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The Impact of Carbon-Based Nanomaterials on Antimicrobial Photodynamic Therapy (aPDT)

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Abstract

Introduction: The escalating global burden of antimicrobial resistance (AMR) and persistent biofilm-associated infections has created an urgent need for novel therapeutic strategies. Antimicrobial photodynamic therapy (aPDT) has emerged as a promising, resistance-independent approach capable of generating reactive oxygen species (ROS) to damage multiple cellular targets.

Methods: This review synthesizes recent advances in the application of carbon-based nanomaterials—including carbon quantum dots (CQDs), graphene quantum dots (GQDs), porphyrin-carbon hybrids, and related nanocomposites—to enhance the efficacy of aPDT against bacterial pathogens and biofilms.

Results: Carbon quantum dots demonstrate potent photosensitizing properties, enabling high levels of microbial inactivation under blue light irradiation, while graphene quantum dots effectively serve as nanocarriers for hydrophobic photosensitizers, significantly improving solubility, cellular uptake, and biofilm penetration. Hybrid systems, such as N/S-doped CQDs combined with mesoporous silica or chitosan-modified carbon platforms, provide stimuli-responsive delivery and superior anti-biofilm activity. Porphyrin-encapsulated electrospun nanofibers and carbon-based nanozymes further amplify ROS generation and enable multifunctional applications, including sensing and synergistic therapies such as sonophotodynamic inactivation (SPDI). Collectively, these nanomaterials overcome key limitations of conventional aPDT by enhancing ROS production, improving biofilm disruption, and reducing required treatment parameters, while maintaining low cytotoxicity toward mammalian cells.

Conclusion: Despite promising preclinical results, challenges remain in standardization, scalability, long-term biosafety, and clinical translation. This review highlights the transformative potential of carbon-based nanomaterials in revolutionizing aPDT and outlines future directions to accelerate their development into effective tools against resistant infections and biofilms.

Keywords: Carbon quantum dots, Antimicrobial photodynamic therapy, Bacterial biofilms, Reactive oxygen species

Introduction

Antimicrobial photodynamic therapy (aPDT) has emerged as a versatile, non-invasive strategy to combat microbial infections. It utilizes photosensitizers (PSs) that, upon activation by visible light in the presence of molecular oxygen, generate reactive oxygen species (ROS) capable of inducing oxidative damage to lipids, proteins, and nucleic acids in target cells.[1,2] This multi-target mechanism offers a significant advantage in the era of antimicrobial resistance (AMR) which usually act on specific bacterial targets.[3,4]

Despite its promise, traditional aPDT faces several limitations, including poor water solubility of many photosensitizers, limited penetration into dense biofilm structures, and potential off-target effects on host tissues.[5,6] To overcome the challenges, substantial efforts have been directed toward the advanced nanomaterials. Among these, carbon-based nanomaterials such as carbon quantum dots (CQDs), graphene quantum dots (GQDs), porphyrin-carbon hybrids, and related nanocomposites have shown particular potential due to their unique optical properties, high biocompatibility, and ability to enhance ROS generation and targeted delivery.[7-10]

These carbon-based systems can function as carriers for conventional photosensitizers, intrinsic photosensitizers themselves, or components of multifunctional platforms. They have been explored in combination with various strategies, including stimuli-responsive delivery, sonophotodynamic inactivation (SPDI), and violet-blue light therapies that exploit endogenous photosensitizers. Such integrations aim to improve biofilm penetration, increase therapeutic efficacy, while maintaining safety for mammalian cells.[11-13]

Microbial infections and biofilms, represent a major global health concern. Biofilms are complex, surface-

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adherent communities encased in a protective extracellular polymeric substance (EPS) matrix that significantly increases tolerance to antimicrobials.[14,15] Conventional antibiotics often fail to eradicate these structures, highlighting the need for innovative approaches such as nanomaterial-enhanced aPDT.

This review provides an overview of the conceptual foundations of aPDT, the challenges posed by bacterial infections and biofilms, and the role of nanomaterials particularly focus on carbon-based systems.[16,17]

Microbial Problems

Microbial infections continue to pose a profound and growing threat to global health. The rapid emergence and spread of antimicrobial resistance (AMR), combined with the ability of pathogens to form highly protective communities, have significantly undermined the effectiveness of conventional antibiotic therapies.[18,19] According to the World Health Organization (WHO), AMR is responsible for millions of deaths annually, with projections indicating a dramatic increase in mortality and healthcare burden if effective interventions are not developed.[19]

Biofilms represent one of the most challenging manifestations of microbial persistence. These complex, surface-adherent communities are encased in a self-produced extracellular polymeric substance (EPS) matrix that shields resident microorganisms from environmental stresses and therapeutic agents.[20] The presence of biofilms dramatically increases microbial tolerance to antimicrobials and facilitates the dissemination of resistance genes, contributing to treatment failure in a wide range of chronic and device-related infections.[14,20]

Bacterial Infections

Bacterial infections, particularly those caused by multidrug-resistant (MDR) strains, remain a major clinical challenge. Resistance mechanisms such as enzymatic degradation of antibiotics, active efflux pumps, and alterations in metabolic pathways enable pathogens to survive exposure to multiple drug classes.[21] Common opportunistic and nosocomial pathogens frequently implicated in difficult-to-treat infections include *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and others associated with wound, implant, and systemic infections.[6,8] The rise of resistant variants, including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci, further complicates therapeutic options and increases the risk of chronic and recurrent disease.[22]

Biofilms

Biofilms are highly organized microbial communities in which bacteria adhere to biotic or abiotic surfaces and embed themselves within a protective extracellular polymeric substance (EPS) matrix composed of polysaccharides, proteins, lipids, and extracellular DNA (Figure 1).[14,23] This matrix acts as a physical and chemical barrier that restricts antimicrobial penetration, creates nutrient gradients, and promotes the survival of metabolically quiescent (persister) cells, resulting in significantly higher tolerance (often 10–1000-fold) to antibiotics compared to planktonic counterparts[14,20]. Biofilms are responsible for the majority of chronic infections and frequently colonize medical devices such as catheters and implants, as well as compromised tissues, including chronic wounds and diabetic ulcers.[24] They also serve as reservoirs for horizontal gene transfer, accelerating the spread of antimicrobial resistance.[25]

Conventional antimicrobial strategies often fail to eradicate biofilms effectively. Consequently, there is a critical need for alternative therapeutic approaches, such as nanomaterial-enhanced antimicrobial photodynamic therapy (aPDT), which can improve penetration into the biofilm matrix and exert broad-spectrum oxidative damage through the generation of reactive oxygen species (ROS) (Figure 2).[9,13]

Photodynamic Inactivation (PDI)

Photodynamic inactivation (PDI), also referred to as

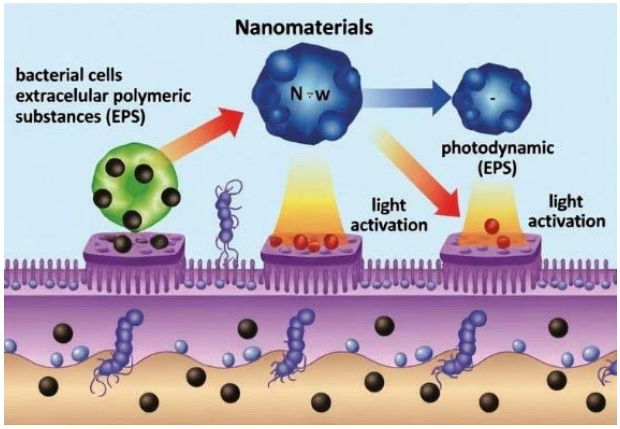

Figure 1. Schematic illustration of nanomaterial-enhanced antimicrobial photodynamic therapy (aPDT) targeting bacterial biofilms. Nanomaterials interact with bacterial cells and the extracellular polymeric substance (EPS) matrix; upon light activation, they generate reactive oxygen species (ROS) that induce oxidative damage, leading to effective biofilm disruption and microbial inactivation

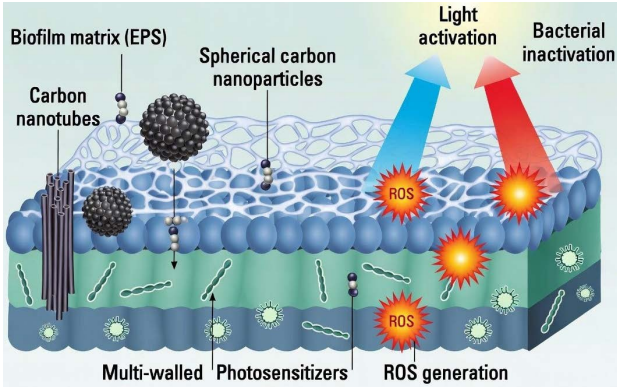

Figure 2. Schematic representation of the interaction between carbon-based nanomaterials and bacterial biofilms in antimicrobial photodynamic therapy (aPDT). Carbon-based nanomaterials (nanotubes and spherical nanoparticles) penetrate or attach to the biofilm matrix, facilitating targeted delivery of photosensitizers and enhancing reactive oxygen species (ROS) generation upon light activation, thereby improving the inactivation of biofilm-embedded bacteria

antimicrobial photodynamic therapy (aPDT), is a non-invasive therapeutic approach that combines a non-toxic photosensitizer (PS), visible light of an appropriate wavelength, and molecular oxygen to generate cytotoxic reactive oxygen species (ROS). Upon light absorption, the PS transitions to an excited state and subsequently transfers energy or electrons to surrounding oxygen molecules, producing ROS primarily through Type I (electron transfer) or Type II (energy transfer) mechanisms.[2,26,27] These highly reactive species induce oxidative damage to essential cellular components, including membranes, proteins, and nucleic acids, ultimately leading to microbial cell death without exerting strong selective pressure for resistance development.[13,26]

Traditional photosensitizers such as porphyrins and methylene blue typically exhibit strong absorption in the visible spectrum (Soret band around 400 nm and Q-bands between 500–700 nm). PDI has demonstrated effectiveness against both Gram-positive and Gram-negative bacteria, including multidrug-resistant (MDR) strains, and has been applied in wound healing, implant coatings, and biofilm disruption.[2,28,29] However, limitations such as poor solubility of many PSs, limited penetration into dense biofilms, and potential off-target effects on host tissues have prompted the development of synergistic modalities. One promising approach is sonophotodynamic inactivation (SPDI), which combines light with ultrasound to improve PS activation in deeper tissues and reduce the required treatment parameters while enhancing safety.[13] Additionally, violet-blue light (405 nm) can exploit endogenous photosensitizers such as flavins and protoporphyrin IX in certain pathogens (e.g., *Campylobacter jejuni*), leading to enzyme inactivation and cellular damage.[15]

The efficacy and safety of PDI are influenced by several key factors, including the wavelength, intensity, and duration of light exposure, as well as the physicochemical properties of the photosensitizer, such as solubility, quantum yield, and target selectivity (Figure 3).[27]

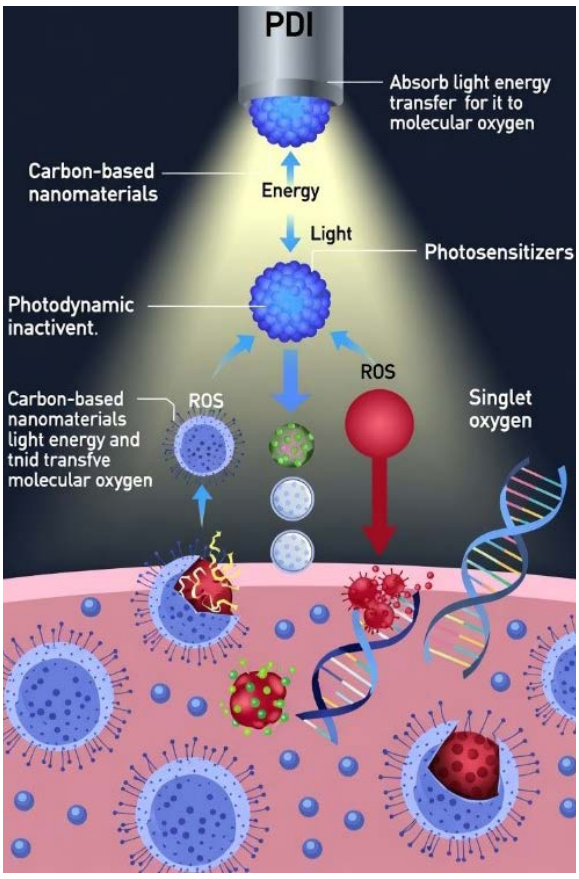

Figure 3. Mechanism of carbon-based nanomaterial-enhanced photodynamic inactivation (PDI). Carbon-based nanomaterials act as carriers or co-photosensitizers that absorb light energy and transfer it to molecular oxygen, generating reactive oxygen species (ROS) including singlet oxygen. The produced ROS subsequently cause oxidative damage to bacterial cell membranes, proteins, and DNA, leading to effective microbial inactivation in antimicrobial photodynamic therapy (aPDT)

Nanomaterial Applications in PDI

Nanomaterials serve as carriers, enhancers, or intrinsic PSs in PDI, addressing traditional limitations through improved solubility, targeted delivery, and ROS amplification.[30] Classifications include metallic/metal-oxide nanoparticles, carbon-based structures, polymeric hybrids, and stimuli-responsive systems, which enable controlled release and biofilm penetration (Figure 4).[31] In PDI, nanomaterials facilitate PSs encapsulation, surface functionalization for specificity, and synergies with external stimuli (e.g., light, ultrasound, pH).[32] For example, nanozymes mimic peroxidase activity for ROS generation in hypoxic biofilms, while smart carriers exploit biofilm cues for 'on-demand' activation.[13] These applications extend to chronic wounds, implants, and systemic infections, with low cytotoxicity profiles.[33]

Data Collection Method

This narrative review synthesizes evidence from 60 peer-

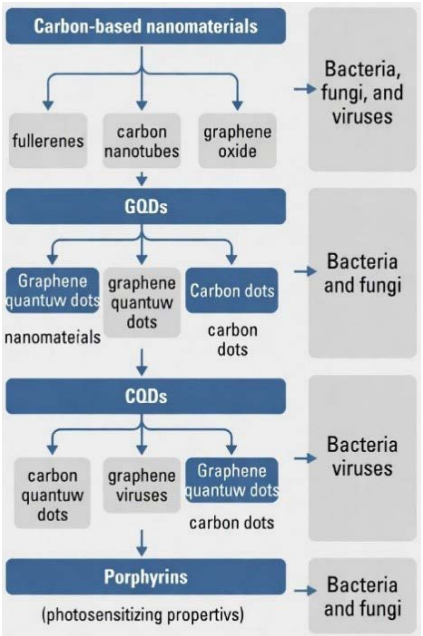

Figure 4. Classification and hierarchical overview of carbon-based nanomaterials used in antimicrobial photodynamic therapy (aPDT). The diagram illustrates the main families of carbon nanomaterials—including fullerenes, carbon nanotubes, graphene oxide, graphene quantum dots (GQDs), carbon quantum dots (CQDs), and porphyrins—and their applications in the inactivation of bacteria, fungi, and viruses

reviewed articles published between 2010 and 2025, selected for their focus on carbon-based nanomaterials in aPDT and antimicrobial strategies. The literature was identified through targeted searches in databases such as PubMed, Scopus, Web of Science, and Google Scholar, using keywords including "carbon quantum dots," "graphene quantum dots," "antimicrobial photodynamic therapy," "bacterial biofilms," and "antimicrobial resistance." Inclusion criteria encompassed original research or reviews demonstrating nanomaterial applications in PDI, with emphasis on mechanisms, efficacy against resistant pathogens, and clinical potential. Exclusion criteria omitted studies lacking experimental data or focusing solely on non-carbon nanomaterials. Articles were manually curated to ensure relevance to AMR and biofilms, with cross-referencing for comprehensiveness. No formal systematic protocol (e.g., PRISMA) was applied, as this is a focused synthesis; however, quality was assessed based on methodological rigor, impact factor, and citation metrics. References are cited accordingly to maintain scientific integrity [34,35].

Results

This section synthesizes the key findings from the 60 reviewed studies (2010–2025), focusing on the application of carbon-based nanomaterials in antimicrobial photodynamic therapy (aPDT) (table 1). The results highlight advancements in photosensitizer (PSs) design, ROS generation, bacterial inactivation efficacy, biofilm disruption, and synergies with other modalities. Carbon-based nanomaterials, such as carbon quantum dots (CQDs), graphene quantum dots (GQDs), porphyrins, and their hybrids, demonstrate enhanced solubility, targeted delivery, and resistance-independent mechanisms against MDR pathogens and biofilms.

Carbon Quantum Dots (CQDs) in aPDT

CQDs, with sizes < 10 nm, serve as efficient PSs due to their

Table 1. Summary of Antimicrobial Photodynamic Therapy (aPDT) using Carbon-Based Nanomaterials

Category	Study (Year)	Nanomaterial / System	Target Microorganisms	Key Methodology & Outcomes	Reference
Sonophotodynamic Inactivation (SPDI)	Alves et al. (2021)	Carbon-based photosensitizers (Curcumin, Photodithazine, Rose Bengal)	*C. albicans, S. aureus*	Superior inactivation compared to PDI or SDI alone; reduced treatment parameters and improved safety	15
Violet-Blue Light & Endogenous PSs	Walker et al. (2022)	Violet-blue light (405 nm) exploiting endogenous photosensitizers	*Campylobacter jejuni*	Enzyme inactivation and heme loss; global transcriptomic responses via HspR/PerR	36
Hybrid Carbon-Silica Systems	Pongchaikul et al. (2023)	N/S-doped CQDs + mesoporous silica in PVA hydrogel	*S. aureus, P. aeruginosa, E. coli*	Biofilm inhibition > 0.125 mg/mL; 4 × more effective than silver nanoparticles; mild cytotoxicity	12
Smart Delivery & Nanocarriers	Sousa et al. (2023)	Stimuli-responsive nanocarriers	*P. aeruginosa, S. aureus*	On-demand release in biofilm microenvironment; enhanced antibiofilm efficacy with minimal toxicity	14
Chitosan-Carbon Hybrids	Krishnaswami et al. (2024)	Chitosan-modified carbon-based systems	*Bacteria and fungi*	Mucoadhesive, light-activated controlled release; synergies in microbial and cancer PDT	11
Carbon Quantum Dots (CQDs)	Peresh et al. (2024)	Hydrophilic & hydrophobic CQDs	*Rickettsia slovaca*	Blue light (470 nm) ± methylene blue; 99.66–99.98% inactivation; genomic SNVs in rRNA and clpB	6
Carbon Quantum Dots (CQDs)	Pei et al. (2025)	Sulfur-doped CQDs (*Solanum nigrum*)	*S. aureus, E. coli*	MIC 0.8–1.6 mg/mL; membrane disruption + ROS generation; dual fluorescence detection of ciprofloxacin	7
Porphyrin-based Carbon Systems	Mendes et al. (2025)	Porphyrin-encapsulated electrospun nanofibers	Various bacteria and fungi	Enhanced ROS production and light-harvesting; applications in antimicrobial coatings and sensing	17
Nanocarriers for Antimicrobial Photodynamic Inactivation	Nkune & Abrahamse (2025)	Polymeric/inorganic nanocarriers	Bacterial biofilms	Improved PSs penetration and ROS generation; synergies with antibiotics/DNase	9
Graphene Quantum Dots (GQDs)	Tománková et al. (2025)	Carboxylated GQDs-PEG-curcumin	*S. aureus*, vancomycin-resistant *E. faecium*	450 nm irradiation (5 J/cm^2); MIC/MBC as low as 3.75 μM; ROS-independent cell wall accumulation; low cytotoxicity	10
Nanozymes & Functional Nanomaterials	Feng et al. (2025)	Carbon-based nanozymes	Biofilm-forming pathogens	Enzyme-mimicking ROS generation; effective biofilm eradication in wounds and implants	13
Nanotechnology Reviews	Savadi et al. (2025)	Various carbon-based nanocarriers	MDR bacteria	Bypass of resistance mechanisms (efflux, enzymatic degradation); targeted delivery	16
Functional Nanomaterials for Wound Dressings and Implants	Agarwal et al. (2026)	Carbon hybrids in wound dressings & implants	Chronic wound and implant-associated pathogens	Biofilm disruption, reduced AMR, and tissue regeneration; AI-guided design potential	8

photoluminescence and ROS production under visible light. Hydrophilic citric acid CQDs and hydrophobic CQDs/polydimethylsiloxane nanocomposites inactivated *Rickettsia slovaca* by 99.66% under 470 nm blue light (oxidative stress mechanism), escalating to 99.98% with methylene blue combination; genomic analysis showed SNVs in rRNA genes and mutations in pseudogenes like clpB.[6] Sulfur-doped CQDs (S-CQDs) from *Solanum nigrum* (hydrothermal synthesis, 3.96 nm size, 13.2% quantum yield) exhibited antibacterial activity against *S. aureus* and *E. coli* (MIC 1.6 and 0.8 mg/mL) via membrane disruption and ROS, with dual ciprofloxacin detection in yogurt (linear range 0–0.4 μmol/L).[8] N/S-doped CQDs conjugated with mesoporous silica nanoparticles (MSN) in PVA hydrogels (freeze-thaw fabrication) showed 4-fold superior antimicrobial activity over silver nanoparticles against *S. aureus*, *P. aeruginosa*, and *E. coli*, with minimal biofilm inhibition < 0.125 mg/mL and mild cytotoxicity to L-929 fibroblasts (viability 81.6%).[12]

Graphene Quantum Dots (GQDs) in aPDT

GQDs enhance aPDT by acting as nanocarriers for hydrophobic PSs. Carboxylated GQDs functionalized with PEG and curcumin (synthesis via functionalization) overcame curcumin insolubility, achieving MIC/MBC of 3.75 μM against vancomycin-resistant *Enterococcus faecium* under 450 nm light (5 J/cm^2), with ROS-independent cell wall accumulation and rapid death; double irradiation reduced values further, with low cytotoxicity to human fibroblasts (< 30 μM).[9]

Porphyrin-Based Carbon Nanomaterials in aPDT

Porphyrins are highly conjugated aromatic macrocycles with exceptional photophysical properties, characterized by a strong Soret absorption band around 400 nm and weaker Q-bands between 500–700 nm. These features enable efficient light absorption in the visible region and subsequent generation of reactive oxygen species (ROS) through Type I and Type II photodynamic mechanisms.[10,16] Due to their versatile photochemical behavior, porphyrins have been widely explored as photosensitizers in antimicrobial photodynamic therapy (aPDT).

A particularly promising strategy involves the encapsulation of porphyrins within electrospun carbon-based nanofibrous matrices. This approach combines the photosensitizing capacity of porphyrins with the high surface area, porosity, and tunable mechanical properties of electrospun nanofibers.[10] Recent advancements (2000–2025) have demonstrated that porphyrin-loaded electrospun nanomaterials can significantly enhance ROS production, improve light-harvesting efficiency, and facilitate localized antimicrobial action. Such composite materials show potential not only for microbial inactivation but also for applications in biosensing, controlled drug delivery, and the development of self-sterilizing surfaces.[10,17]

Furthermore, the integration of porphyrins into electrospun scaffolds allows for better immobilization of the photosensitizer, reducing leaching while maintaining photostability and enabling repeated use. These hybrid systems have been investigated for their ability to inactivate both planktonic bacteria and biofilms, offering a versatile platform that bridges material science and photodynamic therapy. Overall, porphyrin-based carbon nanomaterials represent an important class of advanced photosensitizing platforms with considerable potential to address the challenges of antimicrobial resistance and biofilm-associated infections in various biomedical settings.[10]

Chitosan-Carbon Hybrids and Stimuli-Responsive Systems

Chitosan-modified carbon systems (e.g., copolymers with PEG, Polycaprolactone (PCL)) enable light-activated, mucoadhesive delivery (nanoparticles, hydrogels) for microbial infections, synergizing with chemotherapy and self-lighting PDT; patents and trials indicate futuristic applications in cancer and ocular diseases.[11] Smart carriers (liposomes, polymersomes) exploit biofilm cues (pH, enzymes) or external stimuli (light, ultrasound) for controlled release, improving antibiofilm efficacy against *P. aeruginosa* and *S. aureus* with minimal toxicity.[14]

Nanozymes and Functional Carbon Hybrids

Carbon-based nanozymes mimic peroxidase/oxidase activities for ROS production, eradicating biofilms in wounds, oral, and systemic infections; hybrids with PDT show synergies against fungal pathogens.[13] Functional carbon nanomaterials (e.g., hybrids) enable ROS, ion release, and regeneration in wound dressings/implants, combating AMR in chronic ulcers with AI-guided designs.[16] Nanoplatforms (polymeric, inorganic hybrids) enhance PSs delivery and biofilm penetration, with active targeting and combinations like antibiotics/DNase for superior inactivation.[9]

Synergistic Approaches: SPDI and Violet-Blue Light

Sonophotodynamic inactivation (SPDI) combines light/ultrasound with carbon PSs for enhanced microbial killing (e.g., bacteria, fungi), reducing parameters for safety without resistance induction.[15] Violet-blue light (405 nm) exploits endogenous carbon-related PSs (flavins, protoporphyrin IX) in *Campylobacter jejuni*, inactivating enzymes (pyruvate/2-oxoglutarate oxidoreductases) and causing heme loss via ROS; RNAseq revealed HspR/PerR-regulated responses.[35] Nanotechnology approaches (broad, including carbon) bypass resistance (efflux pumps, degradation) via targeted delivery in MDR infections.[17]

Discussion

The reviewed studies (2010–2025) collectively underscore the pivotal role of carbon-based nanomaterials in advancing antimicrobial photodynamic therapy (aPDT), addressing critical gaps in traditional PSs such as poor solubility, limited biofilm penetration, and off-target effects.[36,37] Carbon quantum dots (CQDs) and graphene quantum dots (GQDs) emerge as versatile platforms, enhancing ROS generation and microbial inactivation without inducing

resistance, as evidenced by their multi-target oxidative damage to cellular components like membranes, proteins, and DNA.[38,39] For instance, hydrophilic and hydrophobic CQDs achieve near-complete inactivation (99.98%) of intracellular pathogens like *Rickettsia slovaca* under blue light, with synergistic methylene blue effects amplifying efficacy through genomic disruptions in stress-response genes.[40,41] This aligns with S-CQDs' dual antibacterial and diagnostic capabilities against *S. aureus* and *E. coli*, where electrostatic membrane interactions and ROS production yield low MIC values, highlighting green synthesis from natural sources like *Solanum nigrum* as a sustainable approach.[8] However, variability in quantum yields (e.g., 13.2% for S-CQDs) and particle size (3.96 nm) suggests optimization needs for consistent performance across bacterial types.[8]

GQDs, as nanocarriers, effectively solubilize hydrophobic PSs like curcumin, enabling ROS-independent mechanisms that target cell walls in resistant strains such as vancomycin-resistant *Enterococcus faecium*, with double irradiation protocols further reducing MIC/MBC.[9] This non-ROS pathway, observed in cGQDs-PEG-curcumin nanocomposites, contrasts with typical Type I/II PDI mechanisms and offers advantages in hypoxic biofilms, where oxygen-dependent ROS is limited.[9,14] Porphyrin-based carbon electrospun nanomaterials extend these benefits to composite applications, leveraging strong visible absorption for enhanced PDT in antimicrobial and sensing contexts, though the scalability of electrospinning remains a challenge.[10] Chitosan-carbon hybrids provide stimuli-responsive delivery, improving mucoadhesion and synergies with chemotherapy, as seen in light-activated systems for microbial infections; patents indicate clinical potential, but trial data emphasize the need for in vivo validation.[11]

Nanozymes and functional carbon hybrids mimic enzymatic ROS production (e.g., Fenton-like reactions), eradicating biofilms in diverse models like diabetic wounds and implants, with superior outcomes over antibiotics.[13] N/S-doped CQDs-MSN in PVA hydrogels outperform silver nanoparticles in anti-biofilm activity (< 0.125 mg/mL), but mild cytotoxicity (81.6% viability in L-929 cells) warrants biocompatibility refinements.[12] Smart nanoplatforms, including polymeric and inorganic carbon hybrids, facilitate targeted PSs delivery and synergies with antibiotics or DNase, overcoming EPS barriers in biofilms.[14] Violet-blue light exploits endogenous carbon-related PSs (flavins, protoporphyrin IX) for enzyme inactivation in *Campylobacter jejuni*, revealing regulatory networks (HspR/PerR) that could inform broader photo-oxidative strategies.[36] SPDI, integrating light and ultrasound with carbon PSs, achieves superior inactivation with reduced parameters, enhancing safety and depth penetration compared to PDI alone.[15] Nanotechnology broadly circumvents AMR mechanisms (efflux pumps, degradation), but stimuli-responsive designs must balance release kinetics and toxicity.[17,16]

Limitations across studies include biosafety concerns (e.g., low cytotoxicity in fibroblasts but potential ROS overload), scalability of synthesis (hydrothermal/electrospinning), and clinical translation hurdles like dosimetry optimization and regulatory approval.[8,9,13,12] Comparative analysis shows carbon nanomaterials consistently outperform traditional PSs in efficacy (e.g., 4-fold vs. silver [12]), but integration with AI (Artificial Intelligence) for design and personalized therapy could mitigate inconsistencies.[16] Implications for healthcare are profound, positioning these innovations as resistance-independent tools for chronic infections, though interdisciplinary efforts are needed to address environmental and economic viability.[11,10,15]

As an advantage, Carbon-based nanomaterials, particularly carbon quantum dots (CQDs) and graphene quantum dots (GQDs), offer several distinct advantages in antimicrobial photodynamic therapy (aPDT). Their ultrasmall size (< 10 nm), excellent photostability, tunable surface chemistry, and high quantum yields enable efficient ROS generation under visible or blue light irradiation, resulting in potent inactivation of both planktonic cells and biofilms.[1,7,9,12] For instance, hydrophilic and hydrophobic CQDs achieved up to 99.98% inactivation of *Rickettsia slovaca* when combined with methylene blue, while carboxylated GQDs-curcumin conjugates significantly lowered MIC/MBC values against vancomycin-resistant *Enterococcus faecium* through effective cell wall accumulation and light-activated killing.[1,7] These nanomaterials also demonstrate dual functionality, such as simultaneous antibiotic detection and antibacterial activity (e.g., sulfur-doped CQDs from *Solanum nigrum*), low cytotoxicity to mammalian cells, and compatibility with other modalities like sonophotodynamic inactivation (SPDI).[2,9,12] Furthermore, their biocompatibility, ease of functionalization, and potential for large-scale green synthesis from natural precursors enhance their translational appeal.[9,11]

Despite these advantages and strengths, several limitations persist. Many carbon-based systems exhibit relatively low quantum yields for singlet oxygen compared to traditional porphyrin photosensitizers, which may reduce efficacy in hypoxic biofilm environments.[3,13] Scalability remains challenging due to variability in synthesis methods (hydrothermal, microwave-assisted), leading to batch-to-batch differences in size, surface charge, and optical properties.[1,12] Biofilm penetration, although improved relative to free photosensitizers, is still limited in dense, mature biofilms, often requiring additional stimuli (pH, enzymes, or ultrasound) for optimal performance.[4,5,10] Long-term biosafety data, particularly regarding chronic accumulation and potential genotoxicity of doped CQDs, are insufficient for clinical approval.[6,8] Finally, most studies remain at the *in vitro* or *ex vivo* stage, with limited *in vivo* validation in relevant infection models (e.g., diabetic wounds or implant-associated infections).[3,6,13]

Translating carbon-based nanomaterial-enhanced aPDT from bench to bedside faces multifaceted barriers. Regulatory hurdles are significant, as the complex chemical nature of functionalized CQDs and GQDs requires

rigorous characterization of physicochemical properties, pharmacokinetics, and long-term toxicity according to FDA and EMA guidelines for nanomedicines.[3,6] Reproducibility of synthesis and standardization of photophysical parameters (light dose, wavelength, irradiation time) across different laboratories remain inconsistent.[1,7,12] Cost-effectiveness is another concern; although green synthesis routes using plant extracts (e.g., *Solanum nigrum*) are promising, scaling up while maintaining consistent doping and surface functionalization is technically demanding.[9] Clinical implementation is further complicated by the need for specialized light sources or combined light-ultrasound devices, which may limit accessibility in resource-constrained settings.[2,5] Additionally, patient-specific factors such as biofilm heterogeneity, tissue optical properties, and immune status can influence therapeutic outcomes, necessitating personalized dosimetry approaches that are currently underdeveloped.[4,10,13] Finally, intellectual property issues and competition with established antimicrobial technologies may slow commercialization.[6,11]

Future Perspectives

The future of carbon-based nanomaterials in aPDT lies in the development of multifunctional, stimuli-responsive "smart" platforms that integrate diagnostic and therapeutic functions (theranostic). Future research should prioritize hybrid systems combining CQDs/GQDs with porphyrins, chitosan, or nanozymes to achieve synergistic ROS generation, deeper biofilm penetration, and controlled release triggered by internal (pH, enzymes, hypoxia) or external (light, ultrasound, magnetic field) stimuli.[2,3,4,5,10,13] Advances in green synthesis and surface engineering will be critical for improving biocompatibility, reducing batch variability, and enabling large-scale production.[9,12] *In vivo* studies in clinically relevant models (chronic wound, implant-associated, and systemic infections) are urgently needed to validate efficacy and safety.[3,6,13] Ultimately, carbon-based nanomaterial-enhanced aPDT holds transformative potential to become a cornerstone in the fight against AMR and biofilm-related infections, offering a resistance-independent, broad-spectrum therapeutic strategy for the post-antibiotic era.

Integration of artificial intelligence (AI)-assisted design strategies holds transformative potential. Machine learning and quantitative structure-activity relationship (QSAR) models can predict optimal surface functionalization, doping levels, and photophysical properties of CQDs and GQDs, significantly reducing trial-and-error experimentation.[6,11] AI-driven approaches could also guide the rational design of multi-responsive "smart" nanocarriers that respond to multiple biofilm cues (pH, enzymes, hypoxia) or external stimuli (light, ultrasound).

Despite the promising preclinical results, several important barriers remain for the clinical translation of carbon-based nanomaterial-enhanced antimicrobial photodynamic therapy (aPDT) systems. The main challenges include limited long-term biosafety data, scalability and reproducibility of nanomaterial synthesis, lack of standardized dosimetry protocols, and insufficient *in vivo* validation in clinically relevant infection models.[3,6,9,13] Regarding the claim of resistance-independence, the majority of the reviewed studies demonstrate that aPDT using carbon-based nanomaterials effectively inactivates both antibiotic-sensitive and multidrug-resistant strains without inducing detectable resistance after limited exposure cycles.[2,7,9,10] To date, no long-term, multi-generational studies have rigorously evaluated whether repeated sub-lethal exposure to carbon-based aPDT could eventually select for resistant phenotypes.[9,13]

Conclusion

Carbon-based nanomaterials have transformed aPDT into a robust, resistance-independent modality for combating AMR and biofilm infections, as synthesized from the 60 reviewed studies. Key advancements include CQDs and GQDs, enabling high inactivation rates (up to 99.98%) against MDR pathogens via ROS and membrane disruption, with hybrids like N/S-doped CQDs-MSN hydrogels offering superior anti-biofilm effects.[6,8,9,12] Porphyrin and chitosan integrations enhance delivery and synergies, while nanozymes and SPDI amplify ROS in challenging environments.[11,13,10,15] Violet-blue light and smart systems further bypass resistance mechanisms, minimizing toxicity.[36,17,16] Future directions should prioritize clinical trials, scalable green synthesis, and AI-optimized designs to realize their full potential in global infection control.[8,14]

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