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MINI-REVIEW

Iron and zinc ions, potent weapons against multidrug-resistant bacteria

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Abstract

Drug-resistant bacteria are becoming an increasingly widespread problem in the clinical setting. The current pipeline of antibiotics cannot provide satisfactory options for clinicians, which brought increasing attention to the development and application of non-traditional antimicrobial substances as alternatives. Metal ions, such as iron and zinc ions, have been widely applied to inhibit pathogens through different mechanisms, including synergistic action with different metabolic enzymes, regulation of efflux pumps, and inhibition of biofilm formation. Compared with traditional metal oxide nanoparticles, iron oxide nanoparticles (IONPs) and zinc oxide nanoparticles (ZnO-NPs) display stronger bactericidal effect because of their smaller ion particle sizes and higher surface energies. The combined utilization of metal NPs (nanoparticles) and antibiotics paves a new way to enhance antimicrobial efficacy and reduce the incidence of drug resistance. In this review, we summarize the physiological roles and bactericidal mechanisms of iron and zinc ions, present the recent progress in the research on the joint use of metal NPs with different antibiotics, and highlight the promising prospects of metal NPs as antimicrobial agents for tackling multidrug-resistant bacteria.

Keywords Metal ions · Metal NPs · Multidrug resistance · Bactericidal mechanism

Introduction

The large-scale misuse of antibiotics in agriculture, animal husbandry, and medical practice causes a crisis of antimicrobial resistance worldwide (McEwen and Collignon 2018). Antimicrobial resistance is an evolutionary phenomenon in which microorganisms such as bacteria, certain parasites, and viruses adapt to circumvent the action of antimicrobial drugs (Pham et al. 2019). Over the past decades, in which pathogenic bacteria, virus, and certain parasites, antimicrobial

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resistance has rapidly developed and disseminated, especially along with emergence of the severely resistant "ESKAPE" pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*), which makes common medical procedures such as surgery, organ transplants, and chemotherapy increasingly risky, leading to severe hospital-acquired infections. Recently, antimicrobial resistance has become a major challenge in the global medical field, seriously threatening human health and causing high significant mortality (Post et al. 2019). How to meet this challenge is consequently of great concern all over the world. The development of new antibiotics is a conventional way to solve this problem, which began with the commercial production of penicillin in the late 1940s and entered the golden age until the 1970s. However, in the ongoing competition with microorganisms, antimicrobial agents seem to always be the loser (Huh and Kwon 2011; Taubes 2008). The development of antibiotics is therefore having difficulty keeping up with the speed of bacterial evolution, and the lack of available drugs for certain strains is a pressing problem (Payne et al. 2007; Tommasi et al. 2015).

Since the production pipeline of new antibiotics has almost "dried up", researchers are turning their sights to development of new antimicrobial strategies, such as antibacterial peptides (Lakshmaiah Narayana and Chen 2015), phage therapy (Dedrick et al. 2019), metal ions (Zhang et al. 2019a), and similar non-conventional active substances (Belbekhouche et al. 2019). The antibacterial action of metal ions has been known since antiquity and containers made of copper and silver were used for water disinfection and food preservation during the time of Persian kings (Alexander 2009). Silver has been used as a topical preparation or as an additive to surgical sutures and other materials to prevent infection (Medici et al. 2019). In fact, the use of metals as antibacterial materials was widespread before the discovery of antibiotics by Alexander Fleming in the 1920s (Lemire et al. 2013). Recently, with the development of nanotechnology, metal NPs have become one of the most sensible strategies to treat multidrug-resistant microbial infections, and the use of antimicrobial metals is being revived (Pelgrift and Friedman 2013; Shnoudeh et al. 2019). Compared with traditional metal-ion preparations, metal NPs possess the characteristics of smaller size and larger surface area, which makes them better adsorb on the bacterial cell surface, allow more metal ions to penetrate the cell wall of bacteria, and enhance the bactericidal effect (Hajipour et al. 2012; Pelgrift and Friedman 2013). NPs composed of metals such as gold (Au), silver (Ag), copper (Cu), zinc (Zn), and iron (Fe) show biocidal activity against a variety of microorganisms (Pelgrift and Friedman 2013). Among them, iron and zinc ions have been widely studied due to their widespread presence in nature and their frequent use in daily life.

Like all other organisms, bacteria require certain essential metal ions to perform their physiological functions, including iron and zinc. However, excess iron, zinc, and other metal ions also cause different forms of damage, such as oxidative stress, protein dysfunction, and damage to membrane integrity (Saqib et al. 2019; Wang et al. 2016; Xu et al. 2016). In this review, we outline the principles of iron and zinc ions as antimicrobial agents, update the application progress of metal NPs to treat multidrug-resistant bacteria, and focus on the combined utilization of metal ions, especially iron and zinc, with antibiotics.

Toxicity of iron and zinc ions to bacteria

Iron ions

Iron is an essential micronutrient for bacteria, involved in many biological pathways, such as DNA synthesis and energy metabolism (Dev and Babitt 2017). It is also the key factor determining bacterial virulence (Eijkelkamp et al. 2011). In the host, iron usually binds tightly with biomolecules like heme, causing an iron-depleted environment in vivo, in which bacteria have to adapt to by employing a series of iron acquisition mechanisms (Eijkelkamp et al. 2011). One of the strategies is siderophore, which has a high affinity for iron ions that can capture iron from the host's protein iron complexes (Lamont et al. 2002). Another way for uptake of iron relies on direct contact between the pathogen and the iron source (Miethke and Marahiel 2007; Mosbahi et al. 2018). However, excess ions can lead to catastrophic damage to bacterial cells. It was found that both Gram-negative (G^-) and Gram-positive (G^+) bacteria can absorb Fe^{3+} and rapidly reduce it to Fe^{2+}. The resulting Fe^{2+} is a catalyst for the formation of reactive oxygen species (ROS), generating large amounts of hydroxyl radicals (·OH) through both the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \cdot OH$) and the Haber-Weiss reaction ($O_2^- + H_2O_2 + Fe^{3+} \rightarrow Fe^{3+} + O_2 + H_2O + \cdot OH$) (Belenky et al. 2015; Rachmilewitz et al. 2005). These hydroxyl radicals, which cannot be removed by the corresponding enzyme system, will cause crippling damage to bacteria, such as lipid peroxidation in the cell membrane, protein and DNA damage, and even cell death (Dharmaraja 2017; Gambino and Cappitelli 2016) (Fig. 1).

Iron oxide nanoparticles (IONPs) are one of the few nanomaterials that can penetrate small capillaries of the tissue and blend into natural human metabolism (Iqbal et al. 2017). Compared with ordinary iron ions, IONPs have a larger specific surface area, smaller volume, and higher activity. These advantages make it easier to contact with bacterial cells and complete the process of crossing the cell wall and cell membrane (Wang et al. 2017). At first, the IONPs adhere to bacterial cell closely and form a stable entity via electrostatic forces, intermolecular forces, and cell adhesion. Then, they pass through the cell wall, interact with lipids and proteins on the cell membrane, and change the osmotic pressure, leading to

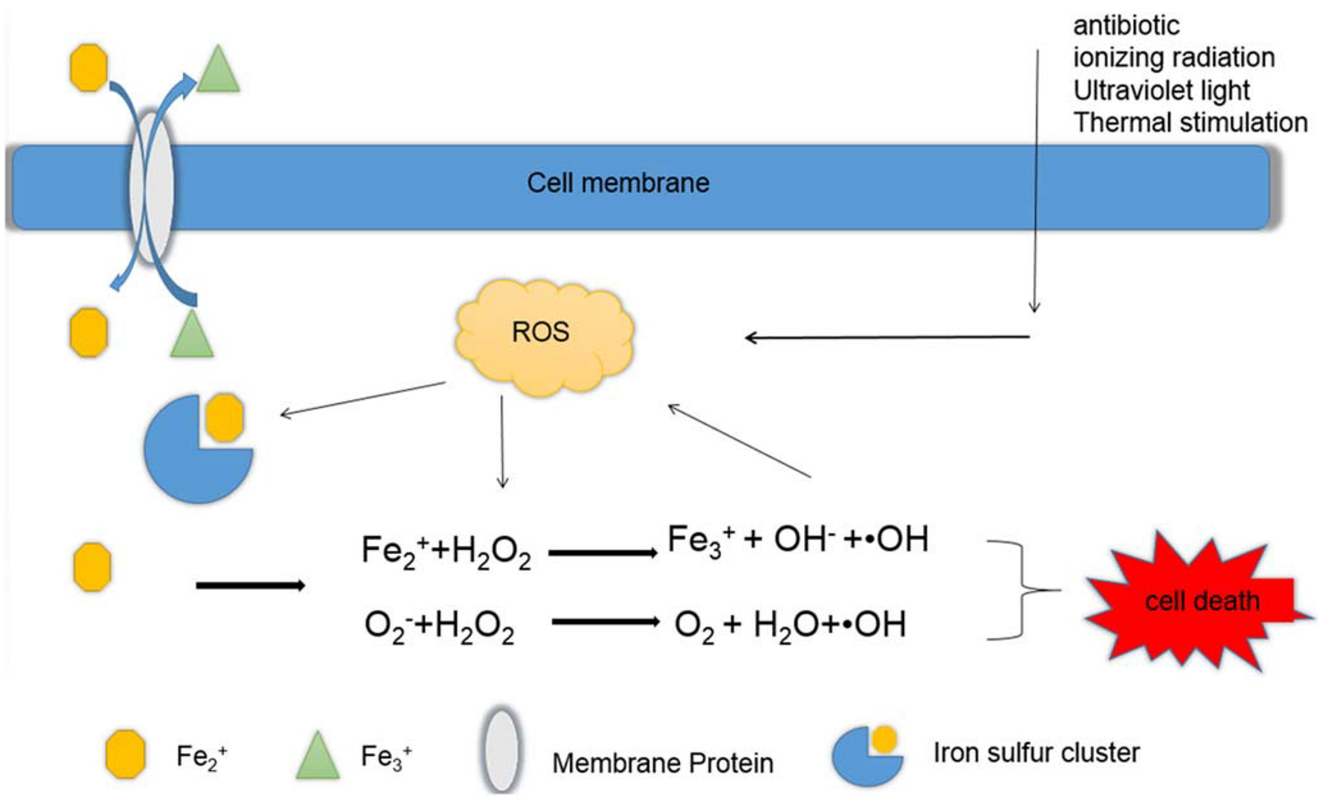

Fig. 1 Schematic diagram of the bactericidal effects of iron by promoting reactive oxygen species production. Fe^{3+} reaching the surface of the cell membrane is rapidly converted to Fe^{2+}, and then reaches the inside of the cell through the iron transporter, where it catalyzes the conversion of H_2O_2 and O_2^- to ·OH, causing bacterial cell death. Excessive reactive oxygen species produced by external stimulants (antibiotics, ionizing radiation, ultraviolet light and heat stress) can also directly stimulate the release of Fe^{2+} from iron-sulfur clusters and catalyze the formation of (·OH)

membrane disruption. Once upon reaching the inside of the cell, IONPs may also generate a large amount of ROS (Arakha et al. 2015), disrupt DNA replication, and induce DNA double-strand breaks (Dinali et al. 2017) (Fig. 2). The ability of IONPs to kill bacteria via multiple described mechanisms simultaneously increases its drug-resistance barrier, making it harder for bacteria to adapt than conventional single-target antimicrobials (Saqib et al. 2019; Wang et al. 2017). For example, Fe_3O_4 NPs can inhibit the growth of *E. coli*, *Bacillus subtilis*, *Staphylococcus epidermidis*, *K. pneumoniae*, and *P. aeruginosa* (Rodrigues et al. 2019). Fe_2O_3 NPs have the ability to kill bacteria and inhibit their biofilm formation against *Serratia marcescens*, *E. coli*, *P. aeruginosa*, and *Listeria monocytogenes* (Al-Shabib et al. 2018).

Recently, iron oxide-based magnetic NPs, composed of maghemite (-Fe_2O_3) and hematite (*a*-Fe_2O_3), have drawn great attention and are listed for human biomedical applications by the World Health Association owing to their magnetic property (Dinali et al. 2017; Rodrigues et al. 2019). These iron oxide-based magnetic NPs have been broadly used as drug delivery and magnetic hyperthermia agents to treat bacterial infections (Chaurasia et al. 2016; Laurent et al. 2011). Under the action of a high-frequency amplitude alternating magnetic field, iron oxide-based magnetic NPs convert magnetic energy into local heat and inhibit the growth of bacteria, which are more sensitive to temperature than host cells (Hantke 2005; Jafarirad et al. 2016). For example, when exposed to Fe_3O_4@SiO_2-NH_2 (complex consisted of an Fe_3O_4 core and SiO_2-NH_2 shell), the multidrug-resistant *S. aureus* and *E. coli* could be killed completely within 30 min in the radio frequency electromagnetic field owing to a disorder of membrane surface potential and defects of protein function (Chaurasia et al. 2016). In addition, incubation of *E. coli* and *P. aeruginosa* bacteria with 100-μg/mL magnetite hybrid nanocomposites for 30 min also caused death of all bacterial cells. In the case of magnetic field treatment, the survival rate of *E. coli* and *P. aeruginosa* biofilms decreased significantly compared with controls that were not exposed to the magnetic field (Zhang et al. 2019a).

Zinc ions

Similar to iron ion, Zn^{2+} is also an important trace metal for the metabolism of microorganisms, found in the active sites of various enzymes. Zn^{2+} takes part in many important metabolic pathways, like synthesis and degradation of sugars, lipids, and proteins (Hantke 2005). Additionally, the zinc ion is involved in the regulation of cell proliferation, differentiation, and maintenance of the membrane structure of cells (Jafarirad

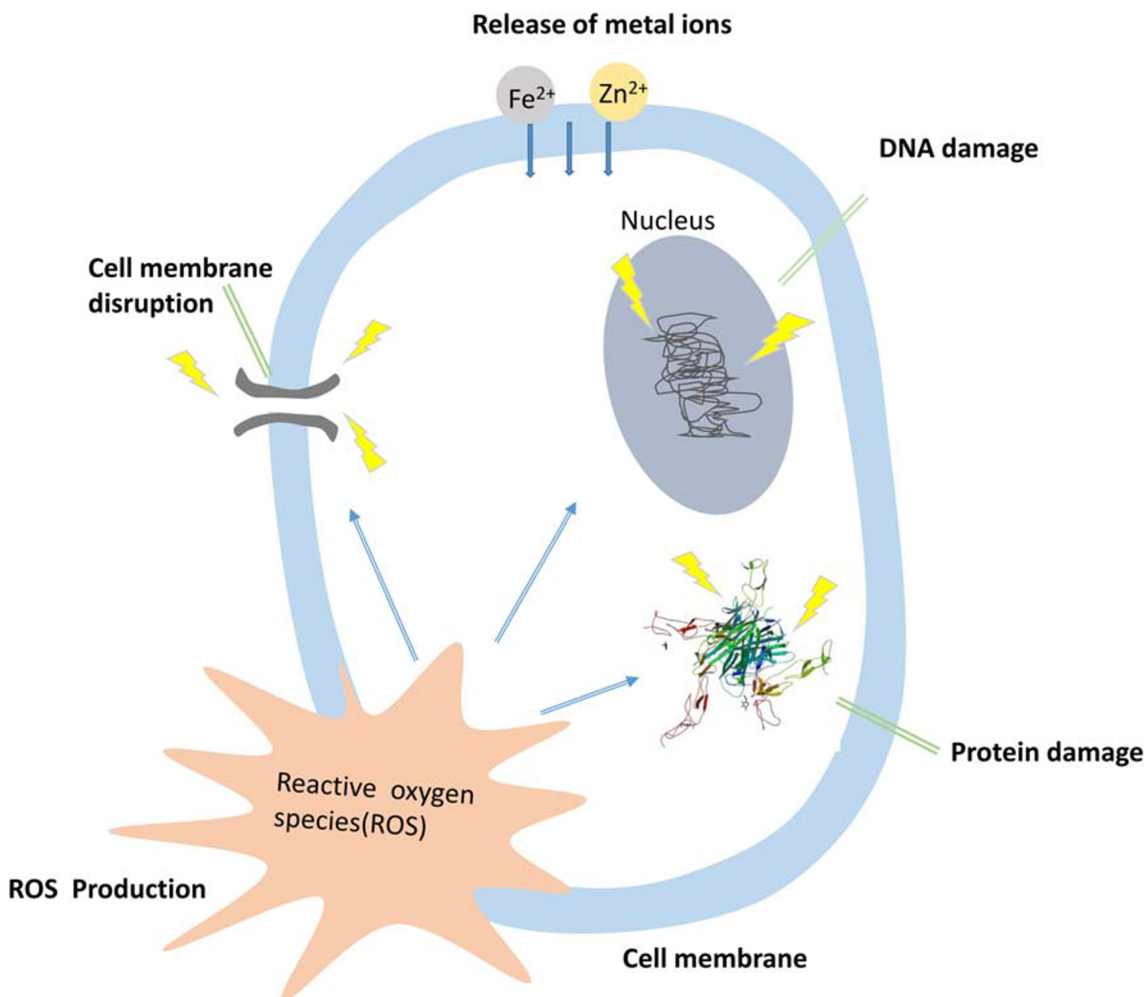

Fig. 2 The essential role and bactericidal effect of iron and zinc ion

et al. 2016). The concentration of Zn^{2+} is a key factor influencing the growth of bacteria. At low concentrations, the promoting effect is predominant, but when the concentration is too high, excessive Zn^{2+} inhibits bacterial growth. At first, excessive Zn^{2+} can compete with other metals and cause a metal mismatch in non-target metal-binding proteins (McDevitt et al. 2011; Nairn Brittany et al. 2016), leading to protein denaturation, enzyme inactivation, and even cell death (Blencowe and Morby 2003). Secondly, when too many Zn^{2+} reach the bacteria, they can be firmly adsorbed onto the cell surface by Coulombic forces. Then, Zn^{2+} will penetrate the cell membrane and cause it to rupture, followed by cytoplasmic outflow that eventually leads to cell death accompanied by production of large amounts of ROS (Blecher et al. 2011). Moreover, at sub-bactericidal concentrations, Zn^{2+} can prevent biofilm formation in many bacteria (Wu et al. 2013). Compared with the common Zn^{2+}, zinc oxide nanoparticles (ZnO-NPs) possess some special advantages that enable them to cross the cell membrane smoothly. This is mainly related to their small particle size and high surface energy. Like other NPs, ZnO-NPs kill bacteria by destroying the cell membrane as well as inducing oxidative stress and ROS generation (Taylor and Webster 2011) (Fig. 2). For example, ZnO-NPs showed a significant inhibitory effect against *L. monocytogenes*, *E. coli*, *S. aureus*, and *K. pneumoniae* (Mirhosseini and Arjmand 2014; Reddy et al. 2014). It was observed that 15 μg/mL of ZnO-NPs can inhibit the growth of *E. coli* and *S. aureus*, and the MIC (minimum inhibitory concentration) was as low as 5 μg/mL against *K. pneumoniae* (Siddiqi et al. 2018).

Ci-ZnO NPs (ZnO-NPs were synthesized using leaf extract of *Costus igneus*) at concentrations of 25, 50, 75, and 100 μg/mL produced inhibition zones against *Vibrio parahaemolyticus* of 4.2 ± 0.1, 5.13 ± 0.17, 6.56 ± 0.11, and 8.16 ± 0.15 mm, respectively (Vinotha et al. 2019). Interestingly, ZnO-NP showed higher activity against G^+ bacteria than G^-, which may be related to differences of their cell wall composition (Premanathan et al. 2011; Sekar et al. 2016).

Furthermore, ZnO-NPs have photocatalytic bactericidal activity. Under ultraviolet irradiation, electrons in the valence band of ZnO-NPs are excited to the conduction band, forming free-moving electrons and positively charged holes (Mirhosseini and Arjmand 2014; Pimpliskar et al. 2019).

These holes can react with oxygen, hydroxyl groups, and water adsorbed on the surface of the material to produce large amounts of ROS, which react with biological macromolecules, damage cells, and inhibit growth or killing bacteria (Lipovsky et al. 2009; Sharma et al. 2012; Siddiqi et al. 2018). Zn-phthalocyanines can inactivate about 70% of *E. coli* within 30 min (Bertoloni et al. 1990).

Application of iron and zinc ions in conjunction with antibiotics

Iron ion conjunction with antibiotics

Antibiotics can be combined with inhibitors of their degradation enzymes, such as cephalosporin and sulbactam, where the former kills bacteria by inhibiting bacterial cell wall synthesis, and the latter works as a competitive inhibitor of β-lactamase to overcome bacterial resistance (Williams 1997). Similarly, different metal ions and antibiotics can also be used together. When antibiotics alone are used to treat bacterial infection, only a small proportion of the active molecules reach the target because bacteria possess many mechanisms to exclude antibiotics, such as membrane selectivity and efflux pumps (Ahmad et al. 2020). However, studies have shown that adsorbing antibiotics onto the surface of nano-carriers can increase their local concentration and potentiate their antibacterial effects (Hassan et al. 2016; Hussain et al. 2018) (Table 1). For example, IONPs have been used to help antibiotics penetrate these barriers. Notably, under the action of an external magnetic field, IONPs facilitate the passage of antibacterial agents through the cell membrane to the target position, protect the drugs from degradation, and help them exert the maximum bactericidal effect (Armenia et al. 2018).

In vitro studies of gentamicin-coated IONPs had significant antibacterial effect against *S. aureus*, *B. subtilis*, and *P. aeruginosa*, whereby 0.2 mg/mL of granules was able to kill 98% of bacterial cells (Bhattacharya and Neogi 2017). Vancomycin-loaded Fe_3O_4 (van-IONPs) not only successfully inhibited 50% of vegetative cell growth after 48 h of treatment, but also inhibited spore germination better than an equal dose of free vancomycin. In the meanwhile, IONP-targeting helps antibiotics reach the bacterial surface at higher concentration. In a mouse model of *Clostridium difficile* infection, van-IONPs significantly protected the mice, reducing intestinal inflammation and adhesion of spores. Microscopy showed that van-IONPs can completely cover the spore surface, significantly blocking the interaction of the spores with mucosal cells, reducing the number of residual spores in the intestines (Chen et al. 2019). In another line of research, the Van-LaB6 @ SiO_2/Fe_3O_4 (vancomycin and Fe_3O_4 NPs were successfully bound onto the surface of LaB6 NPs with a silica coating) complex, which displays super-paramagnetism, was developed as a novel nanomaterial for the near-infrared photothermal ablation of bacteria. The complex was shown to be very effective for the magnetic separation and near-infrared photothermal ablation of *S. aureus* and *E. coli*. The complex can cover the bacterial cell surface, allowing the targeted magnetic separation of the cells. Following near-infrared light illumination for 5 min in the presence of Van-LaB6@SiO_2/Fe_3O_4, the survival of the two bacterial species was reduced to 0.12 ± 0.03 and $0.4 \pm 0.18\%$, respectively (Lai and Chen 2013).

In addition to vancomycin, IONPs also showed synergistic effects with teicoplanin and cephalexin. The nanomaterial iron-coupled teicoplanin (tei-IONPs) showed antibacterial activity against methicillin-resistant *S. aureus* and vancomycin-resistant *E. faecalis*. Moreover, they also inhibited the biofilm formation of *S. aureus* (Armenia et al. 2018). The nanomaterial iron-conjugated cephalexin (cep-IONPs) showed inhibitory activity against *S. aureus*, *Bacillus* sp., *E. coli*, and *Salmonella* sp., and its inhibition zone was greater than that of cephalexin alone (Rayegan et al. 2018). Additionally, IONPs also have the ability to destroy bacterial biofilm structure and inhibit biofilm formation by generating local heat when exposed to a pulsating magnetic field. Combined with IONPs (gm-IONPs), gentamicin led to a 3.2- and 4.1-fold increase in the killing effect against planktonic cells and biofilms, respectively, compared to it alone (Nguyen et al. 2015). Furthermore, biocompatible multi-compartment nanocarriers containing both 20 μg/mL hydrophobic super-paramagnetic IONPs and 40 μg/mL of methicillin were able to kill methicillin-resistant *S. epidermidis*. Importantly, the formulation is selectively toxic to methicillin-resistant bacteria but not to mammalian cells (Geilich et al. 2017).

Zinc ion conjunction with antibiotics

In addition to iron ions, many antibiotics can also be used in combination with zinc ions. Typically, zinc ions are used to promote action of antibiotics such as vancomycin (Zarkan et al. 2016), quinolones (Uivarosi 2013), aminoglycosides (Gokhale et al. 2007), tetracycline (Novák-Pékli et al. 1996), and macrolides (Hamdan 2003).

Compared with vancomycin alone, co-administration of vancomycin and zinc sulfate increased the size of inhibition zone of vancomycin-resistant *Streptomyces coelicolor* M600 and *E. faecalis* JH2-2::I in the paper disk separation test. The MIC tests showed that the sensitivity of both strains to the combination sulfate increased 4 to 8 times than single antibiotics. Notably, Zn^{2+} has the ability to mediate the assembly of vancomycin monomers (Zarkan et al. 2017). Similarly, the norfloxacin-Zn^{2+} complex showed obviously higher antibacterial activity against *E. faecalis* and *Shigella dysenteriae* than norfloxacin alone (Ahmadi et al. 2013).

Table 1 Examples of complexes of iron or zinc ions with antibiotics and their inhibitory effect on microorganisms

Composition	Inhibitory effect	Action bacteria	References
Fe			
Fe_3O_4/LaB6 @ SiO_2 Vancomycin	Showed higher antibacterial activity than vancomycin only	*S. aureus* and *E. coli*	Lai and Chen (2013)
Fe_3O_4-Vancomycin	Inhibited the growth of vegetative cell and spore	*C. difficile*	Chen et al. (2019)
IONPsGentamicin	Inhibit bacterial growth	*S. aureus*, *B. subtilis* and *P. aeruginosa*	Bhattacharya and Neogi (2017)
IONPs-Gentamicin	Revealed a 3.2- and 4.1-fold increase in killing planktonic cells and biofilm	*P. aeruginosa*	Nguyen et al. (2015)
IONPs-Teicoplanin	Inhibit bacterial growth	Methicillin-resistant *S. aureus* and *E. faecalis* with vancomycin-resistant	Armenia et al. (2018)
IONPs-Cephalexin	Showed higher antibacterial activity than cephalexin only	*S. aureus*, *Bacillus*, *E. coli*, and *Salmonella*	Rayegan et al. (2018)
IONPs-Methicillin	Showed selectively toxic to methicillin-resistant bacteria	methicillin-resistant *S. epidermidis*	Geilich et al. (2017)
Zn			
Zn^{2+}-Vancomycin	The susceptibility towards vancomycin increased by 4 to 8 times	*E. faecalis* JH2-2::I and *S. coelicolor* M600	Zarkan et al. (2017)
ZnO-NPs + Ciprofloxacin	Bacteriostatic zone size increased 27% and 22%, respectively	*S. aureus* and *E. coli*	Banoee et al. (2010)
Zn^{2+} + Aminoglycosides	Inhibit bacterial growth	multidrug-resistant bacteria *E. coli* and *A. baumannii*	Li et al. (2015); Lin et al. (2014)
Zn^{2+} + Norfloxacin	Showed higher antibacterial activity than norfloxacin only	*E. faecalis* and *S. dysenteriae*	Ahmadi et al. (2013)

The combination of ZnO-NPs with ciprofloxacin can enhance its antibacterial effect against *S. aureus* and *E. coli*. The presence of ZnO-NPs increased the inhibition zone of ciprofloxacin against these two bacterial species by 27% and 22%, respectively (Banoee et al. 2010). The increase of antibacterial activity of small molecules against *S. aureus* by ZnO-NPs may be due to interference with the pumping activity of the NorA protein, which mediates the active efflux of hydrophilic antibiotics, conferring resistance to fluoroquinolones (Hassanzadeh et al. 2017; Yu et al. 2002). Another explanation is that ZnO-NPs can enhance the absorption of antibiotics by bacterial cells, for example by changing the permeability of the OmpF protein, which is considered to be the main conduit for the penetration of quinolones into the cell (Chevalier et al. 2000; Paulsen et al. 1997). In addition, Zn was found to increase the effects of carbapenems and fluoroquinolones against *P. aeruginosa* biofilms (Elkhatib and Noreddin 2014).

G^- pathogens, who are resistant to amikacin and other clinically significant aminoglycosides, usually carry 6′-N-acetyltransferase type Ib [AAC (6′)-Ib], which catalyzes the inactivation of antibiotics by acetylation using acetyl-CoA as donor substrate (Ramirez et al. 2013; Ramirez and Tolmasky 2017). However, Zn^{2+} can effectively inhibit the normal progress of the reaction as an inhibitor of the enzymatic acetylation of aminoglycosides by AAC (6′)-Ib and sensitize the bacteria (Lin et al. 2014).

Zinc ions can be used in combination with aminoglycosides against multidrug-resistant *E. coli* and *A. baumannii* (Li et al. 2015; Lin et al. 2014). It is confirmed that three classes of ionophores pyrithione, clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) (CI_8HQ), and pyrithione (N-hydroxypyridine-2-thione) when complexed to Zn^{2+} or Cu^{2+}, can significantly reduce the levels of resistance to amikacin in *K. pneumoniae* and *A. baumannii* isolates (Magallon et al. 2019; Chiem et al. 2015).

Combination of iron and zinc ions with other materials

Beside antibiotics, metal-based nanomaterials can also combine with other materials to form hybrid nanomaterials. The doping of these hybrid nanomaterials with other components can improve the physical, optical, and electrical properties and antibacterial activity of metal ions, often with synergistic effects (Guo et al. 2015; Khatami et al. 2018; Ma et al. 2014; Mao et al. 2005; Rajiv et al. 2013) (Table 2).

Combination of iron and zinc with other metal ions

Multi-metal composite nanomaterials have the potential to control a wider range of bacterial infection than single metals (Alzahrani et al. 2017). In addition, there are synergistic effects between metal ions that can lead to greater bactericidal effects in smaller amounts, thereby reducing cytotoxicity and other undesired side effects. Meanwhile, multi-metallic NPs generally have higher catalytic activity and selectivity than single-metal NPs (Madhumitha et al. 2015; Roopan et al. 2014). For example, the AgI/CuFeO complex is capable of killing *E. coli* and *S. aureus* under visible light, and its photoactivity is much higher than that of a single metal (Zhang et al. 2019b). An Au-Fe_2O_3 nanocomposite showed

Table 2 The combined application of metal ions (iron and zinc) with other antibacterial materials

Composition	Shape, size	Action bacteria	References
Combination of iron and zinc with other metal ions			
ZnO-V_2O_5	–	*S. aureus*	Sun et al. (2019a)
ZnO-Ag	–	*C. difficile*	Zare et al. (2019)
Fe_2O_3/NiO	Hexagonal shape, nanometer range	*S. aureus*, *B. subtilis* and *P. aeruginosa*	Bhushan et al. (2019)
AgO-Fe_3O_4-poly (with vinyl pyrrolidoneand conjugated catechol)	–, 72 nm	*S. aureus*, *E. coli*	Mosaiab et al. (2013)
Ag-Au/ZnO	Stick shape, 20–25 nm	*E. coli*, *S. aureus*	Nithya et al. (2019)
TiO_2-ZnO-MgO	Near-spherical shape, 17–23 nm	*E. coli*, *S. paratyphi*, *S. aureus* and *L. monocytogenes*	Luis Miguel et al. (2019)
Ag-ZnO	Hexagonal rod, 30 nm	–	Pimpliskar et al. (2019)
Combined application of metal ions with other substances			
Chitosan/a-Fe_2O_3	Spherical-shaped, 30 nm	*S. aureus*, *E. coli*	Kavitha et al. (2012)
Chitosan-Fe_3O_4-chlorhexidine	Spherical shape, 40 nm	*C. albicans*, *S. mutans*	Vieira et al. (2018)
IONPs-glycol chitosan	–, 8–9 nm	*E. coli* ATCC 8739, *S. enteritidis SE 01*	Inbaraj et al. (2012)
Oxidized starch-ZnO	–, 35–70 nm	*S. aureus*, *E. coli*	Namazi et al. (2018)
ZnO-alginate biopolymer solutionamoxyclav/amikacin	Spherical shape, 120–236 nm	*E. coli* DH5-α, *P. aeruginosa*	Baek et al. (2019)
IONPs-polyvinyl alcohol	Chain-like particles, 140 nm	*S. aureus*	Tran et al. (2010)
ZnO-collagen/chitosan	Geometry structure, 20~50 nm	*E. coli*, *S. aureus*	Sun et al. (2019b)
Si_2O-Fe_2O_3	Ellipsoidal morphology, 5.89~19.89 nm	*C. parapsilosis*, *A. niger* *B. subtilis and E. coli*	Arshad et al. (2019)

excellent antibacterial activity against multidrug-resistant *E. coli* and *B. subtilis*, because the gold coating prevented oxidation of iron NPs and maintains their magnetic properties (Shams et al. 2019). In addition, studies have shown that the loading of precious metals onto the surface of zinc NPs can significantly improve their photocatalytic activity (Chen et al. 2018). Ag/ZnO synthesized by Prashant et al. showed higher photocatalytic activity than pure ZnO nanorods. Addition of silver ions increased the photoconductivity and effectively separated electron-hole pairs, which plays an important role in improving the photocatalytic performance. The experimental results showed that the conductivity of 10 mol% Ag-ZnO is nearly 20 times higher than that of pure ZnO (Pimpliskar et al. 2019). More importantly, the incidence of bacterial resistance is very low because few mutations lead to resistance against multiple metal ions at the same time (Alzahrani et al. 2017).

Combination of metal ions with biocompatible polymers

In addition to other metals, different types of biocompatible polymers such as chitosan have also been conjugated to metal NPs. On the one hand, the polymers protect the drug from rapid degradation or release, thereby increasing its bioavailability and reducing the dose required for successful treatment (Khan et al. 2015; Vieira et al. 2018). On the other hand, the encapsulation of metal NPs can improve their biocompatibility and stability, improving the functionalization of the resulting nano-systems (Liakos et al. 2014).

Chitosan ($CS\text{-}C_6H_{11}O_4N)_n$ is a deacetylated form of chitin that is commonly found in the shells of marine animals and fungal cell walls. It has excellent physical and chemical properties, including biocompatibility, bioactivity, biodegradability, osteoconductivity, low toxicity, and cost effectiveness (Li et al. 2013; Lu et al. 2010). Chitosan has natural antimicrobial properties against bacteria, fungi, and yeasts due to inactivation of enzymes or blocking of enzyme activity by electrostatic interactions of positively charged amino groups with the surface of the shell membrane (Costa et al. 2014; Kurniasih et al. 2018). Recently, chitosan has become one of the most important biomaterials in pharmaceutical development, bone tissue engineering, cosmetics, drug delivery, surgical sutures, biological dressings, and wound-healing materials (Frohbergh et al. 2012; Hajji et al. 2019; Patel et al. 2014; Wang et al. 2012). It is often used in combination with other polymers and metal oxides as antimicrobial agents (Anandhavelu et al. 2017; Romainor et al. 2014).

The application of chitosan can control the particle size and crystal phase of ZnO-NPs and IONPs, prevent occurrence of aggregation, and increase their antibacterial activity. The corresponding complexes exhibited effective antibacterial activity against *S. aureus* and *E. coli* (Kavitha et al. 2012; Nithya and Jothivenkatachalam 2015). The antibacterial properties of five compounds composed of ZnO and chitosan were studied using *E. coli*, *Salmonella typhi*, and *K. pneumoniae* as indicator strains, and two of the compounds produced inhibition zones for *S. typhi* and *E. coli* larger than amikacin (Packirisamy et al. 2019). In addition, the complex ZnO-chitosan is widely used in surgical dressings because it can promote cell proliferation and effectively accelerate wound healing.

Moreover, a pyridone carrier can transfer more Zn^{2+} to the cytoplasm, increase its intracellular concentration, and effectively inhibit growth of *A. baumannii*. When 4 μM Zn pyridine was added to the medium, the MIC of amikacin for *A. baumannii* was reduced from 16 to 3 μg/mL (Lin et al. 2014). Another interesting example is the combination of ZnO-NPs with graphene oxide, which helps Zn^{2+} enter the bacterial cells rapidly and reduce its dissolution, allowing more ZnO-NPs to reach their target and kill the bacteria (Wang et al. 2014).

PBT2 (Prana Biotechnology) is a metal protein-attenuating compound, which has progressed to phase 2 of clinical trials for Alzheimer's and Huntington's disease treatment, and is a safe-for-human-use zinc ionophore (Ayton et al. 2020; Xu et al. 2019). When PBT2 combined with Zn^{2+}, it showed significant antibacterial activity and could disrupt the homeostasis of erythromycin-resistant *group A Streptococcus*, methicillin-resistant *S. aureus*, and vancomycin-resistant *Enterococcus* (Bohlmann et al. 2018). In addition to this, PBT2-zinc ions can synergistically with several clinically relevant antibiotics to improve bactericidal rate. For example, it can increase the sensitivity of *Neisseria gonorrhoeae* to Polymyxin B and Colistin (Jen et al. 2020). In addition, Arshad et al. synthesized a-Fe_2O_3@SiO_2 NPs by co-precipitation and demonstrated their good inhibitory effects against *Candida. parapsilosis*, *Aspergilus niger*, *E. coli*, and *B. subtilis*. The antibacterial effect of a-Fe_2O_3@SiO_2 NPs was comparable to that of rifampicin, and their antifungal activity was slightly lower than that of nystatin. This finding suggested that NPs synthesized on the basis of SiO_2 and Fe_2O_3 are effective antibacterial agents (Arshad et al. 2019).

Synthesis of iron and zinc nanomaterials

In addition to doping and decoration with different substances, the antibacterial effect of nanomaterials is also significantly affected by their own morphology and particle size (Bai et al. 2015; Itoh and Sugimoto 2003). The relative antibacterial activity of ZnO-NPs is in the order of petals > fusiform > rod-shaped flowers. This difference in antimicrobial ability is affected by their physical parameters, such as specific surface area, pore size, and surface energy (Cai et al. 2016). It is well known that different synthesis methods can produce NPs with different antibacterial effects. The synthesis of metal NPs by traditional physical and chemical methods produces higher yields and a more uniform size distribution. Nevertheless, with development of technology, some drawbacks of traditional synthesis methods were revealed, including high capital cost, high energy demand, and utilization of toxic or otherwise hazardous chemicals (Haq et al. 2017). In addition, previous studies have shown that the NPs synthesized by traditional methods are less biocompatible (Raouf Hosseini and Nasiri Sarvi 2015). These problems limit the clinical and biomedical applications of metallic nanomaterials. Therefore, it is necessary to explore and develop cleaner, environmentally safe, and economical alternatives to synthesize biocompatible NPs.

In recent years, the biocatalytic green synthesis of NPs has entered the stage and becomes a substitute for traditional purely physicochemical methods. The biosynthesis of NPs composed of metals and their oxides relies on biologically active products from plants (Happy et al. 2018; Singh et al. 2016), bacteria (Kundu et al. 2014), fungi (Shamsuzzaman et al. 2017), yeasts (Moghaddam et al. 2017), viruses (Nam et al. 2006), and algae (Azizi et al. 2014). Biocatalytic synthesis using plant extracts makes use of complex chemical components, such as phenols, alcohols, terpenes, saponins, proteins, etc., extracted from different parts of plants, including leaves, roots, stems, fruits, and flowers. These compounds act as reducing and capping agents in the synthesis of nanomaterials (Basnet et al. 2018). Furthermore, microbes can be used as whole-cell biocatalysts to reduce metal ions to metal NPs, with the participation of enzymes and other biomolecular compounds secreted or produced by the cells (Boroumandmoghaddam et al. 2015) (Table 3).

In general, the IONPs and ZnO-NPs formed by biocatalytic methods are safer and more stable, displaying more toxicity to bacteria with little side effect on animal cells. Consequently, they are widely used in pharmaceutical carriers, cosmetic ingredients, and medical filling materials (Lee et al. 2008; Machado et al. 2015).

The environmental risks for nanoparticle emissions

It should be noted that most studies on the toxicity of NPs investigated their use on a small dose, where these materials are considered to be non-toxic. However, with the increasing use of NPs in industrial processes, these substances are being inadvertently released and concentrated in the environment, and the influence of these materials is becoming more and more significant (Nel et al. 2006; Santos-Martinez et al. 2007; Zhu et al. 2012).

In fact, the leakage of NPs has become one of the most serious threats to beneficial microorganisms, microbial communities, and public health in ecosystems (Auffan et al. 2009; Gajjar et al. 2009). For example, Ag-NPs (< 5 nm) can inhibit plant growth by interacting with bacterial membranes, inducing ammonia oxidase to produce reactive oxygen species, which inhibit the growth of nitrifying bacteria and interfere with conversion of ammonia nitrogen in the soil to nitrite (Choi and Hu 2008). FeO-NPs at 3.2 mg/kg significantly reduced mycorrhizal clover biomass by 34% by significantly reducing the glomalin content and root nutrient acquisition of Arbuscular mycorrhizal fungi (Feng et al. 2013).

Table 3 Microorganisms and plants that mediate the synthesis of zinc and iron NPs

Name	Irons	Size	Shape	References
Plant				
Sageretia thea	Fe_2O_3	30 nm	Tetragonal	Khalil et al. (2017)
Costus igneus Nak	Ci-ZnO	26.55 nm	Hexagonal	Vinotha et al. (2019)
Annona squamosa	ZnO	20–50 nm	Hexagonal	Ruddaraju et al. (2019)
Azadirachta indica	Fe_2O_3	38.2 nm	Hexagonal cone	Sharma et al. (2015)
Peltophorum pterocarpum	Fe_2O_3	16.99 nm	Rod-like	Anchan et al. (2019)
Bacteria				
Escherichia coli	IONPs	27.7 nm	Spherical	Mahmood and Hassan (2019)
Lactobacillus plantarum VITES07	ZnO	7–19 nm	Spherical	Selvarajan and Mohanasrinivasan (2013)
Staphylococcus aureus	ZnO	10–50 nm	Acicular	Rauf et al. (2017)
Bacillus subtilis	Fe_3O_4	60–80 nm	Spherical	Sundaram et al. (2012)
Yeast				
Pichia kudriavzevii	ZnO	10-61 nm	Hexagonal	Boroumandmoghaddam et al. (2017)
Fungi				
Alternaria alternata fungus	Fe_2O_3	9 ± 3 nm	Cubic shapes	Affifi et al. (2015)
Aspergillus niger	ZnO	61 ± 0.65 nm	Spherical	Kalpana et al. (2018)

Of course, nano-ions can also be directly absorbed by some plants, affecting plant survival and development. For example, Al_2O_3-NPs significantly inhibited root elongation in corn, cucumber, soybean, cabbage, and carrot (Lin and Xing 2007; Yang and Watts 2005). High concentrations of TiO_2-NPs reduced the fresh weight of roots and shoots of wheat (Mahmoodzadeh et al. 2013). Ag-NPs can hinder shoot and root growth of common beans and corn (Salama 2012). In addition, it also exerted several harmful effects on the water, air, soil systems, and food web, which are intimately linked with human health (Rizwan et al. 2017; Rai et al. 2018). Therefore, dealing with the increasing pollution of the environment with NPs, or improving the recovery of these NPs, is a problem we have to face in the future.

Conclusions

Nowadays, multidrug resistance is widespread, and the development of antibacterial drugs cannot keep pace with the evolution of bacteria. Therefore, researchers are paying increasing attention to novel antibacterial substances that differ from conventional antibiotics. Metal ions can achieve bactericidal effect by catalyzing production of ROS, destroying the structure of cell membranes, and binding with intracellular DNA. In addition, they can also be applied in combination with other materials, like metal ions, antibiotics, and biocompatible polymers. At present, by modulating the synthesis processes and combinations, new antibacterial agents can be obtained, which may have broader or specialized antibacterial effects (Bouazizi et al. 2018; Cai et al. 2016; García-Quintanilla et al. 2013). These phenomena provide new ideas for the development of new antibacterial drugs and antibacterial surgical materials, which gives them significant practical significance for hospital management and the clinical treatment of multidrug-resistant bacteria.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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