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Antibacterial activity and mechanistic insights of gallium-based nanoparticles: an emerging frontier in metal-based antimicrobials

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The global rise of antimicrobial resistance has intensified the search for novel therapeutic agents that act through non-conventional mechanisms. Gallium-based nanoparticles (GaNPs) represent a promising yet underexplored class of metal-based antimicrobials. Owing to their unique ability to mimic iron(III), GaNPs disrupt key bacterial metabolic processes, particularly those dependent on iron acquisition and utilization. This mini-review provides an overview of recent advances in the development and application of GaNPs for antibacterial therapy. Emphasis is placed on their mechanisms of action, spectrum of activity, and potential biomedical applications. The review also discusses emerging insights into bacterial responses to gallium, including resistance dynamics and synergy with existing antibiotics. As an innovative approach to combat multidrug-resistant pathogens, GaNPs offer a compelling alternative to traditional antimicrobials.

1. Introduction

The escalating global health crisis of antimicrobial resistance (AMR) represents one of the most pressing medical challenges of the 21st century. Conventional antibiotics are rapidly losing efficacy against a growing number of multidrug-resistant pathogens, prompting an urgent need for novel antimicrobial agents that operate through alternative and non-traditional mechanisms.[1–3] In recent years, metal-based nanoparticles (MNPs) have emerged as a promising class of therapeutic agents owing to their broad-spectrum activity and ability to engage multiple microbial targets simultaneously. Their physicochemical versatility enables them to disrupt bacterial membranes, generate reactive oxygen species, interfere with DNA replication, and inhibit critical metabolic pathways, often with reduced risk of resistance development.[4–6]

Among the various metallic nanoparticles investigated, gallium-based nanoparticles (GaNPs) have garnered increasing attention due to their unique mechanism of action rooted in bioinorganic chemistry. Gallium(III) closely resembles iron(III) in ionic radius and coordination behaviour, allowing it to hijack bacterial iron acquisition systems. However, unlike iron, gallium is redox-inactive under physiological conditions and cannot fulfill the catalytic roles of iron in enzymatic processes. As a result, gallium effectively disrupts iron-dependent bacterial pathways, impairing essential functions such as DNA synthesis, respiration, and biofilm formation.[7,8] This iron mimicry without redox functionality not only inhibits bacterial growth and virulence but also limits adaptive resistance, making GaNPs a particularly attractive candidate for addressing infections caused by iron-dependent and biofilm-forming pathogens.[8,9]

This review explores the antibacterial activity and underlying mechanisms of gallium-based nanoparticles, highlighting their emerging role as a potent, metal-based antimicrobial strategy in the fight against drug-resistant infections.

2. Overview of gallium and its antibacterial properties

Gallium (Ga), a group 13 post-transition metal, has gained increasing scientific and biomedical attention due to its

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distinctive chemical behaviour and promising antimicrobial potential. A key feature that underpins gallium's biological activity is its remarkable chemical mimicry of iron(III), particularly in terms of ionic radius, coordination number, and overall trivalent charge. This structural similarity allows gallium to hijack bacterial iron acquisition pathways, which are vital for numerous microbial processes, including DNA synthesis, respiration, and oxidative stress management.[10,11] However, unlike iron, which cycles between Fe^{2+} and Fe^{3+} oxidation states to catalyze redox reactions essential to life, Ga^{3+} remains redox-inactive under physiological conditions. This single but significant difference enables gallium to function as a "Trojan horse" within microbial cells. Once taken up *via* siderophore-mediated or heme-uptake mechanisms, gallium is incorporated into iron-binding proteins and enzymes but cannot perform the requisite redox chemistry, leading to disruption of critical metabolic pathways and ultimately bacterial cell death.[12–15]

This iron mimicry without redox competence forms the mechanistic basis for gallium's potent antimicrobial action. Gallium-based nanoparticles (GaNPs) exploit this feature further by enhancing gallium's cellular delivery and interaction with bacterial iron-dependent systems. Importantly, several physicochemical properties of GaNPs have been shown to critically influence their antimicrobial efficacy and spectrum of activity. Among these, particle size is particularly impactful; nanoparticles in the range of 10–100 nm has been demonstrated to facilitate optimal uptake through bacterial membranes and biofilm matrices, increasing intracellular gallium concentration. Smaller nanoparticles generally exhibit higher surface area-to-volume ratios, enhancing ion release and biological interaction.[16] Additionally, surface charge plays a pivotal role—positively charged GaNPs more effectively adhere to negatively charged bacterial surfaces, increasing their local concentration at the infection site and improving antimicrobial performance. Morphology, such as spherical or rod-like shapes, also influences interaction with bacterial membranes and cellular uptake. These structural characteristics collectively determine how effectively GaNPs can reach and disrupt their microbial targets.[17,18]

Despite the significant progress in designing bioactive GaNPs, challenges remain with respect to the reproducibility and scalability of their synthesis. Achieving consistent control over nanoparticle size distribution, surface charge, crystallinity, and chemical composition is essential for ensuring batch-to-batch uniformity in both experimental and clinical settings. Minor fluctuations in synthesis parameters—such as pH, temperature, solvent system, precursor purity, or stabilizing agents—can lead to considerable variability in physicochemical properties, which in turn affects antimicrobial performance. Moreover, while laboratory-scale synthesis techniques such as sol–gel, hydrothermal, or co-precipitation methods have demonstrated promise, scaling these methods up to industrial production levels without sacrificing quality and consistency remains a non-trivial challenge. These factors must be carefully optimized to enable future translational applications and regulatory approval. However, as previously noted, detailed synthetic procedures and scalability evaluations are outside the direct scope of this current study. Our focus remains on the biological interactions and mechanistic underpinnings of gallium's antimicrobial efficacy, although we acknowledge these technical aspects are critical to the compound's translational potential.[7,8]

The combination of gallium's unique redox-inert iron mimicry, targeted uptake *via* microbial iron-scavenging systems, and the ability to tailor its delivery through engineered nanoscale formulations makes GaNPs a particularly attractive strategy against antimicrobial resistance. Their selective disruption of bacterial iron metabolism—without significantly impairing mammalian cells—offers a safer, mechanistically distinct alternative to conventional antibiotics. These attributes reinforce gallium's role as a next-generation antimicrobial agent, especially as multidrug-resistant infections become a growing global health concern.

3. Mechanisms of antibacterial action

3.1 Iron mimicry and disruption of iron–dependent pathways

Gallium's antibacterial efficacy primarily derives from its chemical and structural mimicry of iron(III) (Fe^{3+}), allowing it to exploit bacterial iron acquisition systems, which are fundamental to microbial growth, metabolism, and virulence. Bacteria have evolved intricate and highly regulated mechanisms for acquiring iron due to its essential role in numerous enzymatic and redox reactions. Under iron-deprived conditions—often imposed by the host's nutritional immunity during infection—bacteria upregulate a range of iron uptake pathways to ensure survival. These include siderophore-mediated transport systems, the Feo system for ferrous (Fe^{2+}) uptake, ATP-binding cassette (ABC) transporters such as HitABC for ferric (Fe^{3+}) uptake, and heme acquisition proteins. As shown in Fig. 1, these diverse systems work collectively to scavenge iron from the extracellular environment, internalize it, and incorporate it into iron-dependent proteins.[19,20]

While GaNPs primarily target bacterial iron metabolism by mimicking Fe^{3+} and disrupting iron-dependent processes, emerging evidence suggests that gallium can also influence other aspects of bacterial metal homeostasis and general cellular metabolism. Due to overlapping pathways or shared transporters, GaNPs may interfere with the uptake and regulation of other essential metal ions such as manganese and copper, potentially causing broader disruptions in metal ion balance. Furthermore, gallium's interference with iron-dependent enzymes and redox reactions indirectly impacts cellular energy metabolism and oxidative stress responses. Although these off-target effects are less well-characterized, they contribute to the multifaceted antimicrobial action of GaNPs, enhancing their efficacy beyond simple iron mimicry. This comprehensive view underscores the potential of GaNPs to disrupt multiple bacterial metabolic pathways critical for survival and pathogenicity.[19,20]

Gallium(III) (Ga^{3+}), by virtue of its close physicochemical similarity to Fe^{3+}—including nearly identical ionic radii and coordination geometries—can hijack these iron uptake

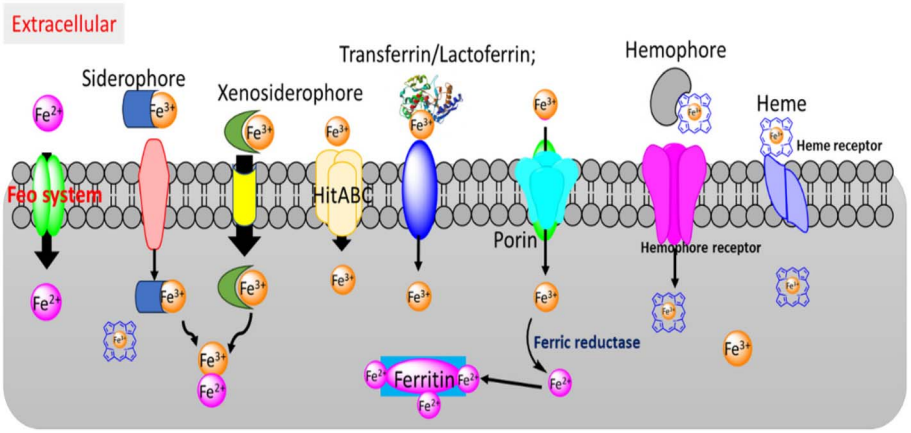

Fig. 1 Bacterial iron/heme uptake pathways. Feo system: bacterial ferrous iron transport. HitABC: a ferric iron ABC transport system. Ferritin: there are two types of bacterial iron storage proteins, bacterial ferritin and bacterioferritin.[21]

pathways. Importantly, gallium is able to form stable complexes with siderophores and heme analogs, thereby entering the bacterial cell *via* the very systems designed for iron acquisition. However, unlike Fe^{3+}, Ga^{3+} is redox-inactive under physiological conditions. This fundamental difference becomes biologically disruptive once gallium is internalized, as many essential bacterial processes rely on iron's redox cycling between Fe^{2+} and Fe^{3+}. Consequently, gallium substitution leads to irreversible inhibition of these processes, severely compromising bacterial viability.

One of the most critical intracellular targets disrupted by gallium is ribonucleotide reductase (RNR)—a highly conserved, iron-dependent enzyme responsible for converting ribonucleotides into deoxyribonucleotides, the building blocks of DNA. By mimicking Fe^{3+}, Ga^{3+} competes for the iron-binding site within RNR but fails to support the redox chemistry required for catalysis. This interference effectively halts DNA synthesis. Choi *et al.* (2024) provided compelling evidence that Ga^{3+} forms biologically inert complexes with nucleotide diphosphates, preventing their proper engagement with RNR, thus stalling DNA replication and cell proliferation.[22]

In addition to RNR, gallium disrupts the bacterial electron transport chain, particularly the function of cytochromes, which are heme-containing proteins essential for respiration. Gallium can substitute into the heme-binding sites of these proteins when introduced in the form of gallium protoporphyrin IX (GaPP)—a structural analog of heme. Once incorporated, GaPP binds to cytochromes but is unable to undergo the necessary electron transfer reactions, thereby collapsing the proton motive force and inhibiting ATP synthesis. This mechanism has been shown to have potent bactericidal effects, even against multidrug-resistant strains. Zhang *et al.* (2023) demonstrated that water-soluble GaPP analogs inhibit bacterial respiration by targeting these heme-dependent systems, further emphasizing the critical role of iron-mimicry in gallium's antibacterial action.[21]

The specificity of Ga^{3+} delivery is further enhanced by its ability to form conjugates with bacterial siderophores—molecules that bacteria secrete to bind and import extracellular iron. Gallium–siderophore complexes, such as those formed with desferrioxamine (DFO) or native siderophores like pyochelin and mycobactin, are actively transported into bacterial cells *via* high-affinity siderophore receptors. Once inside, the Ga^{3+} exerts its toxic effects by substituting for iron in essential enzymes, rendering them inactive. Studies involving Ga(III)–DFO complexes have consistently shown improved antibacterial efficacy compared to gallium salts alone, highlighting the importance of targeted delivery through iron acquisition pathways. In *Mycobacterium tuberculosis*, which utilizes unique siderophores such as mycobactin and carboxymycobactin, gallium-based therapies have shown iron-reversible growth inhibition, further validating the approach of exploiting siderophore-mediated uptake for antimicrobial action.[19,20]

Moreover, beyond siderophore pathways, gallium-based compounds can exploit bacterial heme acquisition systems. Some bacteria express specialized receptors and transporters to scavenge heme from the host. Gallium-substituted heme analogs, such as GaPP, are recognized and transported *via* these heme uptake mechanisms. Once internalized, they integrate into the bacterial respiratory chain, but due to gallium's redox inactivity, they arrest the electron transfer process critical for cellular respiration. This not only leads to ATP depletion but also to the buildup of toxic metabolic intermediates. Mechanistically, this process is outlined in Fig. 2, which illustrates how gallium compounds, by mimicking iron or heme, are selectively internalized and subsequently interfere with intracellular redox-dependent enzymes such as RNR and cytochromes.

The structural mimicry of Ga^{3+} at the molecular level enables it to act as a "Trojan horse" within bacterial cells. By hijacking iron uptake pathways and irreversibly binding to iron-dependent enzymes, GaNPs (gallium nanoparticles) create a multifaceted antibacterial strategy. This mode of action is particularly valuable because it exploits bacterial vulnerabilities intrinsic to their iron metabolism and biosynthetic machinery—traits that are not easily circumvented through

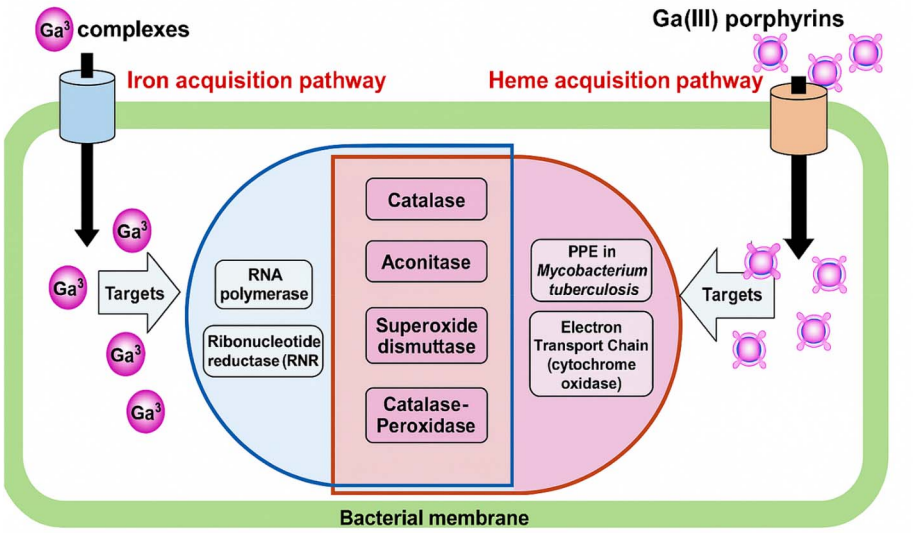

Fig. 2 Schematic diagram of the uptake of gallium-based compounds through iron/heme acquisition pathways and their proposed intracellular targets.[21]

traditional resistance mechanisms. Furthermore, since gallium targets fundamental metabolic processes rather than cell wall biosynthesis or protein translation, the likelihood of developing cross-resistance with existing antibiotics is minimal. This positions gallium-based antimicrobials as a promising therapeutic strategy in the ongoing battle against antimicrobial resistance.

Duffin and Andrews (2023) offer valuable insights into the mechanism by which gallium exerts antibacterial effects through its interference with bacterial iron acquisition systems, aligning with the understanding that gallium acts as a competitive inhibitor of iron uptake.[23] The study investigates a series of dimethylgallium quinolinolate complexes, [$GaMe_2L$], for their antibacterial activity against drug-resistant strains of *Klebsiella pneumoniae*. Crucially, the compounds exhibited potent activity only in iron-depleted environments, such as RPMI-HS media, while remaining inactive in iron-rich LB broth. This highlights the central role of iron scarcity in facilitating gallium's antibacterial mechanism, as bacteria activate high-affinity iron acquisition pathways under such conditions. These findings support the model wherein gallium enters bacterial cells *via* iron uptake pathways—particularly siderophore-mediated mechanisms—but, unlike iron, gallium is redox-inactive and cannot participate in essential redox reactions, thereby inhibiting key iron-dependent enzymes like ribonucleotide reductase and cytochromes.

In the context of iron acquisition, the activity profile of these gallium complexes reflects bacterial reliance on iron transport systems under iron-limited conditions. Gallium's mimicry of Fe(III) enables it to hijack these transport routes; however, once internalized, its inability to engage in redox cycling renders it biologically disruptive. As detailed in the study, the [$GaMe_2L$] complexes show minimal exchange with iron-binding proteins at early time points and maintain structural integrity in biological media, thereby resisting rapid sequestration by host proteins. This slower uptake into iron-binding proteins (Fig. 3) is hypothesized to increase the likelihood of gallium entering bacterial cells *via* siderophore-mediated or other iron transport mechanisms, bypassing premature host clearance and enhancing antimicrobial potency. This mechanistic insight strengthens the concept of exploiting gallium's iron-mimicking behaviour while capitalizing on its biochemical inertness to sabotage iron-dependent bacterial metabolism.

The delayed exchange of these gallium complexes with host proteins, even after 24 hours, as evidenced by the low initial and gradual increase in gallium incorporation into the protein phase, further supports their improved pharmacological profile compared to traditional gallium salts. In standard gallium compounds like gallium nitrate or citrate, rapid hydrolysis and transformation into highly soluble gallate forms reduce bioavailability. Conversely, the [$GaMe_2L$] complexes retain a degree of lipophilicity and hydrolytic stability, favouring their cellular uptake and persistence in physiological environments, and likely enhancing their interaction with bacterial iron transporters. These properties contribute to their observed efficacy against multi-drug-resistant *K. pneumoniae* and underline the potential of tailored organogallium compounds in targeting iron uptake pathways for antimicrobial therapy. This study underscores the therapeutic strategy of leveraging bacterial iron acquisition mechanisms to facilitate gallium uptake, with gallium then acting as a redox-inactive disruptor of critical iron-dependent enzymatic systems. The observed media-dependent activity of the dimethylgallium quinolinolate complexes reaffirms the necessity of low-iron physiological conditions for gallium's antibacterial efficacy, in accordance with its mode of entry and mechanism of action. Fig. 3 effectively illustrates this concept by highlighting how these compounds interface with bacterial iron pathways and

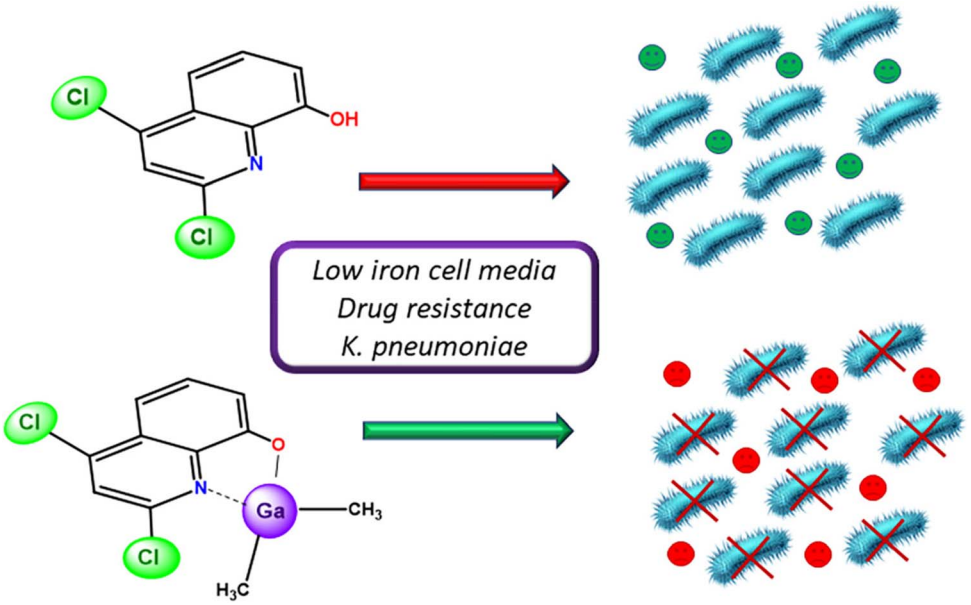

Fig. 3 The enhanced anti-bacterial activity of four dimethyl gallium 8-quinolinol complexes was determined in physiological relevant low-iron media. Exceptional activity was observed toward a multi-drug resistance strain of the ESKAPE pathogen *K. pneumoniae*. Protein-uptake studies suggest the methyl substituted complexes do not undergo rapid uptake or exchange with iron-binding proteins.[23]

underscores their intracellular targets. As such, this work exemplifies a precise alignment with the mechanism of gallium as a competitive, non-functional iron mimic that ultimately impairs bacterial survival by targeting iron metabolism.

Kelson *et al.* (2013) emphasized this concept by demonstrating that gallium complexes can hijack siderophore and heme uptake routes to enter bacterial cells, acting as iron mimics but without fulfilling iron's biological roles.[24] This "Trojan horse" mechanism differentiates gallium from conventional antibiotics and makes it particularly attractive in the face of mounting antimicrobial resistance.

The effectiveness of gallium in mimicking iron was further elaborated by Kircheva *et al.* (2024), who explored gallium's competition with ferric ions for binding to pyochelin and pyoverdine, the principal siderophores of *Pseudomonas aeruginosa*.[20] Through computational models, they demonstrated that gallium formulations such as gallium nitrate and gallium maltolate effectively compete with iron for siderophore binding, thereby allowing gallium entry through established iron uptake pathways. Once inside, its inability to participate in redox reactions renders iron-dependent bacterial systems dysfunctional. This competitive inhibition is not only pivotal for gallium's antimicrobial activity but also helps prevent resistance development, as altering iron uptake systems could severely compromise bacterial viability.

Extending this mechanistic insight, Kircheva and Dudev (2020) investigated the thermodynamic factors governing gallium's affinity for various siderophores under physiological conditions.[20] Their findings underscored the importance of ligand denticity, charge, and environmental pH in dictating Ga^{3+}/Fe^{3+} competition. These subtle physicochemical variations determine whether gallium can outcompete iron for transport into bacterial cells. This adds a critical layer of understanding to gallium's mechanistic action, reinforcing the need to design gallium compounds that optimally engage with bacterial iron-binding structures.

The direct consequence of gallium's interference in iron metabolism was experimentally demonstrated by Goss *et al.* (2018), who reported that gallium exposure resulted in the inhibition of iron-dependent enzymes in *Pseudomonas aeruginosa*, thereby impairing bacterial growth and increasing oxidative stress.[16] Their *ex vivo* and *in vivo* data showed that gallium reduced bacterial viability in sputum from cystic fibrosis patients and improved lung function in clinical trials. Importantly, gallium's activity did not provoke rapid resistance nor did it suppress host immune function, highlighting its promise as a novel therapeutic agent grounded in metabolic disruption rather than conventional bactericidal mechanisms.

Minandri *et al.* (2014) also emphasized that gallium's antimicrobial efficacy is closely tied to environmental iron levels and the metabolic state of the bacterial cell.[25] They showed that gallium is especially potent under iron-depleted conditions, which closely resemble the *in vivo* environment. By replacing iron in cellular targets without supporting the necessary redox reactions, gallium induces profound metabolic disturbances in respiring and fast-growing bacteria. This aligns with the mechanism of iron mimicry leading to lethal functional blockades within the microbial cell.

Best *et al.* (2020) further expanded gallium's application by embedding it into biopolymeric carriers, such as carboxymethyl cellulose, which acted as bioresponsive delivery platforms. These systems ensured targeted gallium release, enabling gallium to effectively enter bacteria *via* iron uptake routes while minimizing cytotoxicity to human cells. Notably, the gallium-

loaded carriers consistently inhibited bacterial growth across both Gram-negative and Gram-positive strains, illustrating the robustness of this iron-competition-based strategy.

Scott *et al.* (2023) consolidated the therapeutic promise of gallium by discussing its potential to become a class-defining antimicrobial targeting bacterial iron metabolism. The review covered gallium's activity against ESKAPE pathogens and its synergistic potential when used alongside traditional antibiotics. This synergy likely arises because gallium disrupts iron acquisition, a metabolic bottleneck, while conventional antibiotics attack structural or reproductive pathways, providing a multipronged attack that bacteria struggle to resist.

The mechanistic theme continues with the work of Wang *et al.* (2024), who designed a novel gallium-based nanostructure where gallium ions were released from polydopamine-coated nanocores.[26] This system enhanced bacterial uptake *via* iron transport mechanisms and allowed *in situ* formation of silver nanoparticles for additional antibacterial effects. The gallium ions, once internalized, replicated the iron mimicry mechanism—disrupting redox enzyme systems—while photothermal enhancement through NIR laser irradiation delivered near-complete bacterial eradication. *In vivo* studies confirmed the efficacy of this platform in eliminating *MRSA* infections and promoting tissue repair, making it an exemplary model of how gallium's metabolic interference can be clinically harnessed.

The study by Duffin and Andrews (2023) adds further mechanistic depth by showing how dimethylgallium quinolinolate complexes exhibit potent antibacterial activity specifically in iron-poor media, a condition that maximizes gallium uptake through siderophore-mediated transport.[23] In standard LB broth, the complexes were inactive, but in iron-depleted RPMI-HS, they demonstrated remarkable activity in the nanomolar range. This reinforces the central role of iron competition in gallium efficacy. Their protein binding studies confirmed that these organometallic gallium complexes do not rapidly exchange with iron-binding proteins, suggesting prolonged bioavailability and increased uptake through bacterial iron acquisition pathways rather than immediate sequestration by host proteins. This slow exchange, alongside hydrolytic stability, ensures that the gallium remains available for bacterial targeting long enough to disrupt iron-dependent processes, thus maximizing therapeutic outcomes.

In totality, these studies construct a cohesive and compelling narrative around gallium's role as a competitive inhibitor of bacterial iron acquisition. Whether delivered as simple salts, organometallic complexes, or within advanced nanoplatforms, gallium's capacity to mimic iron yet fail to engage in essential redox biology constitutes its primary antibacterial mechanism. This strategy subverts a vital nutrient pathway and incapacitates core metabolic functions, offering a promising avenue for addressing antimicrobial resistance through a mechanistically distinct, metabolism-based approach.

3.2 Inhibition of biofilm formation

The inhibitory effect of gallium-based nanoparticles (GaNPs) on biofilm formation has garnered considerable attention in recent years, driven by the increasing prevalence of antibiotic-resistant infections, especially those associated with persistent biofilms. Biofilms—structured communities of bacteria embedded within a self-produced extracellular polymeric substance (EPS) matrix—pose a formidable challenge in clinical settings. This matrix not only shields bacteria from immune responses but also significantly reduces the efficacy of antimicrobial agents, contributing to chronic and recurrent infections. Among the most clinically significant biofilm-forming pathogens are *Pseudomonas aeruginosa* and *Staphylococcus aureus*, notorious for their resilience and roles in conditions such as cystic fibrosis-associated pneumonia, chronic wound infections, osteomyelitis, and device-related infections. GaNPs have emerged as promising anti-biofilm agents due to their unique mechanism that targets critical bacterial pathways involved in biofilm development and maintenance, particularly bacterial iron metabolism and quorum sensing.[27,28]

Gallium's effectiveness lies in its ability to mimic iron (Fe^{3+}), an essential nutrient that bacteria require for growth and biofilm maturation. However, unlike iron, gallium cannot undergo redox cycling under physiological conditions, rendering it catalytically inactive in biological systems. This property enables a "Trojan horse" strategy where gallium is actively taken up by bacterial iron acquisition systems, but once inside the cell, it sabotages downstream iron-dependent metabolic processes. This disruption has a pronounced effect on bacterial growth and viability, particularly within the iron-deprived microenvironments found in biofilm cores. Moreover, quorum sensing—the bacterial communication mechanism that regulates biofilm formation, virulence factor production, and resistance gene expression—is intimately linked to iron availability. By interfering with iron uptake and intracellular iron homeostasis, GaNPs indirectly suppress quorum sensing pathways, effectively inhibiting both the initiation and structural integrity of biofilms.[29,30]

This dual mechanism—disrupting iron metabolism and interfering with quorum sensing—has been visualized and validated in several experimental studies and is succinctly illustrated in Fig. 4, which depicts the inhibitory effect of GaNPs on biofilm formation by *P. aeruginosa* and *S. aureus*. As shown, GaNPs impair essential signaling and metabolic pathways required for biofilm maturation. Bacteria exposed to GaNPs demonstrate reduced production of key biofilm matrix components such as polysaccharides, extracellular DNA, and proteins, leading to a weakened biofilm architecture that is more permeable and less resistant. This weakening is significant because mature biofilms can exhibit up to 1000-fold greater resistance to antibiotics than free-floating (planktonic) bacterial cells, rendering many conventional treatments ineffective. By disrupting quorum sensing and iron uptake, GaNPs enhance biofilm susceptibility not only to immune clearance but also to co-administered antimicrobial agents.[31,32]

Experimental evidence further supports the effectiveness of GaNPs in not only preventing biofilm formation but also destabilizing established biofilms. Morphological analyses using scanning electron microscopy (SEM) and atomic force microscopy (AFM) have revealed that bacteria within GaNP-

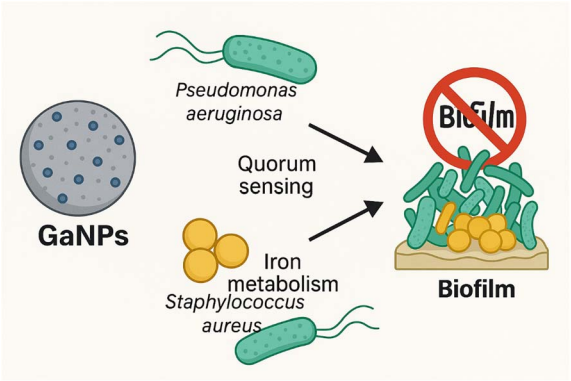

Fig. 4 The inhibitory effect of gallium-based nanoparticles (GaNPs) on biofilm formation in *Pseudomonas aeruginosa* and *Staphylococcus aureus*. GaNPs disrupt bacterial quorum sensing and iron acquisition pathways, impairing biofilm maturation and enhancing susceptibility to treatment.

treated biofilms undergo significant surface damage, exhibit irregular shapes, and show a marked reduction in extracellular matrix content. These structural disruptions correlate with biofilm collapse, improved penetration of antibiotics, and increased bacterial cell death. Importantly, gallium's antibiofilm activity is broad-spectrum, acting against both Gram-negative bacteria like *P. aeruginosa* and Gram-positive bacteria such as *S. aureus*, underscoring its versatility in targeting diverse pathogenic biofilms.[31,32]

An additional advantage of gallium-based therapies is their reduced propensity to induce bacterial resistance. Unlike traditional antibiotics that target specific molecular pathways, gallium's mechanism exploits essential iron-dependent metabolic and regulatory processes that are less amenable to compensatory mutations. The iron mimicry and metabolic sabotage exerted by GaNPs challenge bacterial survival at a fundamental level, making resistance development difficult. This distinction is crucial in an era of escalating antimicrobial resistance.[33–35]

The comprehensive mechanistic insights into GaNPs' mode of action demonstrate their capacity to inhibit biofilm formation, disrupt existing biofilm structures, and potentiate antimicrobial treatments. The illustration in Fig. 4 highlights this multifaceted effect, showing how GaNPs interfere with quorum sensing and iron acquisition to render biofilms vulnerable. Consequently, GaNPs represent a promising adjunct or alternative to conventional antibiotics for combating persistent biofilm-associated infections caused by *P. aeruginosa*, *S. aureus*, and other problematic pathogens.[7,16]

In this context, the work of Xie *et al.* (2021) provides compelling evidence for the potential of gallium-based nanomaterials to combat multidrug-resistant (MDR) bacterial infections through innovative mechanisms.[36] The study describes the development of ultrasmall, non-antibiotic nanoparticles (ICG-Ga NPs) composed of clinically approved gallium(III) and liver-targeting indocyanine green (ICG), designed to synergistically disrupt bacterial viability through photodynamic therapy (PDT) and iron metabolism interference. Upon exposure to 808 nm laser irradiation, the photodynamic effect damages bacterial membranes, facilitating enhanced Ga^{3+} uptake. Once inside the bacteria, Ga^{3+} disrupts iron metabolism by substituting for Fe^{3+}, thereby impairing essential cellular processes and leading to bactericidal effects. This dual action not only eradicates planktonic bacterial cells, such as extended spectrum β-lactamase (ESBL)-producing *E. coli*, but also effectively inhibits biofilm formation. As shown in Fig. 5, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) analyses reveal extensive morphological damage to bacterial cells treated with ICG-Ga NPs and laser, including wrinkled cell surfaces, lesions, and loss of internal contents. Elemental mapping further confirms Ga^{3+} accumulation at damaged sites, suggesting targeted interaction with bacterial membranes (Fig. 5A–C). Crucially, the biofilm elimination capability was visually confirmed *via* fluorescence microscopy, where the combination of ICG-Ga NPs and laser exposure resulted in near-complete eradication of biofilms, unlike in control or ICG-only groups (Fig. 5D). These findings align with the broader evidence that gallium's interference with quorum sensing, and iron metabolism underlies its potent antibiofilm action. The results underscore the potential of Ga-based nanoplatforms as a next-generation strategy for managing resistant infections, particularly where biofilm resilience poses a significant clinical challenge.

This growing body of evidence is further reinforced by He *et al.* (2024), who tackled the problem of dormant bacteria within biofilms—bacteria which typically exhibit low metabolic activity and are highly resistant to antibiotics.[37] They developed an aerosolized nanosystem integrating gallium and catalase, modified with maltohexaose for specificity to *P. aeruginosa*, to reverse the hypometabolic state of these bacteria. By reconciling the oxygen gradient within the biofilm, their strategy effectively "woke up" the dormant bacteria, increasing metabolic activity and iron demand. As gallium mimics iron but disrupts its metabolic roles, the metabolically reactivated bacteria internalized more Ga^{3+}, which subsequently interfered with iron acquisition, utilization, biofilm formation, and quorum sensing pathways. This study supports the notion that gallium's biofilm-disrupting properties are intricately tied to its ability to hijack bacterial iron metabolism and exploit their physiological stress responses, particularly under nutrient-limited and hypoxic biofilm conditions.

This understanding connects seamlessly with findings from Limantoro *et al.* (2023), who further emphasized the unique role of GaNPs in targeting biofilms, even when they do not inhibit planktonic bacterial growth.[38] In their study, gallium nanoparticles were tested against various clinical strains of *P. aeruginosa* and *Acinetobacter baumannii*. Interestingly, while GaNPs showed negligible effects on bacterial proliferation in suspension cultures, they induced profound morphological disruptions in biofilms. Using atomic force microscopy, they revealed that both *P. aeruginosa* DFU53 and multidrug-resistant *A. baumannii* biofilms developed rough, irregular surface features upon treatment with GaNPs. This morphological destabilization, though occurring independently of classical bactericidal

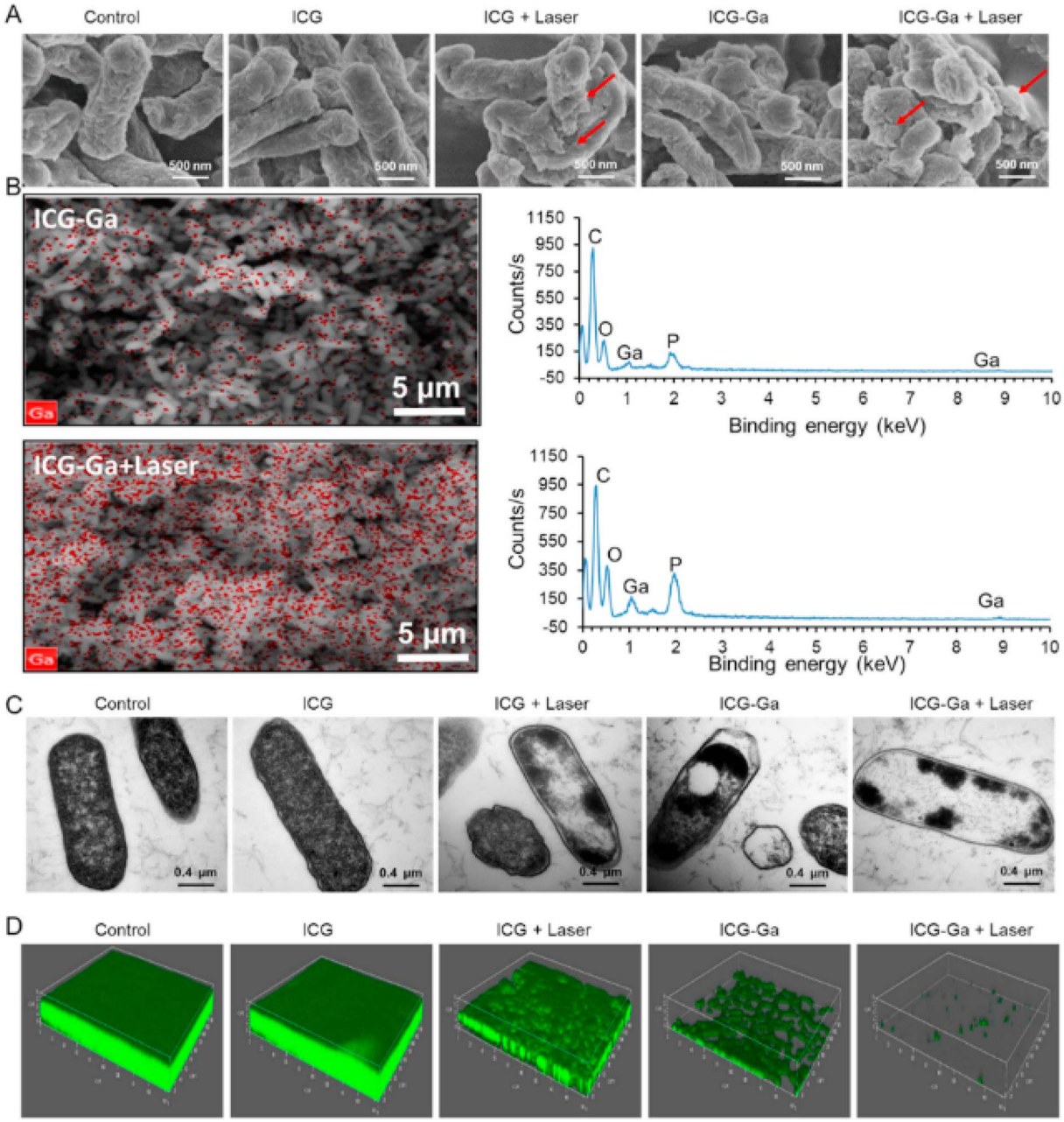

Fig. 5 *In vitro* bactericidal effect and inhibiting biofilm formation of ICG-Ga NPs against ESBL *E. coli*. (A) The SEM images of ESBL *E. coli* after different treatment and (B) the respective mapping analysis. (C) TEM images of the treated ESBL *E. coli*. (D) 3D confocal laser scanning microscopy images (size: 630 μm × 630 μm) of ESBL *E. coli* biofilms after different treatments. Biofilms were stained by SYTO9. The live bacteria can be observed with green fluorescence.[36]

effects, underscores gallium's role in altering biofilm integrity, potentially through interference with structural components or extracellular matrix formation, again reinforcing the role of gallium in modulating biofilm-specific metabolic or regulatory pathways rather than merely exerting direct bactericidal activity.

The observations made by Limantoro *et al.* (2023) are further extended by Xia *et al.* (2021), who provided a detailed mechanistic insight into gallium's role in breaking down mature biofilms, particularly in *Staphylococcus aureus*.[38] Their work demonstrated that gallium can reduce the antibiotic tolerance of methicillin-resistant *S. aureus* (MRSA) biofilms by inducing eDNA-dependent dispersal of the biofilm matrix. Gallium-treated biofilms displayed disrupted three-dimensional architecture and reduced extracellular matrix integrity, resembling the structural features of immature biofilms. Notably, these altered biofilms became more susceptible to antibiotics, and when gallium treatment was followed by low-dose vancomycin, complete eradication of biofilm-embedded MRSA was achieved within a week. This study not only reiterates the importance of gallium in biofilm dispersal but also introduces a valuable

strategy of combining gallium with conventional antibiotics to overcome drug resistance by weakening biofilm-mediated defenses.

Similarly, Shamkani *et al.* (2023) reported the effective antibiofilm action of gallium when used in combination with minocycline in niosome-encapsulated formulations against *A. baumannii* in a murine pneumonia model.[32] Their strategy of using biocompatible drug carriers allowed for improved delivery, stability, and sustained release of both drugs, leading to successful disruption of 1-, 3-, and 5-days-old biofilms in clinical lung isolates. The infected lungs treated with gallium-containing niosomes showed significant histological improvements, with reduced inflammation and structural damage. This study demonstrates that Ga^{3+} not only has independent antibiofilm activity but also acts synergistically with conventional antibiotics when appropriately formulated and targeted, aligning with gallium's broader mechanism of weakening biofilm resilience *via* metabolic interference and membrane destabilization.

The foundational basis for many of these findings can be traced back to the pioneering work of Kaneko *et al.* (2007), who first introduced the concept of gallium as a "Trojan horse" that exploits bacterial iron metabolism.[33] They showed that gallium can effectively replace iron in many bacterial systems, thereby disrupting essential iron-dependent pathways such as Fe uptake and signaling *via* regulators like *pvdS*. Importantly, Ga disrupted both planktonic growth and biofilm formation in *P. aeruginosa* and was effective in murine models of lung infection. Their work established that gallium-induced iron deprivation is not just a supportive mechanism but a central axis of gallium's antibacterial and antibiofilm activity. These results offered one of the earliest comprehensive demonstrations of gallium's dual biofilm-disrupting and antibacterial action and underscored the therapeutic potential of exploiting bacterial metabolic vulnerabilities.

Adding to this mechanistic clarity, Sahoo *et al.* (2013) provided molecular-level evidence of GaN nanoparticles disrupting bacterial cells and inhibiting biofilm formation across both Gram-positive and Gram-negative species.[40] Using Raman spectroscopy, they captured changes in microbial vibrational modes, particularly in protein signatures, that confirmed membrane damage and cellular leakage—key indicators of mechanical and metabolic stress. The remarkable inhibition of biofilm formation (>80%) at sub-micromolar concentrations suggested that gallium's effect could be attributed not only to interference with iron metabolism but also to its nanoscale interaction with bacterial cell structures. The close similarity in ionic radius between Ga^{3+} and Fe^{2+} may allow gallium to infiltrate iron-dependent systems at a molecular level, thereby exerting toxicity through both metabolic disruption and structural compromise.

Taken together, this growing body of literature demonstrates a cohesive narrative: GaNPs, through their mimicry of iron and interference with iron-regulated systems, profoundly disrupt biofilm formation and maintenance in multiple clinically relevant bacterial species. Whether by waking dormant bacteria to increase gallium uptake, destabilizing mature biofilms to enhance antibiotic efficacy, or physically compromising bacterial membranes, gallium represents a multifaceted tool in the fight against antibiotic-resistant, biofilm-associated infections.

3.3 Membrane disruption and oxidative stress

Although gallium itself is redox-inactive and does not directly participate in redox cycling like iron, recent studies have uncovered that certain formulations of gallium-based nanoparticles (GaNPs), particularly those involving eutectic gallium–indium alloys (EGaIn), can indirectly induce oxidative stress in bacterial cells, thereby enhancing their antibacterial potency. This surprising capability is strongly formulation-dependent and often synergistic with other components such as metal oxides or specific surface coatings that modulate gallium's bioavailability and interaction with microbial membranes. One compelling example is demonstrated by Li *et al.* (2021), who investigated the antibacterial effects of EGaIn alloys against both Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*.[41] The results revealed complete inhibition of bacterial growth, with antibacterial rates reaching 100%, emphasizing the robust efficacy of this gallium formulation.

The underlying mechanism of bacterial inhibition by EGaIn was multifaceted. First, surface analysis of the EGaIn films and measurements of ion release confirmed the presence of dissolved gallium ions, which mimic Fe^{3+} and interfere with bacterial iron metabolism. However, more strikingly, the study found that exposure to EGaIn also led to substantial generation of reactive oxygen species (ROS) within bacterial cells. This oxidative stress is critical, as it damages cellular macromolecules such as lipids, proteins, and nucleic acids, leading to compromised membrane integrity and eventual cell death. Morphological evaluations using electron microscopy supported this finding, showing significant structural alterations in bacterial cells after exposure to the liquid metal alloy. Cell walls appeared wrinkled, with visible lesions and irregular shapes, indicating severe membrane disruption and stress.

Interestingly, the EGaIn alloy demonstrated even stronger antibacterial effects compared to gallium nitrate solutions at equivalent gallium ion concentrations. This suggests that the liquid metal matrix itself may facilitate a more efficient or sustained delivery of gallium ions or might promote direct physical interaction with bacterial surfaces, intensifying the toxic effect. The enhanced antibacterial activity could also stem from the physical properties of the EGaIn film, including its fluidity and surface tension, which may enable it to spread over and coat bacterial surfaces more effectively, further contributing to mechanical and oxidative damage.

This formulation-dependent behavior of GaNPs reveals the critical importance of nanoparticle design in achieving optimal antibacterial activity. By harnessing the unique physicochemical characteristics of materials like EGaIn, researchers can create multi-functional nanomaterials that not only exploit gallium's traditional role as an iron mimetic but also introduce auxiliary killing mechanisms such as ROS generation. This synergy is particularly valuable in overcoming microbial resistance, as it presents a multi-pronged assault on bacterial

survival mechanisms. Moreover, the fact that these effects were observed against both Gram-positive and Gram-negative bacteria underscores the broad-spectrum potential of EGaIn formulations.

In a nutshell, while gallium in its ionic form primarily disrupts bacterial iron metabolism, certain GaNP formulations—such as those incorporating eutectic gallium–indium alloys—can also trigger oxidative stress and membrane damage, thereby amplifying their bactericidal efficacy. These findings not only expand our understanding of gallium's antibacterial mechanisms but also highlight the potential of material engineering in enhancing the therapeutic effectiveness of metal-based antimicrobials.

3.4 Synergy with conventional antibiotics

Gallium-based nanoparticles (GaNPs) have emerged as a promising adjunct to conventional antibiotics, particularly in combating multidrug-resistant (MDR) bacterial strains. The synergistic potential of GaNPs when combined with antibiotics such as tobramycin, ciprofloxacin, and colistin has attracted significant research attention due to its capacity to enhance antimicrobial efficacy beyond what either agent can achieve alone. This synergy is of critical importance in addressing infections caused by notoriously resistant pathogens like *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, which pose major therapeutic challenges due to their ability to evade multiple antibiotic classes. The mechanistic basis of synergy between GaNPs and existing antibiotics—whether these effects are additive, synergistic, or antagonistic depending on the antibiotic class—is multifaceted and involves a complex interplay of biochemical and biophysical processes within the bacterial cell. This includes gallium's ability to disrupt essential metabolic pathways, such as iron-dependent enzymatic functions, which weakens the bacterial defense systems and makes them more susceptible to antibiotic action. Additionally, GaNPs can modulate membrane permeability and inhibit resistance mechanisms like efflux pumps, thereby enhancing antibiotic uptake and retention. The overall outcome of these interactions can vary depending on the specific mode of action of the antibiotic involved, the bacterial species, and the environmental conditions, resulting in a spectrum of effects from purely additive to strongly synergistic or, less commonly, antagonistic.[42,43]

At the core of this synergistic interaction is gallium's disruption of bacterial iron metabolism. Gallium mimics ferric iron (Fe^{3+}) structurally and chemically, allowing it to enter bacterial cells *via* iron uptake pathways; however, unlike iron, gallium cannot undergo redox cycling. This inability to participate in redox reactions leads to metabolic dysfunctions such as impaired DNA synthesis and energy production. The resulting intracellular iron starvation weakens bacterial cells and compromises essential physiological processes, which makes them more vulnerable to the bactericidal effects of co-administered antibiotics. For example, gallium-mediated iron deprivation disrupts membrane integrity and enzymatic functions, thereby facilitating enhanced penetration and retention of antibiotics like ciprofloxacin and tobramycin, which otherwise may be limited by active efflux or enzymatic degradation mechanisms within the bacterial cell.[43–45]

Beyond metabolic interference, GaNPs impact key resistance mechanisms such as efflux pumps–protein complexes that bacteria use to expel toxic substances including antibiotics. GaNPs have been observed to downregulate or inhibit these efflux systems, thereby increasing intracellular antibiotic concentrations and allowing drugs to achieve effective therapeutic levels inside resistant bacterial cells. This phenomenon is particularly notable in combination with colistin, a last-resort antibiotic for MDR Gram-negative infections. GaNPs' capacity to restore or enhance colistin's activity holds clinical significance by potentially lowering the required dosage and thus reducing the nephro- and neurotoxicity associated with colistin therapy.[45,46]

In addition, GaNPs can increase bacterial membrane permeability, further augmenting antibiotic uptake. This is attributed both to their physicochemical surface properties and the generation of localized oxidative stress, which transiently compromises membrane integrity by forming pores or inflicting damage. Such membrane perturbations facilitate the intracellular access of antibiotics like tobramycin that generally struggle to penetrate the robust bacterial outer membrane. The combination of increased permeability, efflux pump suppression, and metabolic disruption underpins a potent multi-targeted attack on bacterial defenses, making GaNPs highly effective synergists in antimicrobial therapy.[9,47]

The precise nature of the interaction between GaNPs and antibiotics, whether additive or synergistic, depends on the antibiotic class and bacterial strain involved. Studies consistently demonstrate synergy with antibiotics targeting DNA synthesis (*e.g.*, fluoroquinolones), protein synthesis (*e.g.*, aminoglycosides), and membrane integrity (*e.g.*, polymyxins), while antagonistic interactions are rarely observed. This supports the versatility of GaNPs as broad-spectrum adjuvants capable of restoring or amplifying the efficacy of various antibiotic classes. The synergistic mechanisms are succinctly summarized in Fig. 6, which visually depicts how GaNPs weaken bacterial physiological and structural defenses to enhance antibiotic potency.[48]

Collectively, these mechanistic insights highlight GaNPs as powerful enhancers of antibiotic action. By simultaneously disrupting iron-dependent metabolic pathways, suppressing efflux pumps, and increasing membrane permeability, GaNPs enable existing antibiotics to overcome bacterial resistance mechanisms more effectively. This multifaceted synergy provides a promising therapeutic avenue to rejuvenate the utility of current antibiotics, offering hope in the global fight against antimicrobial resistance.

Rezzoagli *et al.* (2019) provided foundational evidence for this synergistic potential by systematically investigating combinations of gallium—a siderophore mimic and iron metabolism disruptor—with a panel of frontline antibiotics against *Pseudomonas aeruginosa*, a notorious MDR pathogen.[43] By constructing a 9 × 9 drug concentration matrix, they demonstrated that the interaction patterns between gallium

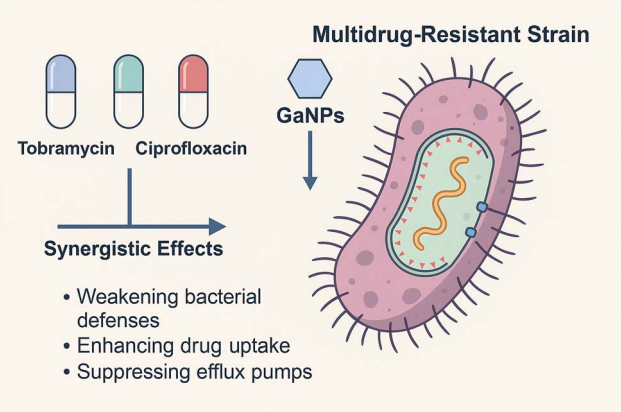

Fig. 6 Synergistic antibacterial mechanisms of gallium-based nanoparticles (GaNPs) and antibiotics.

and antibiotics like ciprofloxacin, colistin, meropenem, and tobramycin was highly concentration dependent. Importantly, at intermediate concentrations, gallium significantly potentiated antibiotic activity, even against resistant clones. The authors noted that gallium's interference with iron acquisition not only weakened bacterial fitness but also rendered certain resistance mechanisms, particularly those not involving efflux pumps, ineffective. In fact, in cases where antibiotic resistance involved the restoration of protein synthesis, the combination with gallium reversed selection for resistance, likely due to gallium's indirect impairment of metabolic pathways essential for these restorative mechanisms. This work underscores the potential of GaNPs to sensitize bacteria to antibiotics by dismantling critical aspects of bacterial physiology, such as iron metabolism and virulence, without selecting strongly for resistance themselves.

Extending these findings, Huang *et al.* (2022) addressed a more complex therapeutic challenge: treating persistent bacteria that exist in intracellular niches or within biofilms—environments notoriously impermeable to conventional antibiotics.[49] They designed a gallium-based metal–organic framework (GaMOF) nanoparticle system that could act both as a drug carrier and an intrinsic antimicrobial agent. The GaMOF's nanostructure, characterized by a high BET surface area and uniform morphology, allowed for effective delivery of antibiotics across cellular and biofilm barriers. Simultaneously, the GaMOF disrupted bacterial iron metabolism, a mode of action similar to that highlighted by Rezzoagli *et al.*[43] further weakening bacterial defenses. The resulting effect was a marked enhancement in the intracellular potency of the carried antibiotics, described as "super-penetrating bombs." The GaMOF-antibiotic system was not only capable of eradicating bacteria within biofilms and host cells but also attenuated the inflammatory response by mitigating bacterial pyroptosis. This study reinforces the notion that GaNPs can effectively amplify antibiotic performance by modifying the microenvironment of infection and impairing bacterial survival mechanisms, particularly those used to evade drug penetration.

Liu *et al.* (2023) introduced another level of synergy by combining GaNPs with antimicrobial peptides (AMPs), specifically melittin, within a gallium-based MOF structure.[50] The resulting nanocomposite exhibited antibacterial activity far exceeding that of either component alone, illustrating a clear case of synergistic enhancement. Here, gallium's iron-mimicking toxicity and melittin's membrane-disrupting action formed a dual mechanism that overwhelmed bacterial defenses, including those in methicillin-resistant *Staphylococcus aureus* (MRSA). Notably, the formulation not only eradicated the bacterial infection more effectively but also promoted tissue healing by modulating inflammatory responses—an important therapeutic outcome in chronic and wound-associated infections. This finding is directly aligned with the observations of Huang *et al.*, whose GaMOFs similarly acted as both carriers and antibacterial agents, although Liu's work emphasized synergy with non-traditional therapeutics rather than standard antibiotics. Together, both studies highlight how GaNPs can serve as versatile platforms that are not only intrinsically bactericidal but also capable of enhancing the therapeutic index of co-administered agents, whether conventional or peptide based.

The convergence of these studies paints a coherent and compelling picture: GaNPs act as strategic adjuvants by weakening bacterial iron metabolism, modulating virulence pathways, and enhancing permeability or retention of antibiotic agents. Whether used to restore the efficacy of failing antibiotics, as shown by Rezzoagli *et al.*[43] to penetrate protective biological barriers like biofilms and host cell membranes, as demonstrated by Huang *et al.*, or to synergize with alternative therapies such as AMPs, as illustrated by Liu *et al.*[50] GaNPs consistently disrupt bacterial homeostasis in a manner that potentiates antibacterial therapy. This growing body of evidence supports the integration of GaNPs into combination therapies, particularly in the face of escalating resistance, and underscores their potential to reinvigorate the clinical utility of existing antimicrobials.

4. Spectrum of antibacterial activity

Gallium-based nanoparticles (GaNPs) exhibit broad-spectrum antibacterial activity against a wide array of clinically significant and often drug-resistant bacterial pathogens. Among the most notable targets are *Pseudomonas aeruginosa*, *Staphylococcus aureus* (including methicillin-resistant *S. aureus*, or MRSA), *Escherichia coli*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*. These pathogens are frequently implicated in hospital-acquired infections and are known for their formidable resistance to many conventional antibiotics, posing substantial challenges to treatment. The efficacy of GaNPs against such a diverse range of organisms underscores their potential as a versatile and powerful antimicrobial strategy.[50,51]

Importantly, studies have demonstrated a clear dose-dependent relationship between GaNP concentration and antimicrobial effects. Higher concentrations of GaNPs typically result in increased bacterial growth inhibition and enhanced disruption of biofilms, illustrating the potency of these

nanoparticles in overcoming bacterial defences.[39] However, establishing a therapeutic window is critical, as this range must maximize antimicrobial efficacy while minimizing toxicity to host cells. The therapeutic window varies depending on nanoparticle formulation, including factors such as size, surface charge, and coating materials. Optimizing these physicochemical properties is therefore essential to achieve effective bacterial killing with minimal adverse effects on mammalian cells, as thoroughly discussed in the manuscript. This balance highlights the promise of GaNPs as targeted antimicrobials that can be fine-tuned for safe and effective clinical application.[58,77]

Regarding generalizability, GaNPs have demonstrated activity against both Gram-positive and Gram-negative bacteria, although differences in cell wall architecture influence their efficacy. Gram-negative bacteria possess an outer membrane containing lipopolysaccharides, which can act as a barrier to nanoparticle penetration, while Gram-positive bacteria have a thicker peptidoglycan layer but lack an outer membrane. Despite these structural differences, GaNPs effectively target critical iron acquisition and metabolic pathways common to both groups. Studies have reported potent antibacterial effects in Gram-negative pathogens like *Pseudomonas aeruginosa* and *Acinetobacter baumannii,* as well as Gram-positive bacteria such as *Staphylococcus aureus* and MRSA.[59] This broad-spectrum action reflects the fundamental reliance of diverse bacteria on iron metabolism, which GaNPs exploit, making their effects generally applicable across bacterial classes, though some variation in susceptibility may occur due to membrane permeability and nanoparticle uptake dynamics.[52–54]

The mechanism underlying this wide-ranging activity is primarily linked to gallium's unique ability to interfere with bacterial iron metabolism. Gallium ions (Ga^{3+}) mimic ferric iron (Fe^{3+}) in biological systems due to their similar ionic radii and coordination chemistry. However, unlike iron, gallium cannot undergo redox cycling under physiological conditions, making it catalytically inactive. When Ga^{3+} is mistakenly incorporated into bacterial iron acquisition pathways, it disrupts essential cellular processes, including respiration, DNA synthesis, and enzyme function. This mechanism is particularly effective against pathogens that rely heavily on iron acquisition for survival and virulence, such as *P. aeruginosa* and *A. baumannii*, both of which exhibit high siderophore activity and aggressive biofilm formation.[51,52]

Importantly, GaNPs have demonstrated potent effects not only against planktonic bacteria but also against biofilm-embedded communities. Biofilms provide a physical and chemical barrier that protects bacteria from antibiotic penetration and immune clearance, often leading to chronic and recurrent infections. GaNPs are capable of penetrating these biofilms and disrupting their structural integrity by inducing oxidative stress and inhibiting iron-dependent metabolic processes within the microbial community. This antibiofilm activity is particularly critical when dealing with resilient pathogens like MRSA and *K. pneumoniae*, which can persist in hostile environments and evade antibiotic treatment through biofilm-mediated resistance mechanisms.[53,54]

Moreover, the nanoscale design of GaNPs enhances their therapeutic potential by improving solubility, cellular uptake, and target specificity. The nanoparticle formulation facilitates sustained release and localized delivery of Ga^{3+} to the infection site, optimizing antibacterial efficacy while minimizing systemic toxicity. Studies have shown that GaNPs, especially when engineered for synergistic interactions (*e.g.*, combined with photodynamic agents or polymeric carriers), can outperform traditional gallium salts and exhibit increased potency across a range of bacterial strains.[55,56] Their ability to act independently of conventional antibiotic pathways also makes them a promising tool in the fight against multi-drug-resistant organisms, potentially filling a critical gap left by the dwindling efficacy of traditional antimicrobials. The spectrum of antibacterial activity demonstrated by GaNPs encompasses several of the most challenging Gram-negative and Gram-positive pathogens encountered in clinical settings. Their unique iron-mimicking mechanism, coupled with strong antibiofilm activity and adaptability to various nanoparticle delivery platforms, positions them at the forefront of emerging non-antibiotic antibacterial therapies. As resistance to existing treatments continues to rise, GaNPs represent a compelling and much-needed addition to the antimicrobial arsenal.[57,58]

For example, the study by Xie *et al.* (2021) offers an innovative and clinically promising strategy for combating aggressive bacterial infections, particularly those caused by multi-drug resistant (MDR) strains such as extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL *E. coli*).[39] By focusing on the synergistic use of gallium (Ga^{3+}), a metal known for its ability to interfere with iron metabolism in bacteria, and indocyanine green (ICG), a photosensitizer, the authors created ultrasmall, non-antibiotic nanoparticles (ICG-Ga NPs) capable of targeting bacterial infections through both iron metabolism disruption and photodynamic therapy (PDT). This dual mechanism is especially significant considering the persistent difficulty in treating iron-dependent and biofilm-forming pathogens, which often demonstrate strong resistance to conventional antibiotics.

The antibacterial spectrum of these ICG-Ga NPs was primarily assessed against ESBL *E. coli*, a highly resistant Gram-negative pathogen of urgent clinical concern. The *in vitro* results revealed a clear dose–response relationship between Ga content and bacterial viability, with significant inhibition observed at 25 μg mL^{-1} Ga concentration. Fig. 7A illustrates that bacterial viability decreased by approximately 65% solely due to gallium-mediated interference in iron metabolism, confirming the standalone antimicrobial potential of Ga^{3+} in these nanostructures. When combined with 808 nm near-infrared (NIR) laser irradiation, a dramatic enhancement in antibacterial efficacy was observed. The synergistic action reached its peak at a laser power density of 1 W cm^{-2}, which reduced bacterial survival by over 99.5% (Fig. 7B), while avoiding significant photothermal effects—temperature increases were negligible, not exceeding 41 °C. This ruled out hyperthermia as a cause of bacterial death and highlighted the dominant roles of ROS generation and Ga^{3+}-mediated metabolic interference.

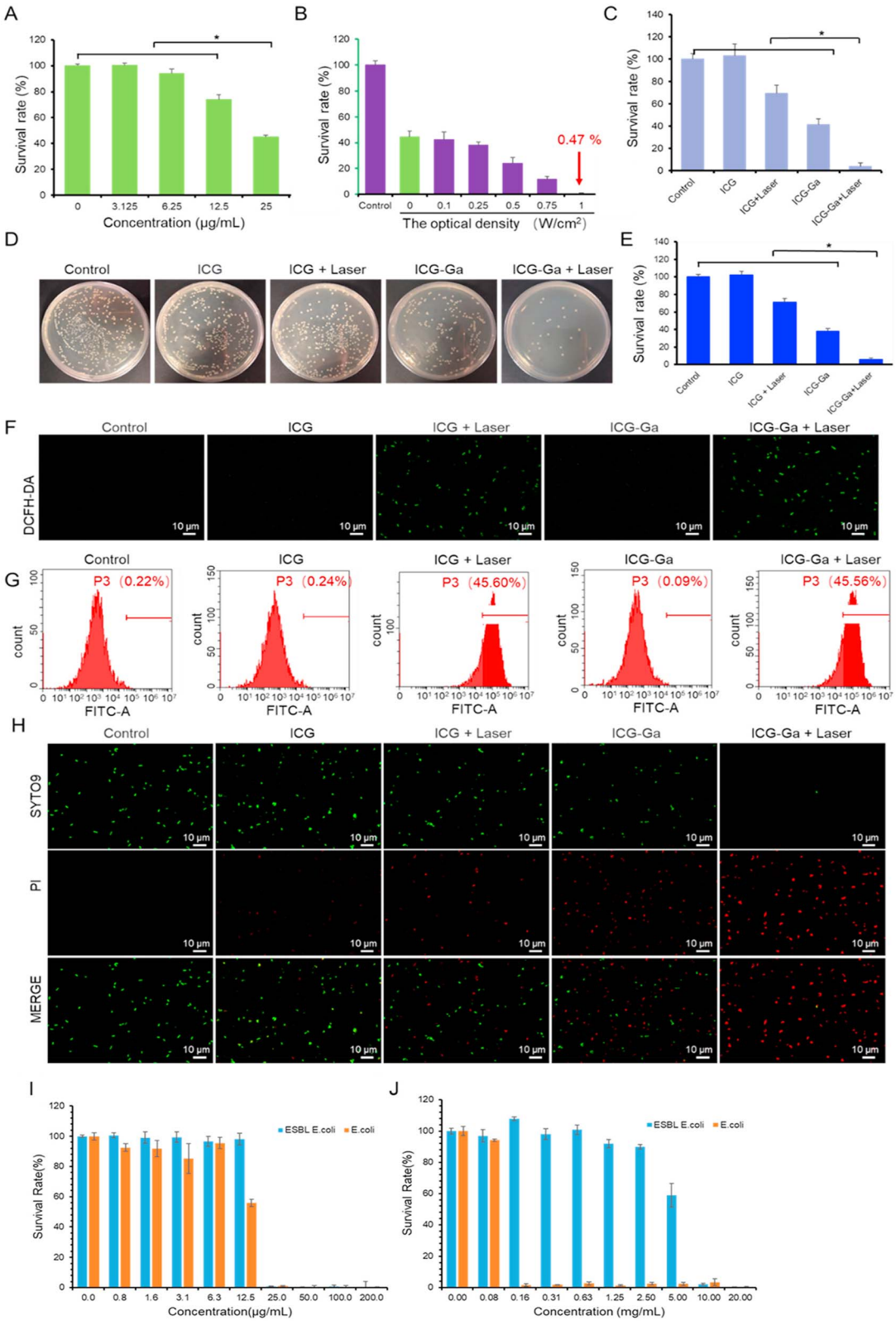

Fig. 7 *In vitro* antibacterial viability of ICG-Ga NPs against ESBL *E. coli*. (A) Survival rates of ESBL *E. coli* after incubation with ICG-Ga NPs at different concentrations (0, 3.125, 6.25, 12.5, and 25 μg mL^{-1}) at 37 °C in LB medium for 24 h. (B) Survival rates of ESBL *E. coli* under an 808 nm laser irradiation at the different power intensity (0, 0.1, 0.25, 0.5, 0.75, and 1 W cm^{-2}) after incubation with ICG-Ga NPs of 25 μg mL^{-1} at 37 °C in LB medium for 24 h. (C) Survival rates of ESBL *E. coli* irradiated by an 808 nm laser irradiation at the power density of 1.0 W cm^{-2} for 10 min after incubation with 25 μg mL^{-1} ICG-Ga NPs or ICG. (D) Optic photographs of bacterial colonies formed by the treated ESBL *E. coli* in all groups and (E) the corresponding CFU counts. (F) Fluorescent images of ESBL *E. coli*, stained by DCFH-DA, upon an 808 nm laser irradiation (1 W cm^{-2}, 10 min) after incubation with 25 μg mL^{-1} ICG-Ga NPs or ICG. (G) Flow cytometry analysis of ESBL *E. coli* quantifies the generation of ROS by staining with DCFH-DA. (H) The fluorescence images of the treated ESBL *E. coli*, stained by SYTO9 and propidium iodide (PI) dyes. (*$p < 0.05$) Comparison of *In vitro* antibacterial ability on ESBL *E. coli* and *E. coli* between (I) ICG-Ga NPs and (J) *Penicillin*.[39].

Crucially, the study dissected the contributions of individual treatment components. While ICG alone or ICG + laser treatments had minimal antibacterial effect, the full ICG-Ga NP formulation combined with laser exposure demonstrated markedly superior efficacy, killing more than 95% of the bacteria (Fig. 7E). This synergy is attributed to increased ROS levels induced by photodynamic activation, as demonstrated through DCFH-DA fluorescence assays (Fig. 7F and G), and the facilitated intracellular delivery of Ga^{3+} due to compromised bacterial membranes. Live/dead staining (Fig. 7H) corroborated these findings, showing substantial membrane damage only in the ICG-Ga + laser group. Moreover, the ICG-Ga NP treatment outperformed traditional antibiotics like penicillin, which were ineffective against ESBL *E. coli* (Fig. 7I and J), reinforcing the nanoparticles' potential for treating antibiotic-resistant infections.

Beyond planktonic bacterial cells, the study delved into structural and morphological disruptions caused by the treatment. Scanning electron microscopy (SEM) images (Fig. 8A) revealed wrinkled, damaged bacterial surfaces following laser-

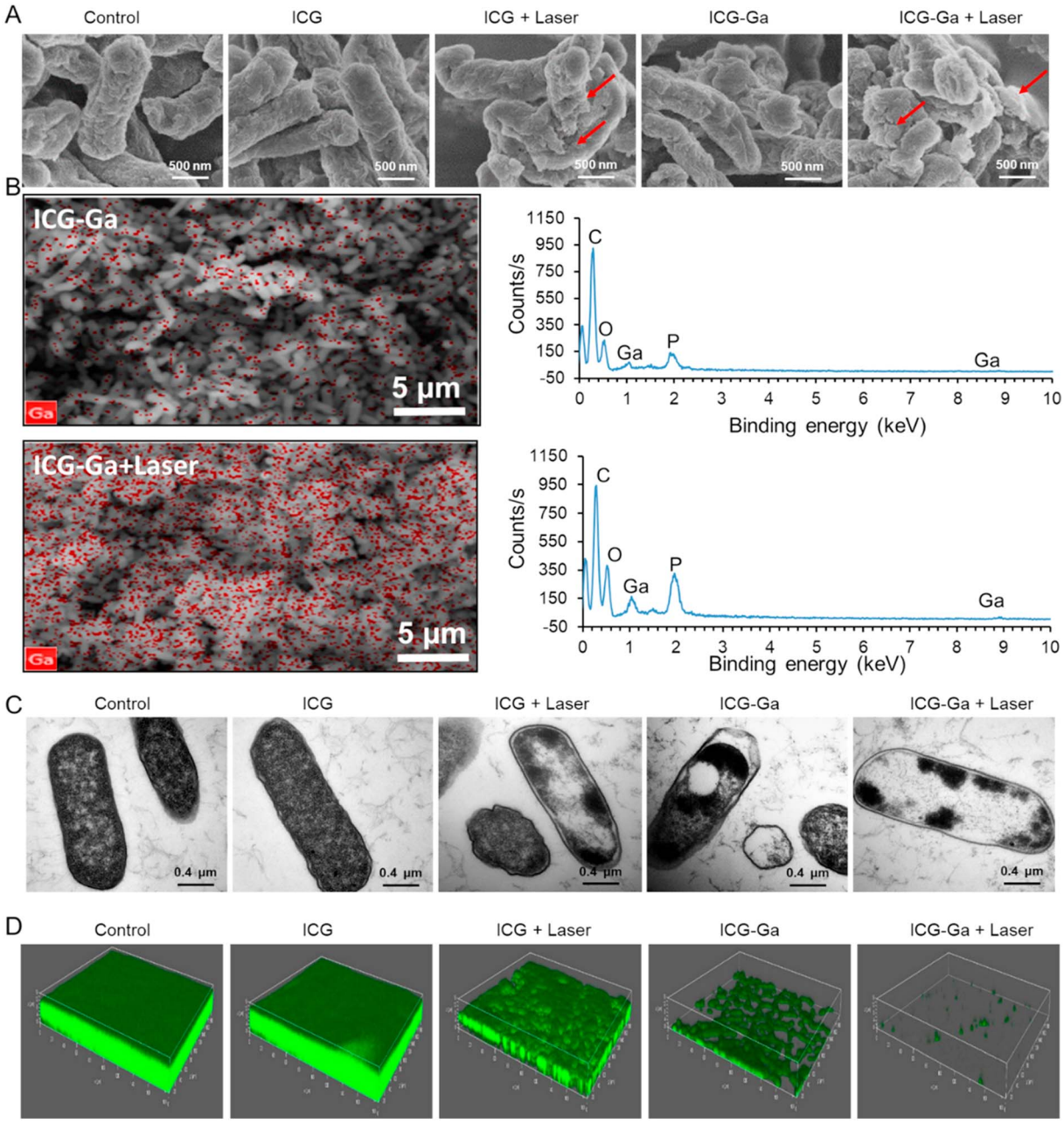

Fig. 8 *In vitro* bactericidal effect and inhibiting biofilm formation of ICG-Ga NPs against ESBL *E. coli*. (A) The SEM images of ESBL *E. coli* after different treatment and (B) the respective mapping analysis. (C) TEM images of the treated ESBL *E. coli*. (D) 3D confocal laser scanning microscopy images (size: 630 μm × 630 μm) of ESBL *E. coli* biofilms after different treatments. Biofilms were stained by SYTO9. The live bacteria can be observed with green fluorescence.[39]

activated ICG-Ga NP exposure, while energy-dispersive X-ray spectroscopy mapping confirmed the accumulation of Ga^{3+} at the damaged sites (Fig. 8B). Transmission electron microscopy (TEM) further demonstrated that these physical alterations extended deep into the bacterial ultrastructure, with pronounced membrane disruption and cytoplasmic leakage (Fig. 8C). These observations underline the severe damage inflicted on cellular integrity, leading to bacterial death.

Particularly relevant to the scope of GaNPs' effectiveness against biofilm-forming pathogens, the study also investigated the nanoparticles' antibiofilm properties. As biofilms represent a major mechanism of resistance in pathogens such as *P. aeruginosa*, *S. aureus*, and *A. baumannii*, their eradication is a critical therapeutic goal. Fluorescent imaging of biofilms formed by ESBL *E. coli* (Fig. 8D) revealed a near-complete elimination of viable bacteria in the ICG-Ga + Laser treatment group. These findings suggest that the ICG-Ga NPs not only penetrate biofilms but also dismantle their structural cohesion through the combined effects of oxidative stress and metabolic interference. This positions GaNPs as a particularly potent option for biofilm-associated infections, which are typically recalcitrant to standard treatments.

In sum, the ICG-Ga nanoparticle platform developed by Xie *et al.* significantly expands the antibacterial spectrum of gallium-based therapeutics, offering a highly effective, non-antibiotic approach against pathogens such as ESBL *E. coli*. By leveraging the pathogen's reliance on iron acquisition and augmenting it with targeted photodynamic disruption, these nanoparticles provide a robust alternative to traditional antibiotics. Their demonstrated efficacy in both free-living and biofilm-embedded bacterial populations reinforces the broad-spectrum potential of GaNPs against other critical pathogens, including *P. aeruginosa*, *S. aureus*, *A. baumannii*, and *K. pneumoniae*. Moreover, the favorable biocompatibility and renal clearance of the ICG-Ga NPs enhance their translational relevance, pointing toward a future where such multi-modal nanomedicines could form the foundation of a new antibacterial paradigm.

The study by Goss *et al.* (2018) offers a foundational clinical and experimental validation of gallium's antimicrobial spectrum, particularly its efficacy against *P. aeruginosa*, a notoriously resilient Gram-negative bacterium prevalent in chronic lung infections of cystic fibrosis (CF) patients.[16] By mimicking iron and thereby deceiving bacterial iron uptake systems, gallium disrupts critical metabolic pathways that depend on iron, leading to bacterial growth inhibition. Their *ex vivo* analysis using sputum from CF patients, mouse lung infection models, and even preliminary human clinical trials illustrates not only gallium's potent bacteriostatic effects but also its therapeutic safety. Notably, gallium demonstrated synergistic potential with existing antibiotics and a slow rate of resistance development. These findings underscore GaNPs' promise as a robust alternative or complement to conventional treatments, particularly for persistent *P. aeruginosa* infections in clinical settings.

Building on this, Zhao *et al.* (2025) extended the application of gallium nanoparticles into orthopedic infections by addressing chronic osteomyelitis—a condition often caused by *S. aureus* and *E. coli*. These pathogens form biofilms that are inherently resistant to antibiotics and immune clearance.[59] The researchers engineered GaNPs anchored onto graphene oxide and embedded them within a poly-L-lactic acid scaffold, achieving not only high antibacterial efficacy (exceeding 99% against both *S. aureus* and *E. coli*) but also excellent biocompatibility and osteogenic potential. The physical integrity of the scaffold allowed targeted delivery of GaNPs, where they exerted antibacterial effects by disrupting iron metabolism and mechanically damaging bacterial membranes. This dual-action approach demonstrates how GaNPs can be tuned for tissue-specific infections, effectively extending their utility to bone infections where both Gram-positive and Gram-negative pathogens are prevalent.

Meanwhile, Choi *et al.* (2019) investigated the antibacterial spectrum and mechanisms of gallium porphyrin compounds—GaPP and GaMP—against *P. aeruginosa* and *A. baumannii*, both of which are known for forming robust biofilms and surviving intracellularly in host cells.[60] The researchers formulated these gallium compounds into nanoparticles to facilitate both extracellular and intracellular antimicrobial activity. The nanoparticles maintained sustained antibacterial effects even when administered prior to infection in macrophages, highlighting their preventive and therapeutic potential. Moreover, the formulations demonstrated strong antibiofilm activity, a crucial advantage when targeting biofilm-mediated infections in hospital settings. The ability to maintain prolonged intracellular efficacy is especially valuable for treating latent or chronic infections where pathogens persist within host cells, shielded from immune responses and antibiotics.

Adding a photodynamic dimension to gallium's antibacterial profile, Awad *et al.* (2022) developed gallium protoporphyrin-loaded liquid crystalline nanoparticles (GaPP-LCNPs) for antimicrobial photodynamic therapy (aPDT) specifically against *P. Aeruginosa*.[61] This bacterium, a prime example of a biofilm-forming and antibiotic-resistant pathogen, was used in both planktonic and biofilm states to evaluate the effectiveness of the platform. Upon light activation, the GaPP-LCNPs produced reactive oxygen species (ROS), dramatically reducing bacterial viability—by 7 $\log_{10}$ in planktonic cells and 6 $\log_{10}$ in biofilms—at remarkably low dosages. These results not only emphasize gallium's versatility but also showcase its potential in non-antibiotic antibacterial modalities, making it a candidate for tackling recalcitrant infections where biofilms are a major therapeutic barrier.

Taken together, these studies collectively reinforce the conclusion that gallium-based nanoparticles possess a uniquely broad and potent antibacterial spectrum, with specific effectiveness against *P. aeruginosa*, *S. aureus* (including MRSA), *E. coli*, *A. baumannii*, and by extension, *K. pneumoniae*. Their ability to disrupt iron metabolism, penetrate biofilms, and function both intra- and extracellularly makes GaNPs a promising frontier in the treatment of infections that are otherwise unmanageable with traditional antibiotics. These findings converge to support the rationale for further translational development of GaNP-based therapeutics across multiple infection models.

5. Resistance considerations

Resistance to gallium-based antibacterial agents presents a notably different profile compared to that observed with traditional antibiotics. One of the most compelling advantages of gallium lies in its mechanism of action: it targets bacterial iron metabolism by mimicking ferric iron (Fe^{3+}), a fundamental nutrient required for many essential bacterial processes. Once gallium is taken up by bacterial cells through iron acquisition systems, its inability to undergo redox cycling renders it metabolically inactive, thereby sabotaging critical pathways such as respiration, DNA synthesis, and enzymatic activity. This mode of action is not easily circumvented by single-point mutations, making resistance to gallium both rare and slow to develop under most conditions.[61,62]

The rarity of resistance is further supported by studies demonstrating that even under extended exposure to sub-inhibitory concentrations of gallium, bacterial populations develop resistance at a significantly slower rate than they do against conventional antibiotics. This likely stems from the evolutionary conservation and indispensability of iron acquisition systems, which bacteria cannot easily discard or modify without incurring a substantial fitness cost.[63] Furthermore, gallium exerts additional pressures through indirect mechanisms, such as the generation of reactive oxygen species (ROS) and disruption of biofilm integrity, which together create a multi-targeted assault that is difficult for bacteria to endure or adapt to rapidly. Nonetheless, emerging evidence indicates that resistance to gallium, while less frequent, is not entirely impossible. Some bacterial strains have shown signs of reduced sensitivity, which can arise from adaptive changes such as the upregulation of efflux pumps that expel gallium ions or nanoparticles from the cell before they can exert their toxic effects. Other mechanisms may involve alterations in siderophore production or the selective expression of alternative iron uptake systems that preferentially avoid gallium mimicry. For example, changes in the expression of transporters that discriminate between Ga^{3+} and Fe^{3+} could hypothetically reduce gallium uptake, thereby diminishing its antimicrobial effectiveness.[63,64]

To address these potential resistance pathways, combination therapies have emerged as a promising strategy. When gallium is used alongside conventional antibiotics or other stress-inducing agents, the likelihood of resistance development appears to decrease, possibly because bacteria are forced to manage multiple, distinct modes of action simultaneously. In particular, synergistic combinations that pair gallium with antibiotics targeting cell wall synthesis, protein production, or nucleic acid replication may overwhelm bacterial defense mechanisms and reduce the selective pressure on any single pathway. Additionally, combining gallium with photodynamic therapy or nanoparticle delivery systems has shown enhanced bactericidal effects, further lowering the chance of resistance emergence.[17]

Overall, while gallium-based antimicrobials are not entirely immune to the evolution of resistance, their unique mechanism and multi-faceted action make them considerably more resilient than traditional antibiotics. Continued research into gallium's interactions with bacterial physiology, as well as strategic combination approaches, will be critical for maintaining its long-term efficacy and mitigating the risk of emerging resistance.

6. Biomedical applications

GaNPs have been explored in various clinical and translational contexts, including:

6.1 Wound dressings and topical gels for infected wounds

Wound infections, particularly those involving multi-drug resistant (MDR) bacterial strains, present a persistent and serious clinical challenge. Topical antimicrobial therapies, such as wound dressings and gels, have emerged as key strategies for localized infection control and enhanced healing. Among these, gallium-based formulations are gaining momentum due to their ability to disrupt bacterial iron metabolism and interfere with structural integrity in ways that standard antibiotics cannot. Gallium oxide nanoparticles (Ga_2O_3 NPs), in particular, offer promising therapeutic avenues when integrated into hydrogel systems for direct application to infected wounds.[65–67]

In the study conducted by Wang *et al.* (2024), Ga_2O_3 NPs were synthesized *via* high-temperature thermal decomposition and incorporated into a chitosan-based hydrogel, resulting in a light-responsive, multilayered, three-dimensional porous dressing.[68] This Ga_2O_3 NPs hydrogel exhibited potent photocatalytic antimicrobial activity under light exposure, a feature that makes it especially suitable for photo-catalytic antimicrobial therapy (PCAT). The hydrogel not only maintained excellent biosafety and biocompatibility but also demonstrated broad-spectrum antibacterial efficacy against *Escherichia coli* and *Staphylococcus aureus*, two prominent culprits in wound infections, including MDR strains. *In vitro* and *in vivo* models consistently showed that the Ga_2O_3 NPs hydrogel could effectively disrupt biofilm formation—a common cause of chronic infection and delayed healing—through the generation of reactive oxygen species (ROS) that destabilize bacterial membranes and induce nucleic acid leakage, culminating in bacterial cell death. The hydrogel's ability to create a moist wound environment further supported tissue regeneration and minimized scar formation, illustrating its dual role in both antimicrobial defence and tissue repair.

In a complementary context, Xu *et al.* (2017) explored the antibacterial capacity of gallium nitrate ($Ga(NO_3)_3$) in the setting of burn wounds, another high-risk environment for bacterial infection.[69] Their findings echoed those of Wang *et al.*[68] confirming that gallium ions exert broad-spectrum bactericidal activity against pathogens commonly isolated from infected burn wounds, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, and *Acinetobacter baumannii*. Minimum inhibitory concentration (MIC) testing revealed that $Ga(NO_3)_3$ was effective at relatively low concentrations (256–512 μg mL^{-1}), supporting its practical potential for clinical use. Furthermore, transmission electron microscopy

(TEM) analyses provided mechanistic insight into the morphological changes induced by Ga^{3+} treatment. Normal *E. coli* cells displayed uniform electron density and intact, smooth membranes, whereas Ga^{3+}-treated cells exhibited disrupted membranes, shrinkage, and detachment of both the cell wall and membrane. Most strikingly, Fig. 9 revealed severe intracellular disorganization characterized by electron-light regions and aggregated electron-dense granules within the cytoplasm and along the cell wall. These features likely correspond to the intracellular accumulation of gallium ions or gallium–bound complexes, further underscoring gallium's invasive and destructive action on bacterial integrity.

These two studies jointly demonstrate the unique potential of gallium-based wound dressings to address both planktonic and biofilm-associated infections, which are frequently resistant to conventional antibiotics. The incorporation of gallium into hydrogels enhances localized delivery, ensures a moist healing environment, and offers the flexibility to harness light-activated catalytic effects for amplified bactericidal outcomes. Notably, Wang *et al.* provide compelling evidence that such systems not only arrest infection but actively promote wound healing, while Xu *et al.*'s detailed morphological characterizations (as seen in Fig. 9) reveal the extent to which gallium can compromise bacterial structure at the cellular level. The combination of mechanistic insights and translational efficacy underscores gallium's promise as a central component in next-generation antimicrobial wound dressings, especially in the face of rising antibiotic resistance.

Valappil *et al.* (2023) introduced a novel gallium–lactoferrin (Ga–LTf) complex designed for topical application to *P. aeruginosa*-infected wounds.[70] Gallium ions, known for their ability to disrupt bacterial iron metabolism and biofilm integrity, are paired with lactoferrin—a natural iron-binding protein with known affinity for infection sites and mucosal tissues—thus

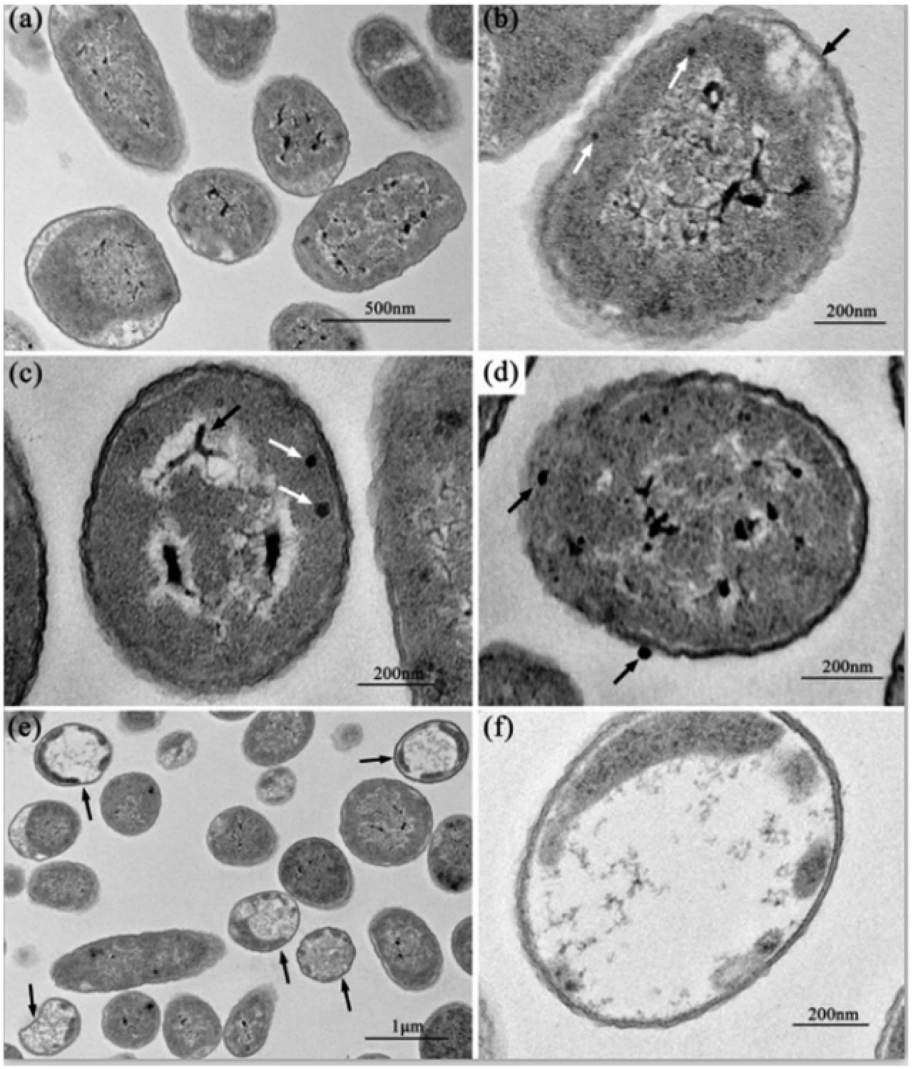

Fig. 9 Microstructure of Ga^{3+} -treated *E. coli* cells. (a) An overview. (b) A large gap between the cell membrane and cell wall (black arrow) and intracellular high-density electronic granules (white arrow). (c) Strip-type electron-dense substances inside the electron-light region (black arrow), and intracellular high electron density granules (white arrow). (d) High electron density granules adhere to the cell wall. (e) and (f) Cells composed of a large electron-light region with substances sporadically distributed.[69]

creating a synergistic complex for localized antimicrobial therapy.

The Ga–LTf complex was extensively characterized using differential scanning calorimetry (DSC), infrared spectroscopy (FTIR), and inductively coupled plasma optical emission spectrometry (ICP-OES). These analyses confirmed the successful binding of gallium ions to lactoferrin, showing thermal and molecular features consistent with complexation and ensuring controlled delivery of Ga^{3+} at the wound site. *In vitro* antimicrobial testing, including planktonic broth and biofilm inhibition assays, demonstrated the efficacy of Ga–LTf, with a modest 0.57 $\log_{10}$ CFU reduction in planktonic cells and a significantly higher 2.24 $\log_{10}$ CFU reduction in biofilm-forming populations within 24 hours. These results underscore the particular strength of Ga–LTf in tackling biofilms, which are notoriously difficult to eradicate and often underlie chronic wound infections.

The *in vivo* performance of the Ga–LTf formulation was evaluated using a rat model of artificially induced *P. aeruginosa* wound infection. Rats were treated twice daily with 200 μL of Ga–LTf solution (2 μg/100 μL Ga^{3+}), with treatment outcomes compared to a tobramycin-treated group (8 mg L^{-1}) and a sterile distilled water-treated control. As shown in Fig. 10, Ga–LTf-treated wounds exhibited visibly accelerated healing over the 7 days observation period. The wound contraction and reduction in surface area occurred more rapidly in the Ga–LTf group compared to both the antibiotic-treated and untreated groups, suggesting a potential therapeutic advantage in promoting wound closure. Although quantification of bacterial burden at the end of the study revealed no statistically significant difference in CFUs recovered between the groups, the enhanced wound healing observed in the Ga–LTf group highlights the multifaceted benefit of the formulation—combining antimicrobial action with a conducive environment for tissue regeneration.

Importantly, systemic biocompatibility and safety were also key aspects of the study. Histological analysis of major organs—including the brain, liver, kidney, and spleen—was conducted to assess both systemic infection and potential toxicity of the Ga–LTf complex. No signs of inflammation, structural

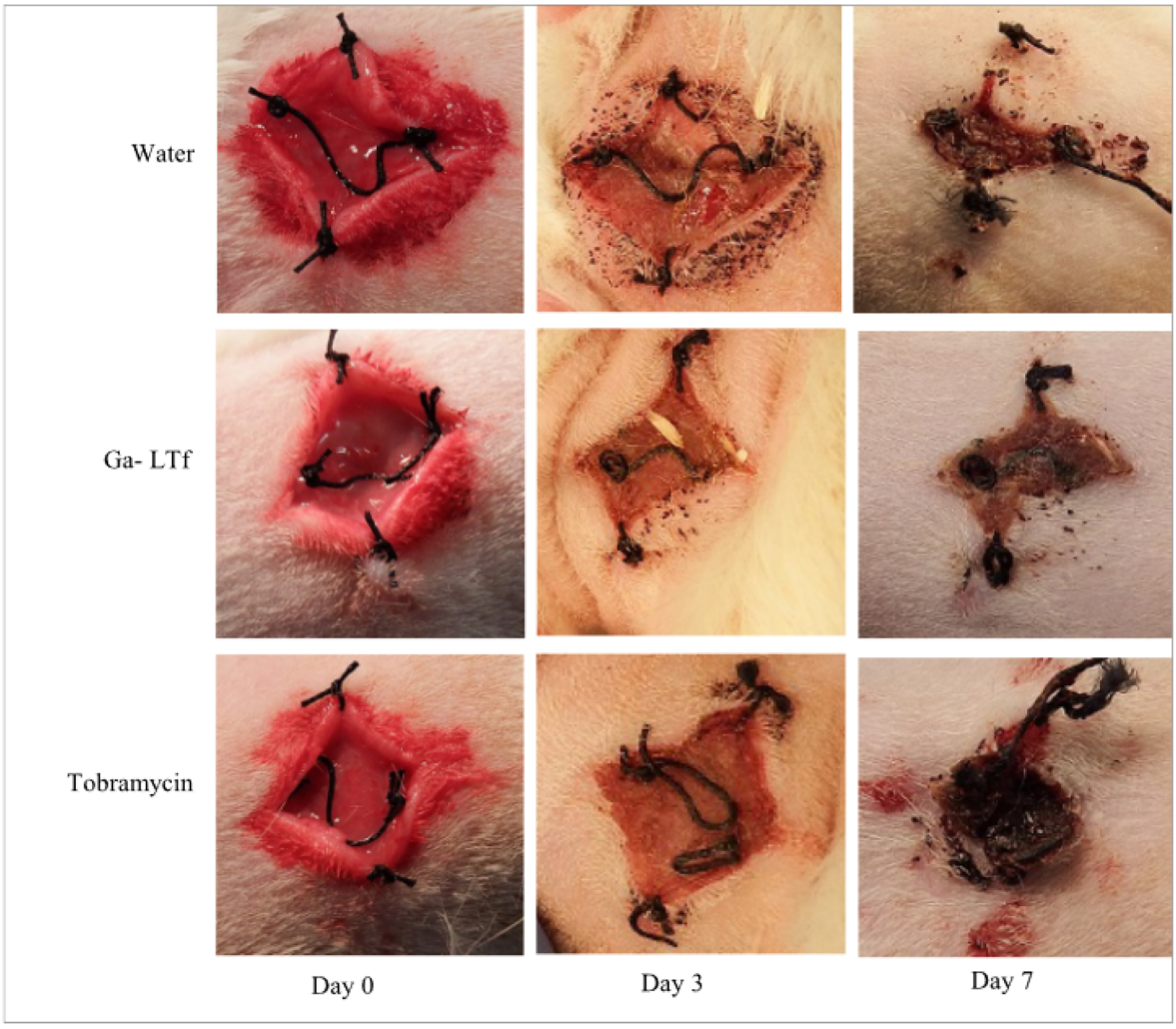

Fig. 10 Representative photographs taken at the beginning, 3rd day and 7th day of the *P. aeruginosa* infected wound after being treated with distilled water (negative control), Ga–LTf (experimental group) and tobramycin (positive control)[70]

abnormalities, or histopathological damage were found in any of the organ tissues from rats treated with Ga–LTf, tobramycin, or sterile water. This absence of systemic toxicity or infection further validates the safety profile of Ga–LTf and supports its suitability for topical wound application. The findings of Valappil *et al.*[70] reinforce the concept that gallium-based biomolecular complexes can serve as effective and biocompatible wound treatments. The Ga–LTf formulation, by leveraging the targeting and transport capabilities of lactoferrin, achieves localized gallium delivery, inhibits biofilm development, and promotes wound healing without systemic toxicity. When integrated into hydrogel dressings or topical gels, such complexes represent a next-generation approach for managing stubborn and resistant wound infections. This aligns strongly with emerging strategies focused on non-antibiotic, multifunctional wound dressings that provide both antimicrobial activity and support for tissue repair, crucial in an era of rising antibiotic resistance.

Zou *et al.* (2025) introduced a multifunctional, cost-effective hydrogel composed of chitosan (CS), tannic acid (TA), and Ga^{3+} assembled *via* a straightforward one-step method.[67] The resulting CS-TA-Ga^{3+} (CTG) hydrogel demonstrated not only self-healing and injectability but also exhibited potent antimicrobial activity against resistant bacteria through Ga^{3+}-mediated interference in iron metabolism. Its pH-responsive behavior and antioxidant, hemostatic, and anti-inflammatory properties positioned it as a holistic wound care agent. *In vivo* studies further confirmed its efficacy in promoting follicle regeneration and collagen deposition while modulating the inflammatory environment, which collectively led to rapid and organized tissue healing. What stands out in this study is how the simple yet multifunctional composition achieves therapeutic sophistication, offering an accessible yet potent dressing solution.

Complementing this, Bright *et al.* (2024) leveraged a different strategy by synthesizing gallium-based nanoalloy hydrogels through galvanic replacement, introducing multimetallic interactions with silver and bismuth.[66] This approach further enhanced antimicrobial efficacy against both *Staphylococcus aureus* and *Pseudomonas aeruginosa*, without compromising cellular biocompatibility. Importantly, the gallium nanoalloy hydrogels showed a strong enhancement in *in vitro* wound closure rates, suggesting synergistic antimicrobial and regenerative effects. Bright *et al.*'s[66] use of gallium in an alloyed nanoparticulate form, embedded within a hydrogel scaffold, complements Zou *et al.*'s[67] chemically bonded hydrogel system by expanding the design space for gallium-based materials while reinforcing the fundamental role of Ga^{3+} in bacterial inhibition.

Li *et al.* (2024) added a unique photonic dimension to this material platform by combining black phosphorus nanosheets (BPNSs) with Ga^{3+} ions to overcome the inherent instability of BP and amplify its antibacterial power.[71] Upon near-infrared (NIR) irradiation, the BP/Ga^{3+} complex engaged in both photothermal therapy (PTT) and photodynamic therapy (PDT), mechanisms that synergized with Ga^{3+}'s metabolic disruption to kill pathogens effectively. The complex's ability to simultaneously act as a photonic agent and Ga^{3+} reservoir connects with Wang *et al.* (2024)'s parallel work, which also exploited NIR-triggered mechanisms.[9] In Wang's study, gallium nanocores modified with polydopamine served as Ga^{3+} ion reservoirs and supported secondary *in situ* reactions to form silver nanoparticles.[9] This system enabled an almost complete bactericidal effect when paired with NIR light, while also enhancing ROS generation and photothermal action.

Wang's study further extended its innovation by incorporating these nanoparticles into a microneedle patch, applied to MRSA-infected mice.[9] The patch demonstrated substantial bacterial clearance, reduced inflammation, and enhanced angiogenesis and collagen deposition—paralleling the healing outcomes observed in Zou's CTG hydrogel but with the added benefit of minimally invasive delivery and photothermal augmentation.[67] Both studies highlight that gallium's versatility can be effectively amplified through nanotechnology and external stimuli, resulting in advanced therapeutic platforms that can be precisely tailored for complex wound environments.

In a similar vein of material functionality, Qin *et al.* (2022) developed a gallium-mediated hydrogel based on sodium alginate, with Ga^{3+} serving as both the cross-linking agent and antimicrobial component.[65] The dual-cross-linked hydrogel was further stabilized *via* photo-cross-linking, ensuring robust mechanical properties while maintaining gallium release. Their findings confirmed that the hydrogel retained homogeneity, displayed consistent Ga^{3+} ion diffusion, and significantly accelerated wound healing in infected models. This work bridges the strategies seen in both Zou's[67] and Wang's[9] research by demonstrating that gallium can be structurally embedded into hydrogels while retaining controlled release capabilities and therapeutic activity.

Collectively, these studies represent a converging narrative around the multifunctionality and therapeutic adaptability of gallium-incorporated hydrogels. Each formulation—whether based on phenolic networks, nanoalloys, photonic composites, nanocore reservoirs, or alginate matrices—leverages Ga^{3+} not just as a bacteriostatic agent but as a modular therapeutic component. The hydrogel platforms also extend beyond antimicrobial functions to support hemostasis, inflammation control, angiogenesis, and matrix remodelling. This integrative approach mirrors the complex needs of chronic and infected wounds, particularly in multidrug-resistant contexts, and underscores the clinical promise of gallium-cantered biomaterials in wound care.

Rather than functioning in isolation, each hydrogel system echoes the findings of the others: that gallium ions, when intelligently incorporated into tunable and biocompatible matrices, can simultaneously suppress infection and facilitate tissue regeneration. Whether through simple chemistries as in Zou *et al.*[67] nanostructural innovations as in Wang[9] and Bright,[66] or photonic synergy as in Li, the common thread is gallium's unique duality as a material scaffold component and an antimicrobial agent. In turn, these studies collectively define a new paradigm in advanced wound management—one in which antimicrobial efficacy, biocompatibility, structural versatility,

and regenerative support coalesce into a single therapeutic platform.

6.2 Drug delivery systems incorporating gallium for controlled release

The exploration of gallium as a key component in controlled drug delivery systems has opened a promising avenue for combating bacterial infections, especially those involving antibiotic-resistant strains and biofilm-associated complications. Central to this development is the capacity to regulate the release of gallium ions (Ga^{3+}) to maintain therapeutic efficacy while minimizing systemic toxicity. Across different platforms, from phosphate-based glasses to liquid metal nanoparticles and dynamic hydrogels, researchers are harnessing gallium's unique biochemical and physicochemical properties to engineer smart, responsive, and efficient delivery systems that align with the growing demand for precision medicine.[43,72–75]

In this regard, one of the earliest and most structurally stable approaches has been the use of gallium-doped phosphate-based glasses (PBGs), as demonstrated by Valappil *et al.* (2009). Their study underscores the importance of material composition in modulating drug release.[72] By adjusting the calcium oxide (CaO) content within the glass matrix, they were able to precisely control the degradation rate of the glasses, thereby directly influencing the release kinetics of Ga^{3+} ions. A lower CaO concentration (14 mol%) led to a higher degradation rate and, consequently, a more substantial release of gallium ions, which correlated with a greater reduction in *Pseudomonas aeruginosa* viability—both in planktonic form and within biofilms. Importantly, biofilm inhibition was validated using confocal microscopy, revealing significant bacterial death on the glass surface. This system effectively demonstrates how compositional tuning of PBGs not only supports sustained ion delivery but also maintains gallium's antimicrobial potency in complex biological environments. The structural coordination of gallium, confirmed *via* ^71 Ga NMR and Ga K-edge XANES, provides further insight into the stability and functional integrity of the ions during the release process, reinforcing the reliability of PBGs as viable drug delivery matrices.

Building upon this principle of controlled and responsive delivery, Zhang (2025) reviewed the emergent potential of gallium-based liquid metal nanoparticles (Ga-based LMPs), which extend the application of gallium far beyond static release from glass matrices.[21] Unlike the passive dissolution seen in PBGs, Ga-based LMPs possess intrinsic responsiveness to physical stimuli such as heat, light, and magnetic fields. These nanoparticles typically exhibit a core–shell structure that enhances stability and allows functionalization for targeted delivery. Their mobility, low toxicity, and photothermal effect enable them to be guided to pathological sites and triggered for drug release under specific conditions, such as near-infrared (NIR) irradiation. While Zhang's review is largely conceptual, it outlines a critical evolution in drug delivery strategies—from passive ion elution systems like PBGs to highly interactive, responsive nanocarriers that can dynamically respond to the body's internal environment or to external control.[21] This marks a significant shift in the drug delivery paradigm, especially in contexts requiring high spatial precision, such as tumor therapy or localized infections.

Yet not all effective controlled delivery systems require sophisticated external stimuli. Abebe *et al.* (2025) demonstrated a remarkably elegant alternative in their development of a strain-controlled transdermal drug delivery (TDD) hydrogel.[73] Inspired by mussel adhesion chemistry, their gallic acid-modified alginate hydrogel forms a robust interpenetrating polymer network with polyacrylic acid, resulting in a highly stretchable, self-adhesive matrix.[74] The critical innovation here lies in the system's mechanical responsiveness; tensile strain alone is sufficient to modulate drug release, eliminating the need for thermal or photonic activation. When strained to 100%, the hydrogel released nearly 78% of its loaded caffeine within an hour, showcasing its potential as a responsive delivery platform. Although gallium was not the active drug in this system, the relevance to the broader gallium delivery narrative is compelling. The gallic acid component shares structural and functional similarities with the polyphenols used in gallium-based hydrogels (as in the case of tannic acid systems), suggesting possible future adaptations of this hydrogel design for gallium-based antimicrobials.

When these different delivery strategies are considered together, a clear continuum emerges from the compositionally regulated, slow-releasing phosphate-based glasses to the dynamic, stimuli-responsive Ga-based nanoparticles, and further to mechanically responsive hydrogels. All these systems demonstrate an evolving sophistication in how gallium can be deployed for therapeutic purposes. The PBGs represent a foundational approach that offers chemical predictability and excellent anti-biofilm efficacy, particularly suitable for implant coatings or *in situ* wound management. In contrast, Ga-based LMPs are more suited for precision targeting and integration with smart diagnostic platforms, allowing not only localized drug release but also potential real-time feedback in clinical applications. Meanwhile, hydrogel systems like that developed by Abebe *et al.*[73] bridge these extremes by offering user-friendly, scalable, and stimulus-free control mechanisms, ideal for outpatient care and minimally invasive administration.

This progression reflects a broader trend in biomedical materials science: moving from static to dynamic, from generalized to tailored, and from chemically to mechanically or physically guided drug release. What unites these systems is gallium's multifaceted therapeutic role—its ionic mimicry of iron, low systemic toxicity, and high antibacterial specificity make it an ideal candidate for controlled release formulations. Each system—whether glass-based, nanoparticulate, or hydrogel—offers unique advantages, but also opens doors for hybrid approaches. For instance, incorporating gallium-doped glass nanoparticles into a strain-responsive hydrogel could theoretically merge the sustained release of ions with user-directed dosing, achieving both long-term efficacy and real-time adaptability. Therefore, the ongoing convergence of materials chemistry, nanotechnology, and biomedical engineering continues to redefine what is possible with gallium-based drug delivery systems. The collective evidence from Valappil,[72]

Zhang,[21] and Abebe[73] provides not only proof of concept but also a roadmap for the next generation of controlled-release platforms, all centered around the unique therapeutic potential of gallium.

6.3 Inhalable formulations for pulmonary infections in cystic fibrosis

Inhalable formulations for pulmonary infections in cystic fibrosis (CF) are emerging as a vital therapeutic approach, particularly in light of the chronic colonization and persistent infections that characterize this condition. The unique pulmonary environment in CF, shaped by the underlying mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, leads to the production of abnormally thick and sticky mucus in the airways. This altered mucus composition impairs mucociliary clearance, which is essential for the removal of inhaled pathogens and debris from the lungs. As a result, the CF lung becomes a highly permissive environment for microbial colonization, with biofilm formation further contributing to the resilience and persistence of pathogens. Among the microorganisms that frequently establish chronic infections in CF patients are *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and increasingly, fungal pathogens such as *Aspergillus fumigatus*, which is not only difficult to treat but is also showing rising resistance to conventional antifungal agents.[18,74]

The treatment of pulmonary fungal infections in CF is further complicated by the limitations of systemic antifungal therapies. These agents often face significant pharmacokinetic barriers, including poor penetration into the thickened airway secretions and difficulty achieving therapeutic concentrations in the lung tissue without eliciting systemic toxicity. This challenge has driven the development of localized, inhaled therapeutic strategies that aim to deliver high concentrations of antifungal agents directly to the site of infection, thereby maximizing efficacy while minimizing systemic exposure. In this context, inhalable formulations represent a particularly promising avenue for addressing the unmet clinical needs in CF-related lung infections.[74,75]

Among the novel classes of antimicrobials being explored for inhalation therapy are gallium-based compounds, which offer a unique mechanism of action by mimicking iron—a critical nutrient for many pathogens—and disrupting microbial iron metabolism. One such compound, a gallium–polypyridyl catecholate complex known as GaS1, has garnered attention for its broad-spectrum antimicrobial properties. Initially investigated for its activity against multidrug-resistant bacteria such as *Escherichia coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, GaS1 has more recently demonstrated significant antifungal potential. In particular, it shows promise against *A. fumigatus*, a leading cause of pulmonary aspergillosis in immunocompromised and CF patients alike.[76,77]

The exploration of GaS1 as an inhalable antifungal agent marks a significant advancement in the field of CF therapeutics. Its ability to retain antifungal activity in complex, CF-mimicking environments, combined with its compatibility with both nebulized and dry powder inhalation delivery systems, positions it as a highly adaptable candidate for localized lung therapy. These characteristics highlight the broader potential of gallium-based therapeutics to address the pressing issue of antimicrobial resistance and to offer effective, targeted treatment options for difficult-to-treat pulmonary infections in the context of cystic fibrosis.

For example, the study by Grassiri *et al.* (2024) epitomizes the innovative use of gallium-based therapeutics tailored for pulmonary delivery.[18] GaS1, initially characterized for its antimicrobial efficacy against various Gram-negative bacteria and methicillin-resistant *Staphylococcus aureus* (MRSA), was further evaluated for antifungal properties specifically against *A. fumigatus*, a fungus of great concern in CF patients.[18] The researchers developed and tested both nebulizable solutions and dry powder inhaler (DPI) formulations of GaS1, recognizing the critical need for optimized drug delivery systems capable of achieving high local concentrations while minimizing systemic exposure. Notably, GaS1 displayed potent antifungal activity against multiple *A. fumigatus* clinical isolates within a CF-relevant artificial sputum medium (ASM), maintaining a consistent minimum inhibitory concentration (MIC) of 63 μg mL^{-1} even in the presence of the sputum's growth-enhancing effects.

Crucially, the study employed an advanced *in vitro* air–liquid-interface (ALI) lung infection model that replicated the complexity of the CF lung microenvironment, integrating human distal lung epithelial cells (NCI–H441), ASM, and clinical *A. fumigatus* isolates. This model provided a more physiologically relevant platform to assess the therapeutic potential of GaS1, simulating both the mucosal interface and the unique nutritional context of the CF lung. In this setting, GaS1 maintained its efficacy, significantly reducing fungal growth in a dose-dependent manner without inducing cytotoxicity, even at concentrations up to 79 times the MIC after short-term exposure and 32 times the MIC after 24 hours. These results underscore GaS1's therapeutic window and reinforce its suitability for pulmonary administration.

Formulation development was meticulously undertaken to translate GaS1 into viable inhalable dosage forms. The nebulization approach, using a hospital-standard Aerogen® Solo mesh nebuliser, yielded a solution with acceptable pH and osmolality for lung delivery and achieved a fine particle fraction (FPF) of 53.8%, demonstrating good lung deposition potential. While nebulization remains a common modality in CF care, the study also addressed the increasing interest in DPI formulations due to their portability, stability, and potential for high-dose delivery. Spray-dried GaS1 powders, both as neat compound (GaS1-pow) and in combination with L-leucine (80GaS1-LL and 70GaS1-LL), exhibited physicochemical characteristics ideal for deep lung deposition, including amorphous morphology and corrugated particle surfaces that reduce interparticle cohesion and improve aerosol performance.

The inclusion of L-leucine, a safe and widely used pulmonary excipient, played a significant role in improving aerodynamic properties. While the geometric particle size remained statistically similar across formulations, the mass median aerodynamic diameter (MMAD) was notably smaller in leucine-

containing powders, correlating with improved FPF values—65% for GaS1-pow and as high as 78% for 70GaS1-LL. The morphological differences, observed *via* scanning electron microscopy (SEM), revealed that L-leucine induced a more spherical and smoother surface topology, minimizing agglomeration and enhancing dispersibility during inhalation. These findings are crucial as they directly impact the deposition efficiency in distal lung regions where *A. fumigatus* colonization is most persistent.

Importantly, the biological activity of GaS1 was retained post-formulation, with MIC values against *A. fumigatus* remaining consistent across both solution and powder formats. This stability, coupled with the excellent *in vitro* deposition profiles, confirms the feasibility of delivering effective and non-toxic doses *via* either nebulization or DPI systems. For instance, based on deposition studies and calculations involving lung lining fluid volumes, both the nebulized solution (4 mL volume) and the 20 mg DPI powder capsule were capable of delivering GaS1 concentrations ranging from 0.4 to 1.4 mg mL^{-1}—within the pharmacologically effective and non-toxic window established by cytotoxicity assays.

Moreover, the strategic simplicity of the formulations—with minimal excipients and reliance on scalable, solvent-free spray drying processes—ensures practical advantages for clinical translation. The use of a common inhalation excipient such as L-leucine, which is already being evaluated in multiple clinical studies, further supports regulatory acceptability and paves the way for potential human application. These findings are particularly timely, considering the pressing need for effective antifungal treatments in CF and other immunocompromised populations. The invasive nature of *A. fumigatus*, exacerbated by its ability to degrade epithelial cells and utilize their debris for nutrient acquisition, makes it a formidable pathogen in pulmonary infections. The use of artificial sputum medium in this study, while not a perfect substitute for patient-derived sputum, provided a controlled and reproducible environment to approximate the infection dynamics in CF lungs. This methodological rigor enhances the clinical relevance of the data, affirming GaS1's promise as a next-generation inhalable antifungal agent.

Collectively, the research led by Grassiri and colleagues represents a significant advancement in the development of gallium-based inhalable therapeutics.[18] It bridges the gap between *in vitro* antimicrobial efficacy and real-world clinical application by integrating formulation science, lung infection modelling, and pharmacological safety assessment. As the landscape of CF treatment increasingly shifts toward precision medicine and targeted delivery systems, the emergence of inhalable GaS1 formulations—capable of addressing multidrug-resistant fungal infections in the complex milieu of the CF lung—offers a powerful and much-needed therapeutic innovation.

6.4 Bone-targeted therapies for osteomyelitis

Bone-targeted therapies for osteomyelitis are emerging as a crucial paradigm in the management of persistent bone infections, especially in the context of implant-associated infections and chronic bacterial colonization. Osteomyelitis, characterized by the inflammation of bone tissue due to microbial invasion, is notoriously difficult to treat due to the complex microenvironment of bone, limited vascularization, and the emergence of antibiotic-resistant strains such as *Staphylococcus aureus* and *Escherichia coli*. Traditional systemic antibiotic therapies often fail to achieve sustained therapeutic concentrations in bone tissue, and surgical interventions, while sometimes necessary, come with substantial morbidity. Therefore, the development of novel, locally deliverable, and bone-integrative therapeutic strategies is essential. In this evolving landscape, gallium-based materials have demonstrated immense promise, primarily owing to their unique mechanism of antimicrobial action that disrupts bacterial iron metabolism, a pathway not easily circumvented by resistance mechanisms. The integration of gallium into bone-targeted delivery systems offers a strategic advantage by enabling site-specific action, minimizing systemic toxicity, and concurrently promoting osteogenesis.

A significant advancement in this area is the development of graphene oxide (GO)-anchored gallium nanoparticles (GaNPs) incorporated into biocompatible scaffolds, as demonstrated by Zhao *et al.* (2025).[59] Recognizing the challenge posed by the inherent fluidity of liquid gallium at room temperature, which impedes its direct application in solid-state biomedical devices, Zhao and colleagues engineered a nanocomposite wherein gallium nanoparticles were stabilized *via* electrostatic interactions with the oxygen-rich surfaces of graphene oxide nanosheets.[59] These GO/Ga nanocomposites were then embedded within poly-L-lactic acid (PLLA), a biodegradable polymer widely used in biomedical engineering and processed into three-dimensional scaffolds using selective laser sintering (SLS) technology. The composite scaffolds thus generated retained excellent structural integrity and mechanical properties while presenting an active antibacterial surface capable of sustained pathogen suppression. The synergistic bactericidal action arises from two mechanisms: the disruption of iron-dependent bacterial metabolic pathways by Ga ions and the physical membrane damage induced by sharp-edged GO nanosheets. The composite scaffolds demonstrated over 99% bactericidal efficacy against both *S. aureus* and *E. coli*, the primary bacterial culprits in osteomyelitis.

Moreover, Zhao *et al.* reported that these scaffolds were not only non-toxic to host cells but actively promoted the proliferation and osteogenic differentiation of rat bone marrow-derived mesenchymal stem cells (rBMSCs).[59] This dual functionality—simultaneous bacterial eradication and osteogenic support—is particularly critical in the context of osteomyelitis, where bone regeneration must proceed in the presence of residual or recurring infections. These findings suggest that the GO/Ga-PLLA scaffolds hold immense therapeutic potential for chronic osteomyelitis, addressing both the infectious and regenerative challenges of the disease in a single platform.

The findings by Zhao *et al.*[59] are complemented and expanded upon by the work of Yang *et al.* (2022), who similarly focused on the creation of GO/Ga nanoplatforms but directed

their investigation toward the surface modification of orthopedic implants.[55] Implant-associated infections, a major subset of osteomyelitis cases, pose unique challenges due to biofilm formation on the implant surface, poor osseointegration, and the propensity for chronic inflammation and osteolysis. Yang *et al.*[55] designed a surface coating composed of graphene oxide and gallium nanoparticles, aiming to endow implants with intrinsic antibacterial properties while enhancing their osseointegration and reducing inflammation-induced bone degradation. Their *in vitro* experiments confirmed robust antibacterial activity and high cytocompatibility, and crucially, revealed that the GO/Ga nanoplatforms actively supported osteoblast differentiation while inhibiting osteoclast formation.

Delving deeper into the cellular signalling mechanisms, Yang and colleagues found that the GO/Ga composites modulated several key pathways involved in bone remodelling.[55] These included the bone morphogenetic protein (BMP)/Smad pathway, mitogen-activated protein kinase (MAPK) signalling, and the nuclear factor kappa B (NF-κB) pathway. By activating osteogenic pathways and suppressing pro-osteolytic signals, the GO/Ga coating created a local environment favourable for bone formation and stability, even in the presence of bacterial challenge. These findings were further corroborated *in vivo* using a rat model of implant-associated femoral osteomyelitis. In this model, implants coated with GO/Ga nanocomposites significantly reduced bacterial colonization at the bone-implant interface, curtailed osteolysis, and promoted new bone growth along the implant surface, all while exhibiting no signs of local or systemic toxicity.

Together, the studies by Zhao *et al.*[59] and Yang *et al.*[55] illuminate a convergent strategy for bone-targeted osteomyelitis therapy that leverages the antimicrobial potency and osteoinductive potential of gallium in combination with the structural and functional advantages of graphene oxide. While Zhao *et al.*[59] emphasize scaffold-based strategies suitable for bone defect filling and chronic infection management, Yang *et al.*[55] target the prophylactic and therapeutic enhancement of implants, thereby covering a broad spectrum of osteomyelitis-related clinical scenarios. The integration of gallium into both resorbable scaffolds and permanent implants presents a versatile toolkit for orthopedic infection control, capable of addressing not only acute microbial threats but also the long-term challenges of bone regeneration and integration.

The synergy between antibacterial efficacy, biocompatibility, and bone regenerative support makes GO/Ga nanocomposites an exemplary model for next-generation bone-targeted therapies. As resistance to conventional antibiotics continues to rise, and as the global burden of musculoskeletal infections grows, these innovative approaches offer not just incremental improvements, but potentially transformative changes in the way osteomyelitis and related conditions are treated. Future directions may focus on the optimization of gallium dosing, controlled release kinetics, and the translation of these materials into clinically deployable devices with scalable manufacturing processes. Furthermore, combining these platforms with other therapeutic modalities such as bioactive growth factors, immunomodulators, or even localized gene therapy could open new frontiers in multifunctional, precision-targeted bone infection treatment.

7. Safety and biocompatibility

Gallium, as a metal-based therapeutic agent, has garnered substantial attention for its antimicrobial, anticancer, and osteogenic applications due to its ability to disrupt microbial iron metabolism without inducing resistance. Gallium ions (Ga^{3+}) mimic ferric ions (Fe^{3+}), thereby hijacking bacterial iron acquisition pathways—a mechanism that allows for selective uptake by bacterial cells over mammalian cells, which rely less heavily on siderophore-mediated iron uptake systems. This biochemical mimicry underpins the preferential accumulation of GaNPs in microbial cells, leading to functional iron deprivation and subsequent disruption of critical cellular processes such as DNA replication and oxidative metabolism. Several studies have demonstrated this selectivity, showing greater internalization and toxicity of GaNPs in bacterial strains such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* compared to human cell lines.[51,78]

In terms of cytotoxicity, GaNPs and other gallium-based compounds have generally exhibited low toxicity toward relevant human cell lines, including keratinocytes, fibroblasts, and epithelial cells, at therapeutically relevant concentrations. For example, *in vitro* studies using human dermal fibroblasts and lung epithelial cell lines have reported cell viabilities above 80% at concentrations that are lethal to bacterial pathogens. Nonetheless, the safety profile of GaNPs remains highly context-dependent, shaped by factors such as nanoparticle size, surface functionalization, dose, exposure time, and route of administration. Therefore, a nuanced understanding of gallium's interaction with biological systems is essential. Continued investigation through both historical and contemporary studies—including advanced cytotoxicity assays, biodistribution analyses, and long-term *in vivo* evaluations—is vital to ensure the safe and effective clinical translation of GaNP-based therapies.[51,77,79]

The foundational toxicological insights into gallium's systemic administration stem from early investigations such as that by Collery *et al.* (1996), who evaluated a novel organo–metallic gallium complex, tris(8-quinolinolato)gallium(III) (KP46), initially developed for anticancer therapy.[77] Their study is instrumental in delineating dose-dependent toxicity thresholds and the tissue-specific distribution of gallium following oral administration in Swiss mice. While KP46 demonstrated improved bioavailability compared to gallium chloride, its toxicity profile warranted caution. Acute toxicity assays revealed LD_{50} values of 2870 mg kg^{-1} and 2370 mg kg^{-1} for male and female mice, respectively. Subacute dosing at 62.5 mg per kg per day proved well-tolerated with no significant impairment to renal, hepatic, or hematological parameters. However, at doses of 125 mg per kg per day and above, toxicity became evident, most notably with a significant reduction in white blood cell count—highlighting gallium's potential to affect immune cell homeostasis at elevated doses. Interestingly, gallium showed high affinity for bone tissue, with concentrations reaching over

7 μg g^{-1} at the lowest dose, which is particularly significant when considering gallium's therapeutic use in bone-targeted strategies such as in osteomyelitis or malignant bone tumors. While the absence of gallium accumulation in sensitive organs like the brain, lungs, and reproductive tissues at therapeutic doses is reassuring, the findings underscore the importance of dose optimization and the need for long-term safety studies before systemic gallium therapy can be widely adopted.

This theme of context-specific biocompatibility continues in more recent research, particularly when gallium is integrated into nanostructured biomaterials. Jewett *et al.* (2012) explored the safety of gallium nitride (GaN), a semiconductor material with growing interest for use in biointerfaces and biosensors.[78] Their work demonstrates that etched and functionalized GaN surfaces remain chemically stable in aqueous environments, even in the oxidative presence of hydrogen peroxide, which is often present in inflammatory or infection-prone physiological sites. Crucially, GaN surfaces leached negligible amounts of gallium, mitigating concerns of local toxicity from ion release. *In vitro* studies with PC12 neuronal cells indicated that these surfaces did not impair cell viability or proliferation. More notably, when modified with the adhesive peptide IKVAV, GaN surfaces not only supported robust cell attachment but also enhanced neurite outgrowth and cell spreading—indicating not just biocompatibility but active promotion of cellular functions essential to neural integration. This work positions GaN as a chemically inert, biologically compatible platform suitable for use in neural prosthetics and potentially for orthopedic applications where nerve–bone interface is critical. The comparison with silicon—a more traditional biomaterial—further underscores GaN's favorable profile in terms of both stability and biofunctionality.

Complementary insights into gallium's compatibility within bone-relevant biomaterials are provided by Melnikov *et al.* (2019), who investigated the *in vitro* cytotoxicity of gallium-doped hydroxyapatite, a compound closely mimicking the mineral component of bone.[79] Their study employed monkey kidney epithelial cells (VERO) and found no statistically significant difference in cell viability between gallium-doped hydroxyapatite and control samples. This suggests that the incorporation of gallium in such a form does not elicit cytotoxic responses and may be safely used in orthopedic implants. Given hydroxyapatite's long-standing use in bone grafts and coatings, the doping of this matrix with gallium introduces a dual-functionality: preserving its osteoconductive nature while endowing it with antimicrobial properties through gallium's bacteriostatic action. This opens exciting clinical possibilities, particularly in combatting implant-associated infections or enhancing healing in osteolytic conditions where infection control and bone regeneration must occur simultaneously.

Taken together, these studies paint a multifaceted portrait of gallium's safety and biocompatibility. On one hand, systemically administered organo–gallium compounds like KP46 exhibit dose-dependent toxicity that must be rigorously evaluated in preclinical models, particularly concerning hematological impacts and long-term tissue retention. On the other hand, gallium, when integrated into localized delivery systems—whether as GaN surfaces or gallium-doped composites—can circumvent many of the systemic risks while retaining therapeutic efficacy. The negligible leaching from GaN and the inert behavior of gallium in hydroxyapatite suggest that structural integration of gallium into biocompatible matrices is a promising route to mitigate toxicity.

These findings collectively underscore a key principle in biomaterial development: safety and biocompatibility are not inherent properties of an element or compound but are contingent upon formulation, application, and delivery context. For gallium, this means that while systemic administration requires careful titration and monitoring, its integration into bone-targeted nanocomposites or implant surfaces holds substantial promise with low cytotoxic risk. As the field advances, future investigations should aim to harmonize efficacy with safety through smart design—tailoring gallium release profiles, optimizing particle characteristics, and pursuing long-term *in vivo* studies to fully establish its role as a safe, multifunctional component of next-generation medical devices.

8. Environmental impact and ecotoxicological considerations of gallium-based nanoparticles

With the expanding application of gallium-based nanoparticles (GaNPs) in antimicrobial therapies and biomedical technologies, understanding their potential environmental impact has become an increasingly critical issue. Despite their promising therapeutic benefits, GaNPs, like other metal-based nanomaterials, present unique challenges due to their persistence, bioavailability, and potential toxicity in ecological systems once released into the environment.

Gallium, as a post-transition metal, shares some chemical properties with metals such as aluminum and indium, which have been studied more extensively for their environmental behaviour.[80–83] However, direct environmental studies specifically on GaNPs remain sparse. Analogous investigations on silver (AgNPs) and copper nanoparticles (CuNPs) provide valuable frameworks for anticipating the environmental fate and effects of GaNPs. For instance, AgNPs, which have been widely studied, exhibit significant toxicity to aquatic microorganisms, algae, and invertebrates, primarily through ion release and oxidative stress mechanisms. Similarly, CuNPs are known for their antimicrobial properties but can induce detrimental effects in non-target microbial communities and aquatic fauna through accumulation and reactive oxygen species (ROS) generation. These studies underscore the complexity of nanoparticle interactions with biotic and abiotic environmental components and highlight the need to carefully evaluate GaNPs from a similar perspective.[84–87]

The environmental pathways for GaNPs include potential discharge through industrial manufacturing wastewater, biomedical waste streams, and leaching from medical devices or coatings. Once introduced into soil or aquatic environments, the physicochemical characteristics of GaNPs — such as size,

surface charge, shape, and coating — critically influence their stability, aggregation, and interaction with natural organic matter. For example, nanoparticles may undergo transformation processes including dissolution, sulfidation, or adsorption onto sediment particles, which can either mitigate or exacerbate their toxicity.[88–90] Microbial communities, which play pivotal roles in nutrient cycling and ecosystem health, may be particularly vulnerable to GaNP exposure. Given gallium's ability to mimic iron and disrupt bacterial iron metabolism, environmental microbes could experience impaired growth or altered community dynamics if exposed to GaNPs at sufficient concentrations. Such perturbations could cascade into broader ecological consequences, including reduced biodegradation capacity and shifts in microbial diversity.[91–94] Furthermore, the possibility of GaNPs affecting non-target organisms such as algae, daphnia, and fish through trophic transfer and bioaccumulation raises concerns about long-term ecosystem impacts.[93,94]

In terms of bioaccumulation and trophic magnification, studies with other metal nanoparticles suggest that nanomaterials can accumulate in lower organisms and biomagnify through food webs, though this process is influenced by nanoparticle dissolution rates and organismal uptake mechanisms. Whether GaNPs exhibit similar behavior remains to be thoroughly investigated.[95,96]

Importantly, the immunological and physiological effects of GaNPs on non-target species, including potential inflammatory or cytotoxic responses, require rigorous *in vivo* and ecotoxicological testing. The development of standardized protocols for environmental monitoring and toxicity assessment of GaNPs is currently lacking but is essential for regulatory risk assessment.[97,98]

As highlighted in the broader nanotoxicology literature, a precautionary approach is warranted. This involves the integration of life-cycle assessment (LCA) methodologies to evaluate environmental release at each stage — from synthesis and application to disposal. Moreover, design of safer-by-design GaNP formulations, such as biodegradable coatings or controlled-release systems, could mitigate environmental risks.[99–102] While GaNPs hold great promise as antimicrobial agents, their environmental release could pose risks to microbial ecology and wider ecosystems due to their persistence and biological activity. The review underscores the urgent need for focused research efforts encompassing environmental fate studies, ecotoxicity assays across multiple trophic levels, and long-term exposure assessments. Such investigations will be pivotal to inform sustainable development, safe deployment, and regulatory oversight of gallium-based nanotechnologies.[103–105]

9. Future perspectives and challenges

While gallium-based nanoparticles (GaNPs) have emerged as promising antimicrobial agents in the fight against multidrug-resistant (MDR) infections, realizing their full therapeutic potential requires addressing a range of scientific, translational, and clinical challenges. Central to this advancement is a more granular understanding of their immunological impact. Although GaNPs are generally considered to be well-tolerated, the potential immunological consequences of GaNP administration, including immunogenicity and inflammatory responses, remain underexplored. Nanoparticles inherently interact with immune cells upon systemic administration, and depending on their surface chemistry, size, and charge, may trigger immune recognition, cytokine release, or complement activation. While some studies report minimal immune stimulation at therapeutic doses, others suggest that nanoparticle-mediated activation of Toll-like receptors or inflammasomes may occur under certain conditions. Thus, a more detailed and systematic investigation of innate and adaptive immune responses to GaNPs is warranted to ensure safe long-term use, particularly in patients with underlying inflammatory or autoimmune disorders. Understanding how GaNPs behave in immunocompromised *versus* immunocompetent hosts will be equally critical in shaping clinical guidelines for their deployment.

Another key challenge in the development of GaNPs is elucidating and mitigating the risk of microbial resistance. While GaNPs circumvent many traditional resistance mechanisms by targeting iron metabolism, bacteria are remarkably adaptable, and the possibility of resistance gene expression changes in bacteria exposed to GaNPs, as revealed through transcriptomic or proteomic analyses, cannot be disregarded. Preliminary studies have indicated alterations in gene expression profiles related to metal transport, stress response, and metabolic reprogramming when bacteria are chronically exposed to sublethal concentrations of gallium. Such adaptations, though not yet fully characterized, could diminish therapeutic efficacy over time. A thorough mapping of bacterial gene and protein expression under gallium pressure is therefore essential to identify early markers of tolerance and to inform combination therapies that pre-empt resistance development. In parallel, the establishment of standardized protocols for minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) assays specific to GaNPs will enable comparative studies and foster predictive models for resistance trends.

Beyond extracellular infections, there is increasing interest in whether GaNPs can address hard-to-treat intracellular bacterial infections. Intracellular pathogens such as *Mycobacterium tuberculosis*, *Salmonella enterica*, and *Listeria monocytogenes* exploit host cell niches to evade immune surveillance and antibiotic treatment. Evidence of GaNP activity against intracellular pathogens, and the mechanisms by which they penetrate eukaryotic host cells, is emerging, albeit limited. Certain studies suggest that GaNPs, especially those functionalized with targeting ligands or optimized for endocytosis, can be internalized by host cells and localize within phagosomes or cytosol, where they exert antimicrobial activity. However, the efficiency of cellular uptake, intracellular trafficking, and release kinetics remains highly formulation-dependent. Engineering GaNPs to exploit host-cell entry pathways without inducing cytotoxicity or altering host cell function represents a pivotal frontier in expanding their clinical applicability to

intracellular infections, which often prove refractory to existing antibiotics.

The issue of dosing and treatment duration also poses a complex challenge. Determining what scale and duration of exposure to GaNPs is required to achieve bactericidal effects without fostering adaptive resistance is critical for both safety and efficacy. While short-term exposure to optimized concentrations has shown strong antimicrobial effects *in vitro*, prolonged or repeated use may exert selective pressures that drive bacterial adaptation or inadvertently disrupt host metal ion homeostasis. Furthermore, understanding the pharmacodynamics of GaNPs *in vivo*—how long they retain activity at the infection site, how they are cleared or retained in tissues, and how they interact with co-administered therapies—will be essential in designing safe treatment regimens. This includes optimizing dosing intervals to balance efficacy with minimization of off-target effects and accumulation risks.

From a materials science perspective, GaNPs must also demonstrate physicochemical stability under physiological conditions to be clinically viable. This includes maintaining their structural integrity and activity in the face of variable pH, ionic strengths, and the presence of serum proteins that could induce aggregation, opsonization, or clearance. In addition to material robustness, scalable and reproducible synthesis methods that adhere to good manufacturing practice (GMP) standards must be established. This is vital not only for regulatory approval but also for ensuring batch-to-batch consistency in therapeutic performance.

Moreover, regulatory pathways for metal-based nanotherapeutics are still evolving. As GaNPs do not fit neatly into conventional pharmaceutical categories, their approval will likely require novel frameworks for safety testing, quality assurance, and pharmacovigilance. Clinical implementation will demand clear dosing guidelines, toxicity thresholds, and contraindications, alongside validated biomarkers for monitoring therapeutic response and side effects. Health care providers must also be educated on the unique mechanisms and applications of GaNPs to prevent misuse and maximize clinical benefits.

The road ahead will undoubtedly require sustained interdisciplinary collaboration. Bridging the knowledge gap between materials engineering, microbiology, immunology, and clinical medicine is paramount. Investment in large-scale, controlled *in vivo* studies that mimic human pathophysiology, coupled with advanced omics technologies, will yield insights into host–pathogen–nanoparticle interactions at unprecedented resolution. Only through such integrated efforts can we anticipate, and strategically overcome, the multifaceted barriers to the successful translation of GaNPs into the clinic.

The clinical translation of gallium-based nanoparticles (GaNPs) presents a complex set of scientific, technical, and regulatory challenges that must be addressed to ensure their safe and effective use in human medicine. As emerging nanotherapeutics, GaNPs do not align neatly with existing regulatory frameworks designed for conventional small-molecule drugs or biologics. Their unique physicochemical properties—including nanoscale size, surface reactivity, and complex biodistribution—necessitate the development of specific regulatory pathways tailored to nanomedicine. Regulatory agencies such as the FDA and EMA are likely to require extensive characterization of GaNPs, encompassing parameters such as particle size distribution, zeta potential, surface chemistry, aggregation behavior, and stability under physiological conditions. These features directly influence cellular uptake, systemic circulation, and interaction with host tissues and microbiota, thereby impacting both efficacy and safety. Batch-to-batch consistency and robustness of synthesis protocols will also be scrutinized to ensure quality control and reproducibility at a commercial scale.

In addition, comprehensive toxicological profiling is essential, with assessments extending beyond acute toxicity to include sub-chronic and chronic exposure studies. Particular attention must be given to organ-specific accumulation (*e.g.*, liver, spleen, kidneys), potential interference with host iron metabolism, immunogenicity, and the risk of inflammatory responses or unintended interactions with host immune systems. These risks are amplified due to the metal-based nature of GaNPs and their ability to mimic iron in biological systems.

Mechanistically, GaNPs disrupt bacterial iron metabolism, a novel approach that calls for the establishment of validated biomarkers and pharmacodynamic endpoints to monitor therapeutic efficacy and off-target effects. The identification of such markers is crucial for both preclinical development and clinical trial design, which may need to adopt novel methodologies tailored to nanoparticle behavior—including flexible dosing regimens, localized delivery strategies, and patient stratification based on infection type or severity.

On the manufacturing front, adherence to Good Manufacturing Practice (GMP) standards is critical. This includes scalability of production methods, purification protocols, and long-term formulation stability, all of which affect product viability and shelf-life. Moreover, regulatory expectations increasingly emphasize environmental safety and lifecycle analysis, calling for data on nanoparticle degradation, waste management, and potential ecological toxicity associated with GaNP production and disposal.

Looking forward, the path to clinical implementation of GaNP-based antimicrobials will depend on multidisciplinary collaboration among materials scientists, microbiologists, clinicians, pharmacologists, and regulatory experts. This includes investing in robust *in vivo* models that closely mimic human disease pathophysiology, incorporating omics technologies to elucidate host–pathogen–nanoparticle interactions, and engaging regulatory authorities early in the development process to ensure alignment with safety and quality standards. While GaNPs hold great promise as next-generation antimicrobials, their successful translation into clinical use hinges on addressing key gaps in toxicology, pharmacokinetics, regulatory classification, and clinical trial design. Proactive efforts to build regulatory frameworks, optimize nanoparticle formulations, and generate robust clinical evidence will be essential to harness their full therapeutic potential.

Gallium-based nanoparticles represent a transformative shift in antimicrobial strategy, offering novel mechanisms to tackle antibiotic resistance. However, fully unlocking their potential hinges on resolving key questions regarding immunogenicity, resistance evolution, intracellular efficacy, optimal dosing, and regulatory integration. By addressing these challenges proactively and comprehensively, GaNPs may ultimately redefine the landscape of infectious disease therapeutics in the post-antibiotic era.

10. Conclusion

Gallium-based nanoparticles (GaNPs) represent a novel and promising class of antibacterial agents with distinct, iron-targeted mechanisms of action that interfere with critical bacterial metabolic pathways. By mimicking iron, gallium disrupts iron-dependent processes, ultimately inhibiting bacterial growth and survival. Their broad-spectrum efficacy against both Gram-positive and Gram-negative pathogens, combined with their ability to prevent and disrupt resilient biofilms, positions GaNPs as highly effective tools in combating persistent and hard-to-treat infections. Moreover, their low propensity for inducing bacterial resistance—a major limitation of conventional antibiotics—further enhances their clinical appeal. As antimicrobial resistance continues to escalate globally, threatening the efficacy of existing treatments, GaNPs offer a sustainable, mechanistically unique, and potentially synergistic alternative. Their versatility, tunable properties, and potential for integration into advanced drug delivery systems underscore the need for continued research, preclinical evaluation, and clinical translation to fully harness their therapeutic potential.

Ethical approval and consent to participate

Not applicable. This review article does not involve studies with human participants or animals performed by any of the authors.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No new data were generated or analyzed in this study. All data supporting the findings of this review are available within the manuscript and the references cited.

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