluorescent siderophores have been developed due to their rapid response rate and high sensitivity, which enable the detection of low concentrations of metals. Sensors use different electrochemical properties of siderophores as fluorescent probes to measure the amount of metals (Nosrati et al., 2018). Simple, user-friendly siderophore-based biosensors are inexpensive and rely solely on spectrophotometers (Gupta et al., 2008). Pyoverdine, which is produced by *Pseudomonas aeruginosa*, is a yellow and green water-soluble fluorescent siderophore that has previously been considered as a promising agent for making biosensors (Chiadò et al., 2013). N-methylanthranyl desferrioxamine (MA-DFB), a chemical derivative of DFB siderophore, has been shown to possess a potential role as an environmental chemosensor in natural waters (Palanché et al., 1999). The concentration of iron in the ocean is measured using a siderophore secreted by *Paracoccus denitrificans* called parabactin (Chung Chun Lam et al., 2006).

5. Conclusion

Siderophores are promising biomarkers to be used in a variety of therapeutic and industrial purposes. The application of iron chelators and iron acquisition mechanisms of bacteria can be a promising option for the production of novel vaccines and antibiotics in the form of conjugates with siderophores (Trojan horse) to inhibit antibiotic-resistant bacteria, which are considered as health problems these days. Indeed, the products of bacteria can be used against themselves to inhibit treatment-resistant bacteria. Moreover, these wonderful molecules can open new horizons in treatment of various cancers without problems associated with the conventional chemicals used for cancer therapy. However, the study of iron uptake pathways and the mechanism of siderophores' action as therapeutic agents need further investigations in animal and human models, and the high potential of iron chelators can be exploited for specific therapeutic purposes and similar applications.

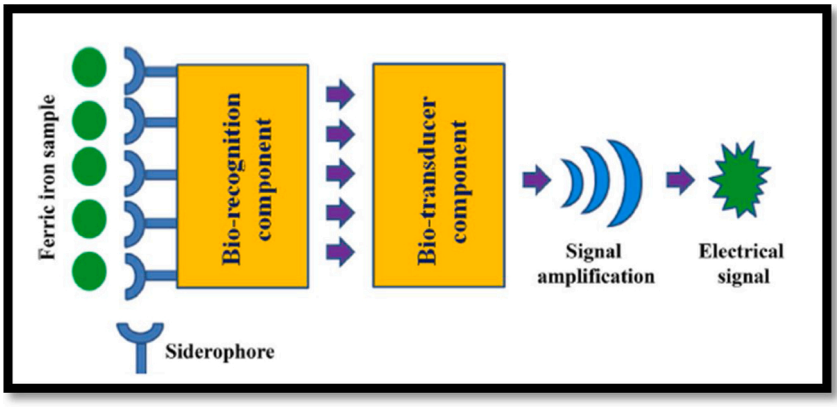

Fig. 5. Schematic representation of siderophore-based biosensor performance. Siderophores act as markers in the interaction with iron analytes *in vitro* and the biotransmitter part converts the signal from the reaction of iron and siderophore into another signal which can be measured through an amplifier and a sensitive detector (Saha et al., 2016).

Authors' contributions

B. Khasheii, P. Mahmoodi and A. Mohammadzadeh have contributed to the concept design of the review. All of the authors are responsible for selecting the references and writing the paper. The manuscript has been read and approved by the authors.

Funding

This work was supported by the Bu-Ali Sina University of Hamadan, Iran.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgements

The authors are grateful for the support of Bu-Ali Sina University of Hamadan, Iran.

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