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NIR-Activated Ag₂S Quantum Dots for Efficient Broad-Spectrum Antibacterial and Biofilm Disruption

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ABSTRACT

Bacterial biofilms, encased in a protective extracellular polymeric substance (EPS) matrix and harboring metabolically dormant persister cells, pose a critical challenge in antimicrobial therapy due to their inherent resistance to conventional antibiotics. To overcome this, we present a near-infrared (NIR)-activated nanoplatfrom based on silver sulfide quantum dots (Ag₂S QDs) that synergistically integrates photothermal therapy (PTT) and photodynamic therapy (PDT). Under NIR irradiation, Ag₂S QDs rapidly generate localized hyperthermia and reactive oxygen species (ROS). This leads to complete eradication (99.99%) of planktonic bacteria within 10 min, as well as significant disruption of pre-established biofilms (69–84% removal). The mechanism involves photothermal-mediated degradation of the EPS barrier to facilitate deep penetration, and ROS-induced oxidative damage to bacterial membranes and intracellular components. This strategy exhibits a physical barrier-disruption paradigm that circumvents conventional antibiotic resistance mechanisms, demonstrating broad-spectrum activity, a well-defined therapeutic index, and spatiotemporally controllable biosafety for the precision treatment of biofilm-associated infections.

1 | Introduction

Chronic and recalcitrant infections caused by bacteria, particularly those forming biofilms, represent a severe global public health challenge due to their strong resistance to conventional therapies [1–3]. Biofilms are structured microbial communities in which bacterial aggregates are encased within a self-secreted, highly hydrated extracellular polymeric substance (EPS) matrix [2, 4]. This matrix, primarily composed of polysaccharides, proteins, nucleic acids, and lipids, not only provides physical anchorage and mechanical stability for the enclosed bacterial community but also constitutes a highly effective defensive

barrier [5, 6]. This barrier significantly impedes the penetration of conventional antibiotics and shields the embedded bacteria from host immune responses and environmental stresses [7, 8], leading to the persistence and recurrence of biofilm-associated infections. The combined effects of the EPS barrier and the resilience of persister cells render biofilm-associated infections often persistent, recurrent, and highly refractory to standard drug treatments, underlying numerous clinical challenges such as implant failure and chronic wound non-healing [9, 10].

Conventional antibiotic development paradigms—focused on “targeting single molecular targets”—have proven increasingly

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inadequate for treating biofilm-associated infections [11, 12]. This strategy not only involves lengthy development cycles and high costs, but, more critically, the pace at which bacteria develop resistance via genetic mutations often outstrips the development of new drugs [13]. Consequently, there is an urgent need to move beyond traditional frameworks and explore novel antibacterial strategies that are independent of bacterial metabolic states and capable of actively disrupting the EPS barrier.

In recent years, light-activated therapies based on nanomaterials, such as photothermal therapy (PTT) and photodynamic therapy (PDT), have offered promising alternatives [10, 14, 15]. These approaches utilize near-infrared (NIR) to activate photosensitive nanomaterials, generating localized hyperthermia or reactive oxygen species (ROS) [16, 17]. By targeting conserved physical structures such as the cell membrane or the EPS matrix itself, these physico-chemical approaches bypass traditional bactericidal mechanisms and offer the potential for achieving “physical barrier disruption” and eradicating biofilms [10, 18, 19]. However, many reported photosensitizing materials are still constrained by complex synthesis processes, limited photothermal conversion efficiency, or slow killing kinetics, hindering their clinical translation potential [20, 21]. Notably, similar synergistic strategies have also shown great promise in the field of cancer phototheranostics, where material design and mechanistic insights offer valuable parallels for antibacterial applications [22–24].

Herein, we report a rapid and efficient integrated antibacterial platform based on silver sulfide quantum dots (Ag_2S QDs) synthesized via a green approach. We selected Ag_2S QDs not only for their documented good biocompatibility and low cytotoxicity but [25, 26], crucially, because they have been identified as versatile agents exhibiting exceptional photostability, photothermal conversion efficiency, and ROS generation capability within the second near-infrared (NIR-II) window [27]. We propose a synergistic antibacterial mechanism of “Physical Barrier Disruption and Pathogen Elimination” (Figure 1): under NIR irradiation, the localized heat generated by Ag_2S QDs instantly denatures proteins and degrades polysaccharides within the EPS matrix, actively “demolishing” the biofilm’s physical barrier. Concurrently, the abundant ROS produced via their photodynamic effect indiscriminately attack the bacteria exposed by this barrier disruption, causing oxidative damage to cell membranes and intracellular components, leading to efficient eradication. Since the core targets of this strategy—the EPS and cell membranes—are highly conserved physical structures rather than variable molecular targets, [28] crucially, this bactericidal activity is spatiotemporally confined to the region of NIR illumination, enabling a high degree of therapeutic precision and minimizing off-target effects on host tissues. We anticipate it will retain strong potential even against future clinical drug-resistant strains.

This study systematically evaluated the synergistic antibacterial effect, biofilm disruption capability, and broad-spectrum activity of Ag_2S QDs combined with NIR irradiation. Integrating biochemical assays, fluorescence imaging, and electron microscopy, we constructed a comprehensive evidence chain tracing from “biofilm barrier disruption” to “bacterial cell membrane permeabilization” and ultimately “ultrastructural collapse,” thereby elucidating the novel antibacterial mechanism centered on “physical barrier disruption.” Our work not only demonstrates

the considerable potential of Ag_2S QDs as potent photoactivated antibacterial agents but also offers robust data supporting the “physical barrier disruption” strategy for combating biofilm-associated infections.

2 | Results and Discussion

2.1 | Photocatalytic Antibacterial and Anti-biofilm Effects of Ag_2S QDs

The antibacterial efficacy of Ag_2S QDs activated by NIR irradiation was systematically evaluated against planktonic cultures of *Escherichia coli* (*E. coli*) and *Staphylococcus epidermidis* (*S. epidermidis*) (Figure 2A,B). Control experiments confirmed that neither a high concentration of Ag_2S QDs (500 $\mu\text{g/mL}$) alone nor NIR irradiation alone induced significant bactericidal effects (Figures S5 and S6), thereby establishing the essential role of NIR photoactivation in triggering the antibacterial function of the QDs.

Upon photoactivation, a potent and rapid synergistic effect was observed. When combined with NIR, Ag_2S QDs at 250 $\mu\text{g/mL}$ achieved a bacterial eradication rate exceeding 80%, while 500 $\mu\text{g/mL}$ resulted in near-complete sterilization (99.99%) within a remarkably short 10-min treatment window. This rapid action, which is significantly faster than that of many reported photoactive materials, suggests a mechanism based on immediate physical disruption rather than slow biochemical inhibition. [29–32]

The concentration-dependent nature of this photothermal synergy was precisely defined. Dose-response analysis revealed a sharp threshold, with identical minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) for both strains (MIC = 250 $\mu\text{g/mL}$, MBC = 500 $\mu\text{g/mL}$), yielding an MBC/MIC ratio of 2 (Figure 2C). This profile indicates a critical concentration point beyond which the system transitions abruptly from bacterial inhibition to complete eradication. This “switch-like” pharmacodynamic behavior is advantageous for designing precise therapeutic dosing strategies to maximize efficacy while minimizing off-target toxicity.

Given the rapid, physical mode of action observed against planktonic bacteria, we hypothesized that this photothermal synergy could be particularly effective against bacterial biofilms—a major clinical challenge due to their protective EPS matrix and dormant persister cells. Consistent with this hypothesis, the combination of Ag_2S QDs and NIR irradiation induced significant, concentration-dependent disruption of pre-formed mature biofilms (Figure 2D). A 10-min treatment at the MIC (250 $\mu\text{g/mL}$) degraded 69.59% (*S. epidermidis*) and 74.79% (*E. coli*) of the biofilm biomass. At the bactericidal concentration (500 $\mu\text{g/mL}$), the eradication rate increased to approximately 84%. Importantly, this anti-biofilm activity was strictly dependent on photoactivation, as control treatments with QDs alone or NIR alone resulted in only modest clearance (<55%) (Figure 2E).

The mechanism underlying this efficient biofilm disruption is fundamentally distinct from that of conventional antibiotics. Rather than relying on passive diffusion and specific

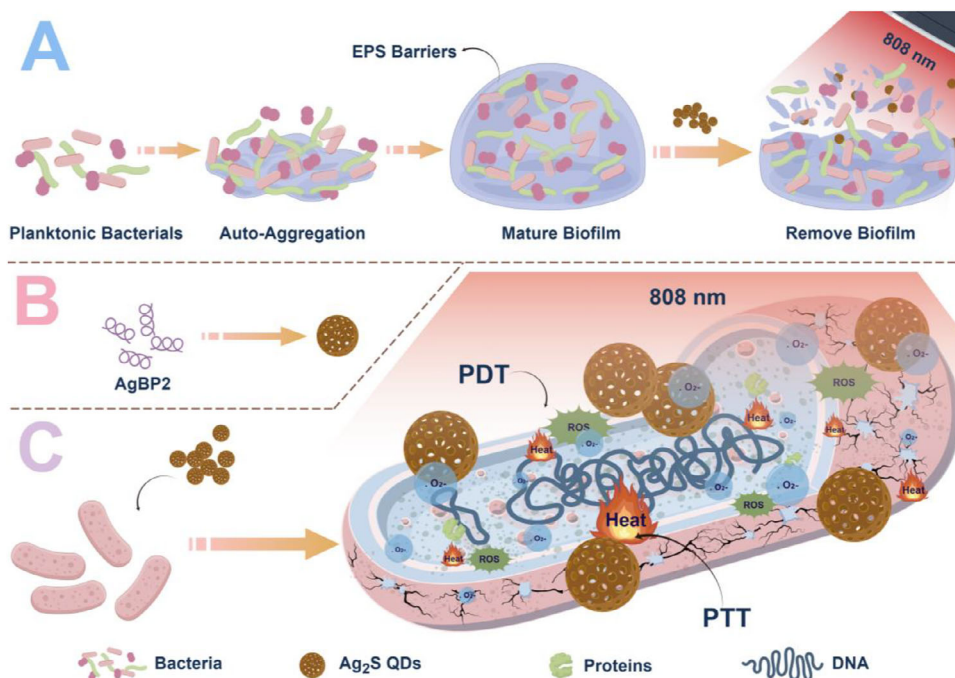


FIGURE 1 | Schematic overview of the study design and the proposed “Physical Barrier Disruption and Pathogen Elimination” mechanism of Ag₂S QDs under NIR irradiation. (A) The lifecycle of a bacterial biofilm and the strategy for its disruption using Ag₂S QDs-NIR (808 nm, 1.5 W/cm², 10 min). (B) Synthesis process of Ag₂S QDs. (C) Proposed multi-modal antibacterial mechanism of Ag₂S QDs-NIR.

molecular targeting, the NIR-activated Ag₂S QDs generate localized hyperthermia and ROS that directly attack the biofilm's structural integrity. [27, 33, 34] This causes rapid denaturation and degradation of key EPS components, leading to the physical collapse of the biofilm architecture. This physical disruption strategy offers a critical dual advantage: it is effective irrespective of the metabolic state of the embedded bacteria (thus targeting dormant persisters), and it acts on the structural scaffold of the biofilm, a target inherently less susceptible to the development of genetic resistance. Ultimately, this work demonstrates that Ag₂S QDs under NIR irradiation exhibit a rapid, threshold-dependent, and synergistic bactericidal effect that extends powerfully to biofilm disruption. It underscores that overcoming biofilm-mediated resistance may be most effectively achieved by rapidly eliminating the structural sanctuary itself, a strategy that can be as consequential as eradicating its inhabitants.

2.2 | Membrane Disintegration Mechanism

2.2.1 | Membrane Permeability Alteration and Leakage of Intracellular Components

Having established the macro-scale disruption of the biofilm barrier, we proceeded to investigate the underlying bactericidal mechanism at the single-cell level. By integrating biochemical assays, single-cell fluorescence imaging, and ultrastructural morphological analysis, we established a comprehensive evidence chain tracing from initial “membrane permeability alteration” to ultimate “cellular disintegration and death,” systematically elucidating the terminal events leading to bacterial death induced by the combined Ag₂S QDs and NIR treatment.

Detection of alkaline phosphatase (AKP) activity, a sensitive indicator of outer membrane integrity, first revealed an early effect of the combined treatment (Figure 3A) [35]. Compared to controls, AKP activity in the culture supernatants of both *E. coli* and *S. epidermidis* increased sharply post-treatment, reaching 2.2-fold and 2.0-fold of control levels, respectively (Figure 3B). This significant change was evident early in the treatment (within 10 min), strongly suggesting that this marker enzyme from the periplasmic space leaked extensively into the extracellular environment due to outer membrane barrier breach. This indicates that altered membrane permeability is one of the key initial biological effects triggered by the combined treatment.

Further evidence came from a comprehensive analysis of macromolecular content in the culture supernatants. After combined treatment, the absorbance values of the supernatants for both bacterial strains at 260 nm (characteristic of nucleic acids) and 280 nm (characteristic of proteins) showed significant increases. Specific data revealed that for *E. coli*, OD₂₆₀ and OD₂₈₀ values increased by 2.9-fold and 2.2-fold, respectively, while the corresponding values for *S. epidermidis* increased by 3.9-fold and 1.8-fold (Figure 3C,D). Together with AKP leakage, this concerted release of nucleic acids and proteins forms a quantitative and corroborative triad of evidence. It conclusively demonstrates that the treatment thoroughly compromises the cell membrane's barrier function, culminating in the collapse of the intracellular microenvironment and cell death.

Notably, the Gram-negative bacterium (*E. coli*) exhibited more pronounced leakage in several indicators compared to the Gram-positive bacterium (*S. epidermidis*). We hypothesize that its complex envelope structure (outer membrane-peptidoglycan-inner membrane), when subjected to photothermal/photodynamic

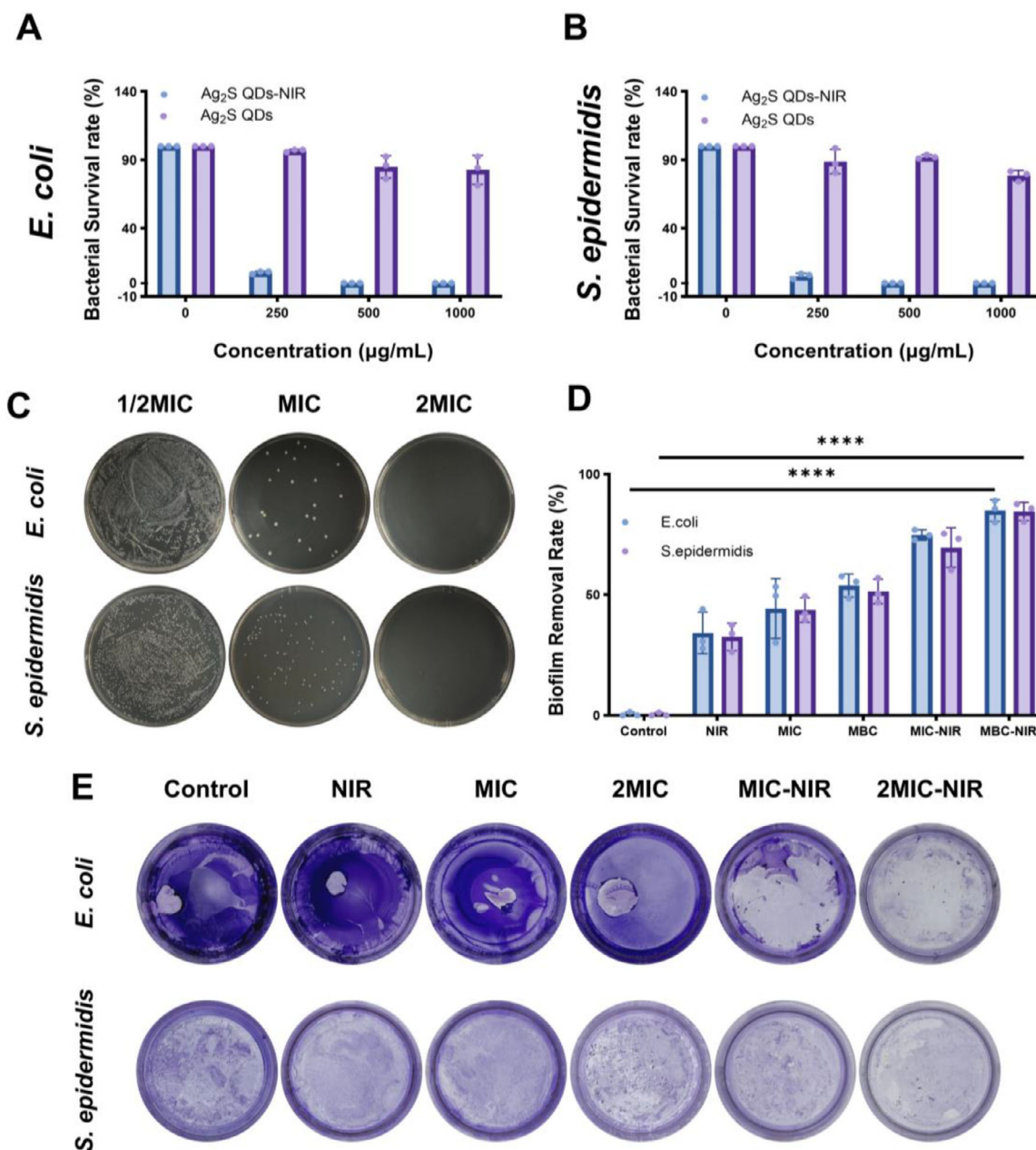


FIGURE 2 | Antibacterial activity against planktonic bacteria and disruption of mature biofilms by Ag₂S QDs under NIR irradiation (808 nm, 1.5 W/cm², 10 min). (A,B) Colony-forming unit (CFU) assays showing the survival of *E. coli* (A) and *S. epidermidis* (B) after treatment with Ag₂S QDs alone or Ag₂S QDs-NIR. (C) Determination of the MBC values for Ag₂S QDs-NIR against *E. coli* and *S. epidermidis*. (D) Quantification of the remaining biofilm biomass for *E. coli* and *S. epidermidis*. (E) CV staining of mature *E. coli* and *S. epidermidis* biofilms after treatment. Data are presented as mean ± SD. **p* < 0.05, ***p* < 0.01, ****p* < 0.001, *****p* < 0.0001 vs. the control group. Images are representative of at least three independent experiments.

impact, might experience stress concentration and interfacial failure due to the heterogeneity in the thermal expansion coefficients and mechanical properties of its components, potentially accelerating the overall structural disintegration [36]. Once the integrity of the outer membrane is rapidly compromised, its inherently thin peptidoglycan layer cannot provide sufficient support independently, leading to more rapid and thorough structural collapse and content leakage compared to the more structurally uniform Gram-positive bacterium. This disparity thus exemplifies the fundamental principle that bacterial susceptibility is dictated by envelope architecture. [37] The validity of this principle is further underscored by recent work on the

synergistic action of TiO₂ and ethyl lauroyl arginate (LAE) under NIR [38, 39], suggesting a convergent mechanism that may be generalizable across diverse antibacterial platforms.

Double-staining experiments using propidium iodide (PI) and the membrane-specific dye N, N-dimethylaniline N-oxide (DAMO) provided direct evidence for assessing membrane integrity at the single-cell level (Figure 3F). Fluorescence microscopy observations showed that bacteria in the untreated control and single-treatment groups exhibited uniform, bright green fluorescence (Figure 3E,G,H), clearly indicating intact cell membranes that effectively excluded the PI dye.

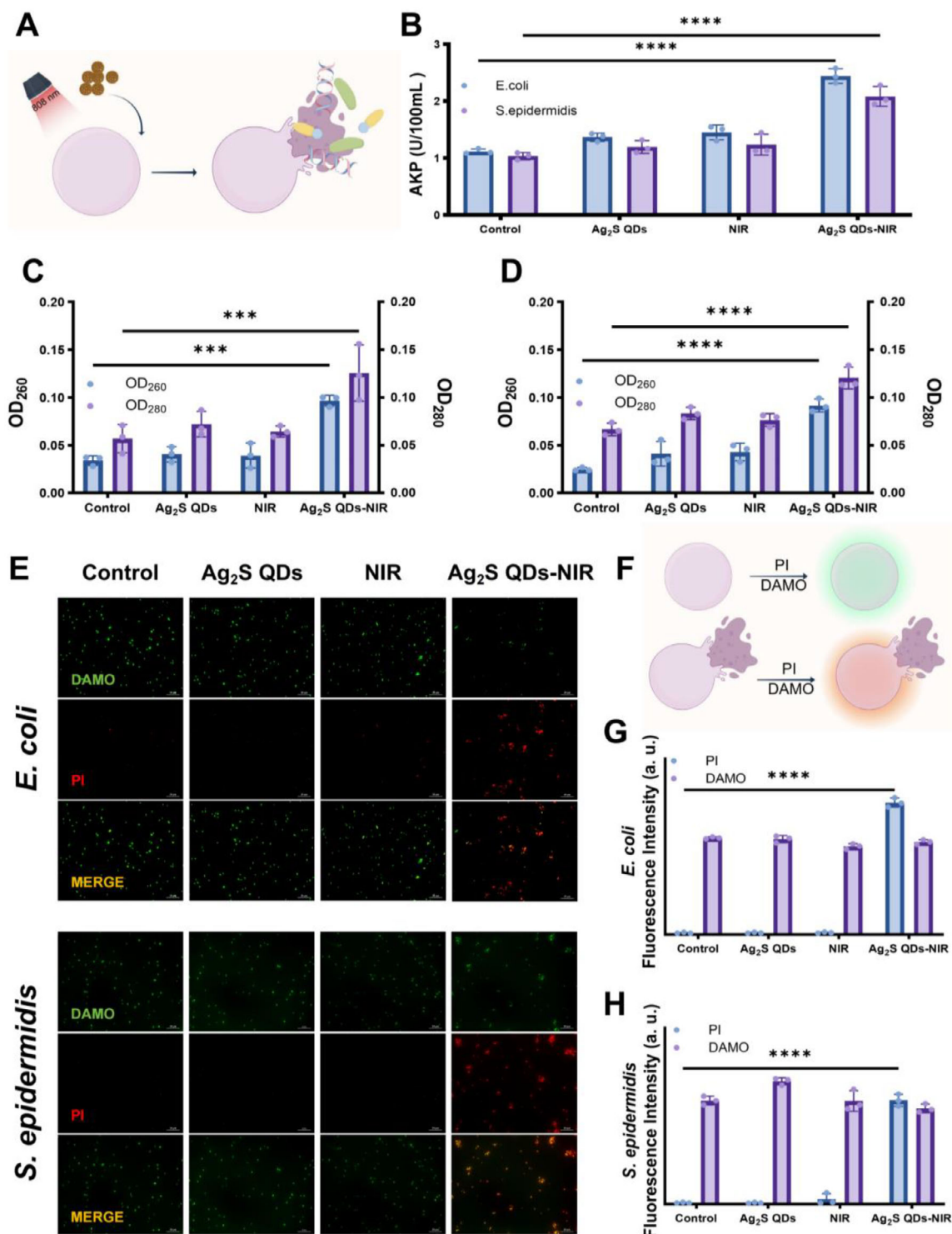


FIGURE 3 | Ag₂S QDs-NIR treatment (808 nm, 1.5 W/cm², 10 min) induces bacterial membrane damage and intracellular content leakage. (A) Schematic of the assay detecting bacterial membrane rupture via the release of intracellular components. (B) Measurement of extracellular AKP activity, indicating outer membrane permeability, in *E. coli* and *S. epidermidis*. (C, D) Spectrophotometric measurement of the release of cytoplasmic nucleic acids (OD₂₆₀) and proteins (OD₂₈₀) from *E. coli* (C) and *S. epidermidis* (D), confirming severe membrane disruption. (E) Representative fluorescence micrographs of *E. coli* and *S. epidermidis* stained with DAMO (live, green) and PI (dead, red). (F) Schematic of the live/dead bacterial staining principle. (G, H) Quantitative analysis of bacterial viability for *E. coli* (G) and *S. epidermidis* (H) by live/dead staining. Scale bars, 20 μ m. Data are presented as mean $\pm$ SD. * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001 vs. the control group. Images are representative of at least three independent experiments.

In stark contrast, fields of view from the combined treatment group contained numerous cells displaying orange–red fluorescence, signifying the superposition of the green membrane signal from DAMO and the red nucleic acid signal from PI. This distinct “fluorescence switch,” reflecting the shift from green (intact) to orange–red (compromised) fluorescence, vividly captures the dynamic transition of bacteria from a viable state to one with lost membrane integrity. This imaging result bridges the population-level “outcome” revealed by biochemical assays with the “process” of individual cell fate, providing indispensable direct visual evidence for understanding the dynamic evolution of the antibacterial mechanism.

Collectively, our multi-faceted analysis delineates a coherent and escalating mechanism of bactericidal action. The combined Ag₂S QDs–NIR treatment initiates with rapid outer membrane permeabilization, propagates into a catastrophic failure of barrier function with massive content leakage, and culminates in the physical disintegration of the cell. This pathway is markedly exacerbated in Gram-negative bacteria, a vulnerability we attribute to the intrinsic structural complexity and interfacial heterogeneity of their cell envelope.

2.2.2 | Ultrastructural Collapse and Morphological Disintegration

Scanning electron microscopy (SEM) observations provided the most direct and compelling morphological evidence for the membrane disintegration mechanism (Figure 4A). Compared to the typical plump and smooth surfaces of control bacteria, both bacterial strains subjected to the combined treatment exhibited severe, albeit distinct, ultrastructural damage.

E. coli samples displayed more violent structural disruption. Their characteristic rod shape was severely distorted and collapsed, with large-scale deep wrinkling, concavities, and apparent tearing of the membrane structure. Notably, some *E. coli* cells exhibited deep, crater-like structural defects on their surface, likely representing physical channels formed after the complete local disintegration of the membrane structure under intense stress (Figure 4B). This catastrophic collapse likely results from the compromised peptidoglycan layer failing to counteract osmotic pressure once the lipid bilayers were breached.

In contrast, the damage pattern observed in *S. epidermidis*, while slightly less severe overall, was equally lethal. Their cell surfaces showed large-area collapse, with distinct pore formation in local regions; some cells even appeared hollowed out due to content leakage (Figure 4C). These morphological changes clearly demonstrate the complete loss of function of the cell membrane as a physical barrier, serving as the ultimate morphological evidence for membrane disintegration and content leakage.

Thus, the three tiers of multidimensional evidence—quantitative biochemical data, single-cell fluorescence imaging, and ultrastructural morphological observation—mutually corroborate each other, collectively establishing the cell membrane as the direct and critical physical target leading to bacterial death induced by the combined treatment. This

mode of action, centered on attacking the highly conserved physical membrane structure, also provides an intrinsic rationale for the broad-spectrum antibacterial activity demonstrated subsequently.

2.3 | Broad-Spectrum Activity and Dose Dependence

After revealing the synergistic bactericidal mechanism involving “physical barrier disruption” and “membrane disintegration” at the mechanistic level, we further conducted a systematic evaluation of the clinical application potential of this combined strategy, with a specific focus on its broad-spectrum antibacterial activity and precise dose dependence.

2.3.1 | Confirmation of Broad-Spectrum Antibacterial Efficacy

As illustrated in Figure 5, Figures S7 and S8, the combined treatment of Ag₂S QDs with NIR exhibited potent growth-inhibitory effects against a panel of clinically prevalent pathogens. The tested standard strains included representatives of Gram-negative bacteria: *E. coli* [40], the highly pathogenic *Pseudomonas aeruginosa* (*P. aeruginosa*) [41–44], and *Acinetobacter baumannii* (*A. baumannii*)—dubbed the “ICU nightmare” [45]. Additionally, Gram-positive bacteria were represented by *S. epidermidis*, a common causative agent of medical device-related infections [46]. The drastic reduction in colony counts across all tested pathogens—including both Gram-positive and Gram-negative species—indicates that the synergistic bactericidal action, rooted in physical membrane disruption, is not constrained by classical bacterial taxonomy. This fundamental feature underscores the strategy’s promise as a broad-spectrum antimicrobial platform for combating diverse infections.

2.3.2 | Systematic Dose-Response Relationship and Tunability

To comprehensively assess the concentration dependence of its antibacterial efficacy, we systematically investigated the dose-response relationship of the combined treatment against all tested strains across a wide concentration gradient (0.98–500 µg/mL) (Figure 5C,E). The results demonstrated that the antibacterial activity exhibited a precise and highly consistent dose dependence. As the concentration of Ag₂S QDs increased (62.5–500 µg/mL), the bacteriostatic efficiency against all strains improved systematically, with a logarithmic reduction in viable bacterial counts. When the concentration reached the maximum of 500 µg/mL, complete eradication of all tested pathogens was achieved (colony survival rate below the detection limit) (Figure 5A,B,D,F).

In summary, through systematic in vitro pharmacodynamic evaluations, this study not only confirms the significant potential of Ag₂S QDs combined with NIR as a broad-spectrum antibacterial platform but, more importantly, delineates a clear translational pathway from basic research to clinical application. The well-defined dose dependence provides a foundation for personalized

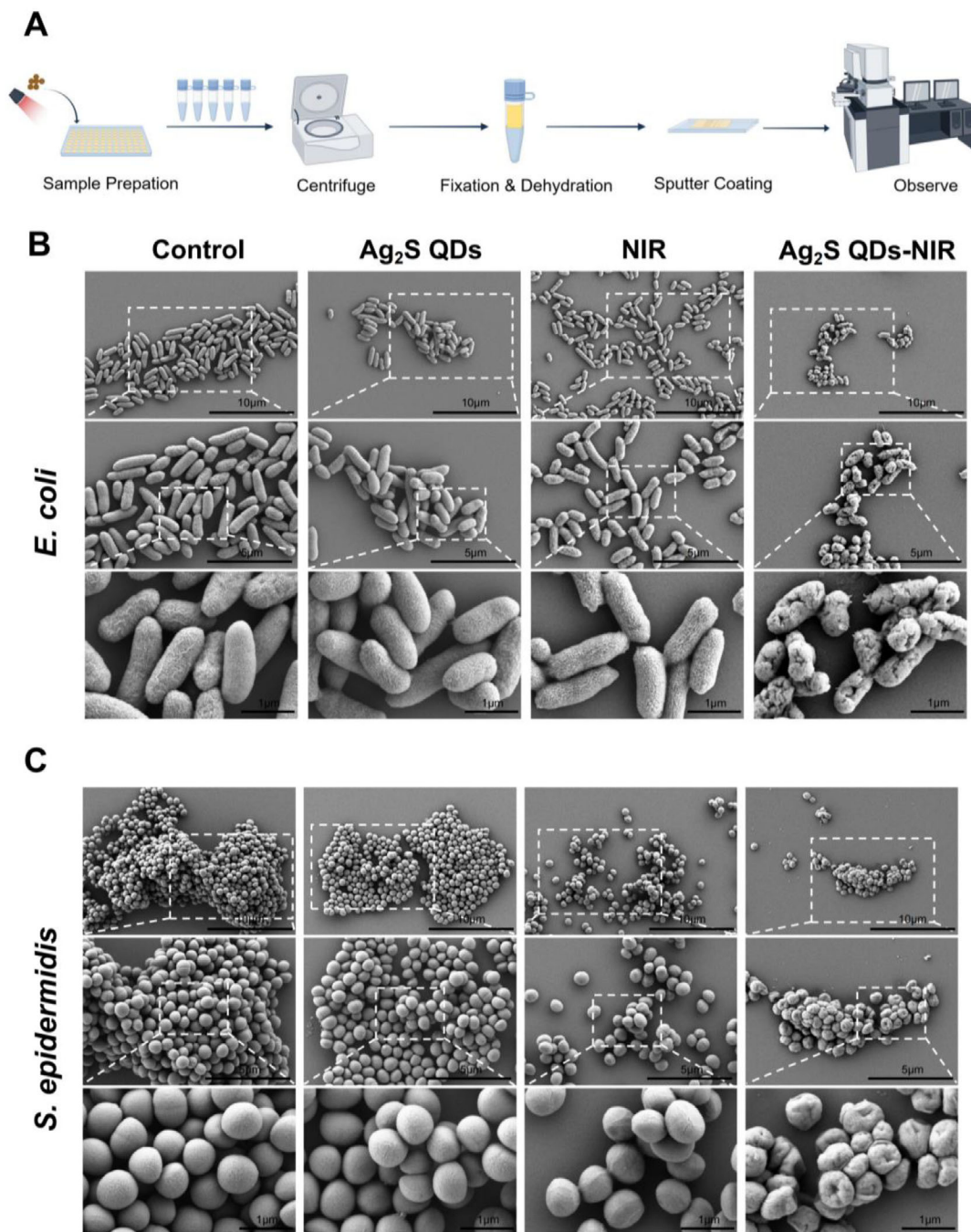


FIGURE 4 | Scanning electron microscopy reveals severe ultrastructural damage in bacteria treated with Ag₂S QDs and NIR (808 nm, 1.5 W/cm², 10 min). (A) Schematic of the sample preparation workflow for SEM. (B, C) SEM images of *E. coli* (B) and *S. epidermidis* (C). Images were acquired at an accelerating voltage of 3.0 kV. Scale bars: top, 10 μm; middle, 5 μm; bottom, 1 μm. Images are representative of at least three independent experiments.

treatment protocols. By adjusting the Ag₂S QDs concentration, this strategy can be tailored to combat specific bacterial challenges, paving the way for safe and highly effective anti-infective therapies.

2.4 | Biocompatibility and Clinical Translation Potential

Having established the superior antibacterial efficacy of Ag₂S QDs in vitro, we next evaluated their biocompatibility, a criti-

cal step toward clinical translation. The hemocompatibility of Ag₂S QDs was systematically evaluated by a standard hemolysis assay to assess their impact on erythrocyte membrane integrity (Figure 6A).

As shown in Figure 6B, after co-incubating murine erythrocytes with a series of Ag₂S QDs concentrations (31.25 to 500 μg/mL) in the absence of NIR irradiation, the supernatants from the 125 to 31.25 μg/mL groups showed no significant difference compared to the negative control (PBS). Critically, at the therapeutically relevant MIC (250 μg/mL), the hemolysis rate was only 4.07% —

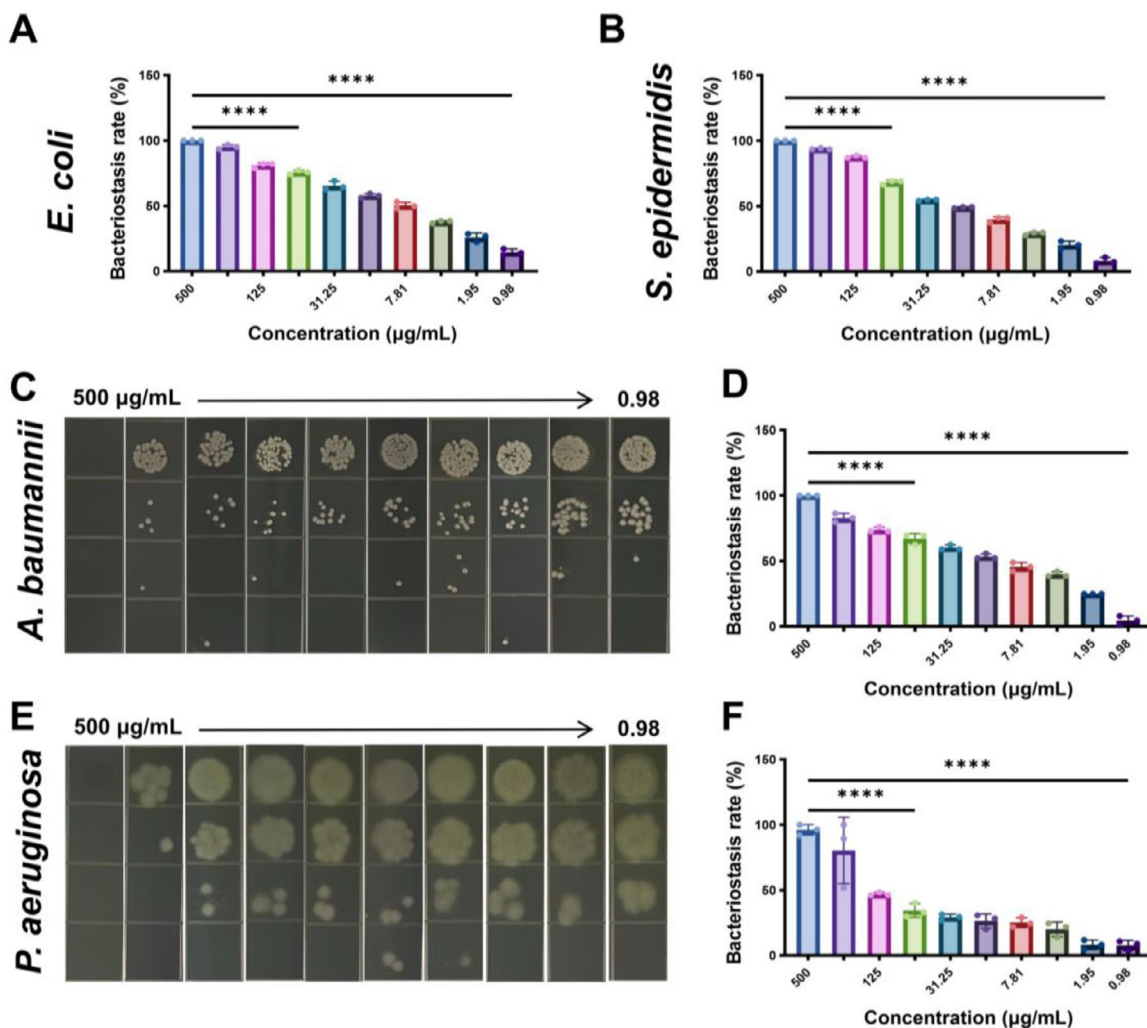


FIGURE 5 | Broad-spectrum antibacterial efficacy of Ag₂S QDs activated by NIR (808 nm, 1.5 W/cm², 10 min) against clinically relevant pathogens. (A,B,D,F) Quantitative analysis of the bactericidal efficacy against *E. coli* (A), *S. epidermidis* (B), *A. baumannii* (D), and *P. aeruginosa* (F). (C,E) CFU assays showing the survival of *A. baumannii* (C) and *P. aeruginosa* (E) after treatment with a concentration gradient of Ag₂S QDs-NIR. Data are presented as mean ± SD. **p* < 0.05, ***p* < 0.01, ****p* < 0.001, *****p* < 0.0001 vs. the 0.98 µg/mL group and 62.5 µg/mL group (A,B,D,F). Images are representative of at least three independent experiments.

well below the 5% safety threshold (Figure 6C). [47] In contrast, a high rate of 72.46% was observed only at the much higher MBC (500 µg/mL). These results clearly demonstrate that Ag₂S QDs in their inactivated state induce no significant disruption to erythrocyte membranes across a broad concentration range up to the MIC (250 µg/mL), indicating excellent hemocompatibility within this therapeutically relevant window.

We next evaluated the hemolytic activity under NIR irradiation. As shown in Figure 6D,E, a drastic and concentration-dependent enhancement in hemolysis was observed upon photoactivation. At the safe MIC concentration (250 µg/mL), NIR irradiation triggered a potent hemolytic response, with the hemolysis rate surging from 4.07% to 76.52%. Even more strikingly, at the MBC (500 µg/mL), the hemolysis rate was amplified from an already high level of 72.46% to a level indicating nearly complete erythrocyte destruction (95.16%) under NIR. This profound contrast definitively uncouples the membrane-disruption activity from passive material toxicity, establishing it as a direct and dominant consequence of photonic activation. Significantly, at 500 µg/mL,

NIR irradiation drove hemolysis beyond the level attributable to intrinsic toxicity alone. This provides compelling evidence that a distinct photophysicochemical mechanism is operative and is dramatically potentiated by NIR.

The comparison between these two states—bio-inert in the dark and potentially membranolytic upon photoactivation—provides crucial insights into the platform's safety and mechanism. First, the significant hemolysis caused by Ag₂S QDs alone at the high MBC concentration (500 µg/mL) underscores that systemic administration of such high doses could pose toxicity risks, highlighting a limitation of relying on intrinsic material properties. However, the critical finding is that at the effective antibacterial concentration (MIC, 250 µg/mL), the powerful membrane-disrupting effect is strictly dependent on and precisely controlled by NIR irradiation. Second, the universal membrane damage inflicted upon activation—affecting both prokaryotic bacteria and eukaryotic erythrocytes—underscores the mechanism's reliance on fundamental physico-chemical disruption rather than specific molecular recognition. This indicates a

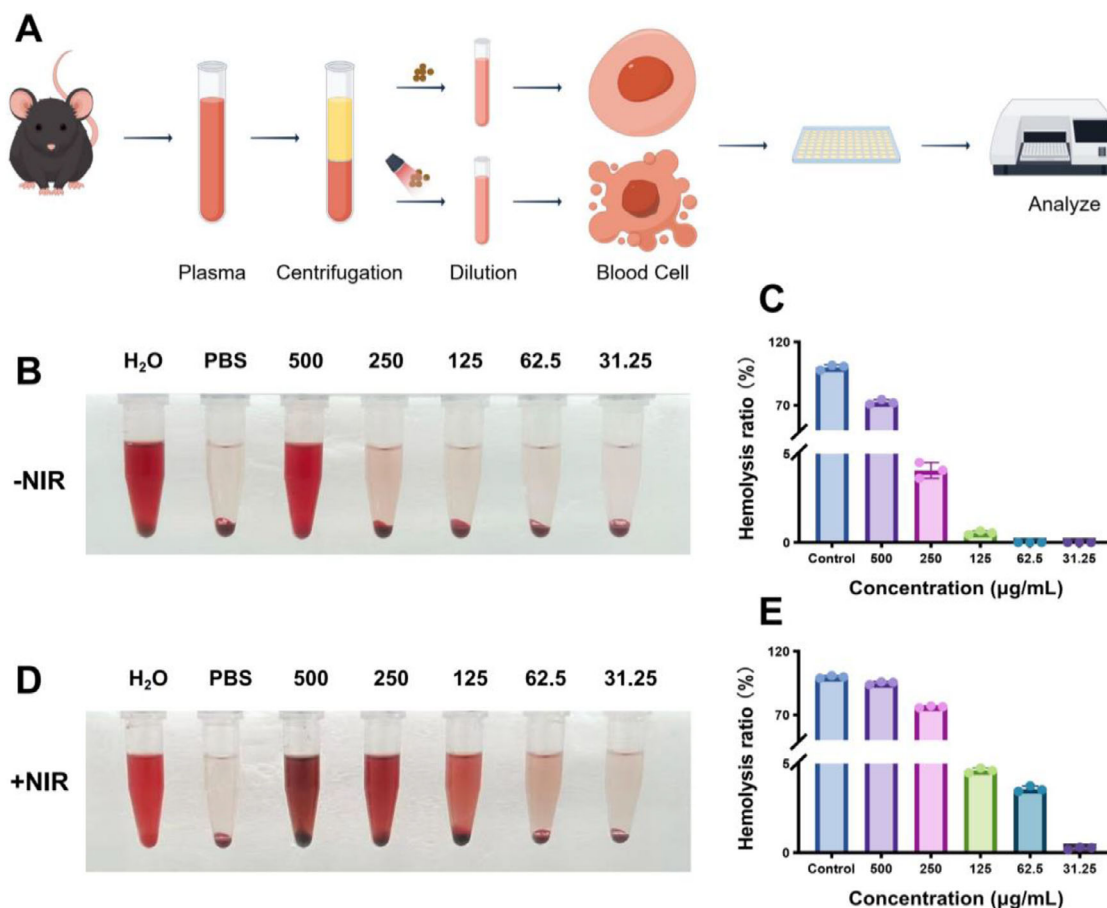


FIGURE 6 | In vitro hemocompatibility assessment of Ag₂S QDs with and without NIR activation (808 nm, 1.5 W/cm², 10 min). (A) Schematic of the hemolysis assay. (B,D) Digital photographs of red blood cells (RBCs) after incubation with Ag₂S QDs (B) or Ag₂S QDs-NIR (808 nm, 1.5 W/cm², 10 min) (D). (C,E) Quantification of the hemolysis percentage induced by Ag₂S QDs (C) and Ag₂S QDs-NIR (E). Data are presented as mean ± SD. Images are representative of at least three independent experiments.

broad-spectrum potential but also reveals that the platform's selectivity is achieved not at the molecular level, but through its unique spatiotemporal controllability. The core targets—cellular envelopes—are universally susceptible. Therefore, the therapeutic window and biosafety critically depend on confining NIR irradiation precisely to the infection site. This spatially confined activation minimizes off-target damage to host tissues while delivering potent antimicrobial action, positioning Ag₂S QDs as a promising on-demand platform for treating localized infections such as deep-seated or surgical site infections.

2.5 | Photothermal and Photodynamic Mechanisms of Ag₂S QDs

2.5.1 | Photothermal Performance Characterization

To elucidate the dual-action mechanism of Ag₂S QDs under NIR irradiation, we first evaluated their photothermal properties. Aqueous solutions of Ag₂S QDs across a concentration gradient (31.25 to 500 μg/mL) were irradiated with an 808 nm laser at a power density of 1.5 W/cm², and the temperature change was monitored in real-time (Figure 7A). The results demonstrate a pronounced concentration-dependent photothermal response. At the MIC (250 μg/mL), the bulk solution temperature reached

approximately 78°C from ambient within the 10-min irradiation period. This final temperature far exceeds the threshold required for protein denaturation and biofilm matrix destabilization (typically 50–55°C), [48] thereby providing direct quantitative evidence for the potent hyperthermia-mediated “physical-barrier disruption” central to our proposed mechanism. The rapid temperature rise kinetics correlate well with the observed fast bactericidal action (Figure 2), underscoring the critical role of instantaneous photothermal effects in biofilm disruption.

2.5.2 | Generation and Mechanism of ROS

The production of ROS is considered a critical step in the photocatalytic sterilization process. To elucidate the types of ROS generated by Ag₂S QDs under NIR irradiation and their respective contributions to the antibacterial mechanism, we conducted systematic investigations using quenching experiments and electron spin resonance (ESR) spectroscopy.

Initially, selective inhibition of active species in the system was performed using different free radical quenchers. TEMPOL, sodium oxalate (Na₂C₂O₄), and isopropanol (IPA) were employed as quenchers for superoxide anion radicals (·O₂⁻), photogenerated holes (h⁺), and hydroxyl radicals (·OH), respectively. The

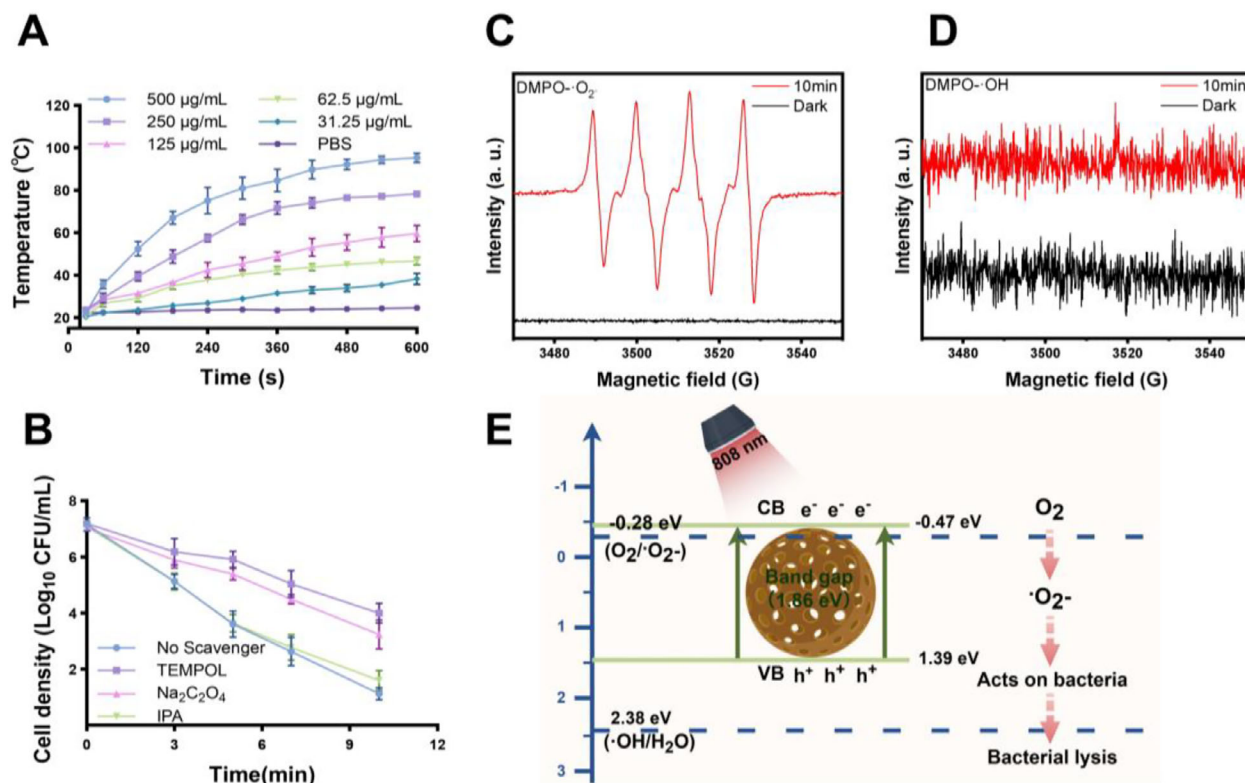


FIGURE 7 | Photothermal properties, photocatalytic antibacterial performance, and reaction mechanism of Ag₂S QDs. (A) Photothermal heating curves of Ag₂S QDs at different concentrations under 808 nm NIR irradiation. (B) Photocatalytic antibacterial activity against *E. coli* with the addition of different scavengers (1 mM TEMPOL, 7.5 mM isopropanol, and 0.5 mM sodium oxalate). (C) ESR spectra of the DMPO/·O₂⁻ adduct in the Ag₂S QDs under 808 nm irradiation. (D) ESR spectra of the DMPO/·OH adduct obtained over Ag₂S QDs under NIR irradiation. (E) Energy level diagram and proposed photocatalytic mechanism of Ag₂S QDs. Data are presented as mean ± SD. Images are representative of at least three independent experiments.

concentrations of the quenchers were optimized to ensure no significant cytotoxic effects on *E. coli* within the 10-min experimental timeframe (Figure S9). As shown in Figure 7B, compared to the control group without quenchers, the bactericidal efficacy of the Ag₂S QDs-NIR system against *E. coli* was significantly reduced upon addition of TEMPOL (quenching ·O₂⁻) or Na₂C₂O₄ (quenching h⁺). In contrast, the addition of the ·OH quencher IPA did not notably alter the antibacterial efficiency. These results indicate that ·O₂⁻ and h⁺ are the predominant active species in this system, whereas the contribution of ·OH is minimal.

To directly confirm the generation of ·O₂⁻, we performed ESR measurements. As depicted in Figure 7C, no significant radical signals were detected under dark conditions. However, under 808 nm NIR irradiation, the Ag₂S QDs system exhibited a characteristic quartet signal (with an intensity ratio of 1:1:1:1), which is indicative of the DMPO/·O₂⁻ adduct. The signal intensity increased with prolonged irradiation time. Under the same conditions, no signal corresponding to the DMPO/·OH adduct (1:2:2:1 pattern) was detected (Figure 7D). The ESR results further confirm that Ag₂S QDs primarily generate ·O₂⁻ rather than ·OH upon NIR excitation.

Therefore, through quenching experiments and ESR analysis, this study identifies ·O₂⁻ and h⁺ as the main active oxygen species in the Ag₂S QDs-NIR system. These two active species act synergistically to induce oxidative damage to bacterial membranes, working in concert with the photothermal effect to achieve

efficient antibacterial activity. This mechanistic insight provides chemical-level support for the proposed synergistic bactericidal model of “physical barrier disruption-ROS attack” presented in this work.

2.5.3 | Band Structure and Redox Processes Underlying Reactive Species Activation

Our previous work has established that the Ag₂S QDs used in this study possess a narrow bandgap of approximately 1.86 eV, with the conduction band (CB) edge at about -0.47 eV and the valence band (VB) edge at about 1.39 eV vs. the normal hydrogen electrode (NHE). [27] This band structure enables efficient electron-hole pair (e⁻-h⁺) generation upon irradiation with 808 nm NIR.

The subsequent charge separation and interfacial redox reactions lead to antibacterial activity, as illustrated in Figure 7E. The relevant energy levels and corresponding redox pathways are outlined below:

2.5.4 | Electron Transfer Pathway

The photogenerated electrons in the conduction band of Ag₂S QDs (CB = -0.47 eV vs. NHE) possess a sufficiently negative reduction potential to reduce molecular oxygen (O₂) adsorbed

on the QD surface to $\cdot\text{O}_2^-$. The standard reduction potential for O_2/O_2^- is -0.28 eV vs. NHE, making this reaction thermodynamically favorable.

The formation of $\cdot\text{O}_2^-$ was directly confirmed by ESR spectroscopy. These radicals can cause extensive oxidative damage to bacterial membranes and intracellular components, constituting a primary photodynamic pathway.

2.5.5 | Oxidative Capability of Holes (Oxidation Process)

While the photogenerated holes in the valence band (h^+ , $\text{VB} = 1.39$ eV vs. NHE) are strongly oxidizing, their potential is considerably lower than that required for the generation of $\cdot\text{OH}$ from water ($\cdot\text{OH}/\text{H}_2\text{O}$, 2.38 eV vs. NHE). As a result, the direct oxidation of water to $\cdot\text{OH}$ is thermodynamically unfavorable in this system. This is consistent with ESR measurements, which did not detect significant $\cdot\text{OH}$ signals (Figure 7D). Importantly, the significant attenuation of bactericidal efficacy by the h^+ scavenger $\text{Na}_2\text{C}_2\text{O}_4$ (Figure 7B) confirms that photogenerated holes are indispensable active species. Instead, the holes likely contribute to antibacterial activity through direct oxidation of bacterial components or via energy dissipation that enhances the photothermal effect.

In summary, the band alignment of Ag_2S QDs governs their redox behavior under NIR excitation. The relatively negative CB potential facilitates the one-electron reduction of O_2 to $\cdot\text{O}_2^-$, which serves as the main ROS responsible for photodynamic action. In contrast, the VB potential precludes $\cdot\text{OH}$ formation, directing hole activity toward alternative oxidative or thermal pathways. This energy-level analysis clarifies the electron-transfer basis of ROS generation and aligns well with the experimental observations, providing a coherent semiconductor-based rationale for the combined photothermal and photodynamic antimicrobial effects.

3 | Conclusions

This study presents an Ag_2S QDs-NIR-activated platform that exerts potent and synergistic antibacterial effects through photothermal and photodynamic mechanisms. Upon NIR irradiation, the localized hyperthermia generated efficiently degrades proteins and polysaccharides within the EPS of biofilms, thereby disrupting the structural integrity of the biofilm matrix. Simultaneously, ROS produced under irradiation directly compromises bacterial membrane integrity, leading to leakage of intracellular contents and cell death. The platform demonstrates broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria. Importantly, these mechanisms target conserved physical structures of bacteria and their protective matrices, independent of bacterial metabolic activity, thereby circumventing conventional antibiotic resistance pathways. A key advantage of this platform lies in its spatiotemporal precision— Ag_2S QDs are activated only within the specific area and duration of NIR exposure, which provides a crucial safety foundation for clinical translation. Given its rapid action against planktonic bacteria and biofilm-disruption capability, the platform holds strong translational promise. Potential applications include intraoperative disinfection protocols for orthopedic implant surfaces

and wound irradiation to prevent postoperative infections, as well as the development of antimicrobial dressings for managing chronic wounds such as diabetic foot ulcers and osteomyelitis. It could also serve as an adjunctive therapy for peri-implantitis. Furthermore, the combined PTT/PDT action, along with its spatiotemporal controllability, suggests potential utility in localized tumor ablation therapies.

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Rui Yao and Peiqing Sun jointly conceived the study and designed the methodology. Rui Yao performed the majority of the experimental investigation and formal analysis. Yaxin Chen contributed to the review and editing of the manuscript. Li Wang and Ying Liu were responsible for data curation and validation. Zhijie Lei secured the necessary resources, and Jianglin Yu developed and implemented the analytical software. Wusimanjiang Hailipitimu provided technical assistance during the investigation. The original draft of the manuscript was written by Rui Yao with critical revision and intellectual input from Peiqing Sun. Wei Wei, Jing Zhao, and Xusheng Qiu provided supervision and assisted in funding acquisition. All authors reviewed and approved the final manuscript. Some cartoon components were from www.figdraw.com for model drawing. Rui Yao and Peiqing Sun contributed equally to this work.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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