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Review Article

Siderophore: A Suitable Candidate for Drug Delivery Using the Trojan Horse Strategy

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ABSTRACT

Increasing antibiotic resistance is a global health problem. In recent years, due to the indiscriminate use of antibacterial compounds, many bacterial pathogens, including staphylococci, members of the *Enterobacteriaceae* family including *Klebsiella pneumoniae* and bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* have become multi-drug resistant. Consequently, it is important to explore alternative approaches for eliminating resistant strains. Bacteria synthesize low-weight molecules called siderophores to chelate iron from the environment as a vital element for their growth and survival. One way to deal with resistant bacterial strains is to utilize siderophore-mediated iron uptake pathways as entrance routes for drug delivery. Therefore, the production of drugs with Trojan horse strategy in the form of conjugated siderophore-antibiotic complexes has recently received much attention for dealing with resistant isolates. In this review, we discuss the efficacy of siderophore-antibiotic conjugates as a Trojan horse strategy for eliminating drug-resistant pathogens.

Keywords: Siderophores, Iron, Drug delivery systems, Drug Carriers, Drug resistance, Anti-Bacterial Agents.

INTRODUCTION

The increasing rate of resistance in bacterial pathogens has contributed to the growing number of incurable infections (1, 2). According to the Centers for Disease Control and Prevention's report in 2019, 2.8 million antibiotic-resistant infections occur in the United States each year that result in almost 35,000 deaths (3). Therefore, development of new antibiotics and novel therapeutic and diagnostic approaches seems crucial. Otherwise, common bacterial infections may re-emerge as potential public health threats (4). Although antibiotic resistance has been discovered in both gram-negative and gram-positive bacteria, it is more common in gram-negative bacteria, such as *Acinetobacter*, *Pseudomonas* and members of the *Enterobacteriaceae* family (5). These bacteria may be resistant to many antibiotics, including carbapenems and third-generation cephalosporins as the drugs of choice for elimination of multidrug-resistant bacteria (6). Bacterial resistance is referred to the ability of bacterial cells to inhibit the bactericidal and bacteriostatic effects of antibiotics (7). Various mechanisms have been described for the development of antibiotic resistance in bacteria, which can be divided into five main categories:

Changes that occur in drug-related receptors and/or molecules that are targeted by specific antibiotics, which can be in complex with enzymes and ribosomes (8). Most of these known types of resistance are in macrolide antibiotics (9). The most well-known example of this resistance is the development of penicillin resistance due to mutations in penicillin-binding proteins in *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Neisseria meningitides* and *Enterococcus faecium* strains (10).

Enzymatic inactivation of antibiotics: In this case, a cellular enzyme changes the antibiotic structure in a way that it will no longer affect the bacterium. Beta-lactamase that hydrolyzes the most widely used antibiotics such as beta-lactams (penicillins and cephalosporins), aminoglycosidase and modifying enzymes of chloramphenicol and erythromycin are among typical examples (11,12).

Excretion of the drug by activating the efflux pumps: These proteins can pump out a wide range of compounds from the periplasmic space of bacterial cells and are activated by bacteria to excrete antibiotics as an important resistance mechanism, especially in *Pseudomonas aeruginosa* and *Acinetobacter* strains (11). This type of resistance has been observed against tetracycline through which the antibiotic is excreted and cannot accumulate in the bacterial cell with the help of an energy-dependent active pumping system (13).

Decreased absorption by changing inner and outer membrane permeability: These changes in the permeability of the inner and outer membranes reduce drug uptake by the cell (14).

Changing drug targets and alternative metabolic pathways: Such alterations can reduce or eliminate the effectiveness of antibiotic binding to its target in the bacterial cells, limiting the potency of the antibiotic (15). However, bacteria can obtain folic acid from the environment instead of synthesizing it, in this way, they become resistant to sulfonamide and trimethoprim (16).

The use of iron delivery systems is an attractive option to deal with antibiotic resistance (17). Iron is an important element for the maintenance, growth and survival of bacterial cells. The siderophore pathway is a route for iron uptake. Siderophores are small organic chelators with a molecular weight of 200-2000 Da, which are synthesized by bacteria to attract iron in the surrounding environment and transfer it into the bacterial cytoplasm through specific pathways involving outer membrane transporters in gram-negative bacteria as well as siderophore-binding proteins, permease and ATPase in gram-positive bacteria (18-21). To date, many siderophores have been characterized and more than 270 of them have been structurally distinguished (22). Based on the functional groups involved in iron binding (Figure 1), siderophores can be classified into three groups: catecholate, hydroxamate and α-hydroxy carboxylate. In addition, there is a fourth unclassifiable category of siderophores called mixed-type that contain more than one functional group (23).

Lack of intracellular iron induces siderophore biosynthesis in microorganisms (25-26) through a non-ribosomal peptide synthetases-dependent and -independent pathways (27). Transporter proteins drive siderophores out of the cell by efflux pumps. The three main types

of these proteins that participate in this process include major facilitator superfamily, resistance nodulation and cell division superfamily and ABC superfamily (28, 29). Then, the iron-siderophore complex enters the cell via two general routs: 1) Iron is released from the complex and reaches the cell as a single cation e.g. in algae and fungi, and 2) The complex enters the cell, which is common in most bacteria (30). Siderophore-mediated iron uptake requires a specific outer membrane receptors in gram-negative bacteria such as FepA, FecA, and FhuA that bind to the ferric-siderophore complex (31). Antibiotics can form covalent bonds with siderophores (32, 33) and after exploration for iron, the siderophore-antibiotic hybrid is identified by bacterial ferric-siderophore uptake pathways. Thus, antibiotics can use siderophore as a carrier (so-called Trojan horse) to take advantage of ferric-siderophore transporters and penetrate bacteria. In other words, antibiotics will be conveyed into the bacterial cell simultaneously with iron transfer by siderophore (5). This strategy can significantly reduce drug resistance due to impermeability through target selection and is particularly useful in the control of multidrug-resistant pathogens (34). Previous studies have also discussed the chemical structure, linker type and binding of various antibiotics to siderophores (35, 36). In this article, we have briefly describe the mechanism of antibiotic resistance, the properties of siderophore and the importance of producing new antibiotics with a special focus on the use of Trojan horse strategy in the production of siderophore-antibiotic conjugates.

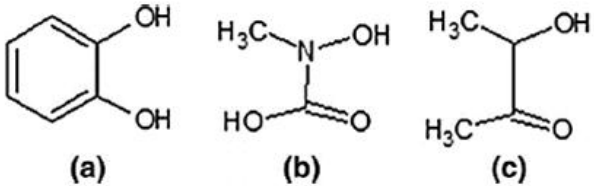

Figure 1- Siderophore functional groups: a) Catecholate, b) Hydroxamate and c) α-Hydroxy carboxylate (24).

The Trojan horse strategy (siderophore-antibiotic conjugate)

It has been shown that bacterial siderophores possess antifungal and antibiotic activity (37, 38). Conjugation with siderophores can be utilized to transfer antibiotics in a manner similar to that of the Trojan horse strategy described by Homer in the Odyssey (Figure 2) (35, 39). The goal of such a strategy is to facilitate the introduction of common or new antibiotics into the bacterial cells, thereby increasing their activity or potentiating them against a wide range of pathogens (32, 39). Drug-siderophore conjugate appears to be a promising approach for the treatment of multidrug-resistant bacterial pathogens belonging to the ESKAPEE group, which includes *E. faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa*, *Escherichia coli*, *Enterobacter aerogenes* and possibly other bacteria distinguished by the Infectious Diseases Society ofc America (40). Interestingly, this clever strategy for the direct transfer of antibacterial agents into the bacterial cells has not been developed by humans. There are several naturally occurring siderophore-antibiotic conjugates called sideromycin. These complexes are produced by a variety of gram-positive and -negative bacteria, including the genera *Streptomyces*, *Salmonella*, *Klebsiella* and *E. coli* so that they can fight for survival against rival bacteria (41). Albomycin, which was discovered in 1947, is a naturally occurring sideromycin produced by some *Streptomyces* strains with antimicrobial activity against several bacteria (42). Other examples include ferrimycin produced by *Streptomyces griseoflavus* (43) and salmycin generated by *Streptomyces violaceus* (44). Albomycin is composed of a trihydroxymate siderophore that binds to a thionucleoside moiety by a serine linker to inhibit aminoacyl−tRNA synthetases. Albomycin has access to the bacterial cytoplasm through a specific membrane transfer pathway for siderophore and when it is established in the cytoplasm, a serine protease detaches part of thionucleoside from the siderophore, blocking protein synthesis by inhibiting aminoacyl tRNA synthetases (45). Ferrimycin also consists of a hybrid of ferrioxamine B with an active antibiotic group

(44). The structure of salmycin consists of a trihydroxamate siderophore known as danoxamine, which is attached to an aminoglycoside antibiotic by a succinyl linker. Salmycin reaches the cytoplasm through the hydroxamate siderophores membrane transport pathway where the pharmacophore or functional part of the aminoglycoside acts by inhibiting protein synthesis. Salmycin is more effective against gram-positive bacteria such as *Staphylococcus* and *Streptococcus* and less effective against many gram-negative bacteria (46, 47). An attractive group of sideromycins is produced by *E. coli*, *K. pneumoniae* and *Salmonella*, which is known as class IIb microcins (47). These compounds are linear antimicrobial polypeptides composed of 60-84 amino acids binding the C-terminal region of salmochelin analog, a glycosylated form of enterobactin (48). Microcin MccE492 15 is transported into the periplasmic space of *E. coli* by catecholate siderophores such as FepA, Cir, and Fiu that are located in the outer membrane (49). The highest *in vitro* antibacterial activity among sideromycins has been observed in albomycin, an antibiotic that has also been shown to possess high antibacterial activity in a mouse model of bacterial infections (41).

Natural examples of sideromycins demonstrate significant drug-siderophore conjugate capability which increase drug reposition in target cell, which ultimately increases antibacterial effectiveness, especially against gram-negative pathogens. Therefore, researchers were encouraged to design and develop drug-siderophore conjugate structures (32).

The successful development of a drug-siderophore conjugate involves designing of a compound containing a siderophore component capable of identification of and entry into the bacterial cell, a suitable and stable binder in the extracellular environment but unstable in cytoplasm or periplasm, and an effective drug component (mainly from the beta-lactam family) (50). All components of such complex have an essential function, and when the siderophore-drug conjugate enters the cytoplasm, the microorganism may be destroyed by several methods, including drug release, complete activation of antimicrobial agents and blockage of iron uptake pathways (51). Up to now, catecholate and hydroxamate siderophores have mainly been used as vectors of antibacterial agents to overcome the problems of drug penetration into the membrane (52), and studies have shown that the use of strong iron chelators, such as triscatechols, increases the chances for conjugates to compete with the natural siderophores (53). However, siderophores of carboxylate type like staphyloferrin A are considered as appropriate candidates for certain applications since this type of siderophore exhibits iron-chelating properties in acidic environments relative to catecholate and hydroxamate siderophores (52). Hydroxamate siderophores and their analogs are good candidates for development of siderophore-antifungal drug conjugates that use iron uptake systems through hydroxamate siderophores molecules (35). The first siderophore-drug conjugates were synthesized by the Zahner group in 1977 by linking ferricrocin and ferrioxamine B to sulfonamides (54). There have been significant changes in the design of siderophore-drug conjugates so that a siderophore-monosulfactam conjugate like BAL30072 showed favorable results and advanced to phase I clinical trial in 2013 (55). In this type of conjugate, a lactam or similar compound is combined with a small molecule mimicking siderophore. BAL30072 is a combination of a dihydroxypyridone moiety and a monocyclic beta-lactam antibiotic moiety. The oxyiminoacyl side-chain allows easy access to the bacterial cell through the iron uptake system, while the second moiety reduces the sensitivity to inactivation by various beta-lactamases (56). The majority of cases associated with the Trojan horse drug delivery rely on beta-lactamases (50). This facilitates penetration of siderophore-bound beta-lactam antibiotics in the outer membrane and allows specific pathogen targeting by the modified siderophore conjugates. For example, triscatecholate siderophore-aminopenicillin conjugate specifically inhibits the replication of gram-negative bacteria such as *P. aeruginosa* (57). Beta-lactam antibiotics are useful as the drug moiety in siderophore-drug conjugate for two reasons. Firstly, penicillin-binding proteins are located in the periplasm and the siderophore-drug conjugate only needs to cross the outer membrane to reach them. Secondly, unlike most other antibiotics, the binding site of beta-lactams to target is different from that of the siderophore moiety so that the conjugate can be completely

activated without detachment of the siderophore moiety (58).

Design of synthetic siderophore-antibiotic conjugate drugs

In 1987, Watanabe et al. synthesized a new siderophore-cephalosporin conjugate called E-0702with antimicrobial activity against gram-negative bacteria such as *K. pneumoniae*, *Salmonella typhimurium*, *P. aeruginosa* and *Serratia marcescens*. They also revealed that E-0702 had the highest antibacterial activity against iron-starved bacteria but had effect on iron-rich bacteria (59).

Milner et al. prepared a panel of carboxylate conjugates of staphyloferrin A siderophore with methyl ester derivatives of fluoroquinolone, ciprofloxacin and norfloxacin as potential anti-*Staphylococcus* agents. Staphyloferrin A was chosen as a carrier since unlike catecholates or hydroxylates, carboxylate-type siderophores have higher affinity for chelating iron in mildly acidic environments. Figure 3 shows the conjugated compounds (52).

18 and 19 (yellow box) and staphyloferrin A (red box) with a fluoroquinolone (blue box)(35). Kinzel et al. isolated and purified two pyoverdine siderophores produced by *P. aeruginosa* ATCC 27853 and *Pseudomonas fluorescens* ATCC 13525, both containing lysine and ornithine, resspectively and ligated ampicillin to them by a non-degradable capric acid binder (Figure 4). The resulting 118 and 119 compounds with respective minimum inhibitory concentration (MIC) of 0.39 mM and 0.024 mM showed strong antibacterial activity against *P. aeruginosa* strains (60). Catechol-cephalosporin conjugate (GR69153) was found to be effective against *E. coli* and *P. aeruginosa* with the lowest MIC in the environments containing very low levels of iron(61).

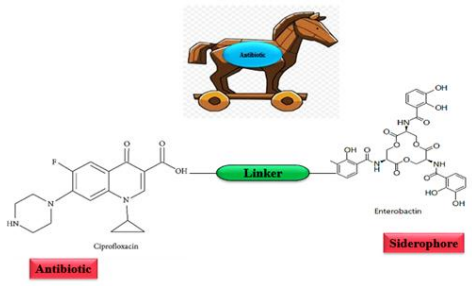

Figure 2- Schematic view of the Trojan horse strategy (siderophore-antibiotic conjugate)

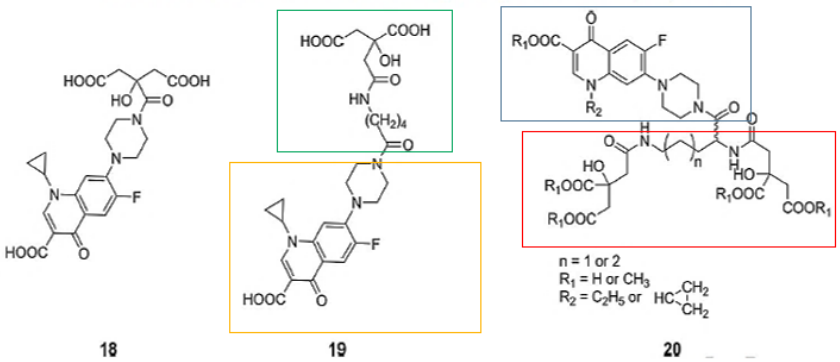

Figure 3- Drug conjugates with α hydroxycarboxylate siderophore: Citrate (green box) with ciprofloxacin 18 and 19 (yellow box) and staphyloferrin A (red box) with a fluoroquinolone (blue box) (35)

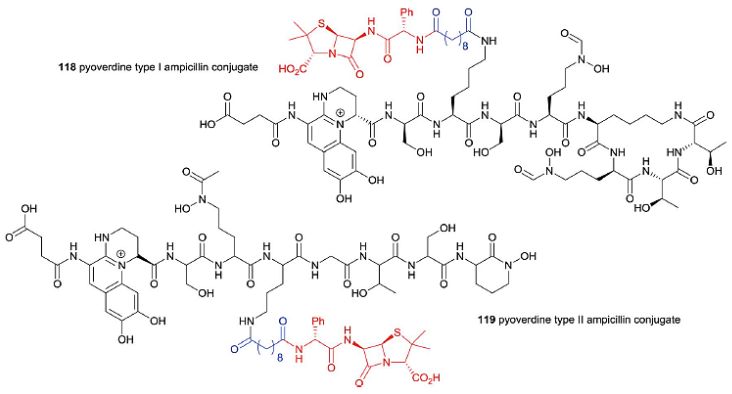

Figure 4- Pyoverdine-ampicillin conjugate, linker (blue), antimicrobial agent (red) (33)

In 2012, Ji et al. synthesized two artificial triscatecholate compounds with ampicillin and amoxicillin that were effective against *P. aeruginosa* strains. Although these gram-negative bacteria contain periplasmic binding proteins as a target of beta-lactam antibiotics, they are resistant to these antibiotics due to impaired passage and arrival at periplasmic space through the outer membrane pores. The researchers showed that both of these beta-lactam-siderophore compounds are effective against *P. aeruginosa* and that their antibacterial activity is higher in environments with low iron concentrations(57).

The most commonly used iron hydroxymate chelator for generation of siderophore-antimicrobial agent conjugate is desferrioxamine B (DFOB), a linear trihydroxamate siderophore sold under the brand name of Desferal (35). In this regard, DFO conjugated with lorabid 24, ciprofloxacin 25 or triclosan showed good activity against several pathogenic bacteria in humans, including *S. aureus*, *E. coli*, and *Mycobacterium vaccae* in vitro (34). The DFO-nalidixic acid conjugate can be synthesized through direct binding of nalidixic acid carboxyl group with N-terminal of DFO. This conjugate was highly active against multidrug-resistant strains of *Plasmodium falciparum* with a MIC of 0.6 µg/ml (62).

In 2013, Duhme-Klair et al. synthesized a staphyloferrin-ciprofloxacin conjugate siderophore with a covalent linkage between fluoroquinolone and carboxylic acid. The prepared conjugates had an average antibacterial activity against a number of gram-positive bacteria and significant antibacterial activity against gram-negative bacteria including *P. aeruginosa*, *Serratia marcescens* NCTC 1998 and *E. coli* NCTC 10418 (52).

In 2014, Sonnet et al. used the Enterobactin analog introduced by Miller et al. to transfer fluoroquinolones, but the resulting conjugate was no effective against *P. aeruginosa* possibly due to the application of non-degradable ligands, which were previously shown to be ineffective for fluoroquinolone conjugates (63,64).

Mycobacterium tuberculosis produces a hydroxamate siderophore known as mycobactin T in order to survive under limited iron conditions. Due to the presence of long fatty acid chains, mycobactin can enter the cell via an energy-independent route. In search of new anti-tuberculosis drugs, a conjugate consisting of a mycobactin T analog and an anti-malarial drug called Artemisinin was designed and found to be highly active against multidrug resistant strains of *M. tuberculosis* (Figure 5) (62).

Flanagan et al. synthesized a siderophore-monocarbam complex (MC-1) conjugate with *in vitro* activity against multidrug-resistant *P. aeruginosa* and *Enterobacteriaceae* producing extended-spectrum beta-lactamases as well as *A. baumannii*. Nevertheless, further research is needed to overcome the hydrolytic instability of this compound. In a study using a rat model of lung infection, the high affinity of this compound to plasma proteins also limited its effect (66).

Cefiderocol (S-649266) was the first siderophore-antibiotic conjugate to reach phase III clinical trial. This catecholate-cephalosporin conjugate siderophore has the structural properties of 3rd and 4th generation cephalosporins, namely ceftazidime and cefepime, which can bind to iron through a catechol moiety at C3 position to enter the cell through siderophore transporter proteins. Cefiderocol has *in vitro* and *in vivo* activity against carbapenem-resistant *Enterobacteriaceae*, *P. aeruginosa*, and *A. baumannii* (67,68).

In 2015, Chairatana et al. designed and prepared a conjugate of glycosylated enterobactin (GlcEnt)-β-lactam antibiotics "ampicillin and amoxicillin" by a chemoenzymatic method. The results of the study showed that the conjugate had 1000-fold higher antimicrobial activity against uropathogenic *E. coli* compared to β-lactams antibiotics alone (69).

In 2017, Ghosh et al. synthesized a conjugate consisting of the mix ligand analog of the selective siderophore fimsbactin (*A. baumannii* siderophore)-daptomycin (abbreviated to conjugate 11) with strong antibacterial activity against multidrug-resistant strains of *A. baumannii* both *in vitro* and *in vivo*. Using the Trojan Horse strategy, their results revealed that conjugation of a drug that are much larger than siderophore facilitates drug uptake and makes it effective against both gram-positive and gram-negative bacteria (4).

In 2018, Ghosh et al. synthesized and tested other conjugates with modified mimetic siderophores-daptomycin (conjugate 5: bis-catechol-daptomycin and conjugate 6: tri-catechol- daptomycin). Conjugate 5 with a MIC of 1.6 µM had stronger activity than conjugate 6 with MIC of 25 µM against *A. baumannii* producing carbapenemase and cephalosporinase. The compound also maintained its activity at lower doses of daptomycin alone against *S. aureus* (70).

In 2018, Neumann et al. reported the synthesis of siderophore (enterobactin)-antibiotic (ciprofloxacin) conjugate, wherein enterobactin was attached to ciprofloxacin by an alkyl linker. This conjugate showed antibacterial activity against *E. coli* strains expressing *IroA* gene cluster. In addition, it had significant antibacterial activity against uropathogenic *E. coli* UTI89 and CFT073 compared to the unmodified ciprofloxacin (71).

In 2020, Boyce et al. designed a conjugate containing a siderophore moiety, a degradable protease linker and an amine-containing antibiotic targeting *E. coli* periplasmic proteases. Using this strategy, daptomycin, which is only effective against gram-positive bacteria became effective against gram-negative bacteria such as *Acinetobacter* species. The results of this study illustrated the usefulness of this platform for the production of protease-activated drugs including Trojan horse antibiotics (72).

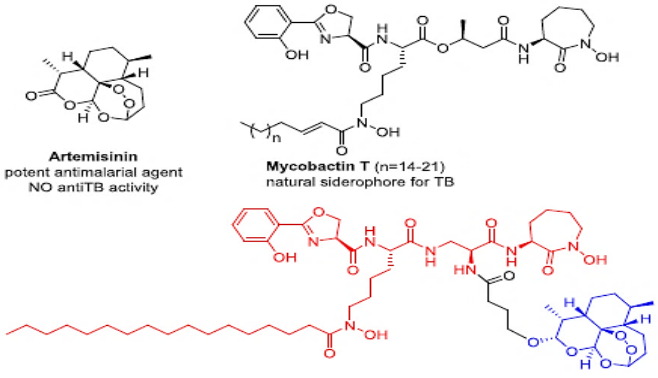

Figure 5- Mycobactin T-Artemisinin conjugate (65)

CONCLUSION

Given the growing number of multidrug-resistant bacteria, the exigency for the development of new drugs and antibiotics is increasingly felt. One way to evaluate the occurrence of antibiotic resistance in bacteria is to use alternative therapeutic strategies, including iron acquisition pathways. Iron chelators such as siderophore molecules can be utilized for the introduction of drugs and antibacterial compounds into bacterial cells, a process known as the Trojan horse strategy. Using this strategy, antibiotics can pass through impenetrable membranes of gram-negative bacteria and destroy them. As discussed in this article, the Trojan horse strategy is a promising and flexible approach for the production of antimicrobials against multi-drug resistant bacteria. Nevertheless, further studies are required to gain a better understanding of the interaction of siderophore and bacterial surface receptors, siderophore uptake mechanisms, dynamic and functional properties of antibiotics and proper linkers.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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