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REVIEW

Iron Oxide-Based Magnetic Nanoparticles in Oral Infection Control

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Abstract: In oral infectious diseases, recalcitrant biofilms, escalating antibiotic resistance, and limitations of local drug delivery within complex anatomical microenvironments necessitate innovative strategies for effective and precise therapy. Among magnetic nanoparticles (MNPs), iron oxide–based nanoparticles (IONPs) have attracted considerable attention in the management of oral infectious diseases because of their unique physicochemical features, including magnetic responsiveness, tunable morphology, and favorable biocompatibility. These properties enable MNPs to exert multimodal antibacterial effects, such as biofilm disruption, magnetothermal therapy, and reactive oxygen species (ROS)-mediated bactericidal activity, thereby allowing them to adaptively target and act within the anatomically constrained, biofilm-rich infection sites of the oral cavity. Recent advances have further explored their applications in caries, endodontic and periapical infections, periodontitis, peri-implantitis, and osteomyelitis of the jaw, highlighting their potential to overcome the limitations of conventional antibiotics. MNPs also enable rapid detection of oral pathogens via magnetic enrichment and point-of-care platforms, complementing their therapeutic potential. Key challenges include complex oral microenvironment interference, uncertain long-term biocompatibility, and obstacles to clinical translation. Future directions focus on omics-guided optimization, theranostic platforms integrating imaging and targeted therapy, and microbiota-modulating strategies. This review provides a comprehensive overview of the antibacterial mechanisms, therapeutic applications, and emerging multifunctional platforms of MNPs in oral infection control, while highlighting their translational potential and supporting their advancement toward safe and effective clinical applications.

Keywords: magnetic nanoparticles, iron oxide nanoparticles, antibacterial, biofilms, oral infections

Introduction

Oral infectious diseases, including dental caries, endodontic infections, periodontitis, and osteomyelitis, affect over 2 billion people worldwide and pose significant challenges to both oral and systemic health.[1] Their pathogenesis is closely linked to complex multispecies biofilms, while conventional treatments such as mechanical debridement and antibiotics have notable limitations: mechanical debridement can remove dental plaque and infected tissue, but pathogens in deep periodontal pockets, furcation areas, and root canal systems are difficult to eradicate completely, and excessive intervention may damage periodontal or dental hard tissues; antibiotics can achieve short-term bacterial suppression, yet prolonged use may induce resistant strains and show limited efficacy against bacteria embedded within mature biofilms.[2–4]

To overcome these limitations, diverse nanomaterials have been developed as promising antibacterial agents owing to their ability to disrupt microbial structures, generate reactive oxygen species (ROS), and modulate local microenvironments.[5,6] Compared with conventional antibiotics or antiseptics, nanomaterials offer superior adaptability, multifunctionality, and controlled physicochemical properties that enable targeted and sustained antibacterial effects. However, their clinical application still requires careful consideration of cytotoxicity, tissue selectivity, and the maintenance of antibacterial activity within complex oral microenvironments.[6–8]

Among them, magnetic nanoparticles (MNPs), including iron-, cobalt-, and nickel-based types, have attracted increasing attention because of their unique magnetic controllability. This magnetic responsiveness enables remote manipulation,

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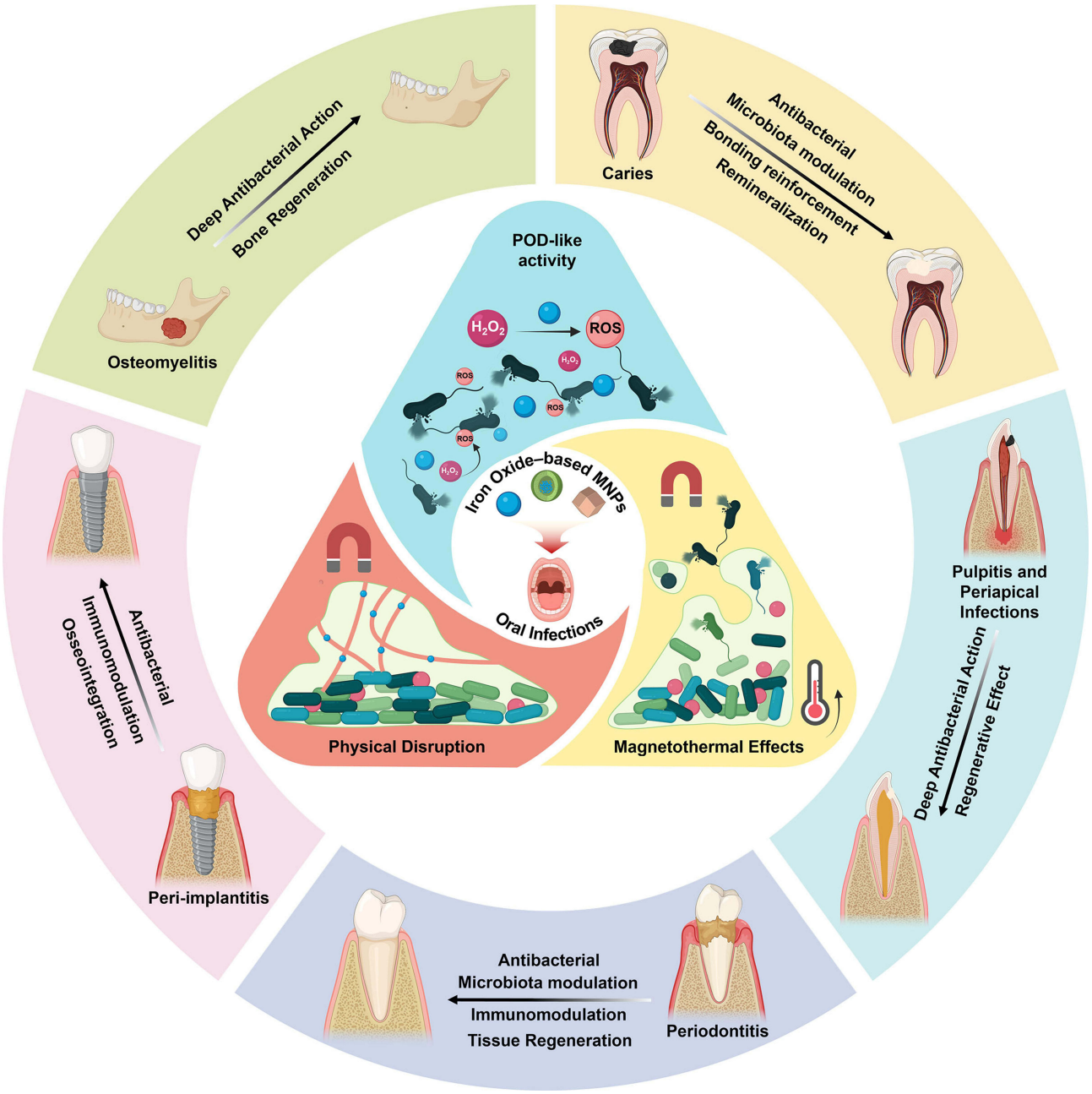
Graphical Abstract



targeted accumulation, and controlled therapeutic activation under external magnetic fields. However, while cobalt- and nickel-based MNPs often suffer from cytotoxicity and oxidation issues, iron-based nanoparticles exhibit higher stability and superior biocompatibility, making them more suitable for biomedical use.[9–12]

Consequently, iron oxide nanoparticles (IONPs), represented by Fe_3O_4 and γ-Fe_2O_3, have become the most extensively studied candidates. FDA-approved Ferumoxytol, a carboxymethyl dextran-coated iron oxide nanoparticle, demonstrates their clinical potential.[13] IONPs typically range from 1 to 100 nm in diameter, and when their size is reduced to a specific nanoscale, they can exhibit superparamagnetism, characterized by minimal remanence and rapid responsiveness to external magnetic fields.[14,15] Their favorable biocompatibility, controllable chemical stability, and facile surface

functionalization further enhance their utility for local controlled delivery, magnetic targeting, and magnetothermal therapy. Collectively, these attributes position IONPs as highly promising candidates for the prevention and treatment of oral infectious diseases.

While IONPs have attracted considerable attention for oral infection control, there remains a notable gap in the literature regarding comprehensive reviews on the application of multifunctional IONP platforms in this context. This review aims to bridge this gap by providing a comprehensive overview of the synthesis, mechanisms of action, and biomedical applications of IONPs in oral healthcare, while critically evaluating associated biosafety and translational challenges. By integrating these perspectives, it establishes a clear framework to guide future research and support the clinical implementation of IONP-based strategies.

Synthesis, Properties, and Functionalization of IONPs

IONPs can be synthesized via coprecipitation, thermal decomposition, microemulsion, hydrothermal, and green methods.[16] Coprecipitation is simple and widely applied but lacks precise control of size and morphology.[17] Thermal decomposition affords uniform and monodisperse particles, though it is energy-intensive and low-yield.[18] The hydrothermal process produces highly crystalline nanoparticles but requires harsh conditions of elevated temperature (>200 °C) and pressure (>6000 Pa), while microemulsion allows superparamagnetic products but often retains surfactant residues.[19,20] Green synthesis, using plant extracts or magnetotactic bacteria, avoids toxic reagents and offers better biosafety.[21] To ensure optimal oral application, the synthesis route should consider feasibility, key physicochemical and magnetic properties, and specific functional requirements.

Magnetic properties are pivotal for oral applications. High saturation magnetization (Ms) enhances magnetic guidance and targeted delivery, facilitating precise transport of antimicrobial agents to periodontal pockets, root canals, or biofilms.[22] Superparamagnetic behavior at small sizes, with near-zero remanence (Mr) and coercivity (Hc), prevents uncontrolled aggregation and canal blockage.[23] Surface and interfacial structures further regulate magnetism and colloidal stability; appropriate coatings preserve dispersion in complex oral environments.[24] Thus, optimizing Ms, Mr/Hc, and interface features is key to effective targeting and biofilm penetration.

Surface functionalization further expands performance. Given the intrinsic hydrophobicity of IONPs, inert hydrophilic coatings such as polyethylene glycol, dextran, or chitosan are often applied to reduce nonspecific adsorption and immune clearance, ensuring stability and safety in the oral environment.[13,23,25] Mesoporous or hollow matrices enable high drug loading and controlled release, while polymer shells or stimulus-responsive gates allow site-specific release.[26–28] Targeting can be reinforced by conjugating strain-specific ligands and modulating surface charge to enhance binding with biofilms.[29] Collectively, advances in synthesis, magnetic tuning, and functionalization establish IONPs as promising candidates for oral infection control.[30]

Antibacterial Mechanisms and the Design of IONPs

Physical Disruption Mechanisms

The size of IONPs plays a critical role in their interaction with biofilms. Smaller IONPs tend to promote biofilm dispersal, and their antibacterial efficacy largely depends on crystal phase, particle size, and surface modification (Table 1). However, this dispersal effect may also increase the risk of bacterial dissemination and bacteremia. In contrast, larger IONPs are more effective in creating "artificial channels" within biofilms, likely due to their sharper morphology that physically disrupts the biofilm matrix (Figure 1A–C).[31,32] This process facilitates the targeted delivery of antimicrobial agents into the biofilm core (Table 2). Moreover, magnetic antibacterial coatings on implant surfaces can release IONPs on demand, generating channels that enhance antibiotic penetration (Figure 1D and E).[33] Importantly, the optimal antibacterial concentration of IONPs requires further investigation, as excessive levels may stimulate extracellular polysaccharide (EPS) secretion and thereby diminish antibacterial efficacy.[33]

For microbial infections of teeth and periodontium, IONPs must adapt to complex anatomical environments by enhancing mobility and deformability. Hwang et al embedded IONPs in agarose gel to design a soft magnetic robot capable of rotating, sliding along irregular tooth surfaces, and removing biofilms.[37] Recently, surface

Table 1 Impact of Small-Sized IONPs Properties on Antibacterial Activity

Magnetic Field	Compositions	Size (TEM)	Surface Modification	Antibacterial Effect	Ref.
Direct current magnetic field (DC)	#1: synthesized large IONPs	65.33 nm ±38.81 nm	Dextran or alginate	#4 is the most effective in combating multispecies biofilms; #3>#2; `alginate > dextran.	[34]
	#2: commercial Fe_2O_3	29.62 nm ±24.97 nm			
	#3: commercial Fe_3O_4	58.75 nm ±19.05 nm			
	#4: synthesized ultrasmall IONPs	8.87 nm ±2.66 nm			
Alternating magnetic field (AMF)and DC rotation field	Fe_3O_4	8 nm, 11 nm and 70 nm	SiO_2	DC rotation field > AMF;in the same magnetic field: 11nm>8nm>70nm.	[35]

topography-adaptive robotic superstructures (STARS) have been developed using magnetic nanoparticles to construct bristle-like architectures with gradient stiffness, enabling them to conform to complex dental and periodontal surfaces for efficient biofilm removal while simultaneously collecting microbial samples for downstream analysis (Figure 2).[38]

Swarming behavior is another effective approach to achieve multimodal motion.[39] Such collective organization enables single magnetic robots to perform diverse movements and generate shear forces under electromagnetic actuation, thereby disrupting biofilms.[40] Sun et al developed magnetic microrobot swarms with fluidity that can traverse complex structures under magnetic control and cut biofilms with their sea-urchin-like morphology.[41] In addition, flowing liquid metal alloys can be shaped into sharp structures under magnetic fields to eliminate planktonic bacteria. These "robots" not only penetrate intricate anatomical sites but also collect and remove fragmented biofilms and planktonic bacteria, preventing biofilm regeneration.

Magnetothermal Effects

Hyperthermia not only reduces bacterial viability but also disrupts the protective barrier of biofilm, thereby rendering embedded pathogens more susceptible to subsequent treatments.[42] The effective and safe antibacterial temperature range is 43–50 °C.[43–45] IONPs generate heat mainly via magnetic and photothermal pathways.

Under an AMF, IONPs produce heat through three mechanisms: Néel relaxation, Brownian relaxation, and hysteresis loss, with the latter being dominant in the ferro/ferrimagnetic size regime.[46,47] When particle size decreases below the superparamagnetic threshold, heating is primarily governed by relaxation losses.[48–50] Optimizing the external magnetic field together with particle size and morphology is crucial to maximize the specific heating power.[51] Compared with nanospheres, anisotropic nanostructures such as nanocubes exhibit superior performance in magnetic hyperthermia.[52] Moreover, Shuai et al demonstrated that hard–soft magnetic biphasic interface exchange coupling can retain the high anisotropy of the hard core while lowering the energy barrier for magnetic reversal via the soft shell, thereby enabling efficient magnetic moment switching and significantly enhancing heat conversion efficiency (Figure 3).[53]

IONPs possess inherent photothermal activity arising from electronic transitions and localized surface plasmon resonance (LSPR).[54] Although their molar absorption coefficient in the near-infrared (NIR) region is lower than that of conventional photothermal agents such as gold nanorods and copper sulfides, the photothermal antibacterial potential of IONPs should not be underestimated. By optimizing parameters such as concentration and irradiation conditions, IONPs can achieve excellent photothermal antibacterial efficacy (Table 3).[55] In addition, combining IONPs with auxiliary photothermal agents, including graphene, polydopamine, and zeolitic imidazolate frameworks (ZIFs), has been widely employed to further enhance therapeutic performance.[56–59]

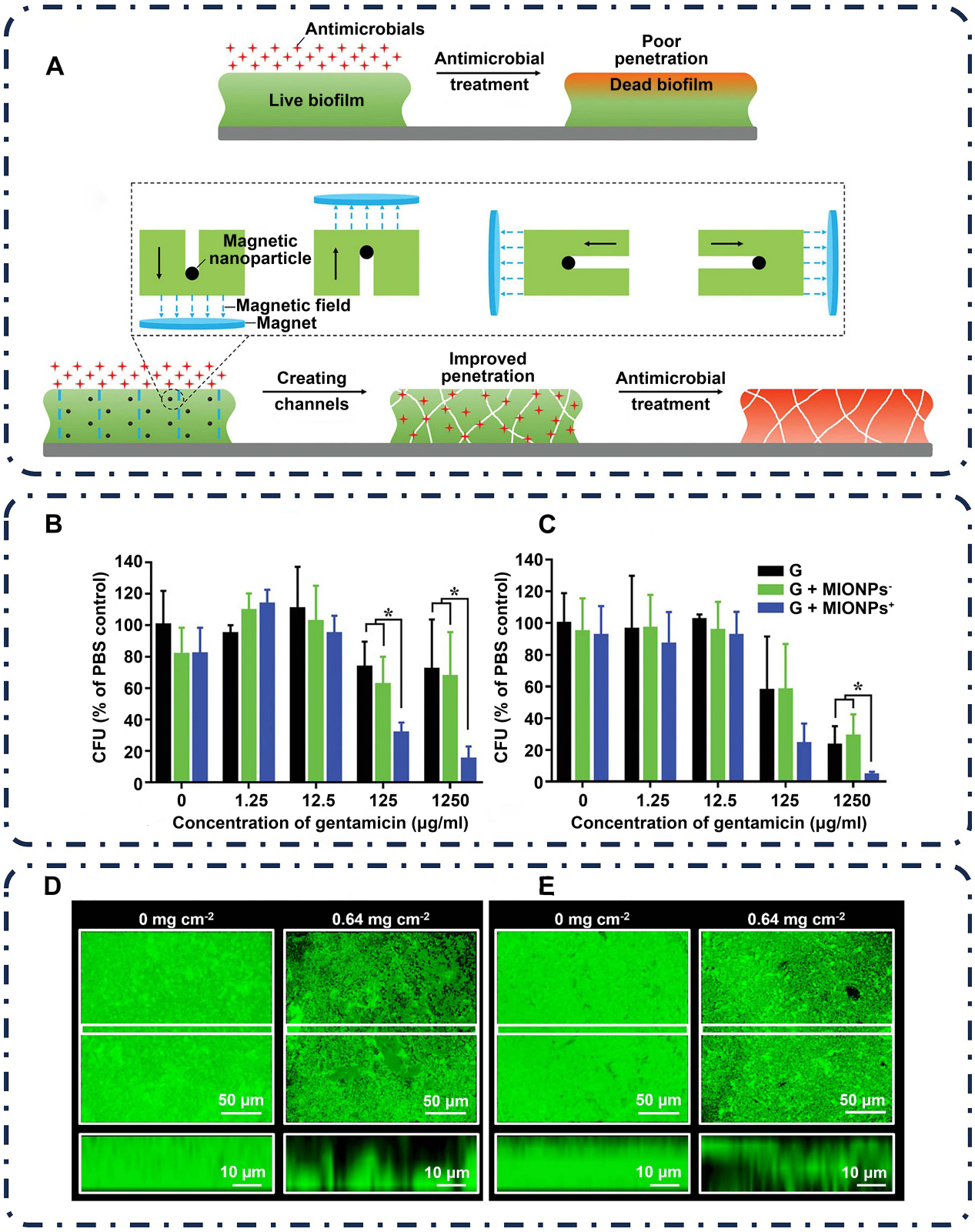


Figure 1 Large-sized IONPs creating artificial channels for antibacterial action. (**A**) Magnetic nanoparticles creating artificial channels in biofilms to enhance drug penetration and bacterial killing.[31] (**B** and **C**) CFU reduction of *S. aureus* strains ATCC 12600 (**B**) and 5298 (**C**) after MIONP exposure with or without magnetically forced movement and varying gentamicin concentrations. *$p < 0.05$ indicates statistical significance.[31] (**D** and **E**) CLSM images showing IONPs penetrating (**D**) *S. aureus* and (**E**) *P. aeruginosa* biofilms from coated surfaces under magnetic guidance.[33]

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Table 2 Large-Sized IONPs for Biofilm Penetration and Drug Delivery

MNPs	Size	Magnetic Field Parameters	Ref.
IONPs + gentamicin	278 ± 61 nm	A disc NdFeB magnet (10 mm diameter, 1 mm height, 1.17–1.21 Tesla residual magnetism)	[31]
Ag@Fe_3O_4 + rhamnolipid and vancomycin	212.5 nm	Cylindrical neodymium magnet	[32]
IONPs + gentamicin and tobramycin	316 ± 77 nm	A cylindrical NdFeB magnet (1 cm diameter, 1 mm height, 1.17–1.21 Tesla residual magnetism)	[33]
Fe_3O_4 + minocycline	273.7 nm	A NdFeB magnet (50×30×10 mm, 2000–2200 Gs surface magnetic field intensity)	[36]

ROS-Mediated Antibacterial Mechanisms

IONPs, particularly Fe_3O_4, exert chemical antibacterial effects primarily by inducing ROS generation. Released Fe^{2+}/Fe^{3+} ions can participate in Fenton or Fenton-like reactions, or catalyze endogenous H_2O_2 via peroxidase (POD)-like activity into highly reactive ·OH and other ROS.[63,64] These ROS trigger oxidative stress, leading to lipid peroxidation, protein denaturation, and DNA damage, thereby compromising membrane integrity and metabolic functions.[65] In addition, IONPs can interfere with key bacterial enzymes, further amplifying oxidative injury. The synergy of oxidative stress and enzymatic disruption underpins the chemical antibacterial activity of IONPs.

The catalytic efficiency of Fe_3O_4 is strongly pH-dependent, showing higher activity in acidic conditions that favor the growth of many oral pathogens.[66,67] Beyond direct bactericidal effects, Gao et al demonstrated that the Fe_3O_4–H_2O_2 system effectively degrades the biofilm matrix, weakening its protective role and limiting regeneration (Figure 4A).[66] While exogenous H_2O_2 supplementation is feasible, a more physiologically relevant approach is to immobilize glucose

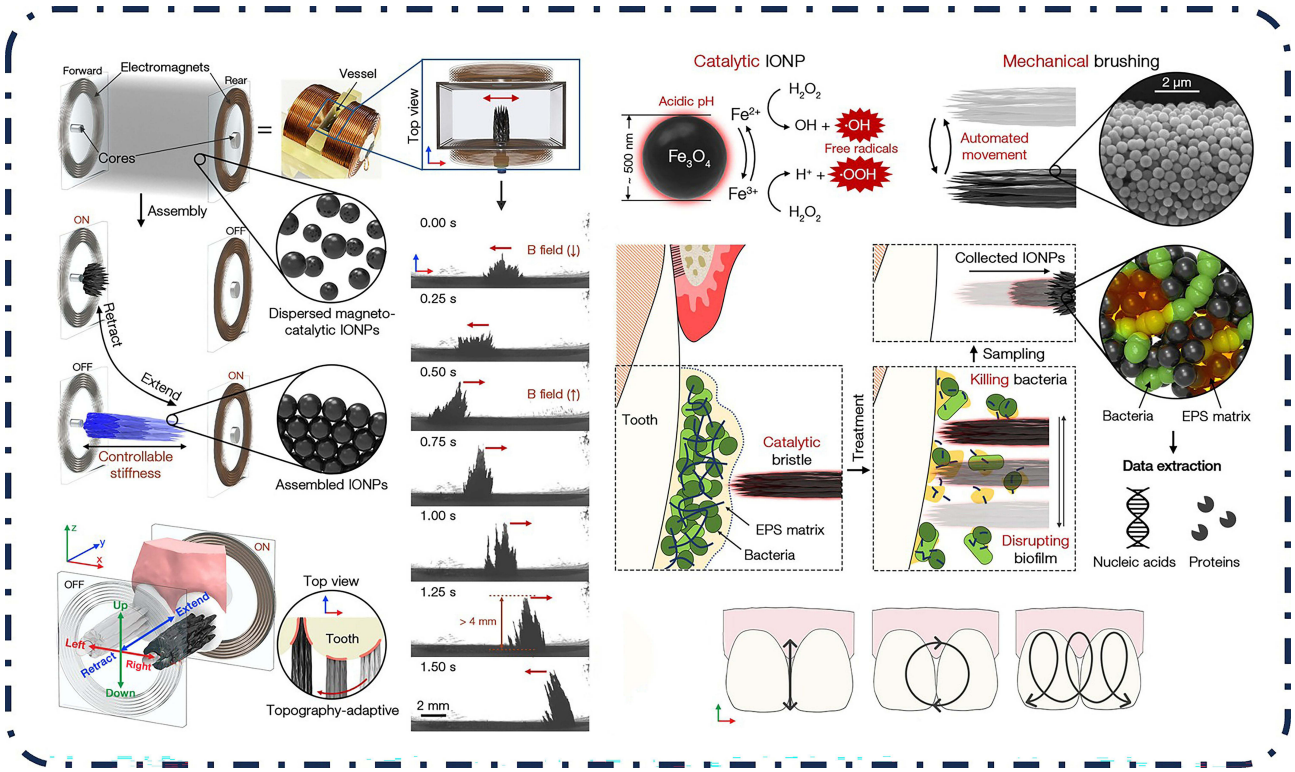

Figure 2 Schematic of STARS formed by magnetic nanoparticles for biofilm removal and microbial sampling. STARs integrate multiple multifunctional and multitasking capabilities, including topography-adaptive behavior, controllable stiffness, catalytic killing activity, mechanical scrubbing for biofilm disruption, and pathogen detection. The upward and downward arrows accompanying the term "B field" indicate the direction of the applied magnetic field.[38]

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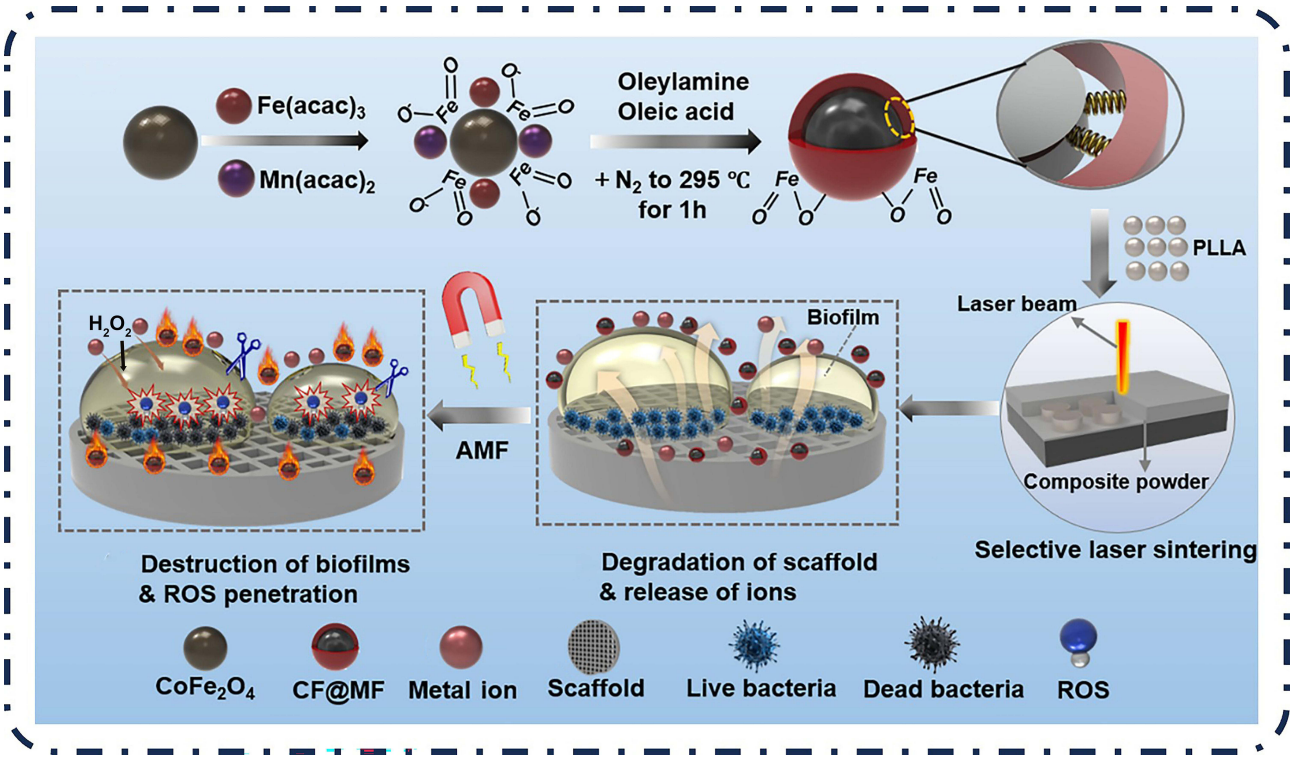

Figure 3 Schematic illustration of CF@MF nanoparticles, scaffold preparation, and antibacterial mechanisms.[53]

oxidase (Gox) on IONPs (GMNP), which not only depletes glucose reserves within the biofilm ("starvation therapy") but also generates local H_2O_2 that is further converted into ROS (Figure 4B–E).[59,68] This dual mechanism endows IONP@Gox systems with promising potential in managing periodontal biofilms, particularly in diabetes-associated oral infections.

In summary, the robust antibacterial efficacy of IONPs-based systems arises from three complementary and synergistic mechanisms: physical disruption of biofilm architecture, magnetothermal inactivation induced by external stimulation, and ROS-mediated catalytic damage. The combined action of these pathways produces significant biological effects, which, together with key clinical and design considerations, are detailed in Table 4. Given this potent, multimodal, and adaptable antimicrobial profile, IONPs represent a promising alternative to conventional antibiotics, particularly for managing localized and persistent oral infections.

Table 3 Photothermal Parameters and Performance of IONPs Under Various Conditions

Materials	Diameter	Concentration	NIR Irradiation	Temperature	Photothermal Conversion Efficiency	Ref.
Orange peel extract-coated IONPs	About 50nm	8 mg/mL	630 nm, 65.5 mW/cm^2, 30 min	50.8 ± 0.2 °C in Deionized water	–	[43]
CS - coated Fe_3O_4	29.62 ± 1.25 d.nm	200 μg/mL	808 nm, 2 W/cm^2,5 min	>55°C in Distilled water	21.53%	[60]
Minocycline (MIN) was loaded onto Fe_3O_4 NPs	>100 nm	250 μg/mL	808 nm, 1 W/cm^2, 10min	About 40°C in PBS	26.42%	[61]
IONPs	–	1000 ug/mL	808 nm, 1 W/cm^2, 10 min	>65°C in aqueous suspension	28.5%	[62]

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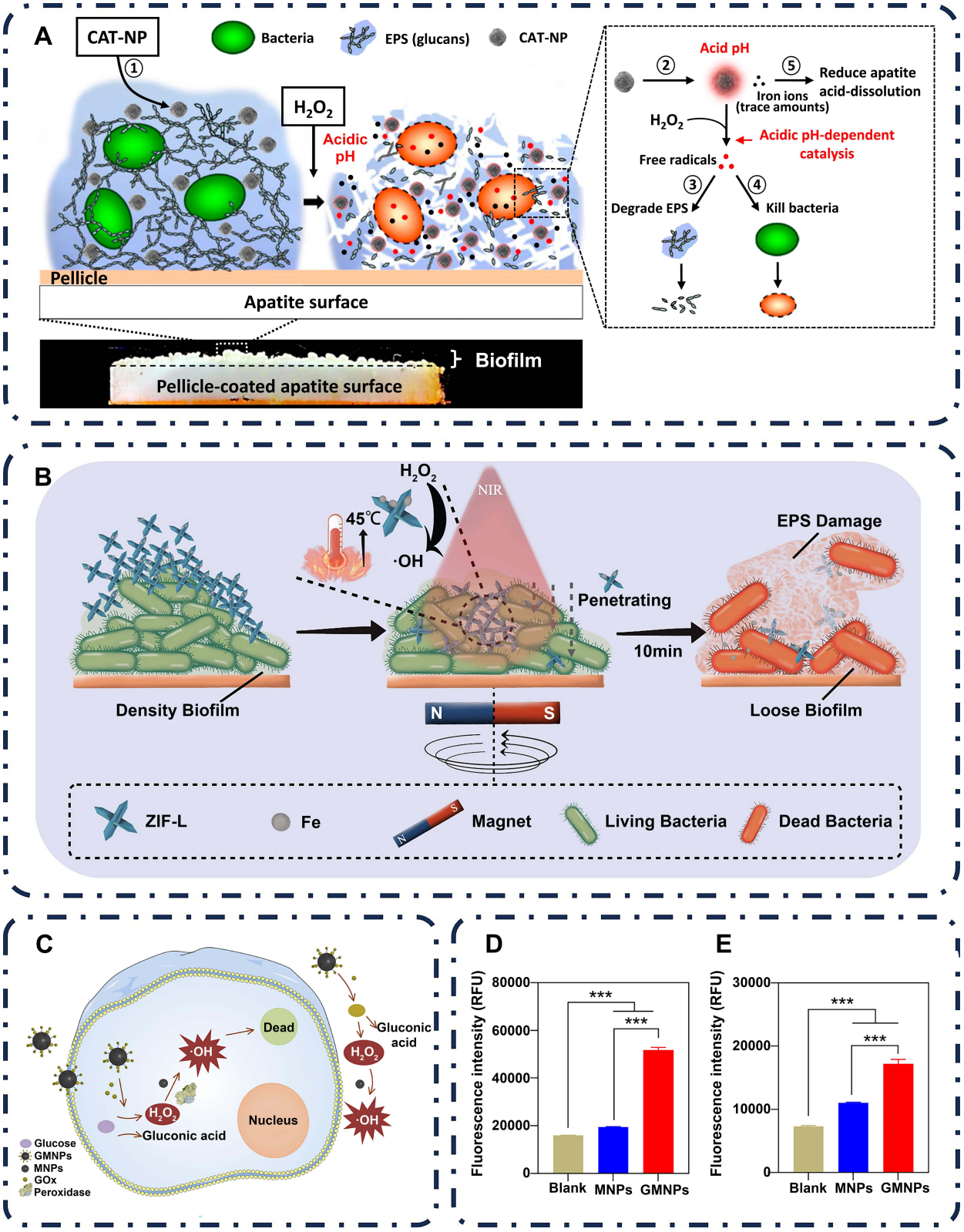

Figure 4 Catalytic biofilm disruption by IONP-based systems. (**A**) Schematic of biofilm disruption under acidic conditions via CAT-NP/H_2O_2. Numerical indicators denote the major biological effects of the CAT-NP–based strategy: ① retention of CAT-NP within the 3D biofilm structure after brief topical exposure; ② rapid catalytic conversion of low concentrations of H_2O_2 into free radicals under acidic conditions; ③ degradation of the EPS matrix; ④ killing of bacteria embedded within biofilms; and ⑤ reduction of acid-induced hydroxyapatite dissolution.[66] (**B**) Schematic illustration of the mechanism of action of ZIF-L-Fe with exogenous H_2O_2 supplementation. The upward black arrow indicates the photothermal heating effect induced by ZIF-L-Fe under light irradiation.[59] (**C**) Schematic illustration of GMNP-induced ROS formation and antimicrobial interactions.[68] (**D** and **E**) Intracellular ROS levels in *E. faecalis* (**D**) and *C. albicans* (**E**) after MNP and GMNP treatment. ***$p < 0.001$ indicates statistical significance.[68]

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Table 4 Key Mechanisms, Biological Effects, and Considerations of IONPs-Enabled Antibacterial Strategies

Mechanisms	Key Principles and Operating Modes	Representative Biological Effects	Considerations
Physical disruption	Morphology-dependent penetration: sharp/aniso particles (nanorods, nanocubes) enhance disruption. Size effects: small IONPs (<20 nm) promote dispersal; large IONPs form channels. Magnetic actuation: soft robots, STARS, microrobot swarms under AMF generate mechanical forces.	EPS penetration via micro-channels. Targeted biofilm removal in complex dental anatomy. On-demand IONP release from implants.	Risk of bacterial dispersal or bacteremia. Requires external magnetic control. Optimal concentration must be defined.
Magnetothermal effects	Magnetic hyperthermia: heat (43–50 °C) via Néel/Brownian relaxation and hysteresis loss. Photothermal: LSPR/electronic transitions enhanced with NIR-responsive coatings (graphene, PDA, ZIFs).	Biofilm barrier disruption and increased permeability. Direct bacterial viability reduction. Synergy with antibiotics or ROS agents.	Risk of off-target thermal damage. Requires AMF or NIR equipment. Photothermal efficiency may remain suboptimal without appropriate parameter optimization.
ROS generation and catalytic activity	Fenton/Fenton-like reactions: Fe^{2+}/Fe^{3+} convert H_2O_2 into ·OH and other ROS. POD-like activity enhanced in acidic pH. GOx immobilization: in situ H_2O_2 generation via glucose depletion.	Oxidative damage to lipids, proteins, enzymes, DNA EPS matrix degradation, impaired biofilm regeneration. Microenvironment-responsive antibacterial action.	Potential host oxidative damage Catalytic activity pH-dependent. Requires long-term biosafety validation.

Applications of IONPs in Oral Infection Control

Caries

Dental caries arises from dysbiosis of the oral biofilm and persistent acidification, leading to demineralization of hard tissues. IONPs offer precise antibacterial and anti-demineralization effects through nanozyme catalysis and magnetic responsiveness.

Recent studies highlight a transition from single antibacterial effects to multimodal strategies. Functionalized and structurally engineered IONPs not only inhibit cariogenic bacteria but also disrupt deep biofilms through magnetic guidance, photodynamic activation, and enzyme-like catalysis. Magnetically guided photosensitizer delivery overcomes the limited penetration of conventional photodynamic therapy, enabling efficient killing within biofilm cores (Figure 5A).[69]

Moreover, peroxidase-mimicking IONPs catalyze H_2O_2 decomposition under acidic conditions to generate ROS, which degrade extracellular polysaccharides and eradicate embedded bacteria, while exerting minimal effects on the oral microbiome and soft tissues (Figure 5B–D).[70] Beyond direct antibacterial effects, emerging strategies also modulate biofilm microecology. For example, integrating cationic antibacterial monomers into multilayer core–shell structures suppresses lactic acid production and reshapes microbial communities, reducing the dominance of cariogenic species.[71]

Incorporating IONPs into dental resins or adhesives imparts durable antibacterial activity, enhances dentin bonding strength, and decreases the risk of secondary caries.[72,73] They further reduce hydroxyapatite demineralization and promote enamel and dentin remineralization, likely through iron-facilitated nucleation or calcium ion substitution (Figure 5E and F).[66,74] Although color compatibility remains a concern, SiO_2- or calcium-based coatings have been shown to mitigate discoloration caused by IONP-containing dental adhesives.[75]

Collectively, these advances illustrate the evolution of IONPs from "single-function antibacterial agents" to multifunctional platforms integrating antimicrobial, restorative, and microecological regulation, offering promising strategies for caries management and clinical translation.

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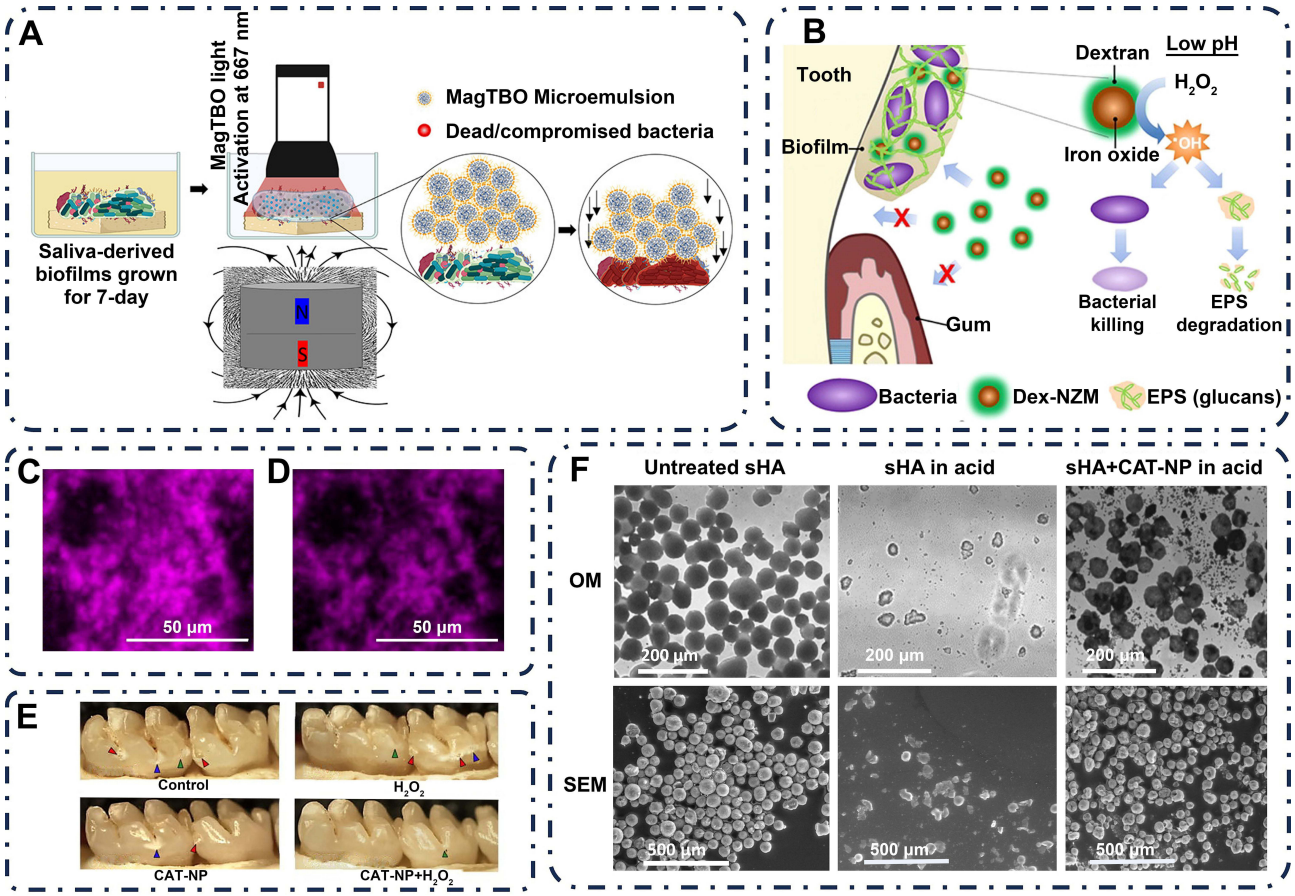

Figure 5 Multimodal antibacterial strategies of IONPs in caries. (**A**) Schematic of magnetically guided photosensitizer delivery for deep biofilm photodynamic killing. Downward arrows indicate the direction of magnetically driven movement of the MagTBO microemulsion.[69] (**B**) Schematic of catalytic IONPs selectively eradicating biofilms with minimal impact on oral soft tissues.[70] (**C**) EPS images before H_2O_2 exposure (EPS in magenta).[70] (**D**) The corresponding region after 100 min of H_2O_2 exposure, revealing pronounced EPS degradation.[70] (**E**) Caries progression and treatment-associated suppression. Green arrows indicate early enamel demineralization; blue arrows show intermediate structural destruction; red arrows mark advanced cavitation lesions.[66] (**F**) CAT-NP reduces synthetic hydroxyapatite(sHA) demineralization. OM and SEM images of sHA beads (80 μm) under different conditions: untreated, in acidic buffer (pH 4.5), and with CAT-NP.[66]

Pulpitis and Periapical Infections

In complex root canal systems, drug-resistant biofilms remain a major barrier to treating persistent pulpitis and periapical infections. To overcome these challenges, IONPs offer a promising strategy by enabling magnetically assisted ultrasonic activation that effectively cleans canal walls, opens dentinal tubules, and enhances antimicrobial penetration into deeper regions without compromising dentin integrity.[76–79] In addition, peroxidase-mimicking IONPs effectively disrupt *E. faecalis* biofilms by generating ROS in situ under low-dose H_2O_2.[80] Ultrasound further triggers amplified ROS bursts, enhancing biofilm eradication (Figure 6A).[81] Engineered platforms extend these functions: magnetically actuated helical nanorobots can penetrate dentinal tubules and achieve targeted killing through localized friction and thermal effects,[82] and nanozyme-shell microcapsules navigate complex anatomies to catalyze localized ROS production (Figure 6B).[83] Clinically, the FDA-approved Ferumoxytol shows antibiofilm efficacy comparable to NaClO but with superior biocompatibility, while also promoting apical papilla stem cell proliferation and osteogenic signaling, highlighting its dual potential for infection control and regeneration (Figure 6C).[84]

Periodontitis

Periodontitis is a chronic disease driven by biofilm infection and host immune dysregulation, leading to progressive alveolar bone loss.[85] Conventional therapies partially control infection but are limited in microecological modulation and tissue regeneration.[86] Recently, IONPs and their composite scaffolds have shown promise in enhancing periodontal

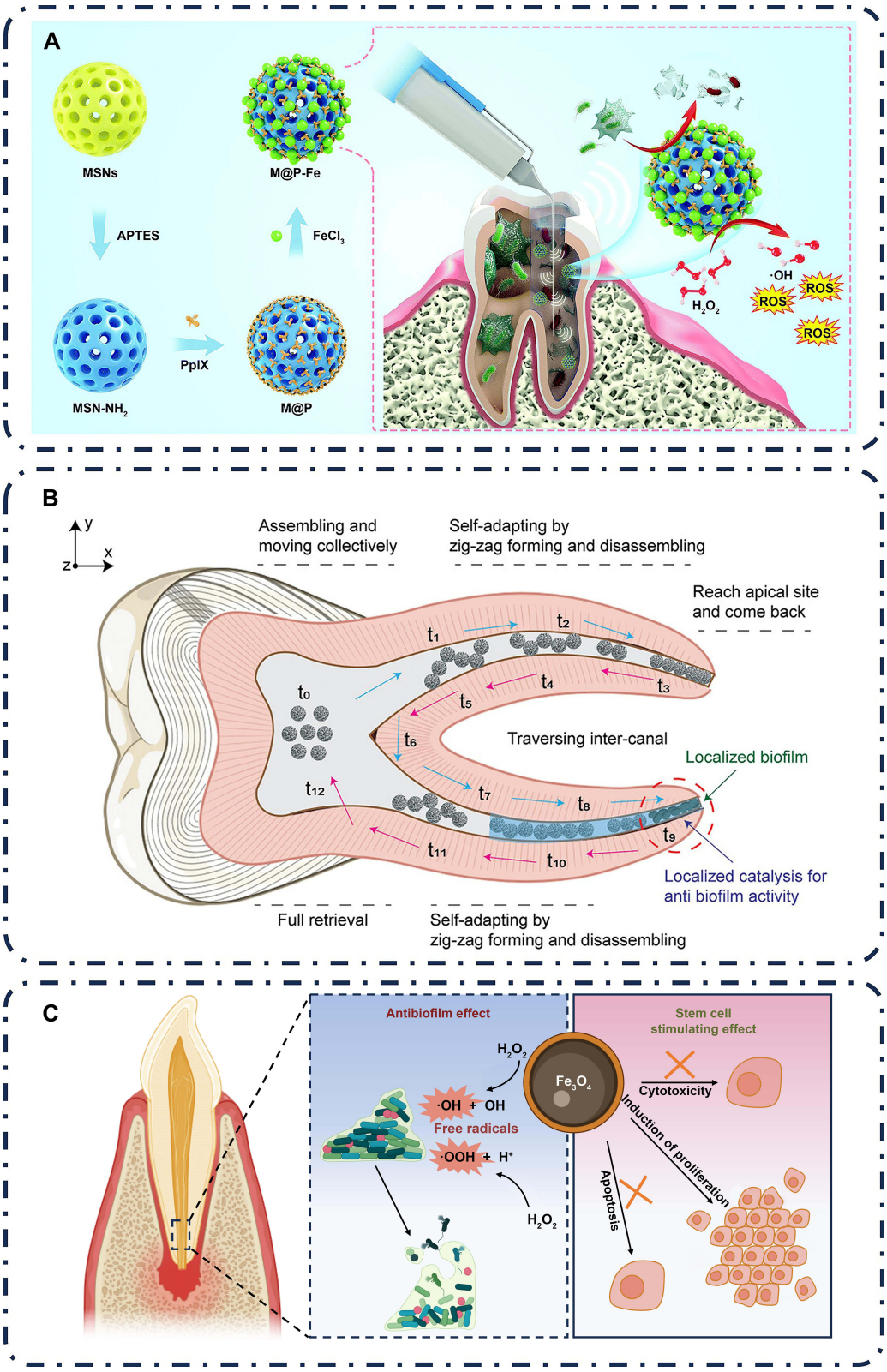

Figure 6 IONP-based strategies for pulpitis and periapical infection management. (**A**) Schematic illustration of a Fenton-enhanced sonodynamic platform enabling ROS-mediated root canal disinfection.[81] (**B**) Schematic of nanozyme-shell magnetic microcapsules showing self-guided navigation and localized ROS-mediated biofilm eradication. Blue arrows indicate the direction of magnetically guided motion of microcapsules toward the narrow apical region, whereas pink arrows denote the direction of their magnetic retrieval. t_0–t_{12} represent sequential time points during microcapsule motion under an out-of-plane rotating magnetic field.[83] (**C**) Schematic illustration of Ferumoxytol showing antibiofilm activity and stem cell–stimulatory effects for regeneration-oriented root canal therapy.[84]

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outcomes via multiple mechanisms. In animal models, SPION-loaded poly(lactic-co-glycolic acid)(PLGA) scaffolds promoted alveolar bone repair and favorably modulated oral microbiota, reducing pathogenic taxa such as *Clostridia* and *Bacteroidaceae* while increasing beneficial *Lactobacillus*.[87] Concurrently, pro-inflammatory cytokines (IL-1β, IL-17) decreased, and anti-inflammatory IL-10 increased, indicating immune regulation and inflammation suppression.[88] Layer-by-layer SPION–PLGA 3D-printed scaffolds further enhanced regeneration by providing antibacterial and anti-adhesive properties, inducing macrophage M2 polarization, inhibiting NLRP3 inflammasome activation, and promoting mesenchymal stem cell osteogenic differentiation.[89] Applying a static magnetic field (SMF) amplified these effects in a manner dependent on field strength, exposure duration, and bacterial species, highlighting magnetic modulation as a potential adjuvant strategy.[89] In summary, IONPs offer a multimodal approach for periodontitis, combining antibacterial, immunomodulatory, and regenerative functions to restore periodontal tissues.

Peri-Implantitis

Peri-implantitis is driven by plaque biofilms and host inflammation, with treatment focusing on infection control, biofilm suppression, and osseointegration. Magnetic IONPs offer multifunctional strategies due to their antibacterial activity, surface modifiability, and magnetic responsiveness.

In surface modification, incorporating SPIONs into 3D-printed hydroxyapatite or PLGA scaffolds preserved osteogenesis while enhancing antibacterial effects and modulating immunity via macrophage M2 polarization and NLRP3 inflammasome inhibition.[90] IONPs combined with polymer brushes reduced bacterial adhesion and biofilm formation at 0.15 mg/mL, lowering peri-implant infection risk.[91] In situ deposition of zero-valent or iron oxide nanoparticles on titanium (Fe-NPs/TOC) enabled electrochemical antibacterial activity against Gram-positive bacteria under dark conditions, maintaining cytocompatibility (Figure 7A).[92]

For drug delivery, magnetic core–mesoporous silica systems with pH-responsive shells provided precise release in acidic microenvironments (pH ≈ 5–6), enhancing local retention and avoiding burst release (Figure 7B).[27] External magnetic fields guided nanoparticles to infection sites, improving targeting and reducing systemic exposure. Carboxyl-modified SPIONs increased bactericidal efficiency against gentamicin-resistant *S. aureus* nearly eightfold and remained

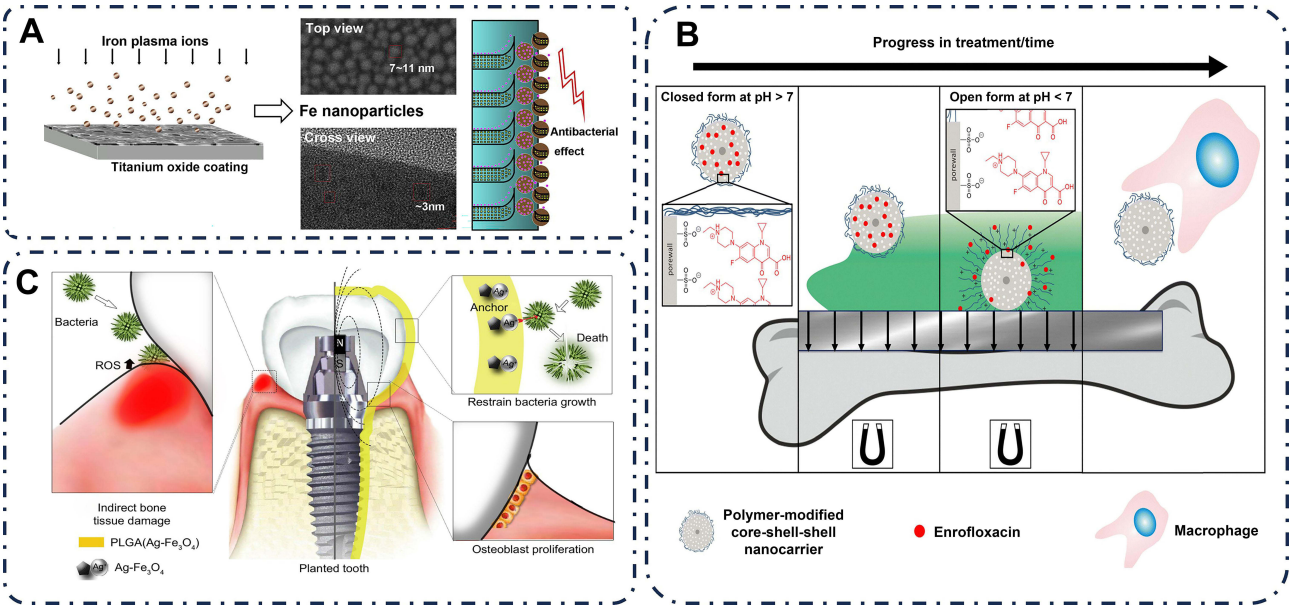

Figure 7 IONP-based strategies for peri-implantitis management. (**A**) Schematic of Fe-NPs/TOC titanium coatings showing electron-storage–enabled and externally driven antibacterial activity against Gram-positive bacteria. Downward black arrows indicate the direction of motion of iron plasma ions toward the TOC under applied bias voltage.[92] (**B**) Magnetic core–mesoporous silica core–shell systems with pH-responsive shells for controlled drug release in acidic infection environments.[27] (**C**) PLGA coatings with Fe_3O_4 and silver enabling magnetically enhanced antibacterial activity while maintaining osteoblast compatibility. The left white hollow arrow indicates the process of bacterial infection, while the black upward arrow represents the increased ROS production during infection. The red arrow in the upper-right region indicates the targeted antibacterial action of silver nanoparticles toward bacteria.[94]

effective against mature biofilms.[93] Embedding silver or other antibacterial agents with Fe_3O_4 into PLGA coatings maintained strong antibacterial activity, enhanced local effects under magnetic control, and ensured osteoblast compatibility (Figure 7C).[94]

In summary, IONPs integrate decontamination, antibacterial action, immune modulation, and osseointegration, functioning as surface modifiers and intelligent drug delivery platforms, providing multimodal strategies for localized infection control and bone regeneration.

Osteomyelitis

Osteomyelitis of the jaw is difficult to treat because deep-seated biofilms and canalicular barriers limit antibiotic penetration. IONPs and their composites offer viable strategies for precision therapy of deep bone infections via targeted delivery, surface modification, physicochemical or stimuli-induced ROS generation, thermal activation, and antibacterial–osteogenic scaffolds.[95]

To overcome the limited penetration and oxygen dependence of conventional ROS therapies, chemical and electromagnetic activation strategies have been developed. Fe^{2+}-activated $Na_2S_2O_8$-modified poly(ether ether ketone)(PEEK) generates sulfate and hydroxyl radicals under hypoxia, inducing ferroptosis and enhancing osseointegration.[96] Microwave-responsive Fe_3O_4/Au "pseudo-macrophage" nanoparticles eradicate *S. aureus* while promoting M2 polarization and osteogenesis in a rabbit osteomyelitis model (Figure 8A).[97] Jin et al further demonstrated that MoS_2/Fe_3O_4 nanostructures, through dielectric–magnetic coupling and interfacial polarization, amplify microwave absorption and synergistically enhance thermal and ROS effects to eliminate bone infections in vitro and in vivo.[98]

In drug-delivery and multimodal therapy, gentamicin-loaded magnetic mesoporous bioactive glass (Gent-MMBG) provides magnetically guided, sustained release and promotes osteogenesis.[101] A microwave-triggered Fe_3O_4/Carbon nanotube(CNT)/Gent system achieves enhanced bactericidal efficacy and healing in Methicillin-resistant *Staphylococcus aureus* (MRSA) models via nanoparticle trapping, magnetic guidance, and synergistic hyperthermia–chemotherapy (Figure 8B).[99] A Fe_3O_4/Prussian blue(PB)/PLGA/Gent composite couples microwave hyperthermia, ROS generation and magnetic targeting to deliver potent anti-*S. aureus* activity; transcriptomic analysis indicates disruption of membrane protein transport and ionic homeostasis as key lethal mechanisms (Figure 8C).[100]

Together, these multimodal strategies integrate targeted delivery, ROS induction, thermal activation, controlled release and osteogenic function, demonstrating considerable potential for precision treatment of deep jaw infections; however, systematic evaluation of long-term safety, in vivo fate, and scalable manufacturing is required to facilitate clinical translation.

IONP-Based Rapid Detection of Oral Pathogens

To enable rapid diagnosis and guide precise treatment of oral infections, there is an urgent clinical need for tools that can quickly identify pathogens and monitor infections in real time. Oral pathogens are typically present at low abundance and reside in complex microenvironments rich in proteins, enzymes, and commensal microbes, which significantly increases detection difficulty. Conventional microbiological methods are time-consuming, lack sensitivity, and fail to capture the dynamic nature of infections.

Rapid detection based on iron oxide nanoparticles exploits the synergistic effect of magnetic enrichment and specific recognition, substantially enhancing the detection efficiency of oral pathogens. Common strategies involve functionalizing nanoparticles with specific recognition elements to selectively capture pathogens from saliva, coupled with PCR or other nucleic acid amplification techniques to markedly lower detection limits.[102–104] Magnetic enrichment can also be combined with biosensing readouts, including colorimetric, fluorescent, giant magnetoimpedance (GMI) sensors or surface-enhanced Raman scattering(SERS) approaches, to construct rapid, sensitive, and field-deployable platforms.[102,105–108] For example, silver-coated magnetic nanoparticles (Fe_2O_3@AgNPs) integrated with a microfluidic chip enable magnetic enrichment and SERS detection of *Porphyromonas gingivalis (P. gingivalis)* and *A. actinomycetemcomitans* (Figure 9).[108] To systematically summarize the materials, targets, and detection performance reported in current studies, relevant data are compiled to guide future methodological optimization (Table 5). Building on this, multimodal designs integrating chromatography, fluorescence, Raman spectroscopy, or magnetic encoding with

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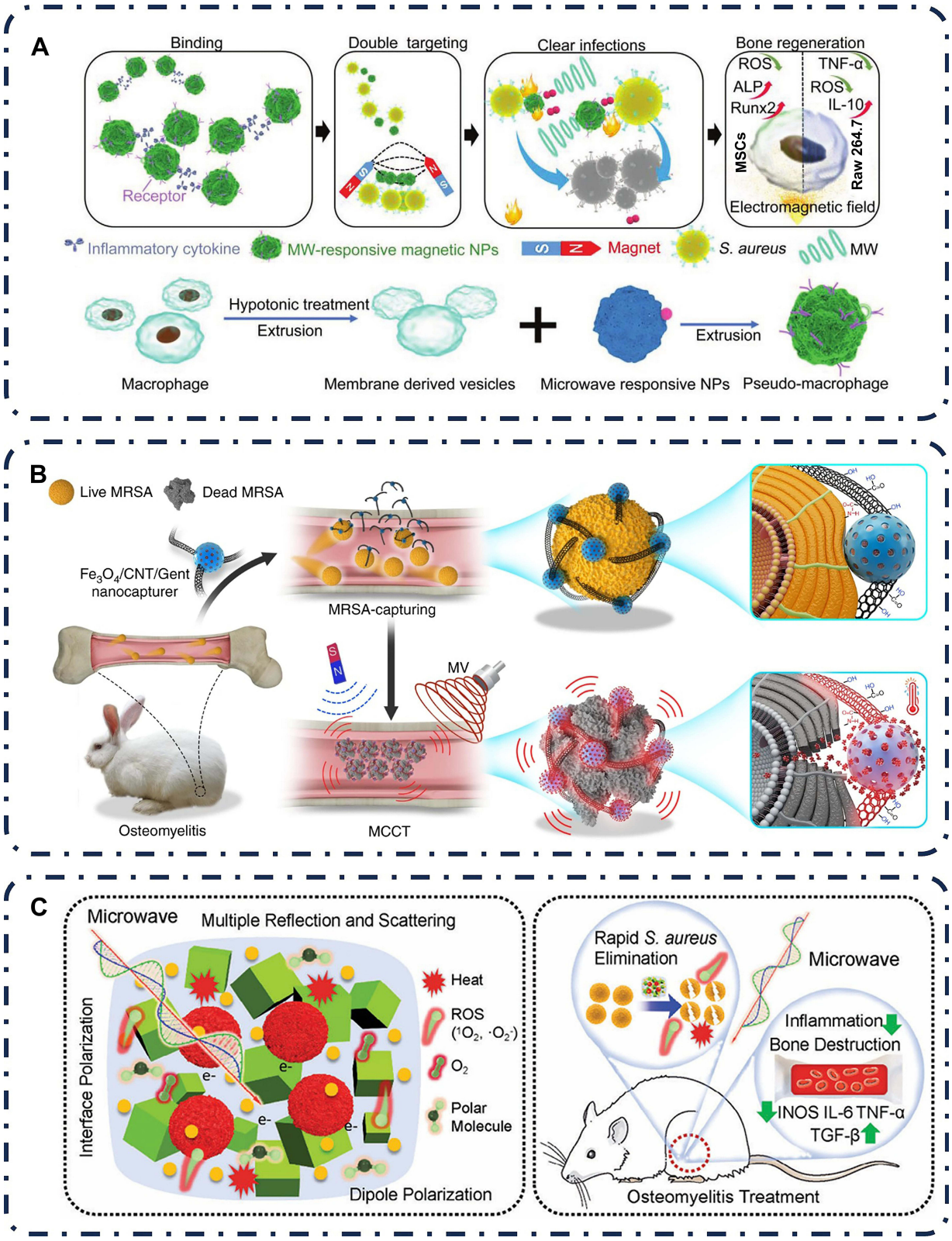

Figure 8 IONP-based strategies for osteomyelitis management. (**A**) Fe_3O_4/Au nanoparticles enabling antibacterial activity, M2 polarization, and mesenchymal stem cell (MSC) osteogenesis under microwave stimulation. Green downward arrows indicate decreased levels of the corresponding biomarkers, whereas red upward arrows indicate increased levels of the corresponding biomarkers.[97] (**B**) Fe_3O_4/CNT/Gent system enabling targeted antibacterial therapy for MRSA-induced osteomyelitis via magnetic guidance and microwave-assisted chemo-thermotherapy.[99] (**C**) Schematic of Fe_3O_4/PB/PLGA/Gent system and its microwave-assisted osteomyelitis treatment mechanism. Green downward arrows indicate a decrease in inflammation and the corresponding inflammation-related factors, whereas upward arrows indicate an increase in the corresponding anti-inflammatory factors.[100]

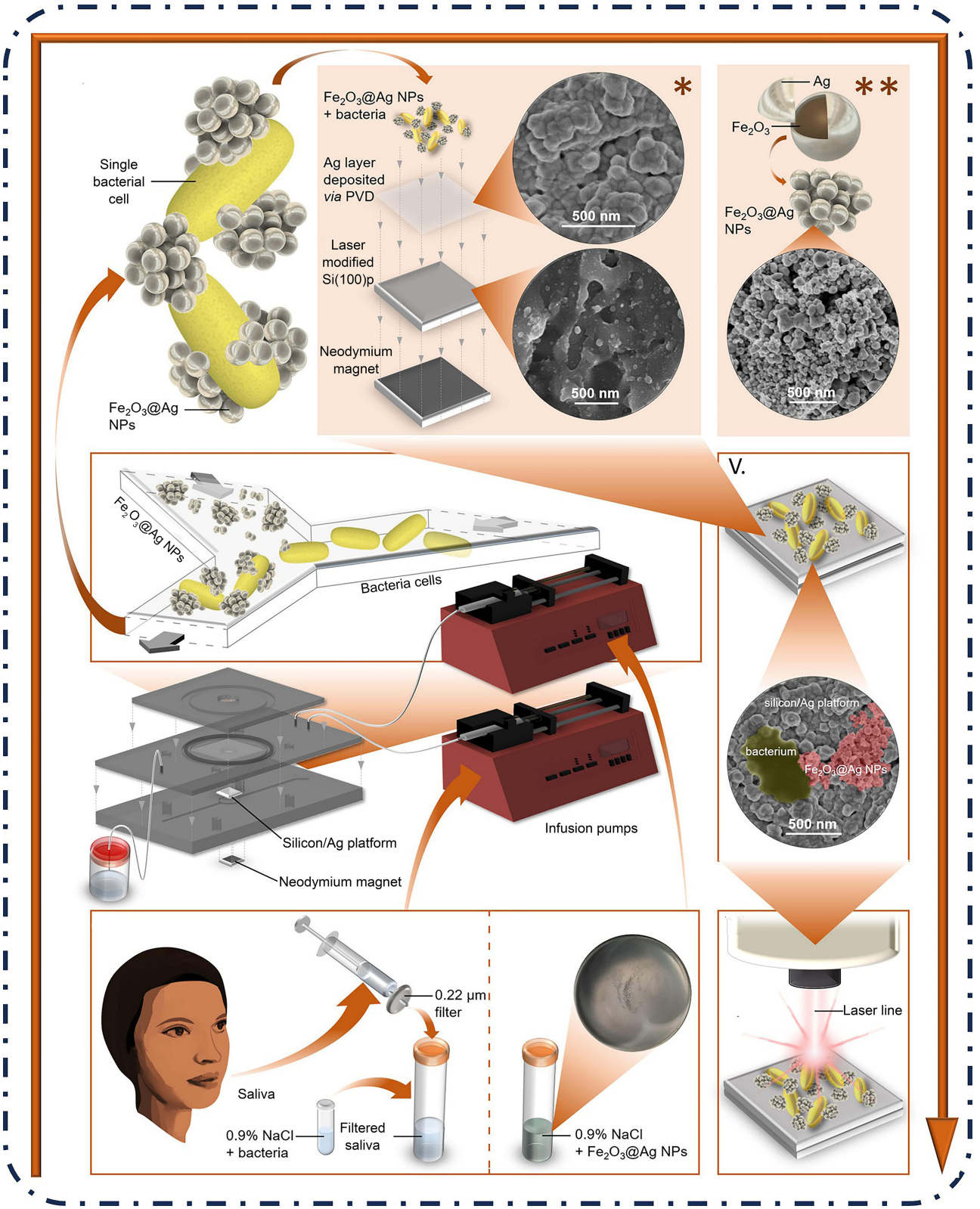

Figure 9 Schematic illustration of bacteria separation and detection using Fe_2O_3@AgNPs integrated with a microfluidic chip, enabling magnetic enrichment and SERS-based identification of *P. gingivalis* and *A. actinomycetemcomitans*. * and ** represent the arrangement and SEM images of the Si/Ag substrate and of Fe_2O_3@Ag magnetic NPs, respectively.[108]

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Table 5 Materials, Targets, and Detection Performance for Oral Diagnostics in Current Studies

Materials	Target Analytes	Biomarkers	Detection Methods	Limit of Detection	Detection Time	Sample Types	Ref.
Magnetic beads-GMI sensor	*P. gingivalis*	Antibody	Magnetic immunoassay	10^3 CFU/mL	1 h	Saliva	[102]
MNPs-cellulose acetate membrane	*Streptococcus mutans* and *Streptococcus sobrinus*	Cell-wall-binding-domain (CWBD)	Colorimetric assay	16 CFU/mL (*S. mutans*), 72 CFU/mL (*S. sobrinus*)	30 min	Saliva	[103]
Amoxicillin-loaded chitosan (CS)-coated magnetic nanocarriers	*P. gingivalis, Parvimonas micra*	–	PCR	10 CFU/mL	30 min (enrichment only)	Saliva	[104]
Magnetic nanobeads + Gold biosensing platform	*P. gingivalis*	Gingipains	Colorimetric assay	49 CFU/mL	30 s	Saliva	[105]
Magnetic beads–gold sensor surface	Periodontitis-associated proteases	Human Neutrophil Elastase (HNE) and Cathepsin-G	Colorimetric assay	1 pg/mL (HNE), 100 fg/mL (Cathepsin-G)	20–30 s	Saliva	[106]
Fluorescent–magnetic encoding nanospheres	*P. gingivalis*	Monoclonal antibody	Fluorescence immunoassay	10 CFU/mL	1 h	Mixed bacterial suspension	[107]
Fe_2O_3@AgNPs+Si/Ag SERS platform	*P. gingivalis, A. actinomycetemcomitans*	–	SERS-based microfluidic assay	10^3 CFU/mL	45 s	Saliva	[108]

optical signals can reduce false positives and false negatives through signal complementarity and improve quantitative reliability. Although these strategies have been explored in food safety and environmental monitoring, their application for oral pathogen detection remains largely unexplored and warrants further investigation.[109,110]

Challenges and Perspectives

Challenges

Despite the promising potential of iron oxide nanoparticles in oral infection control, several challenges remain to be addressed. Firstly, the complex oral microenvironment poses significant interference, as salivary and plaque biomolecules readily adsorb onto nanoparticle surfaces to form a protein corona, thereby altering their dispersibility, cellular interactions, and antibacterial efficacy.[111–113] Moreover, uncertainties persist regarding biocompatibility and long-term safety. Although iron-based nanoparticles are generally regarded as biocompatible, their metabolic pathways—particularly involving iron ion release, ROS generation, immune responses, and potential tissue accumulation—have not yet been fully clarified through systematic and long-term evaluations.[114] In addition, manufacturing consistency and quality control remain critical barriers to clinical translation. Scaling up from laboratory synthesis to clinical-grade production demands precise control of particle size, morphology, surface modification, and drug loading to ensure reproducibility and regulatory compliance. Furthermore, multifunctional or chemically complex nanoparticle systems often face increased regulatory scrutiny, as each additional component may require independent safety assessments and validated analytical characterization.[115] Therefore, establishing standardized physicochemical characterization protocols, scalable production processes, and clear regulatory guidelines is crucial to ensure clinical-grade quality, reproducibility, and safe

translation into clinical practice.[116] Finally, challenges related to delivery routes and clinical adaptation must also be overcome. Oral therapeutic applications require materials with suitable adhesion, retention, and washability, as well as compatibility with clinical workflows and dosage forms such as gels, films, or implant coatings, which should be validated under standardized operational protocols.

Perspectives

As the field of magnetic nanomaterials advances toward clinical translation, it is essential to align future research with precision medicine and microecological balance in oral health. Looking ahead, omics-guided strategies hold great promise for the intelligent optimization of IONPs. Integrating microbiome, metabolome, and proteome data enables comprehensive profiling of the oral lesion microenvironment, covering microbial composition, enzyme activity, pH, and metabolite patterns, to guide surface modifications, controlled release, and targeted delivery of IONPs. Additionally, the construction of theranostic magnetic nanoplatforms that couple imaging, precision delivery, and multimodal antibacterial functions could establish a closed-loop framework encompassing localization, diagnosis, intervention, and post-treatment monitoring, thereby accelerating clinical translation. In addition, future strategies in antibacterial therapy are expected to move beyond broad-spectrum bactericidal approaches toward microbiota-modulating paradigms that restore ecological balance by selectively targeting pathogens while maintaining beneficial commensal species, ultimately supporting sustainable oral health management.

Conclusion

IONPs, with their unique magnetic responsiveness, tunable physicochemical properties, and versatile functionalization strategies, exhibit remarkable potential in oral healthcare. These nanomaterials integrate multiple antibacterial mechanisms, including physical disruption of biofilms, magnetothermal effects, and ROS-mediated bactericidal activity. Across diverse in vitro and in vivo models, IONPs consistently demonstrate superior antimicrobial effects compared to traditional antibiotics, underscoring their significant potential for controlling complex oral infections. Their multifunctionality provides promising approaches for managing oral infections such as caries, pulpitis, periodontitis, peri-implantitis, and osteomyelitis, while also enabling rapid detection of oral pathogens.

Despite promising antimicrobial efficacy and biocompatibility, clinical translation of IONPs is limited by challenges such as complex oral microenvironments, uncertain long-term safety, manufacturing consistency, and delivery adaptability. The integration of multiphase or multiplex theranostic platforms—capable of combining targeted delivery, responsive activation, and real-time diagnostic readouts—could further accelerate the clinical translation of IONPs by enhancing both detection and treatment of oral infections. Future work should focus on omics-guided optimization, multifunctional theranostic platforms, and microbiota-modulating strategies to enable safe and effective next-generation oral antimicrobial and diagnostic applications.

Abbreviations

MNPs, magnetic nanoparticles; IONPs, iron oxide–based nanoparticles; ROS, reactive oxygen species; Ms, saturation magnetization; Mr, near-zero remanence; Hc, coercivity; EPS, extracellular polysaccharide; DC, direct current magnetic field; AMF, alternating magnetic field; STARS, surface topography-adaptive robotic superstructures; LSPR, localized surface plasmon resonance; NIR, near-infrared; ZIFs, zeolitic imidazolate frameworks; POD, peroxidase; Gox, glucose oxidase; sHA, synthetic hydroxyapatite; PLGA, poly(lactic-co-glycolic acid); SMF, static magnetic field; Fe-NPs/TOC, iron oxide nanoparticles on titanium; PEEK, poly(ether ether ketone); Gent-MMBG, gentamicin-loaded magnetic mesoporous bioactive glass; CNT, Carbon nanotube; MRSA, Methicillin-resistant *Staphylococcus aureus*; PB, Prussian blue; MSC, mesenchymal stem cell; GMI, giant magnetoimpedance; SERS, surface-enhanced Raman scattering; *P. gingivalis, Porphyromonas gingivalis*; CWBD, cell-wall-binding-domain; CS, chitosan; HNE, Human Neutrophil Elastase.

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Disclosure

The author(s) report no conflicts of interest in this work.

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