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REVIEW

Ferroptosis-Like Death: An Emerging Innovative Antibacterial Strategy

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Abstract: The increasing global crisis of antibiotic resistance underscores the imperative for innovative antibacterial strategies that transcend conventional mechanisms. Ferroptosis, an iron-dependent form of regulated cell death characterized by lethal lipid peroxidation, is a promising therapeutic approach. This review systematically explores ferroptosis-like death as an emerging antibacterial paradigm. The core mechanism involves exogenous interventions that result in intracellular iron overload, the incorporation of polyunsaturated fatty acids (PUFAs), and the disruption of bacterial antioxidant defenses. A comprehensive evaluation of three key strategies is provided: host-directed approach, in which immune cells are programmed to eliminate intracellular pathogens; small molecule-induced pathway, in which iron agents, PUFAs, and others are used to directly trigger bacterial death; and nanomaterial-mediated precision therapy, in which functionalized nanosystems are employed for synergistic and intelligent targeting. Despite the challenges in mechanistic understanding and biosafety, future advancements through multiomics, intelligent nanosystems, and synergistic cell death pathways are anticipated to propel this field. This strategy indicates a possible transformation in anti-infective therapy from broad-spectrum killing to precision regulation. This shift offers a potentially effective solution to address drug-resistant bacterial infections.

Keywords: ferroptosis-like death, antibiotic resistance, lipid peroxidation, nanomedicine, reactive oxygen species

Antibiotic Resistance

Antibiotic resistance is defined as the capacity of bacteria to resist antibiotics, resulting in failed standard treatment, persistent or recurrent infections, and a heightened risk of pathogen transmission.[1] Since the advent of penicillin, antibiotics have constituted a cornerstone of modern medicine and significantly reduce the incidence and mortality associated with infectious diseases. However, the extensive and indiscriminate applications of antibiotics in human medicine and animal agriculture have resulted in potent selective pressure. This pressure drives microbes to continuously evolve resistant phenotypes through mechanisms like genetic mutation, efflux pump expression, and biofilm formation.[2] The World Health Organization has formally acknowledged the serious harm of antibiotic resistance, classifying it as one of the most pressing concerns to global public health. In 2019, approximately 4.95 million deaths worldwide were associated with antibiotic resistance, with 1.27 million of these deaths being directly attributable to it. This figure exceeds the combined mortality from HIV/AIDS and malaria.[1] In the absence of effective interventions, the number of annual deaths attributable to antibiotic resistance is projected to exceed 1.9 million by 2050, with particularly devastating consequences in regions with limited healthcare resources.[3] The challenges posed by antibiotic resistance have extended beyond health to economic domains, thereby triggering significant global socioeconomic challenges.[4] The fundamental reason for the emergence of antibiotic resistance crisis is the critical disconnection between the rapid evolution of pathogens and the stagnation of the antimicrobial development. The development of novel antibiotics is confronted by multiple challenges, including the rapid evolution of bacterial resistance, prolonged development cycles coupled with high costs and failure rates. Therefore, there is an urgent need for novel antibacterial paradigms that function independently of conventional antibiotic mechanisms.

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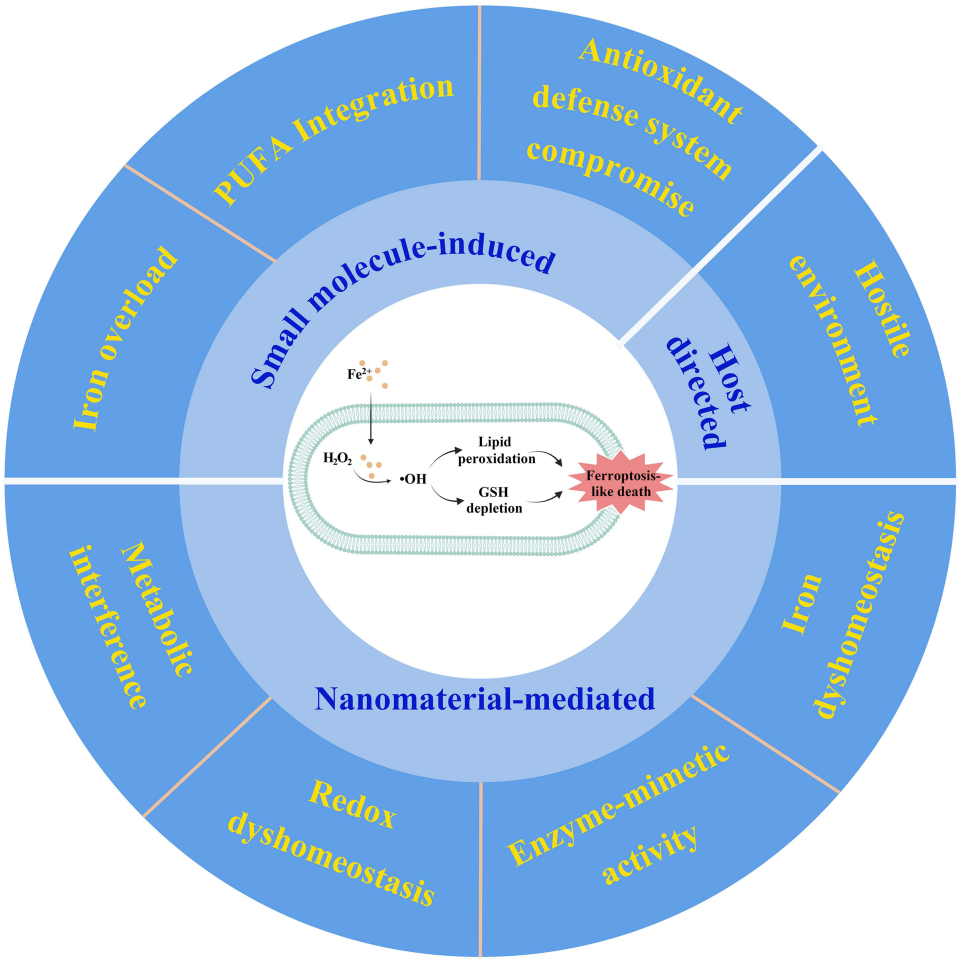
Graphical Abstract



Numerous alternative antimicrobial strategies with distinct mechanisms have been explored. Reactive oxygen species (ROS)-based antimicrobial approaches, such as photodynamic therapy (PDT) and hyperbaric oxygen therapy, primarily induce nonspecific oxidative damage to bacterial lipids, proteins, and nucleic acids.[5] Metal-based antimicrobial strategies, including silver nanoparticles, copper-based coatings, and zinc oxide materials, utilize the intrinsic toxicity and catalytic properties of metal ions or their nanostructured derivatives.[6] Strategies targeting regulated bacterial death involve modulating specific programmed cell death pathways in bacteria, such as apoptosis-like death, pyroptosis, immunogenic cell death, and NETosis.[7] Recently, ferroptosis-like death, which involves the targeting of bacterial iron metabolism and redox homeostasis, has garnered significant attention as a highly promising innovative antibacterial pathway.[8] This strategy is less prone to inducing drug resistance and easily combines with nanocarriers for targeted delivery, significantly reducing off-target damage to host cells. Therefore, it offers a highly promising new direction for mitigating antibiotic resistance crisis.

To date, there are only few reviews addressing ferroptosis-like antibacterial strategies, with primary focus on elucidating ferroptosis mechanisms and its dual role in host–pathogen interactions.[9–11] This review firstly compares the ferroptosis in eukaryotes with ferroptosis-like death in bacteria. The core mechanisms driving bacterial ferroptosis-like death is then outlined, and the strategies utilized are categorized into three types: host-directed, small molecule–mediated, and nanomaterial-mediated approaches. In particular, the nanomaterial-mediated section, a major focus of

current research, is discussed in detail covering mechanisms, multimodal synergy, intelligent responsiveness, and application scenarios. Finally, future directions and clinical translation prospects for ferroptosis-like antibacterial strategies are discussed.

Antibacterial Potential of Ferroptosis

Ferroptosis

Ferroptosis is an iron dependent and nonapoptotic form of regulated cell death formally defined in 2012.[12] It is morphologically characterized by mitochondrial shrinkage and the reduction or disappearance of cristae. The nuclear structure remains intact and lacks typical apoptotic features. Biochemically, this process is characterized by iron-dependent peroxidation of phospholipids on cell membranes, consequently resulting in membrane system failure.

The initiation of ferroptosis is contingent upon the dysregulation and synergistic interaction of three fundamental elements: the catalytic center (iron), the reaction substrate (polyunsaturated fatty acid (PUFA)-containing phospholipids, PUFA-PLs), and the defense system (antioxidant pathways).[13] Intracellular labile ferrous ions (Fe^{2+}) function as the primary catalysts for the Fenton reaction and initiate ferroptosis. The Fenton reaction is a chemical process that involves the conversion of hydrogen peroxide (H_2O_2) into highly reactive hydroxyl radicals (•OH). These radicals subsequently initiate lipid peroxidation, which damages cell membranes and other biological molecules. This process can also be specifically catalyzed by iron-dependent enzymes (eg, lipoxygenases and cytochrome P450 oxidoreductases). The complex formed by ALOX15 and phosphatidylethanolamine-binding protein 1 plays a critical role in phosphatidylethanolamine oxidation and ferroptosis signal transduction.[14] Long-chain PUFA-PLs in the cell membrane, particularly phosphatidylethanolamine, function as the principal fuel for lipid peroxidation. The bisallylic hydrogen atoms of PUFAs are highly susceptible to radical attack and peroxidation chain reactions. The enzymatic esterification of PUFAs, a process facilitated by acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), has been shown to promote the generation and incorporation of oxidizable phospholipids into membranes. Consequently, this results in increased vulnerability to ferroptosis. Conversely, monounsaturated fatty acids have been demonstrated to impede the propagation of lipid peroxidation through two distinct mechanisms: competitive esterification via ACSL3 and membrane fluidity alteration. This results in resistance to ferroptosis. Furthermore, lipid droplets play a pivotal role in providing protection by sequestering PUFAs, thereby reducing their availability for incorporation into membrane phospholipids.[15] Cells are equipped with a sophisticated and multitiered defense system to regulate ferroptosis, thereby preventing the lethal accumulation of lipid peroxides. The Xc^- cystine/glutamate antiporter (consisting of the SLC7A11 and SLC3A2 subunits) is responsible for cystine uptake, which is the rate-limiting step for de novo glutathione (GSH) synthesis. GSH plays a pivotal role as a reducing cofactor, facilitating the action of GSH peroxidase 4 (GPX4). This process entails the reduction of membrane lipid hydroperoxides to nontoxic lipid alcohols. In addition to the GPX4-GSH system, the FSP1-CoQ10-NAD(P)H, GCH1-BH_4, and DHODH-$CoQH_2$ systems have been identified as crucial independent defense systems. Calcium-independent phospholipase A2 beta which catalyzes the hydrolysis of oxidized phospholipids, and the endosomal sorting complex required for transport-III, which facilitates plasma membrane repair, also contribute to delaying the ferroptosis process.[16]

The susceptibility of cells to ferroptosis is precisely regulated by intricate molecular networks. NRF2 is the master regulator of the antioxidant response. It transcriptionally upregulates genes such as SLC7A11, ferritin heavy chain, and FSP1, thereby providing a comprehensive enhancement of cellular defense capabilities. On the other hand, p53 has been shown to play a context-dependent dual role. It can promote ferroptosis by transcriptionally repressing SLC7A11 or exert protective effects by inducing genes such as p21. The hypoxia-inducible factor pathway exerts a regulatory influence on ferroptosis by modulating iron and lipid metabolism. The specific outcomes resulting from this regulatory process vary depending on the particular context. Furthermore, epigenetic mechanisms, including histone modifications and DNA methylation, have been shown to play regulatory roles in the expression of key ferroptosis-related genes, such as GPX4 and ACSL4.[17,18]

Potential of Ferroptosis-Like Death as Antibacterial Mechanism

A similar phenomenon to ferroptosis has been observed in microorganisms, which is also accompanied by hallmark features such as an iron overload-driven Fenton reaction, impairment of the antioxidant system, and membrane lipid peroxidation.[9] This process can be reversed by ferroptosis-specific inhibitors, such as ferrostatin-1 and liproxstatin-1. However, bacteria lack the core molecular machinery functioned in eukaryotic cells in regard to ferroptosis (eg, ACSL4 and GPX4), and their cell membranes usually do not contain many long-chain PUFAs, which can be easily damaged by peroxides. For these reasons, it is defined as ferroptosis-like death rather than canonical ferroptosis (Table 1). Therefore, bacterial ferroptosis-like death should be defined as an iron-dependent cell death driven primarily by the abnormal accumulation of intracellular lipid peroxidation (Figure 1).

The core biochemical milieu of ferroptosis-like death includes the iron overload occurrence, PUFA incorporation, and compromise of the antioxidant defense system.

Iron Overload Occurrence

Direct administration of Fe^{2+} has been identified as the most effective strategy to initiate an ROS burst and subsequent damage in bacteria. The administration of $FeSO_4$ results in a significant increase in intracellular ROS levels within *Staphylococcus aureus* (*S. aureus*).[19] In addition to Fe^{2+}, other metal ions such as Fe^{3+} and Cu^{2+} can also lead to the accumulation of intracellular Fe^{2+}, either directly or by reprogramming bacterial iron metabolism (eg, upregulating iron uptake genes), thereby priming the cell for the Fenton reaction.[20,21]

PUFA Incorporation

The native bacterial membrane is an unsuitable substrate for extensive lipid peroxidation. Consequently, the provision of exogenous PUFAs, such as arachidonic acid (AA) and docosahexaenoic acid (DHA), is often necessary. Specifically, certain microbes (eg, *Vibrio vulnificus* (*V. vulnificus*) and *Saccharomyces cerevisiae*) take up PUFAs from the environment and incorporate them into membrane phospholipids.[8] Once integrated, PUFAs have the capacity to modify membrane properties, potentially resulting in membrane potential hyperpolarization, increased permeability, and even pore formation.[22]

Compromise of the Antioxidant Defense System

Bacteria possess a robust and multifaceted antioxidant defense network, which primarily relies on GSH, other low-molecular-weight thiols, and antioxidant enzymes (eg, catalase and alkyl hydroperoxide reductase). The depletion of intracellular GSH or the inhibition of key antioxidant enzymes is imperative for lowering the threshold for inducing ferroptosis-like death. Multiple nanomaterials can achieve ferroptosis-like antibacterial effects by disrupting the redox systems of bacteria. For example, gold nanoparticles can induce intracellular GSH depletion and inactivation of GPx-like enzymes.[23] The release of polysulfides from diverse nanomaterials, such as iron sulfide (FeS_2) and $Fe^{2+}S_naq$, can directly oxidize and consume GSH. This results in a deleterious disruption of the bacterial GSH/GSSG ratio.[24,25]

Based on the elucidated mechanisms, the targeting of ferroptosis-like death strategies can effectively trigger bacterial death. The precise modulation of host immunometabolism can result in the strategic application of ferroptosis to eradicate intracellular bacteria. The use of small molecule compounds or prodrug has emerged as a promising approach for the exogenous delivery of key effectors, such as iron and PUFAs to induce ferroptosis-like death. In addition, functionalized nanomaterials can achieve both synergistic action and intelligent, targeted delivery. The explorations involving ferroptosis-like antibacterial strategy have considerable translational potential and will be discussed in more detail (Figure 2).

Ferroptosis-Like Antibacterial Applications

Host-Directed Ferroptosis-Like Death

Host cells can transform the potentially self-damaging process of ferroptosis into an effective immune weapon for clearing intracellular pathogens by precisely regulating their own iron metabolism and lipid peroxidation pathways. By creating a harmful intracellular environment for pathogens, precise clearance can be achieved.

Table 1 Ferroptosis vs Ferroptosis-Like Death

	Ferroptosis	**Ferroptosis-Like Death**	**Core Summary**
(1) Cell type	Eukaryotic cells (particularly mammalian)	Prokaryotic cells (particularly bacteria)	
(2) Core biochemical elements			
Catalytic Center (Iron)	• Labile Fe^{2+} via the Fenton reaction • Iron-enzymes (eg., lipoxygenases) directly catalyze lipid peroxidation	• Primarily exogenously supplied Fe^{2+} • Other molecules (eg, Cu^{2+}) can reprogram bacterial iron metabolism to accumulate Fe^{2+} • Lacks canonical lipoxygenase homologs	Common: Central driver is Fe^{2+} and the Fenton reaction Distinct: Eukaryotes have enzymatic pathways; Bacteria rely mainly on chemical pathways
Reaction Substrate (Lipids)	• Membrane PUFAs-containing phospholipids, particularly phosphatidylethanolamine • ACSL4 and LPCAT3 esterify and incorporate PUFAs into membranes	• Native bacterial membranes are poor substrates (low in long-chain PUFAs) • Relies on exogenous PUFAs that are passively or actively incorporated • No ACSL4/LPCAT3 homologs; incorporation mechanism is unclear	Common: Lipid peroxidation, mainly requires the presence of PUFAs in membranes Distinct: Eukaryotes have biosynthetic incorporation; Bacteria rely on exogenous supplementation
Defense System	Multilayered, sophisticated antioxidant systems: • Core: GPX4-GSH axis • Parallel: FSP1-$CoQH_2$, GCH1-BH_4, DHODH-$CoQH_2$ • Repair: iPLA2β, ESCRT-III.	Simpler, general antioxidant network: • GSH, low molecular weight thiols • Enzymes like catalase, peroxidase, superoxide dismutase • Lacks homologs of core ferroptosis defense proteins (eg, GPX4, FSP1).	Common: Both depend on intracellular antioxidants and enzymes to maintain redox homeostasis. Distinct: Eukaryotic system is complex, redundant, and specific; Bacterial system is fundamental and general.
(3) Molecular & Genetic Basis			
Key Genes/Proteins	A well-defined core machinery: • Pro-death: ACSL4, LPCAT3, ALOX15 • Anti-death: GPX4, SLC7A11, FSP1	Lacks the homologous core machinery. The process is mediated by exogenous factors and basal bacterial metabolic/stress pathways.	Ferroptosis is a genetically defined pathway; Ferroptosis-like death is a phenotypic endpoint triggered by external stress.
Regulatory Network	Precisely regulated by transcription factors: • p53: Context-dependent dual role. • NRF2: Master regulator of defense genes. • HIF: Modulates iron and lipid metabolism. • Epigenetic regulation.	Network is ill-defined; Bacterial global stress responses (eg, oxidative stress response, iron homeostasis regulons).	Distinct: Eukaryotic regulation is programmed and networked; Bacterial response is reactive and modular.
(4) Morphological Features	• Mitochondria: Shrinkage, increased membrane density, loss of cristae. • Nucleus: Normal size, no chromatin condensation. • The cell membrane remains intact in the early stages of the process and undergoes lysis in the late stages.	• Plasma Membrane: Pore formation, rupture, dissolution. • Cytoplasmic leakage.	Common: Both involve damage to membrane systems. Distinct: The hallmark organelle of damage differs (mitochondria vs plasma membrane).
(5) Pharmacological Response			
Inhibitors	Effectively suppressed by specific ferroptosis inhibitors: Ferrostatin-1, Liproxstatin-1	Effectively suppressed by specific ferroptosis inhibitors: Ferrostatin-1, Liproxstatin-1	Common: Sensitivity to the same inhibitors confirms the shared core chemistry of lipid peroxidation.
Inducers	• Erastin: Inhibits System Xc^- • RSL3: Directly inhibits GPX4 • Ferritinophagy	• Exogenous Fe^{2+}/Fe^{3+}, Cu^{2+} • Exogenous PUFAs • ROS generator or GSH depletion	Distinct: Eukaryotic inducers target specific proteins; Bacterial inducers provide reactive substrates or disrupt the environment.
(6) Physiological/Pathological Role	Involved in development, immunity, tumor suppression, neurodegenerative diseases, and ischemia–reperfusion injury. A "double-edged sword".	Not a conventional physiological process. Primarily investigated and leveraged as an emerging antibacterial strategy to eliminate drug-resistant and intracellular bacteria.	Distinct: Ferroptosis is an endogenous physiological/pathological process; Ferroptosis-like death is currently primarily an exogenous therapeutic tool.

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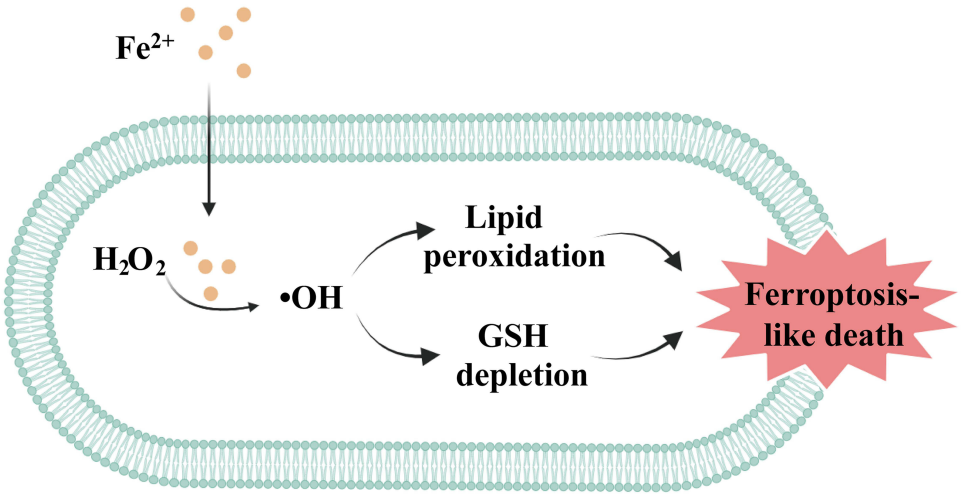

Figure 1 Mechanism of bacterial ferroptosis-like death. This cellular process is driven by iron-dependent ROS generation, predominantly via the Fenton reaction between intracellular Fe^{2+} and H_2O_2. Highly reactive •OH is generated, which triggers membrane lipid peroxidation and simultaneously depletes intracellular GSH. Collectively, the synergistic action of these biochemical cascades culminates in ferroptosis-like death in bacterial cells.

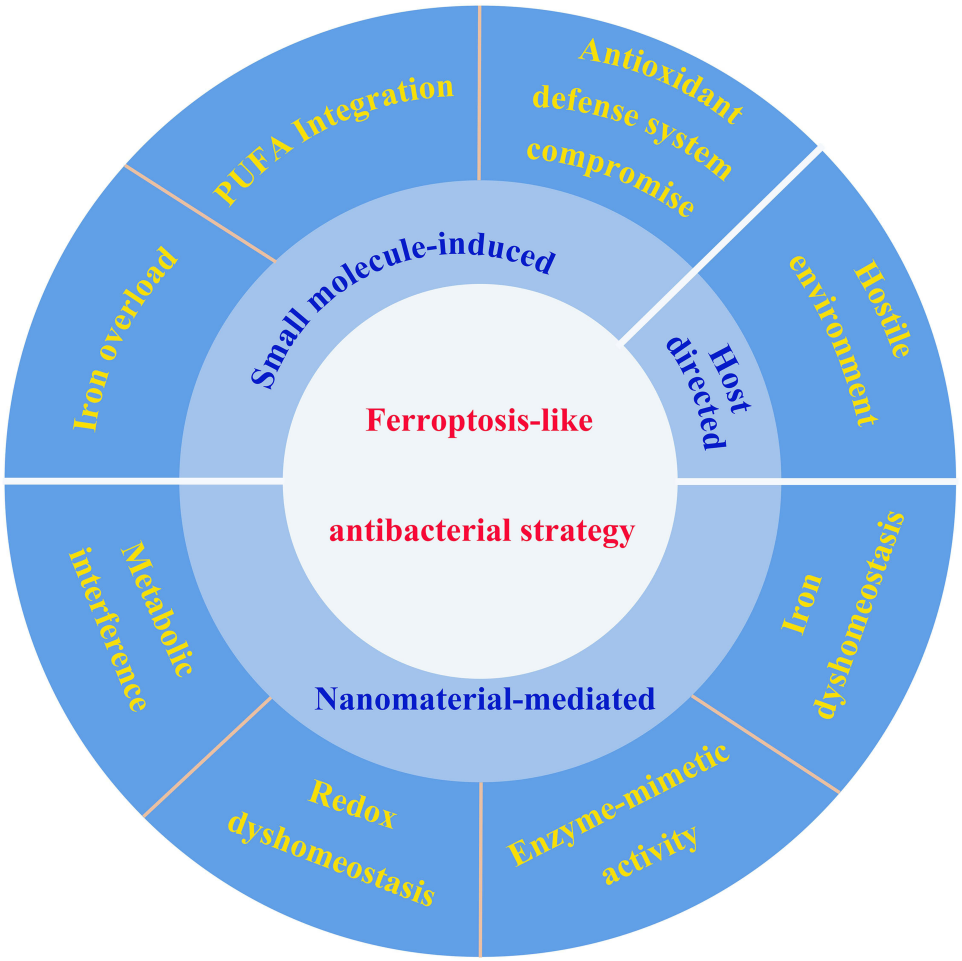

Figure 2 Ferroptosis-like antibacterial strategies. The execution of these strategies is achieved through three primary approaches: the host-directed approach, which engenders a hostile environment; the small molecule-induced pathway, encompassing iron load, PUFA integration, and antioxidant defense system compromise; and the nanomaterial-mediated strategy, involving disruption of metabolic interference, redox dyshomeostasis, enzyme-mimetic activity and iron dyshomeostasis.

The controlled induction of ferroptosis in macrophages enhances the capacity of these cells to eliminate intracellular bacteria.[26] Iron overload within the infection microenvironment can upregulate ACSL4 expression, thereby increasing the efficiency of PUFA incorporation into membranes. This consequently increases the susceptibility of macrophages to ferroptosis.[27] Infection of macrophages with attenuated rough *Brucella* (strain RB14) results in a robust ferroptosis response, as demonstrated by significant decrease in GSH levels, accumulation of malondialdehyde (MDA), lipid ROS burst, and expansion of the labile Fe^{2+} pool. The administration of ferrostatin-1 substantially increased bacterial survival, indicating that in this specific scenario, ferroptosis induction might benefit the host by promoting the clearance of these defective pathogens. The host effectively transforms the damage instigated by the pathogens into a fatal countermeasure against them.[28] p53 functions as a transcriptional repressor of SLC7A11, a critical component of System Xc^-. The level of p53 protein rapidly increases in macrophages infected with the rough *Brucella* strain RB51, leading to decreased expression of SLC7A11 and its partner SLC3A2. This results in the inhibition of cystine uptake, leading to depletion of the cellular GSH pool. Consequently, this depletion inactivates GPX4, which ultimately triggers lethal lipid peroxidation and ferroptosis. Both ferroptosis inhibitors and p53 inhibitors can reverse the aforementioned pathway, thereby increasing intracellular bacterial survival. These observations further confirm the hypothesis that these mechanisms function as active host immune mechanisms that facilitate pathogen clearance.[26]

The functional repurposing of ferroportin (FPN) can target iron delivery. For example, infection of sea cucumber coelomocytes leads to downregulation of GPX4 and elevated levels of intracellular Fe^{2+} and MDA. The iron efflux protein AjFPN post-infection colocalizes with intracellular bacteria (up to 68.5%), delivering iron into bacterial vesicles and effectively "iron poisoning" the bacteria. The knockdown of AjFPN leads to significant reduction in Fe^{2+} and lipid ROS levels within bacteria, resulting in a substantial decrease in antibacterial efficiency.[29] Macrophages exhibit a more sophisticated spatiotemporal control mechanism. Within 1 to 12 hours post-infection with *S. aureus*, macrophages enter a transient phase of ferroptotic stress, characterized by significant increase in Fe^{2+} and lipid ROS levels. Mechanistically, approximately 65% of FPN is internalized and enriched on the membranes of bacteria-containing vesicles in a specific manner. This results in a shift in its function from iron efflux channel to localized conduit for directional Fe^{2+} delivery into the bacterial microenvironment. This strategy significantly reduces the bacterial load. During the later infection stages (approximately 24 hours), as GPX4 expression recovers, macrophages effectively eliminate the accumulated lipid ROS without substantially compromising cell viability. This outcome exemplifies the programmed and self-contained utilization of ferroptosis by the host (Figure 3).[30]

Small Molecule-Mediated Ferroptosis-Like Death

Small molecule-mediated strategies are designed to create the necessary conditions for triggering ferroptosis-like death of pathogens. This approach is distinct from host-directed ferroptosis stress strategies. The primary benefit of this approach lies in its substantial design flexibility and combinability. This methodology has been established through the implementation of individual or synergistic actions that disrupt pathogen iron homeostasis, introduce lipid peroxidation substrates (PUFAs), and disrupt antioxidant defenses (Table 2).

Iron Overload

The most straightforward approach to induce bacterial ferroptosis-like death is direct administration of Fe^{2+}. The efficacy of this treatment has been demonstrated across a variety of bacterial species, although its specific manifestations can vary. $FeSO_4$ can induce rapid (within 15 min) and dramatic increases in ROS levels (12.3-fold), depletion of GSH (from 25 μmol/L to 8 μmol/L), membrane potential collapse (68% decrease), significant MDA accumulation, and membrane rupture in *S. aureus*.[19] Ferrous gluconate efficiently kills *Escherichia coli* (*E. coli*) through a multifaceted mechanism involving the combined processes of lipid peroxidation and DNA damage.[36] Nevertheless, the bactericidal effect of $FeSO_4$ on *Vibrio parahaemolyticus* (*V. parahaemolyticus*) does not involve a substantial increase in ROS, which are categorized as atypical ferroptosis-like death.[45]

A combined strategy has been formulated to increase iron utilization efficiency and achieve synergistic sterilization. Ultrasound treatment generates cavitation effects, thereby increasing membrane permeability. When combined with

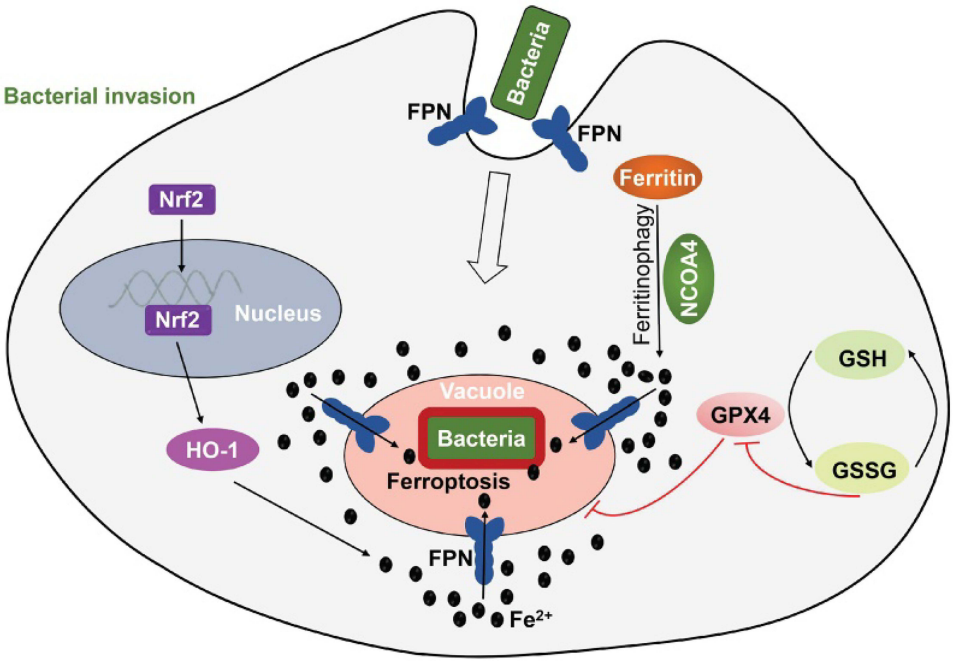

Figure 3 Host-directed vacuolar ferroptosis-like response eliminates bacteria. When bacteria are ingested into the cellular vacuoles by the host cell, NCOA4-dependent ferritinophagy releases cytosolic Fe^{2+}, which is transported into the pathogen-containing vacuole via ferroportin (FPN). Simultaneously, Nrf2 translocates to the nucleus and upregulates HO-1, further modulating cytosolic iron homeostasis. Within the vacuole, elevated Fe^{2+} levels promote GSH oxidation to GSSG, inactivating GPX4 and triggering localized lipid peroxidation. This vacuole-restricted ferroptosis-like response results in bacterial death, ensuring pathogen clearance. Reproduced with permission from Ref.[30] Copyright © 2022 by the authors, Ivyspring International Publisher.

$FeSO_4$, ultrasound can promote the influx of Fe^{2+} and subsequently intensifies the Fenton reaction.[34] The combination of $FeSO_4$ with a cinnamaldehyde nanoemulsion synergistically inhibits *E. coli* O157:H7 and its biofilms through concurrent ferroptosis-like death and direct membrane disruption.[35] This formulation has been developed into active packaging films for food preservation.[46]

The advent of delivery systems has been driven by the need to address two fundamental challenges: the low bioavailability of Fe^{2+} and the associated host toxicity. The ferrous sulfide in glycyrrhizic acid (FeS/GA) hydrogel facilitated the concurrent release of Fe^{2+} and H_2S, thereby achieving a substantial reduction in bacterial ATP levels. This treatment enhanced wound healing rates in diabetic mice, with a documented improvement of up to 78%. Additionally, the FeS/GA hydrogel promoted the polarization of macrophages toward the reparative M2 phenotype, which increased from 18% to 52%.[37] PEGylated liposomes (P/Fe@L-P) successfully codeliver polymyxin B and Fe^{2+}, achieving a high release rate (78%) in the acidic infection microenvironment (pH 5.5). The survival rates in murine pneumonia model increased from 45% (free drug group) to 85% while the nephrotoxicity is reduced.[38]

Other metal ions and compounds can also induce similar iron dysregulation and oxidative damage. $FeCl_3$ can effectively kills *Pseudomonas aeruginosa* (*P. aeruginosa*) and induces classic ferroptosis markers.[20] Catechol-type flavonoids (eg, 7,8-dihydroxyflavone) can reduce Fe^{3+} to Fe^{2+} and inhibit bacterial two-component systems, potently reversing colistin resistance.[33] Fe^{3+}-salophene complex exhibits high levels of bacterial uptake. The bactericidal activity is similar to that of ciprofloxacin and can be reversed via ferrostatin-1.[47] The phenolic compound phloroglucinol can form stable complexes with Fe^{3+} and markedly increases the efficiency of the Fenton reaction, inducing GSH depletion and lipid peroxidation (Figure 4).[39] $CuSO_4$ upregulates the iron-responsive regulator Fur in *S. aureus* and initiates iron metabolism reprogramming which predisposes bacteria to ferroptosis.[21] Vitamin B_6 promotes Fe^{2+} accumulation by inhibiting potassium transport and increases colistin efficacy.[40] In the presence of oxygen and iron, vitamin C drives the Fenton reaction by reducing Fe^{3+} and completely eradicate *Mycobacterium tuberculosis*.[44] The natural product thymol directly promotes ferritin-mediated Fe^{2+} release and induces ferroptosis-like death in *V. parahaemolyticus*.[42] Photosensitizer precursor 5-aminolevulinic acid can be metabolized

Table 2 Small Molecule-Mediated Bacterial Ferroptosis-Like Death

Active Compound	Strain and Disease Type	Characteristics of Ferroptosis-Like Death
5-Aminolevulinic acid[31]	Gram-positive bacteria: *M. abscessus*; No in vivo studies conducted.	Intracellular iron overload; ROS elevation, lipid peroxidation; Membrane integrity disruption; Attenuated by ROS scavenger and ferroptosis inhibitor.
Arachidonic acid, Triclosan[32]	Gram-positive bacteria: *S. mutans*; No in vivo studies conducted.	ROS induction, lipid peroxidation.
Copper sulfate[21]	Gram-positive bacteria: *S. aureus*, MRSA; Skin wound infection.	Intracellular iron overload; ROS burst, lipid peroxidation; Membrane perforation; Inhibited by ROS scavenger, iron chelator, and ferroxidase inhibitor.
7,8-Dihydroxyflavone[33]	Gram-negative bacteria: *S. typhimurium, E. coli, K. pneumoniae*; Typhoid fever.	Intracellular iron overload, and iron homeostasis disruption.
Ferrous sulfate[19]	Gram-positive bacteria: *S. aureus*, MRSA; Keratitis.	ROS burst, lipid peroxidation; Membrane rupture; Alleviated by ROS scavenger and ferroptosis inhibitor.
Ferrous sulfate[34]	Gram-negative bacteria: *V. parahaemolyticus*; No in vivo studies conducted.	Iron influx; ROS burst, lipid peroxidation; Membrane damage; Alleviated by ferroptosis inhibitor.
Ferrous sulfate[35]	Gram-negative bacteria: *E. coli*; No in vivo studies conducted.	ROS increase, lipid peroxidation; GSH/GSSG ratio reduce; Inhibited by ferroptosis inhibitor, iron chelator and antioxidant.
Ferrous gluconate[36]	Gram-negative bacteria: *E. coli*; No in vivo studies conducted.	Labile iron increase; ROS burst, lipid peroxidation; Inhibited by iron chelators.
Ferrous sulfide[37]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*, MRSA; Diabetic wounds.	ROS increase, lipid peroxidation; GSH depletion, GSH/GSSG ratio decrease; Inhibited by ROS scavenger.
Ferrous chloride, polymyxin B[38]	Gram-negative bacteria: *A. baumannii*, polymyxin B-resistant *A. baumannii*, multidrug-resistant *K. pneumoniae*; Gram-positive bacteria: multidrug-resistant *S. aureus*; Pneumonia.	ROS generation and MDA increase; GSH depletion; Inhibited by iron chelator.
Ferric chloride[20]	Gram-negative bacteria: *P. aeruginosa*, drug-resistant *P. aeruginosa*; Full-thickness skin wound infection.	Intracellular iron increase; ROS burst, lipid peroxidation; GSH synthesis reduce; Cell surface collapse and content leakage; Inhibited by iron chelator, ROS scavenger, and ferroptosis inhibitor.
Phloroglucinol[39]	Gram-negative bacteria: *E. coli, Pseudomonas sp., S. typhimurium, K. pneumoniae*; No in vivo studies conducted.	Lipid peroxidation; GSH depletion; Inhibited by ferroptosis inhibitors and ROS scavenger.
Pyridoxal 5′-phosphate[40]	Gram-negative bacteria: *E. coli, S. enterica, K. pneumoniae*; Peritonitis sepsis.	Intracellular iron overload; Lipid peroxidation; GSH homeostasis impairment; Cell membrane lysis; Attenuated by iron chelators and ferroptosis inhibitor.
Ruthenium complex[41]	Gram-negative bacteria: *E. cloacae, K. pneumoniae*; Gram-positive bacteria: *S. aureus*, MRSA; Wounds.	Lipid peroxidation; GSH depletion.
Thymol[42]	Gram-negative bacteria: *V. parahaemolyticus*; No in vivo studies conducted.	Iron homeostasis disruption, and intracellular iron accumulation; ROS burst, lipid peroxidation; Cell membrane damage; Inhibited by both iron chelator and ferroptosis inhibitor.

(*Continued*)

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Table 2 (Continued).

Active Compound	Strain and Disease Type	Characteristics of Ferroptosis-Like Death
Urechistachykinin I[43]	Gram-negative bacteria: *V. vulnificus*; No in vivo studies conducted.	Intracellular iron accumulation; ROS accumulation; Lipid peroxidation; GSH/GSSG ratio decrease.
Vitamin C[44]	Gram-positive bacteria: *M. tuberculosis*; No in vivo studies conducted.	Intracellular free iron increase; Inhibited by iron chelator.

by bacteria into protoporphyrin IX. Subsequent to light exposure, the production of ROS is initiated, in addition to the upregulation of heme oxygenase. This results in the accumulation of Fe^{2+} and the exacerbation of ferroptosis-like death.[31]

PUFA Integration

The properties of bacterial membranes can be altered by the absorption and incorporation of exogenous PUFAs into phospholipids. Low concentrations of AA induce hyperpolarization of the membrane potential and increase permeability in *Streptococcus mutans*. At the minimum inhibitory concentration (MIC), more than 75% of the cells exhibited ATP and K^+ leakage. Electron microscopy revealed the formation of 20–50 nm pores in the cell membrane, and this damage could be reversed by α-tocopherol.[48] DHA and eicosapentaenoic acid also cause bacterial shrinkage and localized membrane dissolution.[49]

However, there are still significant challenges in direct integration of PUFAs into bacterial membranes. Bacteria have evolved multiple mechanisms to withstand such stress. The murophospates of gram-positive bacteria and the lipopolysaccharides of gram-negative bacteria form a physical barrier and impede the transport of hydrophobic PUFAs to the cell membrane. *S. aureus* employs the FarE efflux pump system to expel PUFAs that have entered the cell. *P. aeruginosa* secretes 15-lipoxygenase and utilizes host AAs to generate immune regulatory mediators, which may help regulate host responses. *E. coli* integrates exogenous PUFAs into membrane phospholipids, which unexpectedly increases resistance to antibiotics such as polymyxin B and promoting biofilm formation.[50] Consequently, the development of combination therapies is imperative. Sorafenib derivative SC5005 combined with DHA can rapidly eradicate both planktonic and

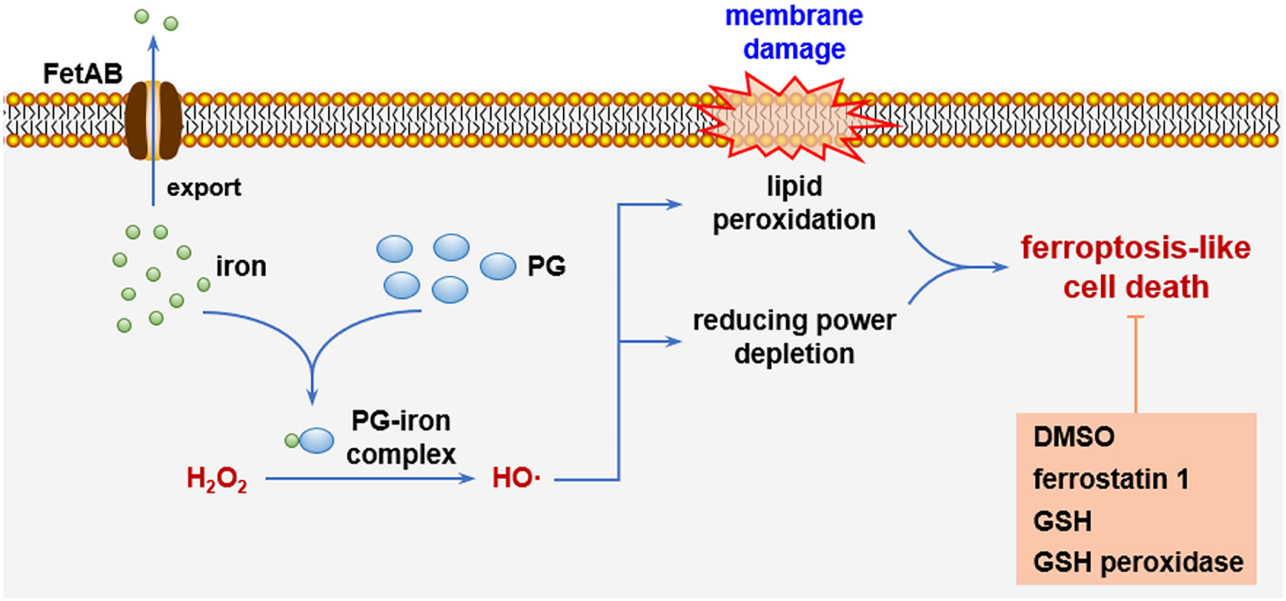

Figure 4 Phloroglucinol–Fe^{3+} complexes induce ferroptosis-like bacterial death. Phloroglucinol (PG) forms stable, redox-active complexes with Fe^{3+}. This complex can drive Fenton-like reactions, producing highly reactive HO•. HO• causes direct peroxidation of membrane lipids, leading to irreversible membrane damage and depletion of cellular reducing power. Collectively, these oxidative disruptions overwhelm bacterial cellular homeostasis, resulting in ferroptosis-like death. Reproduced with permission from Ref.[39] Copyright © 2024 by the Authors, Springer Nature.

persister methicillin-resistance *S. aureus* (MRSA) and is also effective against biofilms.[51] Triple therapy comprising AA, triclosan, and fluoride significantly inhibits oral biofilms.[32]

Antioxidant Defense System Compromise

ROS generation is considered the primary cause of lipid peroxidation which further leads to ferroptosis. The ruthenium complex Ru2 under light irradiation has been shown to generate elevated levels of ROS, which leads to redox imbalance, lipid peroxidation, and a ferroptosis-like bacterial death.[41] Innate immune components, including antimicrobial peptides, directly compromise membrane integrity and disrupt bacterial iron and redox homeostasis. This, in turn, renders bacteria susceptible to ferroptosis-like death. Urechistachykinin I elicits increased levels of ROS in *V. vulnificus*, culminating in a disruption of the GSH/GSSG ratio and lipid peroxidation. The observed reversal by ferrostatin-1 substantiated the involvement of a ferroptosis-like death pathway.[43]

Nanomaterial-Mediated Ferroptosis-Like Death

The implementation of small molecule-mediated strategies is encumbered by considerable challenges, particularly concerning issues related to targeting specificity and stability. Nanomaterials, with high specific surface area, adaptable physicochemical characteristics, and potential for multifunctional integration, provide an optimal foundation for the precise and efficient induction of ferroptosis-like death. These nanomaterials not only function as efficient carriers but also act as intrinsic catalytic centers or active substance donors. Lethal lipid peroxidation storm is synergistically induced by nanomaterials at the site of infection through various mechanisms, including iron ions overload, biocatalytic activation, and disruption of redox homeostasis. The subsequent sections methodically delineate the fundamental mechanisms, multimodal synergistic approaches, intelligent responsive systems, and applications in specific infection scenarios of nanomaterial-induced ferroptosis-like death (Table 3).

Core Mechanisms

Iron Dyshomeostasis

Metal sulfides are highly effective iron ion carriers. These nanomaterials exhibit responsiveness within the infection microenvironment, leading to the release of high concentrations of Fe^{2+}. These ions serve as a crucial catalyst for the Fenton reaction, which is fundamental in the overall antimicrobial response. Biogenic FeS_2 releases approximately 120 μmol/L Fe^{2+} under acidic conditions (pH 5.0), which is significantly greater than other iron sulfides (~45 μmol/L). Concurrently released dimeric sulfur species oxidize and consume GSH, and increased MDA levels approximately 3.5-fold. Bio-FeS_2 remains the initial antibacterial activity against the resistant *E. coli* even after ten passages.[24] Water-soluble ferrous polysulfides ($Fe^{2+}S_n$aq) rapidly kill 99% of planktonic *S. aureus* within 5 min at 50 μg/mL via an oxygen–sulfur exchange reaction. The concomitant release of hydrogen persulfide and Fe^{2+} results in the formation of a "nanodecoction" that rapidly depletes GSH (85% decrease) and induces lipid peroxidation.[25] Fe_3S_4 demonstrated Gram-dependent activity. The MIC for *Gardnerella vaginalis* and *Lactobacillus* is 25 μg/mL and greater than 500 μg/mL, respectively. The released polysulfides can penetrate thin-walled bacteria with greater efficacy, thereby inhibiting glucokinase (~80%) and reducing ATP (~65%). This process occurs synergistic with Fe^{2+}, resulting in the selective killing of bacteria.[59]

Iron-doped carbon dots have been shown to achieve >99.999% bactericidal efficacy against *E. coli*. This efficacy is achieved through a multifaceted mechanism, including membrane disruption, ROS bursts, GSH depletion, and DNA damage. Subsequent analysis via transcriptomics has substantiated the impacts on membrane stress, iron homeostasis, and energy metabolism.[67]

Enzyme-Mimetic Activity

Many nanomaterials possess intrinsic enzyme-like activities (nanozyme) that are capable of triggering endogenous ROS storms. CeO_2@Mn_3O_4 nanorods exhibit notable peroxidase (POD)-like and GPX-like catalytic activity when exposed to H_2O_2. These activities result in the eradication of >99.9% of both MRSA and *E. coli*.[75] Combined with visible light irradiation or H_2O_2, $CuFeS_2$ nanozymes can result in lipid peroxidation through expediting ROS generation, depleting

Table 3 Nanomaterial-Mediated Bacterial Ferroptosis-Like Death

Material	Bacterial Strain	Characteristics of Ferroptosis-Like Death	Treatment
Bio-FeS_2[24]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus, Bacillus spp*.	Intracellular iron overload; GSH depletion; Lipid peroxidation.	None.
Fe(II)$S_n$aq[25]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*, MRSA.	Intracellular iron accumulates; ROS increase, lipid peroxidation; GSH depletion; Inhibited by iron chelators, ferroptosis inhibitors, and antioxidants.	Pneumonia, sepsis.
$CuFeS_2$[52]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: MRSA.	Lipid peroxidation; GSH depletion; Inhibited by ferroptosis inhibitor, iron chelator and antioxidant.	Skin wound infections.
CFp/ HPDA@BNN6[53]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*.	ROS burst, lipid peroxidation; GSH depletion.	Wound infections.
ICG@Fe-Qu[54]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*.	Intracellular iron accumulates; ROS increase, lipid peroxidation; Attenuated by ferroptosis inhibitor, and antioxidants.	Full-thickness skin wound infections.
FeS@Au[55]	Gram-negative bacteria: *E. coli, P. aeruginosa*; Gram-positive bacteria: *S. aureus, S. epidermidis*, MRSA.	ROS increase, lipid peroxidation; Cell membranes deformation and surface collapse; Inhibited by iron chelators and ferroptosis inhibitor.	Type 1 diabetes mellitus complicated with full-thickness skin wound infections.
Pt@FeMOF[56]	Gram-negative bacteria: *P. aeruginosa*; Gram-positive bacteria: MRSA.	Intracellular iron accumulates; ROS increase, lipid peroxidation; GSH/GSSG balance disruption.	Chronic diabetic wound infections.
SP-PFe[57]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*.	Intracellular iron accumulates; ROS increase, lipid peroxidation; GSH depletion.	Infectious bone defects.
MFBH[58]	Gram-positive bacteria: *S. aureus*.	Intracellular iron overload; ROS increase, lipid peroxidation; GSH depletion.	Bacterial endophthalmitis.
D-Fe_3S_4[59]	Gram-variable bacteria: *G. vaginalis*, metronidazole-resistant *G. vaginalis*;	Lipid peroxidation; GSH depletion.	Bacterial vaginosis.
$CuFeO_x$/ IR825@PCM[60]	Gram-positive bacteria: MRSA.	GSH depletion, redox homeostasis disruption; Cell membrane breakage.	Subcutaneous abscesses.
FGO@MN[61]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*.	Intracellular iron overload; Lipid peroxidation; GSH depletion; Cell membrane damage.	Implant-related bacterial biofilm infections, diabetic wound bacterial biofilm infections.
Fe-POM@HA[62]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: MRSA.	ROS burst, lipid peroxidation; GSH depletion, GSH/GSSG ratio decrease; Cell membrane damage.	Chronic diabetic wound infections.
ETN@Fe_7S_8[63]	Gram-positive bacteria: MRSA.	Intracellular iron overload; Lipid peroxidation; GSH depletion, GSH/GSSG ratio decrease; Cell membrane rupture.	Wound infections.
Fe-doped titanite[64]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*, MRSA.	Intracellular iron overload; Lipid peroxidation; GSH depletion, GSH/GSSG ratio decrease; Cell membrane damage.	Implantation-related postoperative infections.

(*Continued*)

Table 3 (Continued).

Material	Bacterial Strain	Characteristics of Ferroptosis-Like Death	Treatment
UPBNPs-MCSNs[65]	Gram-positive bacteria: *E. faecalis, S. mutans*.	Lipid peroxidation; GSH depletion, GSH/GSSG ratio decrease; Inhibited by the metal chelator and antioxidant.	None.
mFe-CA[66]	Gram-positive bacteria: MRSA.	ROS increase, lipid peroxidation; GSH depletion, GSH/GSSG balance disruption; Cell membrane integrity disruption.	Acute pneumonia.
Fe-CDs[67]	Gram-negative bacteria: *E. coli*;	Intracellular iron overload; ROS increase, lipid peroxidation; GSH depletion; Cell membrane integrity disruption.	None.
FZO-APs[68]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*.	Metal ion homeostasis disruption; ROS increase, lipid peroxidation; GSH depletion.	None.
Fe_2O_3/Ti_3C_2-MXene@GOx[69]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*.	Intracellular iron overload; Inhibited by iron chelators and antioxidants.	Diabetic wound infections.
Fe-G@MM[70]	Gram-negative bacteria: *P. aeruginosa*; Gram-positive bacteria: MRSA.	Intracellular iron overload; ROS increase, lipid peroxidation; GSH depletion; Cell membrane integrity disruption.	Acute bacterial pneumonia, acute osteomyelitis.
Fe-GP[71]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*, MRSA.	Intracellular iron overload; Iron transport-related genes (eg, feoB, efeO, isdB) upregulation, and iron export-related gene ftnA downregulation; Lipid peroxidation.	Chronic diabetic wound infections.
FSP[72]	Gram-negative bacteria: Multi-drug resistant *P. aeruginosa*; Gram-positive bacteria: MRSA.	Intracellular iron overload; ROS increase, lipid peroxidation; GSH depletion; Inhibited by iron chelator.	Pyomyositis.
CMCS-OXG @TA-Fe[73]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*, MRSA.	Intracellular iron overload; ROS increase, lipid peroxidation; GSH depletion; Cell membrane integrity disruption.	Acute prosthetic joint infections, chronic osteomyelitis.
EGCG-Au[74]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*, MRSA.	ROS induction; Cell shrinkage, fragmentation.	Skin wound infections, keratitis.
CeO_2 @Mn_3O_4[75]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: MRSA.	Lipid peroxidation; GSH depletion; Cell membrane integrity disruption.	Percutaneous implantation-related infections, orthopedic implantation-related infections.
CuSA-COF[76]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: MRSA.	ROS increase, lipid peroxidation; GSH depletion;	Wound infections.
GTCM[77]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*.	Lipid peroxidation; Inhibited by ferroptosis inhibitor.	Chronic wounds with full-thickness skin defects.
Sp^2c-COF-Ir-ppy_2, sp^2c-COF-Ru-bpy_2[78]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: MRSA.	ROS burst, lipid peroxidation; Cell membrane integrity disruption.	Wound infections, subcutaneous abscesses.
BFBT[79]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: *S. aureus*.	Intracellular iron overload; ROS increase, lipid peroxidation; Cell membrane integrity disruption.	Implant-associated infections (IAIs).
TOMPE[80]	Gram-negative bacteria: *E. coli*; Gram-positive bacteria: MRSA.	Lipid peroxidation; GSH depletion.	Osteomyelitis.

(*Continued*)

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Table 3 (Continued).

Material	Bacterial Strain	Characteristics of Ferroptosis-Like Death	Treatment
P18-TPZ[81]	Gram-negative bacteria: *A. baumannii, K. pneumoniae*, multi-drug resistant *P. aeruginosa*; Gram-positive bacteria: MRSA.	Intracellular iron overload; ROS increase, lipid peroxidation; Cell membrane integrity disruption.	Bacterial pneumonia.

intracellular GSH, and interfering with respiratory metabolisms.[52] The CFp/HPDA@BNN6 nanozyme not only releases Cu^{+} and Fe^{2+} but also initiates cascades generation of •OH, NO and O_2 in the infection microenvironment. It can effectively eliminate bacteria and the associated biofilm via the NO strengthened bacterial ferroptosis-like death, with MICs of 8 μg/mL against planktonic *E. coli* and *S. aureus*. Meanwhile, NO and O_2 can synergistically promote the wound healing.[53]

Single-atom catalysts (SACs) maximize the exposure of catalytic sites and achieve uniform properties by anchoring metal active centers as individual atoms within ordered porous frameworks. The Ir and Ru SACs on sp^2c-COF achieve >99.9% killing of MRSA under light. The mechanism involves the generation of $•OH/O_2^{•-}$ by Ir via electron transfer, and the production of $^1O_2$ by Ru via energy transfer. Besides, the SACs disturb the nitrogen and respiratory metabolisms, leading to ferroptotic damage.[78]

The CuSA-COF material employs a light-controlled proton self-supply strategy to address the issue of reduced nanozyme activity in neutral physiological environments. The local microenvironment pH decreases from 7.4 to 6.2 within a span of 10 minutes upon exposure to 635 nm laser light. This decrease in pH facilitates the maintenance of 67.4% peroxidase-like activity, even at a relatively neutral pH of 7.5. Consequently, CuSA-COF induces ROS surge and disrupts metabolic pathways, ultimately leading to lipid peroxidation-driven ferroptotic damage.[76]

Disruption of Intracellular Redox Homeostasis

The survival of bacteria is contingent on their intracellular redox homeostasis, particularly antioxidant molecules such as GSH. Nanomaterials have the potential to disrupt the defense system via multiple pathways. Materials such as FeS_2, Fe^{2+} $S_n$aq, and CeO_2@Mn_3O_4 can efficiently deplete GSH via reactive sulfur species or catalytic activity.[24,25,75]

Metabolic Interference

Nanomaterials have also been shown to disrupt quorum sensing and core metabolism, thereby promoting ferroptosis-like death indirectly. Fe_3S_4 polysulfides can inhibit glucokinase, a key enzyme of glycolysis.[59] Ga/Cu-MOF nanozymes continuously release Ga^{3+} and Cu^{2+} ions, which independently inhibit NO production and promote the decomposition of S-nitrosothiols. This nanozyme has the unique capacity to induce both ferroptosis-like and cuproptosis-like death concurrently. When vancomycin is loaded on the nanozyme, the rate of MRSA death is 98.66%.[82]

Multimodal Synergistic Strategies

Multifunctional integrated nanosystems that combine ferroptosis with other physical therapies, gas treatments, and immunomodulatory strategies have been shown to generate significant synergistic effects, facilitating the efficient eradication of refractory infections.

Photothermal Therapy

Photothermal therapy (PTT) is a minimally invasive therapeutic modality that employs photothermal agents to convert light energy, typically near-infrared (NIR) radiation, into localized heat. The induced hyperthermia leads to the selective ablation of target cells or tissues, such as cancer cells or pathogenic bacteria. The integration of PTT with ferroptosis-like antibacterial mechanisms represents a powerful and rationally designed synergistic strategy. PTT may further enhance the ferroptosis-like antibacterial efficacy by compromising the bacterial antioxidant defense system, increasing iron bioavailability and Fenton reaction catalytic efficiency, as well as promoting lipid peroxidation. $CuFeS_2$ nanozymes exhibit PTT and catalytic activity, achieving bactericidal rates >99.99% under NIR irradiation.[52] FGO@MN microneedle containing

Fe_3O_4 nanoparticles can catalyze •OH generation in biofilm microenvironment, which can disrupt the bacterial biofilm heat-shock response. When combined with mild PTT, ferroptosis-like bacterial death is induced in biofilms due to iron overload. Meanwhile, neutrophils can acquire iron ions to restore the antibiofilm function.[61] Metal–phenolic nanoparticles (E-Au NPs) achieve 96.62% MRSA killing and >90% biofilm disruption when exposed to NIR irradiation, even with mild heating (to 36°C).[74] The development of a self-sustaining H_2O_2 system has been engineered to overcome the limitations posed by insufficient H_2O_2 in the infection microenvironment. $CuFeO_x$/IR825@PCM exhibits bacterial infection microenvironment/NIR dual-responsive antibacterial efficacy. Under laser irradiation, the hyperthermia effect generated by IR825 induces the rapid release of $CuFeO_x$. $CuFeO_x$ decomposes to release a substantial amount of H_2O_2 and metal ions, which not only consumes GSH but also promotes the generation of •OH. This nanomaterial could effectively destroy the bacterial structure and induce bacterial inactivation with ignored side toxicity.[60]

PDT

PDT employs light-activated photosensitizers to produce ROS, primarily singlet oxygen ($^1O_2$), leading to the destruction of target cells. Emerging research highlights a potent synergistic relationship between PDT and ferroptosis-like antibacterial pathways, offering a promising combinatorial strategy. Fe-doped ZnO nanoparticles exhibit enhanced photocatalytic activity. This phenomenon can be attributed to the effect of Fe doping, which reduces the bandgap of the material from approximately 3.37 eV to 3.18–3.22 eV. When subjected to ultraviolet irradiation, the MIC against *E. coli* and *S. aureus* were determined to be 0.20 and 0.15 mg/mL, respectively. The bactericidal activity was primarily achieved through the generation of $^1O_2$ for PDT and the release of Zn^{2+}/Fe^{2+} for lipid peroxidation.[68]

PTT + PDT

The concurrent or sequential application of PTT, PDT, and ferroptosis-like antibacterial pathways represents a sophisticated multimodal strategy designed to maximize antibacterial efficacy through complementary and mutually reinforcing mechanisms. This tripartite combination holds significant promise for addressing complex infections, particularly those involving drug-resistant bacteria and biofilms. Microneedles loaded with heterojunctions (MoS_2 /FeS_2, MXenes/CuS) penetrate the skin (~0.15 N/needle) with minimal discomfort. When exposed to NIR irradiation, these microneedles can generate enhanced PTT and PDT effects, while concurrently releasing metal ions to induce ferroptosis-like death. These effects result in a substantial disruption of mature biofilms.[77,83] Engineered bioheterojunctions (F-bio-HJs) under NIR irradiation can disrupt membranes via PTT/PDT, promote Fe^{2+} influx, and induce ferroptosis in both extra and intracellular bacteria (99% antibacterial rate), thus promoting the healing in diabetic wounds.[69] The metal–polyphenol platform (ICG@Fe-Qu) disrupts membranes through PTT and enhance Fe^{2+} influx in conjunction with PDT/chemodynamic therapy to augment ROS, thereby initiating lipid peroxidation and circumventing the limitations associated with monotherapy.[54]

Gas

As previously discussed, NO can enhance •OH induced ferroptosis-like death, resulting in a synergy index of 2.8.[53] The FeS@Au nanozymes exhibit glucose oxidase (GOx)-like and POD-like activities. The GOx-like activity catalyzes glucose into gluconic acid and H_2O_2, which further enhance the POD-like activity to generate •OH and induce ferroptosis-like death in drug-resistant bacteria. Furthermore, H_2S is released from nanozymes in the diabetic wound microenvironment, which not only upregulates hypoxia-inducible factor-1α and vascular endothelial growth factor but also reduces the damage to endothelial cells caused by excessive ROS. This, in turn, promotes angiogenesis and combines bactericidal and tissue repair functions.[55]

Immune Modulation

When bacteria undergo ferroptosis-like death, the released bacterial antigens and damage-associated molecular patterns can serve as potent endogenous adjuvants to activate the host's adaptive immune response. Some nanoplatforms possess the capacity to modulate the polarization of macrophages. The piezoelectric signals generated by oxygen vacancy-rich $(BiFe)_{0.9}(BaTi)_{0.1}O_{3-x}$ (BFBT) nanoreactor have been shown to induce M2 polarization.[79] The Fe-POM@HA hydrogel exhibits chronologically adaptive functionality. During the acidic infection phase, it induces bacterial ferroptosis through

ROS generation. Whereas in the new tissue proliferation stage, it can promote wound angiogenesis through by modulating inflammation and polarization of M2 (from ~15% to ~65%). These processes have been shown to achieve nearly complete healing within 14 days in diabetic rats.[62] In addition to inducing of bacterial ferroptosis-like death, the emodin-conjugated and Mn-doped titanium dioxide (TOMPE) platform can also temporally modulate M1 and M2 polarization of macrophages to promote osteogenic differentiation.[80] The biomimetic Fe-G@MM (which utilizes trained macrophage membranes) has been demonstrated to achieve active targeting and immune regulation, thereby reducing the bacterial load and inflammation while increasing the number of repair factors in models of pneumonia and osteomyelitis.[70] The iron-coordinated glycopeptide hydrogel (Fe-GP) facilitates a three-stage repair process for drug-resistant bacteria-infected chronic wounds. First, rapid release of TA/Fe nanocomplexes induces bacterial ferroptosis, eliminating over 98% of MRSA bacteria. Second, sustained release of glucomannan promotes M2 polarization, resulting in a 5-fold increase within 48 h. Third, the 3D peptide nanofibers framework facilitates extracellular remodeling.[71] The Hemin@ER-IR808 system can activate the ferroptosis-like stress of intracellular bacteria under NIR laser. Besides, the system can engenders M1 polarization via glycolysis enhancement and protect the macrophage from ferroptosis, thereby impeding bone loss and promoting repair.[84]

Intelligent Responsive Nanosystems

The advent of intelligent systems has facilitated the optimization of ferroptosis-like antibacterial strategies. This approach achieves a fundamental shift from always-on to on-demand precision targeting. These strategies are initiated by specific internal or external signals. Exogenous control systems provide a remote control for treatment, whereas endogenous response systems endow nanomaterials with autonomous intelligence to sense and adapt to the disease environment.

Exogenous Stimulus-Responsive Systems

These systems facilitate remote, real-time, and controllable antimicrobial treatment through external physical signals such as light and ultrasound, thereby achieving remarkably high temporal and spatial precision. Light-responsive systems typically trigger reactions through PTT and PDT, which has been discussed in section "multimodal synergistic strategies". The use of ultrasound as an external trigger to induce bacterial ferroptosis-like death represents an emerging and innovative antibacterial strategy. The BFBT nanoreactor self-generates H_2O_2 under ultrasound and facilitates ROS generation, resulting in the clearance of more than 85% of mature biofilms.[79] The TOMPE platform (with the bandgap reduced from 3.05 eV to 2.76 eV via emodin/Mn doping) increased the amount of sonocatalytic ROS ($\bullet OH/O_2^{\bullet-}$ increased ~3.5/2.8-fold). The generated ROS disrupts the bacterial cell membrane and facilitates the uptake of Mn ions, ultimately triggers bacterial ferroptosis-like death in MRSA.[80] Carrier-free nanosideromycin is prepared through self-assembly of siderophore-sonosensitizer conjugate and Fe^{3+}. Upon ultrasound irradiation, sonodynamic therapy and sono-Fenton catalysis are simultaneously triggered, resulting in an explosive ROS burst and ferroptosis-like bacterial death.[72] Nanoamplifier is prepared through supramolecular co-assembly of tirapazamine and sonosensitizer purpurin 18. Under ultrasound stimulation, purpurin 18 is activated, resulting in the production of ROS and hypoxia. Consequently, this results in the activation of tirapazamine, which in turn induces ferroptosis cascade via ROS overproduction and extracellular Fe^{2+} influx enhancement.[81]

Endogenous Microenvironment-Responsive Systems

Endogenous response systems possess the capacity to autonomously activate in specific physiological or pathological characteristics at the infection site, such as pH, enzyme, and metabolite levels.

pH

The infected site is slightly acidic. The release of Fe^{2+} from biogenic FeS_2 at pH 5.0 is significantly greater than pH 7.4.[24] $CuFeO_x$/IR825@PCM decomposes and supplies H_2O_2 at pH 6.0 while remaining inert at a pH 7.4.[60] Pt@FeMOF exhibits considerable POD/GOx-like activity at pH 5.5 and converts into CAT-like activity at pH 8.0. This feature enables it to modulate activity in response to changes in wound pH.[56]

GSH

GSH in bacteria serves as an essential target for response mechanisms. The Fe-POM@HA hydrogels deplete more than 90% of the GSH in a 10 mmol/L GSH environment.[62] Polysulfides released from $Fe^{2+}S_n$aq efficiently oxidize GSH.[25] OVT@ADM nanoreactors leverage high intracellular GSH concentrations to reduce Fe^{3+} to Fe^{2+}, thereby triggering structural dissociation and controlled doxorubicin release. The generated H_2O_2 undergoes a self-sustaining Fenton reaction with Fe^{2+}, achieving an inhibition rate of up to 99.3% against *S. aureus*.[85]

Enzyme/Glucose

These systems are designed to target enzymes that are specific to bacteria, or metabolites associated with infection. Phenothiazine-ZnO QDs respond to bacterial amidases, resulting in approximately 6.5-fold enhanced bactericidal activity.[86] FeS@Au nanozymes induce a cascade reaction under conditions of elevated glucose levels. The GOx-like activity consumes glucose and produce H_2O_2. H_2O_2 is subsequently catalyzed by POD-like activity to generate •OH. This leads to reduction of glucose concentration (approximately 45% in local wound glucose levels), highly efficient antibacterial activity (4-log reduction in bacterial load), and promotion of angiogenesis (approximately 2.8-fold increase in CD31-positive vessels). This process achieves synergistic bactericidal effects in diabetic infection microenvironments.[55]

Applications in Specific Infection Scenarios

The ultimate validation of ferroptosis-like antibacterial strategies lies in their effectiveness against specific infections in complex physiological settings. These methods have shown significant potential across diverse scenarios.

Skin and Wound Infections

Chronic wounds, such as diabetic ulcers, pose significant challenges due to the complex microenvironment, drug resistance, and the formation of biofilms. The advent of ferroptosis strategies has emerged as a promising avenue for addressing these challenges, leveraging a multifaceted approach encompassing sterilization, biofilm disruption, and immunomodulation. The Fe-POM@HA hydrogel, when utilized in a diabetic MRSA wound model, enables nearly complete wound closure (99.75% healing rate) within 14 days, which is ~60% faster than the control group.[62] The FeS@Au nanozymes can achieve synergistic effects in diabetic rat models through a multistep intervention strategy. The 14-day healing rate exhibited an exceeded of 90%.[55] F-bio-HJ and ICG@Fe-Qu have also demonstrated effective antibacterial and healing properties in diabetic wounds.[54,69] Nano-iron sulfide integrated with erythrocyte-templated nanozyme (ETN@Fe_7S_8) promotes comprehensive healing via multistage regulation.[63]

Deep Tissue and Implant-Associated Infections

These infections are difficult to treat because of biofilms and poor drug penetration. Nanosystems capable of generating high levels of ROS or possessing physical targeting functionalities demonstrate significant advantages in this field. BFBT piezoelectric nanoreactors, when utilized in conjunction with ultrasound, have demonstrated a remarkable capacity to eradicate bacteria by approximately 3.8 logs, significantly promoting the formation of new bone tissue in vivo.[79] The "Restauro" strategy has been demonstrated to be highly efficacious in the eradication of biofilms in an artificial joint infection model, with a reported reduction in viable bacteria of approximately 99.7%. This approach has the potential to obviate the need for implant removal, thus facilitating implant-preserving treatment.[73] In infection microenvironment, SP-PFe implants can generate $S_2O_8^{2-}$ and release Fe^{2+}, effectively killing bacteria through formation of $•SO_4^-$/•OH and Fe^{2+} triggered ferroptosis-like death. Meanwhile, the concomitant release of SO_4^{2-} promotes osteogenesis via calcium signaling, thereby underscoring the potential biological significance of this process.[57] Nanoswords of Fe-doped titanite can increase the environmental pH to decrease the ATP synthesis in bacteria. Ferroptosis-like bacterial death is triggered by the accelerated influx of Fe^{2+} ions. In addition, the nanoswords can improve osteoblast behavior and bone regeneration.[64] The ultrasmall Prussian blue nanoparticle-mesoporous calcium-silicate nanoparticle composites elicit

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a Fenton reaction, thereby instigating ferroptosis-like death in *E. faecalis*. Concurrently, these nanoparticles can disrupt mature biofilms by up to 4.5 logs, thereby ensuring optimal root canal disinfection.[65]

Systemic and Organ-Specific Infections

The management of systemic and organ-specific infections requires enhanced targeting specificity and systemic biological safety. The administration of a single intravenous injection of $Fe^{2+}S_n$aq (5 mg/kg) resulted in a significant increase in survival from 0% to 80% and the modulation of systemic cytokines in a sepsis model.[25] Hybrid biomimetic membrane particles and the biomimetic Fe-G@MM nanocage showed excellent targeting ability and safety in acute MRSA pneumonia.[66,70] The sonosensitizer purpurin 18-tirapazamine nanosystem enables ferroptosis-immune regulation in bacterial pneumonia.[81]

The MoS_2/Fe@mercaptophenylboronic acid@hyaluronic acid nanoflowers administered at low doses via a single intravitreal injection exhibited potent bactericidal activity against *S. aureus*. This efficacy is analogous to that of vancomycin, and no retinal toxicity was observed (Figure 5).[58] The orally available nanosecoy-lipopeptide nanospecies (CF-Dab/PLGA@RBCNPS) is formed via pH-responsive self-assembly. This nanospecies has been shown to penetrate membranes, resist enzymes, clear luminal and tissue pathogens, alleviate host cell ferroptosis by scavenging lipid peroxides, effectively clear bacteria, and reduce colon inflammation in a mouse model.[87]

Nanomaterials mediated ferroptosis-like antibacterial strategies hold enormous clinical potential owing to their distinctive advantages, such as targeted bactericidal activity via intelligent responsiveness, and enhanced antibacterial and therapeutic efficacy through the integration of multiple functions (eg, PTT/PDT model, immunomodulation and tissue repair). Yet, this field still faces several critical limitations. Most studies lack long-term (more than 14 days) in vivo safety evaluation. The detailed biodistribution profiles, metabolic pathways and clearance mechanisms of nanomaterials remain poorly characterized. Furthermore, the bacterial strains examined in most studies are largely restricted to common pathogenic bacteria (eg, *S. aureus, E. coli*). To effectively advance the translation of these strategies from bench to bedside, it is imperative to clarify the applicable scenarios of different nanoformulations and conduct multidimensional long-term safety evaluations.

For a more comprehensive comparison, the advantages, limitations and development stages of the three strategies discussed above are summarized in Table 4.

Perspectives

The research into ferroptosis-like antibacterial mechanisms is transitioning from phenomenological discovery to clinical translation. It is imperative to acknowledge the potential inherent in this phenomenon. This section proposes a strategic framework by analyzing the core challenges and outlining forward-looking development paths.

Bridging the Cognitive Gap

From Homology Search to Prokaryotic Specificity

Fundamental questions regarding the existence of ferroptosis homologs in prokaryotes has yet to be elucidated. Future research needs to move beyond simplistic analogies of mammalian ferroptosis and commit to elucidating the distinctive molecular underpinnings of bacterial ferroptosis-like death. The integration of multiomics technologies (eg, lipidomics and metabolomics) with large-scale genetic screens (eg, CRISPR-based knockout libraries) can be used to map key molecular networks and specific signaling pathways. It is imperative to elucidate the following critical areas: the failure mechanisms of bacteria-specific antioxidant systems; the pathways of lipid peroxidation in the absence of canonical executors such as GPX4; and the question whether this process is subject to endogenous programmed regulation.

Elucidating the Double-Edged Sword Effect and Developing Specific Tools

The role of ferroptosis in infection exhibits a complex double-edged sword effect. On the one hand, the host can utilize ferroptosis as a defense mechanism to clear intracellular bacteria.[30] On the other hand, pathogens can also exploit ferroptosis to damage host cells (eg, *P. aeruginosa* secretes pLoxA to trigger host ferroptosis).[88] Therefore, particular emphasis should be placed on the biosafety and selectivity of host-directed strategies. Uncontrolled regulation of this

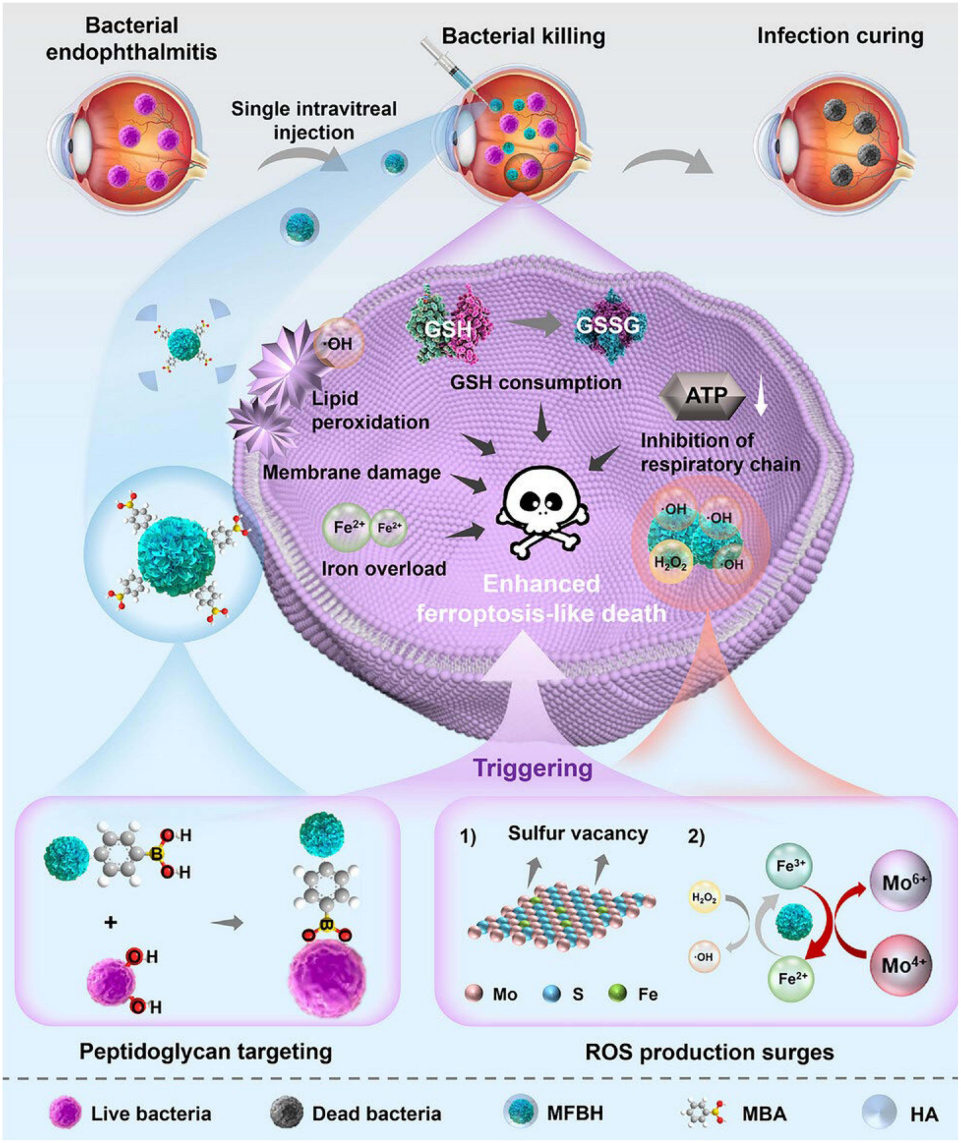

Figure 5 MFBH induces bacterial ferroptosis-like death to cure bacterial endophthalmitis. Following intravitreal administration, MFBH anchors to bacterial surfaces via its peptidoglycan-binding MBA moieties. This platform subsequently triggers a surge in ROS production, driven by sulfur vacancies in the MoS_2 framework and a sustained Mo^{6+}/Mo^{4+} redox cycle to regenerate Fe^{2+}. Concurrently, it promotes the accumulation of labile Fe^{2+} inside bacterial cells, leading to iron overload. The resulting •OH initiates membrane lipid peroxidation, which causes irreversible structural damage to bacterial membranes. Meanwhile, intracellular GSH is oxidized to GSSG, depleting key antioxidant reserves. The bacterial respiratory chain is inhibited, which disrupts the ATP synthesis. These synergistic oxidative and metabolic disturbances exacerbate bacterial ferroptosis-like death, directly eliminating pathogens and ultimately resolving the infection to cure bacterial endophthalmitis. Reproduced with permission from Ref.[58] Copyright © 2025 by the Authors, John Wiley and Sons.

strategy may cause multiple damages due to off-target activation or metabolic disorders, including abnormal activation of ferroptosis in normal host cells, systemic iron homeostasis disorder and organ iron deposition, immune function inhibition and risk of secondary infection.

To enhance the selectivity of this strategy and minimize off-target effects, the following three aspects may be considered. 1) Targeted delivery. Nanocarriers or similar technologies can be utilized to deliver pro-ferroptotic agents specifically to infected cells or to subcellular compartments harboring bacteria, thereby sparing normal tissues. 2) Conditional activation. Stimuli-responsive inducers or genetically engineered circuits that are activated exclusively in the infection microenvironment (eg, specific pH, enzymes, or bacterial metabolites) can enable precise, on-demand induction of ferroptosis. 3) Combined regulation. Integrated approaches that simultaneously exploit synergistic cytotoxicity and bolster host protection are recommended. Examples include co-administering ferroptosis inducers with

Table 4 Summary Comparison of Three Strategies

Strategy Type	Advantages	Limitations	Development Stage
Host-Directed Strategy	Utilizes host immune-metabolic reprogramming to regulate intrinsic iron metabolism and lipid peroxidation pathways, converting ferroptosis into an immune weapon for eradicating pathogens; Enables precise elimination of intracellular pathogens with minimal damage to normal host cells; Offers precise temporal regulation and is less likely to induce bacterial drug resistance.	Involves complex regulatory mechanisms; Exhibits a "double-edged sword" effect, where therapeutic benefits may coincide with unintended host damage; Highly dependent on host immune status, which varies individually; Primarily effective against intracellular bacteria, with limited efficacy against extracellular pathogens.	Preliminary feasibility has been verified in animal studies; Not yet entered clinical research, lacking clinical application data.
Small Molecule-Mediated Strategy	High design flexibility and ease of combination, enable synergistic antibacterial effects through various approaches; Directly delivers key ferroptotic effectors, providing rapid and direct action; Low cost, ease of synthesis, and suitability for large-scale production.	Poor targeting causes oxidative damage and toxicity to normal host cells; Low stability and delivery efficiency limit bioavailability. Bacterial intrinsic barriers hinder small molecule entry, reducing antibacterial efficacy; Bacteria are prone to developing resistance, and monotherapy often requires high doses, increasing the risk of side effects.	Currently in preclinical research; some formulations have been applied in food packaging or topical use, but long-term safety data and large-scale clinical trial evidence are lacking.
Nanomaterial-Mediated Strategy	Targeted delivery and smart drug release in response to the microenvironment; Exhibits strong functional integration, combining mechanisms such as drug loading, catalysis, PTT, PDT, gas therapy, and immunomodulation for efficient synergistic antibacterial effects; Demonstrates strong biofilm penetration and efficacy against both drug-resistant and intracellular bacteria. Supports tissue repair functions.	Long-term in vivo safety remains unclear; Biodistribution, metabolism, and clearance mechanisms of nanomaterials require further study; Current research is largely limited to common pathogens, with insufficient validation in complex infection models.	Advanced preclinical research phase; various smart responsive systems have been developed and show significant efficacy in complex animal models such as diabetic wounds, implant-associated infections, pneumonia, and bone infections. Has not yet entered clinical trials.

endogenous antioxidants or rapidly engaging cellular repair pathways after pathogen clearance, which can widen the therapeutic window and constrain excessive tissue damage.

Developing Spatiotemporally Precise Regulation Platforms

Therapeutic strategies are evolving from static drug administration towards dynamic regulation. The field encompasses the design of dual- or multi-responsive nanosystems that are activated exclusively upon the fulfillment of predetermined conditions to ensure maximal specificity.[56] The use of synthetic biology tools to engineer smart live therapeutics is another key element of this approach. A notable example is the utilization of probiotics that are engineered to synthesize and secrete ferroptosis inducers exclusively at the site of infection.[89] Furthermore, it can combine exogenous physical fields (eg, ultrasound, specific wavelength light) for remote and real-time manipulation, enabling on-demand activation.[90]

Overcoming Technical Bottlenecks

Networked Integration of Death Pathways

Antibacterial therapies should not be restricted to a single death pathway. The integration of ferroptosis-like death with other regulated cell death pathways, such as cuproptosis-like death, represents a promising frontier for overcoming

resistance. For example, the Ga/Cu-MOF nanozyme has been demonstrated to modulate pivotal proteins implicated in ferroptosis-like and cuproptosis-like death, consequently attaining substantial bactericidal efficacy against MRSA by inducing parallel death networks.[82]

Passive Carriers to Active Homing

Contemporary delivery systems are undergoing a transformation from basic drug delivery vehicles to more sophisticated and advanced solutions. Biomimetic nanosystems, such as macrophage membrane-camouflaged nanocages, possess inherent active targeting and immunomodulatory capabilities.[70] Novel formulations, including microneedle-based transdermal delivery and oral targeted nanoformulations, offer diverse solutions for different infection sites.[83,87] These systems comprise an intelligent medical arsenal capable of sensing the environment, actively homing, and executing controlled release.

Anti-Infection to Ecological Regulators

Materials integrating pathogen eradication and tissue regeneration possess enhanced therapeutic potential. The development of stage-adaptive materials (eg, the Fe-POM@HA hydrogel) that induce bacterial ferroptosis-like death during the acute infection phase and transition to an antioxidant, pro-regenerative mode (eg, promoting macrophage M2 polarization) during the resolution phase is a promising avenue for further research.[62] This temporal therapy elevates the anti-infection strategy from mere destruction to more sophisticated reconstruction, which guides tissue back to homeostasis while concurrently addressing off-target effects and biosafety concerns.

Accelerating Clinical Translation

Standardization of Material Platforms

Addressing the synthetic reproducibility and batch-to-batch consistency for complex nanomaterials, especially advanced structures such as single-atom nanozymes, is a prerequisite for scalable manufacturing.[78] To address these challenges, standardized and modular material platforms must be established, which is expected to result in a reduction in production cost and an increase in translation efficiency.

Upgrade of Evaluation Systems

A more comprehensive evaluation system, encompassing antibacterial efficacy, immunomodulatory effects, tissue repair capacity, and long-term safety, must be implemented in more physiologically relevant models, such as large animal models and human organoids. A systematic evaluation of the long-term in vivo fate of nanomaterials, potential organ accumulation, and broader impact on the host microbiome and systemic iron homeostasis is imperative.

Personalization of Treatment Strategies

To ensure optimal patient care, it is imperative to incorporate personalized medicine principles. The integration of artificial intelligence and multiomics data has enabled the development of precision treatment regimens tailored to the pathogen profile, host immune status, and individual iron metabolism. Meanwhile, expanding the antibacterial spectrum to encompass clinically challenging pathogens (eg, fungi and mycobacteria) and actively exploring the synergistic combinations with conventional antibiotics will provide tailored solutions for a range of clinical scenarios.

Summary

Ferroptosis-like death is evolving profoundly as an emerging antibacterial strategy, transitioning from conceptual analogy to mechanistic dissection and technological innovation. Research has established a foundational framework for triggering bacterial lipid peroxidation and disrupting redox homeostasis via exogenous interventions. The strategy can be implemented through multiple approaches, including host-directed, small molecule-induced, and nanomaterial-mediated approaches. The advent of intelligent and responsive nanosystems, in particular, has enabled spatiotemporally precise induction of ferroptosis-like death. Multifunctional composite materials can achieve the integration of synergistic sterilization, immune regulation, and tissue repair.

However, this field still faces significant challenges, including the inadequate definition of the molecular basis of bacterial ferroptosis-like death and the urgent need to clarify its interactions with prokaryote-specific metabolic networks. The intricacies of pathogen defense mechanisms, the potential hazards associated with the viable but non-culturable state, and the translational viability of nanomaterials from laboratory to clinical practice are also pressing concerns. In the future, three strategic transitions are imperative. From a scientific perspective, the research focus should shift from morphological analogy to in-depth exploration of the mechanistic essence. This transition requires the utilization of multiomics and gene-editing tools to elucidate its distinctive characteristics. Technological development should advance from single-function to intelligent and synergistic integrated platforms, fostering innovations such as logic-gated nanosystems and live therapeutics. From a therapeutic standpoint, it is imperative to transition from broad-spectrum killing to precision regulation. This transformation involves the development of temporal treatment strategies that integrate sterilization, immunomodulation, and repair mechanisms.

Ferroptosis-like antibacterial strategies, characterized by profound interdisciplinary integration and systematic innovation, have the capacity to induce a strategic transformation in anti-infective therapy. Developing this mode of cell death into a regulable and on-demand antibacterial tool represents a fundamental strategic innovation in addressing the global antibiotic resistance crisis. Despite the challenges that remain, sustained conceptual iteration and technological convergence will continue to drive the application of this strategy in future anti-infective therapy.

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