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Selective Physicochemical Modulation of Antimicrobial Efficacy by Metal Ions: A Comparative Study of Foodborne Pathogens and Clinical Isolates

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Abstract

Antimicrobial resistance (AMR) is a global challenge in both clinical and food safety. The increasing prevalence of resistant strains is challenging treatment and control measures against microbial pathogens. Metal ions are common in environmental and food systems, and can affect bacterial physiology, resistance mechanisms, and antibiotic activity. This study examines the influence of four metal ions (Fe^{2+}, Mg^{2+}, Mn^{2+} and NH_4^+) on the antibacterial effectiveness of four groups of antibiotics (amoxicillin, ampicillin, erythromycin and ciprofloxacin) against a series of clinically relevant pathogens (Escherichia coli, Staphylococcus aureus Pseudomonas aeruginosa and Serratia marcescens), in addition to foodborne organisms. We show that metal ions potentiate antibiotic activity in a species- and concentration-dependent manner, affecting both resistance and survival of the bacteria. Moreover, Fe^{2+} dramatically decreased both sensitivity to erythromycin and ciprofloxacin in E. coli and abolished antibiotic function completely in S. aureus at high concentrations, which may involve a more rigid cell envelope preventing drug penetration. In P. aeruginosa, Mn^{2+} also caused step-by-step resistance to ciprofloxacin and then enhanced oxidative stress protection and efflux pump were likely involved therein. In contrast, the effect of NH_4^+ on S. marcescens was little and ciprofloxacin showed similar bactericidal activity at different concentrations. These findings point to a complex interplay of environmental metal exposure and antibiotic resistance within clinical and food-associated pathogens, suggesting that the levels of metal ions should be considered when targeting AMR in both food processing and clinical environments.

Keywords: *Antimicrobial resistance, Foodborne pathogens, Metal ion–antibiotic interaction, Physicochemical modulation.*

INTRODUCTION

Antimicrobial resistance (AMR) has become a serious concern to the world community compromising the clinical therapeutic responses and food safety systems. The growing emergence of resistant foodborne pathogens hinders the maintenance of a contaminant-free food supply, is detrimental to public health and imparts considerable financial impact on the food industry 1). AMR not only may enhance persistent infections and therapeutic failure in the clinical field, but it also undermines reliable antibiotics used widely for preservative enhancement, food production and contaminant control. In the foodborne cases resistance can allow microorganisms to reside after processing and storage life, develop as strong biofilms on equipment surfaces, survive along the entire supply chain until product spoilage, outbreaks and mass product recalls 2). In the era of food biotechnology development, more attentions have been paid to molecular, enzymatic and system technology for bettering food quality, safety and function. These approaches depend on accurate knowledge of the physiology of microbes, stress teachings and environments' reactions within food systems 3). Moreover, modern food systems are intricate biological matrices in which a number of parameters (nutrient availability, chemical composition, pH; moisture content; temperature and metal ion levels) interact to modulate bacterial response 4). Some of these physicochemical conditions can inhibit bacteria or inadvertently select for resistance. Consequently, investigating how environmental factors, including metal ions affect bacterial survival and antibiotic resistance is crucial 5).

Metal ions are of particular concern since they naturally occur in agricultural soils, irrigation water, food matrices, as well as fermentation systems and processing machines, and accumulate in foods either by contamination or deliberate supplementation. These ions have the potential to alter microbial cellular architectures, biologically important reactions, stress responses, and antibiotic-microbe interactions 6). In the case of food biotechnology, such physicochemical factors can influence either the effective control or shift pathogen strains to adapt and survive under selective pressure. As a result, an understanding of these interactions is therefore critical for the design of better bioprocesses, minimising of AMR misuse, and more effective preservation strategies as well as advances in the global problem that has become AMR in both food and clinical settings 7).

Metal ions are one of these important but under-examined elements. Elements, including iron (Fe^{2+}), magnesium (Mg^{2+}), manganese (Mn^{2+}) and ammonium (NH_4^+), exist naturally in agricultural soils, water supplies and food matrices as well as in the processing equipment, packaging materials, and microbial environments 8). These ions are cofactors required for bacterial metabolism, stress/stimulus response, enzyme activation or function and maintenance of membrane properties. Nonetheless, these ions may also have a remarkable impact on antibiotic efficacy due to physicochemical interferences that affect drug binding on the cell envelope, uptake and penetration into the cell 9). Metal ions are not well-understood with respect to their antimicrobial activity in the context of food systems, where exposure levels and environmental interactions can be markedly different from clinical settings, despite their prevalence 10).

Awareness of metal–antibiotic interaction is of great relevance, because metals can cause non-genetic resistance or a "physicochemically driven resistance" by stabilizing bacterial envelopes and increasing efflux pump activity, oxidative stress pathways and antibiotic target interactions in bacteria 11). Common foodborne pathogens often experience fluctuating metal levels during processing, storage and environmental exposure, although the consequences of this on antibiotic susceptibility are relatively unknown. Furthermore, clinical isolates of the same species may react in a different way owing to different selection pressure, metabolic adaptation, as well as resistance determinants 12). Thus , comparing foodborne and clinical strains is informative to determine common and divergent metal-induced effects.

The escalating problem of multidrug-resistant (MDR) bacteria represents a significant challenge worldwide by rendering the existing antibiotics ineffective, and increasing threats on human health, food safety and the environmental system 13). Resistant pathogens as a persistent contaminant in clinical and food-processing settings With the continued contamination by antibiotic-resistant organisms, Treatment failures increased cost Public-health consequences. As the pace of new antibiotic discovery decelerates, alternative approaches are needed to potentiate antimicrobial activity and define what in the environment triggers bacterial responses 14).

One of these factors is metal ions that are found to be plentiful in food times, water system, processing machinery and biological hosts. Metal ions profoundly impact bacterial physiology, membrane integrity, activity of enzymes, response to oxidative stress and nutrient uptake 15). Such biochemical interactions can enhance or diminish antimicrobial activity, therefore it is relevant to study these effects in a controlled manner with mechanistic significance. The knowledge of metal–microbe–antibiotic interactions is important for the development of safer food, better strategies in microbial control and avoiding resistance acquisition, both in food biotechnology and public health 16).

In order to maintain biological relevance and to focus in on the mechanism, we took a deliberately single-ion–single-bacterium strategy. Each of the metal ions was matched with a bacterium according to its published chemical role and actual environmental distribution. Fe^{2+} was challenged in E. coli, because iron is the most important metal in Gram-negative metabolism and is also present in host tissues and foods contaminated with *E. coli* 17). Mg^{2+} was tested with S. aureus, as this ion makes up a large proportion of the thick peptidoglycan-rich Gram-positive cell wall and is abundant in dairy, meat and fermented food products that are frequently spoiled by *S. aureus* 18). Mn^{2+} was screened with *P. aeruginosa*, and as this bacterium is more dependent on manganese for oxidative stress defense and efflux systems (specifically in water systems, biofilm formation and food processing 19). NH_4^+ was tested with *S. marcescens*, a physiologically versatile foodborne species that can readily utilize ammonium as a nitrogen source in nutrient-rich and spoilage-associated environments 20). These selective combinations generate physiologically relevant conditions and are useful for the precise determination of antibiotic modulation by different ions.

This article describes an investigation of the impact of four metal ions (Fe^{2+}, Mg^{2+}, Mn^{2+}, NH_4^+) on common antibiotics, including amoxicillin, ampicillin, erythromycin and ciprofloxacin in terms of their antimicrobial efficacy against principal foodborne pathogens as well as clinical isolates. Through analysis of species-specific, ion-specific and concentration-dependent effects, the study provides a new understanding on physicochemical and biochemical determinants to govern antibiotic performance. The results provide insight into resistance acquisition while guiding development of enhanced food safety interventions and underscore the importance of environmental metal exposure in strategies to protect public health more generally against the urgent challenge of antimicrobial resistance.

MATERIALS AND METHODOLOGY

Preparation of Metal Ion Stock Solutions and Metal-Supplemented Mueller–Hinton Agar

The single-ion–single-bacterium approach was used in this study for the analysis of all metal ions to minimize cross-interference and hence to achieve clear, organism-specific responses. The ammonium ferrous sulfate (Fe^{2+} source), magnesium sulfate heptahydrate (Mg^{2+} source), manganese(II) sulfate monohydrate (Mn^{2+} source), and ammonium sulfate (NH_4^+ source) metal salts were steam-sterilized in their solid forms by autoclaving at 121°C for 15 min. All metal salts, after being sterilized, were dissolved in sterile distilled water to form individual 100 mM stock solutions. Mueller–Hinton (MH) agar powder (38 g/L) was dissolved with distilled water and autoclaved at 121°C for 15 min. The molten MH agar was cooled down to a temperature of 50–55°C, then different volumes of each metal stock solution were added in antiseptic conditions to achieve the following final working concentrations: 0 mM (control), 1 mM, 2 mM, 5 mM and 10 mM. Sterile water was topped up in each preparation to match the final volume for all concentrations within a metal set. The melted agar containing added metal was stirred well to homogeneously disperse ions and poured into sterile Petri plates (20–25 mL per plate). Since the majority of the rubrics tested a metal ion against a single bacterium, Fe^{2+} plates for E. coli, Mg^{2+} plates for S. aureus, Mn^{2+} plates for P. aeruginosa and NH_4^+ plates of Serratia marcescens were prepared.

Bacterial Strains and Culture Preparation

Four bacterial species were used: Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Serratia marcescens in combination with one metal ion in each case as described above. All isolates were subcultured on new nutrient agar plates and incubated at 37°C for 18–24 h to allow the bacteria grow actively. Afterward, colonies from these plates were resuspended in sterile physiologic saline solution and adjusted to the 0.5 McFarland turbidity standard to establish a constant number of bacteria for all experiments (approximately 1 × 10^8 cfu).

Inoculation of Plates

Metal-supplemented and its control MH agar plates were prepared as described in the standard method. To each of the organisms, 1 mL of /the 0.5 McFarland bacterial suspension was mixed with the molten MH agar at a temperature of 45–50°C by using appropriate quantity sterile saline The inoculated MH plate was gently mishandling to avoid bubbles and after it had cooled down, the poured out media/ seed agar was aseptically transferred into sterile Petri dishes. The plates were permitted to set on a laminar air flow. After the plates had set, sterile cork borers were used to form uniform 6–8 mm diameter wells in the agar, with a spacing appropriate to avoid overlapping zones of inhibition. 50 microliters of sterile antibiotic solution (Amoxicillin, Ampicillin, Ceftriaxone, or Ciprofloxacin) with the respective concentration was added to each well and a sterile micropipette. The plates were incubated at 37°C for 18–24 hours, followed by leaving the plates undisturbed at room temperature for 30 min to ensure complete diffusion of the antibiotic into agar.

Measurement of Antimicrobial Activity

Following incubation, the diameters of the zones of inhibition surrounding each well were measured in millimeters using a calibrated ruler. The effect of each metal ion on antibiotic activity was determined by comparing inhibition zones on metal-supplemented plates with those on metal-free control plates for the same organism. Only the following metal–bacterium combinations were included in the analysis: Fe^{2+} with *E. coli*, Mg^{2+} with *S. aureus*, Mn^{2+} with *P. aeruginosa*, and NH_4^+ with *S. marcescens*.

Results

1) Effect of Fe^{2+} on Antibiotic Activity Against *Escherichia coli*

Table 1: Effect of Fe^{2+} on Antibiotic Activity Against Escherichia coli

Metal Ion (Fe^{2+})	Concentration	Amoxicillin 30 µg/ml (mm)	Ampicillin 30 µg/ml (mm)	Erythromycin 30 µg/ml (mm)	Ciprofloxacin 30 µg/ml (mm)
		AMX	AMP	ERY	CIP
Fe^{2+}	0 mM	22	20	12	38
Fe^{2+}	1 mM	15	18	0	34
Fe^{2+}	2 mM	20	22	0	28
Fe^{2+}	5 mM	22	22	0	13
Fe^{2+}	10 mM	22	18	20	16

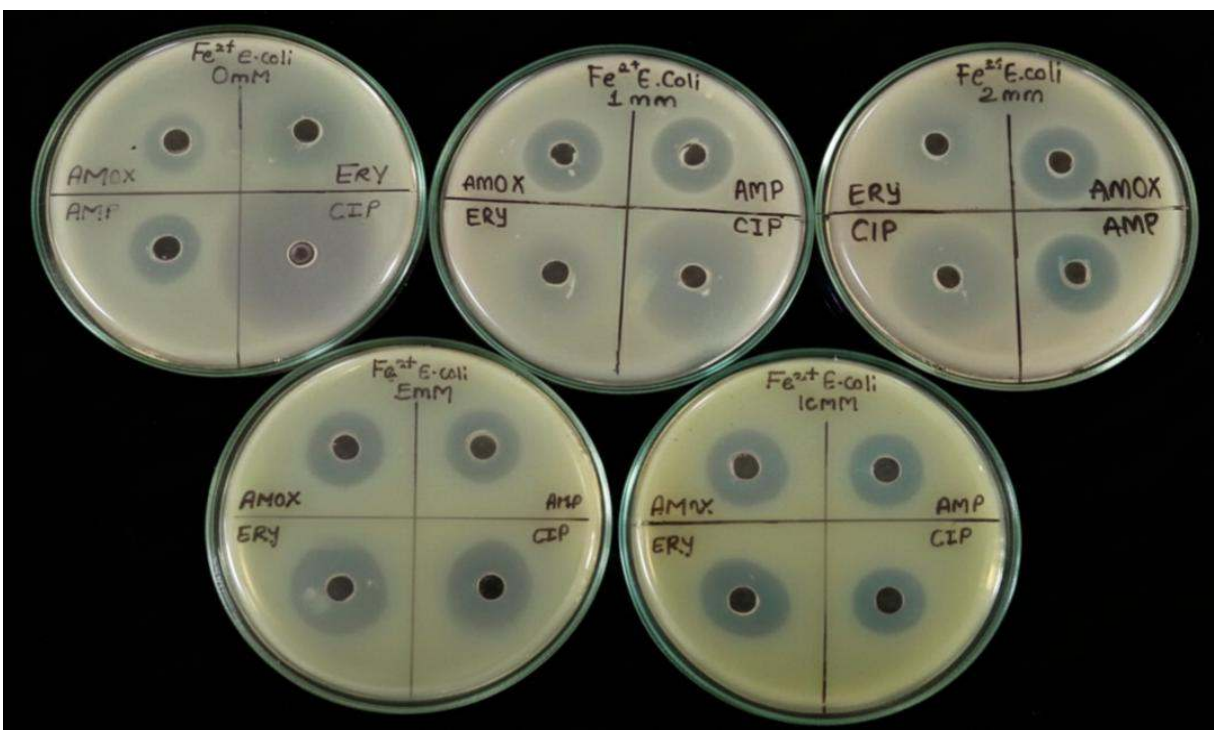

Figure 1. Petri plate image showing E. coli inhibition zones under Fe^{2+} ion treatment

2) Effect of Mg^{2+} on Antibiotic Activity Against *Staphylococcus aureus*

Table 2: Effect of Mg^{2+} on Antibiotic Activity Against Staphylococcus aureus

Metal Ion (Mg^{2+})	Concentration	Amoxicillin 30 µg/ml (mm)	Ampicillin 30 µg/ml (mm)	Erythromycin 30 µg/ml (mm)	Ciprofloxacin 30 µg/ml (mm)
		AMX	AMP	ERY	CIP
Mg^{2+}	0 mM	26	28	0	20
Mg^{2+}	1 mM	26	28	0	18
Mg^{2+}	2 mM	16	32	0	16
Mg^{2+}	5 mM	30	28	0	14
Mg^{2+}	10 mM	0	0	0	0

Figure 2. Petri plate image showing Staphylococcus aureus inhibition zones under Mg^{2+} Ion treatment

3) Effect of Mn^{2+} on Antibiotic Activity Against *Pseudomonas aeruginosa*

Table 3: Effect of Mn^{2+} on Antibiotic Activity Against Pseudomonas aeruginosa

Metal Ion (Mn^{2+})	Concentration	Amoxicillin 30 µg/ml (mm)	Ampicillin 30 µg/ml (mm)	Erythromycin 30 µg/ml (mm)	Ciprofloxacin 30 µg/ml (mm)
		AMX	AMP	ERY	CIP
Mn^{2+}	0 mM	0	0	0	28
Mn^{2+}	1 mM	0	0	0	24
Mn^{2+}	2 mM	0	0	0	24
Mn^{2+}	5 mM	0	0	0	22
Mn^{2+}	10 mM	0	0	0	18

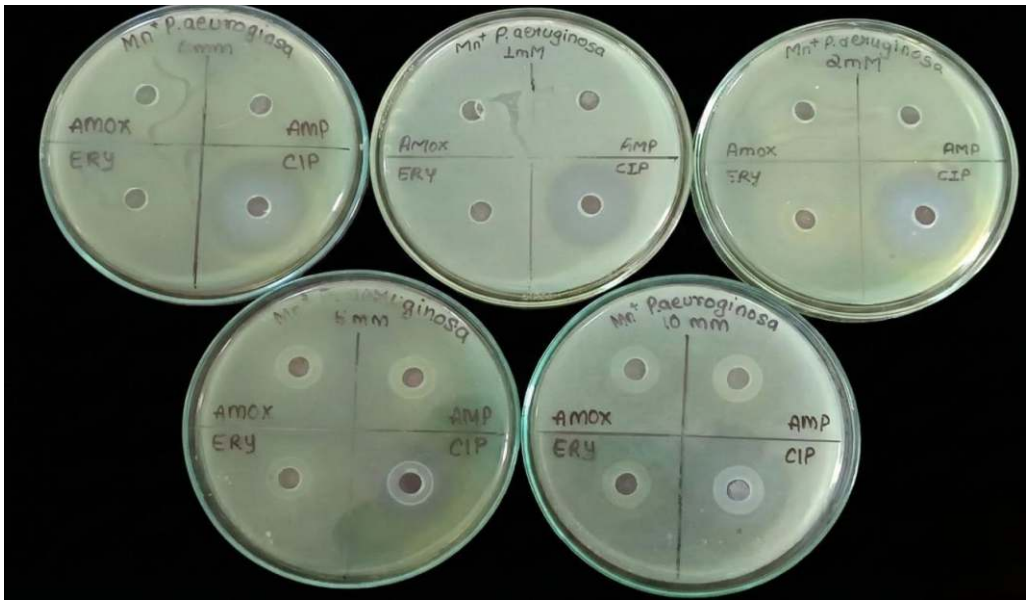

Figure 3. Petri plate image showing Pseudomonas aeruginosa inhibition zones under Mn^{2+} ion treatment

4) Effect of NH_4^+ on Antibiotic Activity Against *Serratia marcescens*

Table 4: Effect of NH_4^+ on Antibiotic Activity Against Serratia marcescens

Metal Ion ($NH4^+$)	Concentration	Amoxicillin 30 µg/ml (mm)	Ampicillin 30 µg/ml (mm)	Erythromycin 30 µg/ml (mm)	Ciprofloxacin 30 µg/ml (mm)
		AMX	AMP	ERY	CIP
NH_4^+	0 mM	0	0	0	30
NH_4^+	1 mM	0	0	0	28
NH_4^+	2 mM	0	0	0	26
NH_4^+	5 mM	0	0	0	30
NH_4^+	10 mM	0	0	0	30

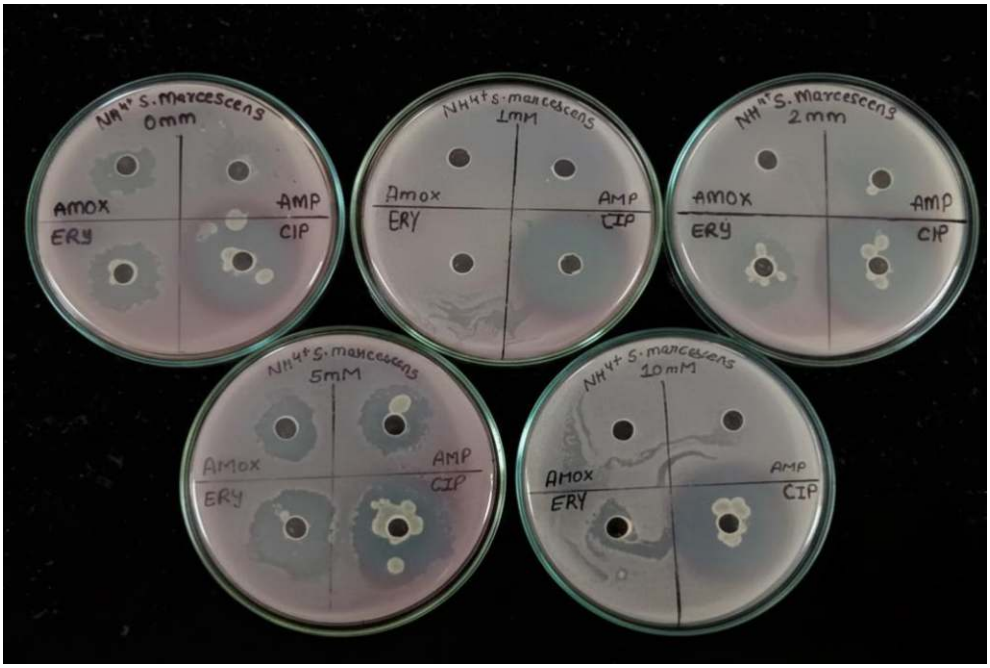

Figure 4. Petri plate image showing Serratia marcescens inhibition zones under NH_4^+ Ion treatment

Discussion

These results highlight that metal ions have selective and concentration-dependent physicochemical effects on the antibiotic activity with significant values for food science, microbial ecology and food biotechnology. In all investigated organisms, the interaction of metal ions with antibiotics is compatible with cell-wall structure, metabolic needs and open cycle drug–metal chelation. In all, Fe^{2+} and Mg^{2+} had the most pronounced 'suppressor' properties, reducing there being activity of many antibiotics in *E. coli* and *S. aureus*, respectively. These results indicate that metal-enriched contexts that are prominent in meats, dairy products, processed foods and water systems can change the rate of drug diffusion, binding or uptake as well as modify the microbial susceptibility.

In *E. coli,* Fe^{2+} demonstrated not only a potent inhibition of erythromycin but also progressive loss of ciprofloxacin activity, both consistent with known Fe^{2+}–macrolide and Fe^{2+}-fluoroquinolone binding effects. This underscores the possibility that iron-containing edible products or equipment surfaces may still serve as a refuge for pathogen survival even after antimicrobial applications. In *S. aureus*, Mg^{2+} concentrations above 10 mM abrogated all β-lactam and fluoroquinolone activity. Magnesium is enriched in dairy, sources of fermentation, and animal tissue, while the stabilization of Gram-positive cell walls may account for the drug interference seen. This result might be particularly important for food environments in which magnesium salts are used as fortificants or buffering agents.

Mn^{2+} had a specific impact on *P. aeruginosa* and decreased ciprofloxacin activity without affecting drugs with no intrinsic effect. This is consistent with the organism's reliance on manganese-induced oxidative-stress pathways. Food-processing waterlines with mineral deposits may thus inadvertently select for low-antibiotic-sensitive *P. aeruginosa.* Conversely, NH_4^+ had weak preferences for *S. marcescens* , and ciprofloxacin activity remained constant. This suggests that spoilage environments determined rich in ammonium will unlikely modify antimicrobial effectiveness for this species.

In general, the study demonstrates that antibiotic efficacy is influenced by food matrices, processing parameters, mineral supplements and environmental metal contamination. These interactions are all the more relevant given current trends in the food industry, which emphasize molecular and bioprocess-oriented solutions for safety. These observations are consistent with a recent call for combined antimicrobial approaches, which include the matrix state in which the microorganisms dwell, rather than chemical compounds alone.

Conclusion

The current work reinforces the importance of metal ions in fine-tuning selective antibiotic activity against major foodborne pathogens, shown to have species- and drug-dependent character. Fe^{2+} and Mg^{2+} exerted the strongest inhibitory effects, significantly compromising the activity of multiple classes of antibiotics, whereas Mn^{2+} specifically decreased ciprofloxacin activity in

P. aeruginosa. NH_4^+ was a less interfering ion with weak modulation in *S. marcescens*. These results highlight the need for an understanding of metal exposure in food and clinical environments because physicochemical interactions such as these can affect antimicrobial activity, contribute to apparent resistance, and affect the success of contamination control measures. More generally, the findings underscore the importance of incorporating environmental chemistry into food biotechnology and safety protocols. Knowledge of the effects of metallic ions on antimicrobial activity can be used to improve processing strategies, modify risk assessment models and develop better engineering methods for reducing microbial hazards. This research contributes to the metal-informed design of antimicrobials for a safer food chain and in support of the global challenge against AMR.

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