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REVIEW

Novel Carbon Dots Nanomaterials for the Precision Diagnosis and Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome: Mechanisms and Applications

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Abstract: Acute Lung Injury (ALI) and its severe manifestation, Acute Respiratory Distress Syndrome (ARDS), represent critical clinical challenges characterized by diffuse alveolar damage, uncontrolled inflammatory storms, and oxidative stress. Despite supportive therapies such as mechanical ventilation have advanced considerably, mortality rates remain persistently high. Over the past five years, Carbon Dots (CDs)—a novel class of zero-dimensional carbon nanomaterials—have demonstrated significant potential for the precision theranostics of ALI/ARDS due to their ultra-small size (<10 nm), tunable photoluminescence, superior biocompatibility, and intrinsic enzyme-mimicking activities. This review comprehensively synthesizes frontier advancements in CDs applications for pulmonary diseases over the past five years. We systematically elucidate eco-friendly synthesis strategies, surface functionalization (eg, mannose and RGD peptide targeting), and the mechanisms by which CDs function as nanozymes (mimicking SOD, CAT, and POD) to scavenge reactive oxygen species (ROS). Particular emphasis is placed on novel therapeutic strategies, including the modulation of the gut-lung axis to remodel intestinal flora and the construction of ROS-responsive smart drug delivery systems (eg, for siRNA and glucocorticoids). Furthermore, we compare the inhalation toxicology of CDs against traditional carbon materials like carbon nanotubes and evaluate their utility in in vivo lung inflammation imaging and microenvironmental sensing (NO, pH). This review aims to provide a theoretical foundation and strategic direction for the clinical translation of CD-based nanomedicine.

Keywords: carbon dots, acute lung injury, oxidative stress, theranostics, nanozymes

Introduction

Clinical Background and Challenges of Lung Injury

ALI is a complex clinical syndrome triggered by diverse factors, including pneumonia, sepsis, severe trauma, and acute pancreatitis.[1] ALI may progress to ARDS, a condition manifested by acute, widespread pulmonary inflammation, compromised gas exchange, and hypoxemia, with mortality rates reaching 35%–40%.[2] The incidence and prognosis of ALI are influenced by variables such as age, gender, seasonality, and lifestyle, underscoring its status as a major public health challenge. The core pathological alterations involve the disruption of the alveolar-capillary barrier, the exudation of protein-rich edema fluid, hyaline membrane formation, and a robust inflammatory response dominated by neutrophil and macrophage infiltration.[3,4] Damage to alveolar type II epithelial cells (AECII) not only impairs surfactant production, but also triggers a programmed cell death pathway in which PANopsis (a mode of death integrating apoptosis, pyrosis, and necroapoptosis) has been shown to be a key mechanism driving barrier dysfunction.[5]

Currently, the clinical management of ALI/ARDS remains predominantly supportive, relying on mechanical ventilation to maintain oxygenation, yet lacking fundamental curative strategies.[6–8] Notably, in the wake of the global COVID-

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19 pandemic, a subset of survivors continues to suffer from varying degrees of pulmonary consolidation and fibrosis, severely impairing quality of life.[9]

At the molecular level, the progression of ALI/ARDS is driven by redox imbalance and the collapse of immune homeostasis. The disease is characterized by the release of pro-inflammatory mediators—such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6)—alongside reactive oxygen species (ROS) and reactive nitrogen species (RNS).[4] Excessive ROS not only induces alveolar epithelial cell apoptosis via oxidative damage, lipid peroxidation, DNA damage, and mitochondrial dysfunction but also amplifies the inflammatory cascade, triggering a cytokine storm.[10–12] The progression of ALI is driven by redox imbalance. Excess ROS generated by mitochondrial electron transport chain leakage trigger ROS-induced ROS release effect, resulting in mitochondrial DNA release into the cytoplasm, which in turn activates the cGAS-STING pathway.[13] Current pharmacological interventions, primarily glucocorticoids, antibiotics, and neuromuscular blockers, are limited by low pulmonary bioavailability, short half-lives, and severe systemic side effects (eg, immunosuppression, hyperglycemia).[14] Consequently, the development of novel agents capable of targeting pulmonary inflammation, exerting dual anti-inflammatory and antioxidant effects, and maintaining high biosafety has become a focal point in critical care research.

Given the complexity of ALI/ARDS pathology, an ideal therapeutic strategy must be multifunctional: capable of efficiently traversing the blood-air barrier and mucus layers to reach the lesion, while simultaneously curbing oxidative stress and inflammation to promote tissue repair. Traditional small-molecule drugs struggle to meet these requirements. Nanomedicine offers a breakthrough, with CDs standing out due to their unique physicochemical properties.

The Rise of CDs: A New Star in Pulmonary Nanomedicine

CDs are quasi-spherical carbon nanomaterials typically smaller than 10 nm.[15] Discovered serendipitously by Xu et al in 2004 during the purification of single-walled carbon nanotubes, CDs have pioneered a new field of fluorescent nanomaterials.[16] Unlike traditional semiconductor quantum dots (QDs), CDs are composed primarily of carbon, oxygen, and nitrogen, avoiding heavy metals like lead and cadmium, which confers superior biocompatibility and lower toxicity.[12,17] Furthermore, their robust photoluminescence, water solubility, resistance to photobleaching, and ease of surface functionalization make them highly advantageous for bioimaging and sensing.[18]

Advanced synthesis strategies—utilizing specific precursors, doping elements, and surface modifications—have endowed CDs with exceptional optical and functional properties. For instance, Sun et al designed manganese-doped CDs with high T1-weighted imaging performance, enabling dual-mode fluorescence/MRI imaging of tumors.[19] Similarly, Wang et al utilized fluorine and nickel co-doped CDs to form stable complexes with Fe^{3+}, achieving significant MRI contrast.[20]

Beyond imaging, CDs can be engineered with intrinsic antioxidant activities. Surface functional groups (-COOH, -OH, and -NH_2) provide abundant electrons, facilitating free radical scavenging.[21] Li et al synthesized red-fluorescent CDs with high superoxide dismutase (SOD)-like activity (>4000 U/mg) using glutathione and folate, effectively guiding ALI treatment via imaging.[22] Additionally, penicillin-derived CDs have been shown to retain antibacterial activity while reducing bacterial infectivity under visible light, offering new strategies against multi-drug resistant strains.[23]

In the context of ALI/ARDS, CDs exhibit a unique theranostic advantage. Many metal-doped or specifically synthesized CDs possess nanozyme activity, mimicking natural enzymes like SOD and catalase (CAT) to directly scavenge pulmonary ROS.[24] As smart drug carriers, their rich surface chemistry allows for conjugation with anti-inflammatory drugs (eg, dexamethasone), genetic agents (eg, siRNA), or targeting ligands (eg, mannose), enabling targeted pulmonary delivery.[25] Furthermore, their fluorescence facilitates the tracing of inflammatory cells and real-time sensing of microenvironmental markers like pH and NO.[26]

The ability of carriers to penetrate lung physiological barriers must be considered when developing lung diagnostic systems. Traditional nanocarriers such as liposomes and polymeric nanoparticles have been used clinically, but their comparison with CDs shows the innovative advantages of the latter[10,27,28] (Table 1).

Table 1 Comparison of Carbon Dots with Liposome and Polymer NPs

Types	Size	Lung Targeting/Penetration Mechanisms	Intrinsic Biological Activity	Stability and Leakage Risk
CDs	<10 nm	Ultra-small size effect, easy to penetrate mucus layer and intercellular space	Inherent nanoenzyme activity and antioxidant capacity	High; covalent binding or core embedding, very low risk of leakage
Liposomes	100–500 nm	Passive accumulation, mainly deposited in conductive airways	Usually none (only as a carrier)	Low; susceptible to membrane rupture due to environmental pH and enzymes
Polymeric Nanoparticles	20–200 nm	Surface charge dependent and ligand mediated targeting	Rare	Medium; depends on the degradation rate of the polymer

Synthesis Strategies and Structural Engineering

The physicochemical properties of CDs (size, charge, quantum yield) dictate their pulmonary deposition, cellular uptake, and biodistribution. Current synthesis strategies for ALI/ARDS applications focus on green synthesis, heteroatom doping, and targeted surface modification.

Green Synthesis and Biomass Precursors

To avoid toxic residues associated with strong acid oxidation, "Green Chemistry" promotes the "bottom-up" synthesis of CDs using natural biomass or pharmacologically active products via hydrothermal or microwave-assisted carbonization.[29] For example, CDs derived from bitter almond (Armeniacae Semen Amarum) carbonized at 300°C effectively reduced serum IL-6, IL-1β, and TNF-α levels in LPS-induced ALI models.[30]

Synthesizing CDs from drug molecules allows the nanomaterial to inherit and potentially enhance the precursor's therapeutic function.[31] Aspirin-based CDs, synthesized via microwave-assisted methods, retained aspirin's anti-inflammatory moieties. They demonstrated superior anti-inflammatory efficacy compared to free aspirin in reducing prostaglandin E2 (PGE2) levels, with no significant hepato-renal toxicity.[32,33] Similarly, CDs derived from traditional Chinese herbs like *Fructus Aurantii* and *Puerariae lobatae* have shown efficacy in suppressing inflammation and cytokine release in gout models.[34,35] Garlic-derived CDs, retaining organic sulfur compounds, have also been highlighted for their immunomodulatory potential in COVID-19-associated lung inflammation.[36]

Sustainable synthesis utilizes food waste and plant extracts (eg, bayberry, orange juice, cabbage) to produce biocompatible CDs with intrinsic anti-inflammatory, anti-gout, and immunomodulatory activities, which are suitable for inhalation delivery.[37–41] These methods reduce production costs and facilitate scalability for clinical translation.

Heteroatom Doping and Nanozyme Engineering

Pristine CDs often suffer from low quantum yields and limited catalytic activity. Doping with non-metals (N, S, P) or metals (Mn, Cu, Fe) modulates the bandgap and electron distribution, conferring enzyme-mimicking properties.[42]

Manganese Doping

Mn-CDs synthesized via hydrothermal methods exhibit multi-enzyme mimetic activities (SOD, CAT, POD, GPx), enabling the cascade scavenging of intracellular $O_2\bullet^-$, H_2O_2, and •OH. This capability is critical for mitigating sepsis-induced oxidative storms.[7]

Red Emission and Deep Tissue Imaging

Novel CDs with high SOD-like activity (>4000 U/mg) and emission at 683 nm allow for deep tissue imaging with minimal background interference.[24]

Functional Tuning

The synthesis temperature of folate-derived CDs significantly impacts carbonization and functional group retention, thereby influencing antibacterial activity and mucosal adhesion—a crucial factor for treating bacteria-associated ARDS.[43]

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Surface Targeting Modification for Pulmonary Delivery

Effective pulmonary delivery must overcome physiological barriers, specifically the airway mucus layer and non-specific uptake by alveolar macrophages.[44]

Mucus Penetration

The airway mucus layer traps positively charged nanoparticles via electrostatic interactions. Modifying CDs with maleamic acid creates a surface with neutral or zwitterionic characteristics, minimizing mucin interaction and enhancing penetration and transfection efficiency by orders of magnitude in mucus-producing cell models.[45,46]

Mannose Receptor Targeting

To target alveolar macrophages (specifically modulating M2 polarization), CDs are functionalized with mannose or D-mannosamine, exploiting the high expression of mannose receptors on these cells for precise uptake.[47–49]

Integrin Targeting

Conjugation with RGD (Arginine-Glycine-Aspartic acid) peptides allows CDs to target integrin αvβ3 receptors upregulated on inflamed endothelium and tumor neovasculature, enhancing tissue penetration and imaging signal-to-noise ratios.[50–52]

It is worth noting that ligand density plays a dual role. While higher density generally increases avidity, excessive surface crowding can lead to steric hindrance, preventing effective receptor binding. Optimal spacing, achieved by using PEG linkers between the CD surface and the RGD/mannose motif, preserves the ligand's spatial conformation and maximizes cellular uptake efficiency.[53,54]

Multidimensional Mechanisms in Lung Injury Treatment

CDs intervene in ALI/ARDS not merely as carriers but through complex biological mechanisms involving redox regulation, immunometabolic reprogramming, and gut-lung axis modulation as shown in Figure 1.

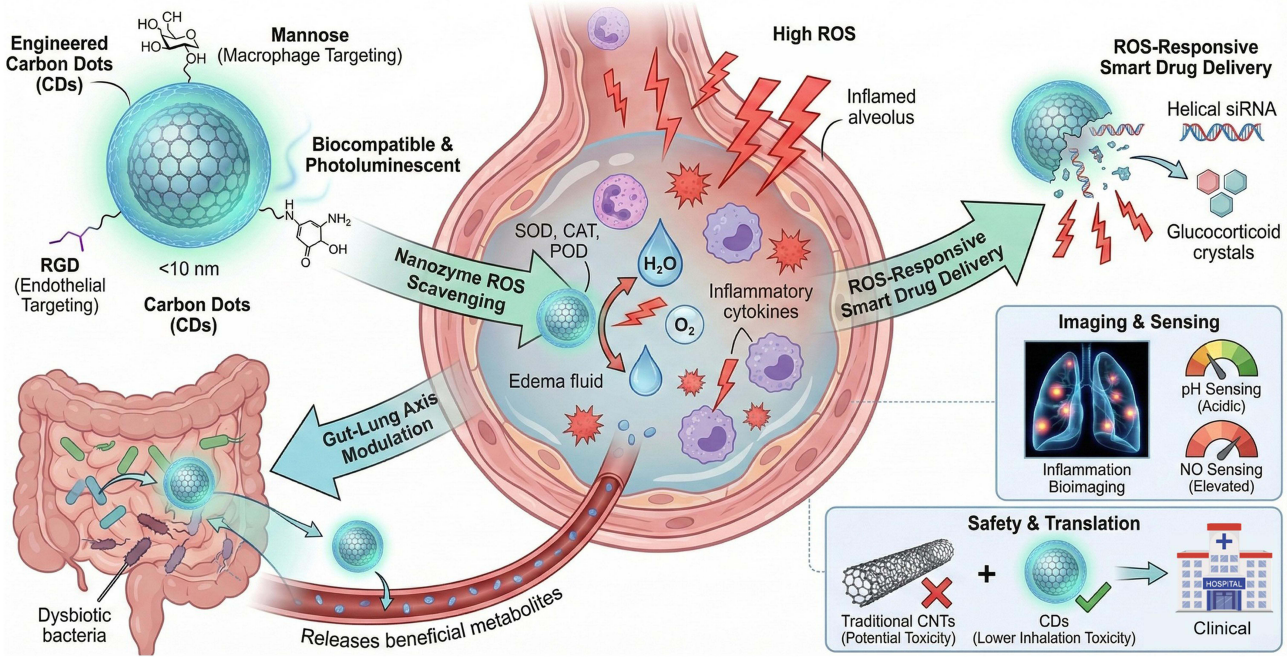

Figure 1 Mechanisms of CD-based therapy for ALI, illustrating ROS scavenging, mitochondrial protection, and gut-lung axis modulation.

Antioxidant Enzyme Activity and Mitochondrial Protection

Mitochondria are the epicenter of ROS generation and cell death signaling in ALI/ARDS.[55,56] While NADPH oxidase is a known ROS source, evidence suggests that mitochondrial electron transport chain (ETC) leakage is the primary driver of the oxidative storm in pathology.[57–59] Inflammatory stimuli compromise Complex I and III activity, causing electron leakage and superoxide ($O_2\bullet^-$) formation.[38] This triggers "ROS-induced ROS release" (RIRR), where local ROS opens the mitochondrial permeability transition pore (mPTP), causing a catastrophic release of ROS and mitochondrial DNA (mtDNA) into the cytosol.[59–63] Thus, mitochondria-targeted CDs (mt-CDs) represent a superior therapeutic design (Table 2).

Mt-CDs

Targeting mitochondria is superior to non-targeted approaches. mt-CDs, often modified with triphenylphosphonium (TPP) or delocalized positive charges, exploit the high negative membrane potential of the mitochondrial matrix to accumulate against the concentration gradient.[24,64,65] mt-CDs with SOD mimetic activity quench ROS at the source, preventing the amplification of oxidative damage.[7]

Anti-Inflammatory Depth

By maintaining mitochondrial integrity, mt-CDs prevent the leakage of oxidized mtDNA (ox-mtDNA). Cytosolic ox-mtDNA is a potent activator of the cGAS-STING pathway, which drives type I interferon and pro-inflammatory cytokine production. Therefore, mt-CDs suppress inflammation at its upstream origin.[66,67,69,70]

NLRP3 Inhibition

Mitochondrial ROS are essential for NLRP3 inflammasome activation. ROS-responsive CDs have been shown to restore macrophage mitochondrial potential, thereby inhibiting NLRP3 assembly and IL-1β maturation.[68,71–73]

Immunomodulation and Anti-Inflammatory Signaling

CDs modulate key inflammatory pathways directly or indirectly.

Table 2 Comparison Between Non-Targeted and Mitochondria-Targeted Carbon Dots

Comparative Dimensions	Non-Targeted / Cytosolic CDs	Mitochondria-Targeted CDs	Mechanistic Advantages	Ref.
Subcellular Localization	Lysosomes, Cytosol	Mitochondrial Matrix, Intermembrane Space	Penetrates the double-membrane barrier to directly target the source of ROS generation.	[64,65]
ROS Scavenging Efficiency	Low; only scavenges ROS leaked into the cytosol.	High; in situ quenching of ROS generated by Complex I/III.	Blocks the ROS-induced ROS release (RIRR) amplification effect, preventing the propagation of oxidative damage.	[62]
Fold Enrichment	1–10 fold (dependent on passive diffusion)	100–500 fold (driven by membrane potential)	Lipophilic cations accumulate exponentially along the potential gradient.	[64]
mtDNA Protection	Weak; unable to prevent intramitochondrial oxidation.	Strong; directly protects mtDNA from oxidation.	Inhibits the release of oxidized mtDNA and the subsequent activation of the cGAS-STING pathway.	[66,67]
Anti-inflammatory Mechanism	Indirect inhibition of NF-κB	Direct inhibition of NLRP3 inflammasome assembly	mtROS is an essential signal for NLRP3 activation; source-targeted inhibition is more effective.	[68]
Macrophage Polarization	Limited effect	Significantly promotes M1-to-M2 transition	M2 polarization relies on the restoration of mitochondrial oxidative phosphorylation (OXPHOS).	[67]

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NF-κB Inhibition

Drug-loaded or bioactive CDs inhibit IκBα phosphorylation, preventing NF-κB p65 nuclear translocation and down-regulating downstream cytokines (TNF-α, IL-6).[74,75]

Macrophage Reprogramming

Promoting the transition from the pro-inflammatory M1 phenotype to the reparative M2 phenotype is vital for resolution. Mn-CDs have been shown to upregulate M2 markers (Arg-1, CD206), accelerating tissue repair.[7]

Modulation of the Gut-Lung Axis

Recent breakthroughs highlight a remote treatment strategy targeting the gut-lung axis. Sepsis and ARDS are often accompanied by gut dysbiosis.[76] Peng et al demonstrated that *oral* administration of Mn-CDs reversed gut microbiota dysbiosis in septic mice, increasing beneficial genera like *Clostridium* and *Bacteroides*.[7] Mn-CDs integrate ROS scavenging and multienzyme (CAT/SOD/POD/GPx) catalytic functions, and enzyme activity is dose-dependent, effectively restoring intestinal microbial homeostasis. The mechanism extends beyond simple abundance regulation. Mn-CDs have been shown to act as electron transfer mediators under anaerobic intestinal conditions. They specifically enhance the activity of tryptophan metabolic enzymes (such as tryptophanase), thereby accelerating the conversion of dietary tryptophan into Indole-3-propionic acid (IPA). This shift elevated levels of IPA. IPA enters the circulation and activates the Aryl Hydrocarbon Receptor (AHR) on pulmonary macrophages, promoting efferocytosis (clearance of apoptotic neutrophils) and anti-inflammatory polarization. This confirms that CDs can treat lung injury via the gut without requiring pulmonary deposition.[7,77]

Theranostic Strategies

ROS-Responsive Drug Delivery

To minimize systemic toxicity, researchers utilize the high ROS levels in ALI lesions as a trigger. For instance, red-emitting CDs conjugated to methylprednisolone via ROS-cleavable thioketal linkers remain stable physiologically but release the drug and fluorophore rapidly upon encountering inflammatory ROS. This ensures targeted therapy and simultaneous imaging.[68] By utilizing Fluorescence Resonance Energy Transfer (FRET) or self-quenching mechanisms, the recovery of fluorescence intensity can be linearly correlated with drug release, allowing for semi-quantitative monitoring of dosage in situ.[78]

siRNA Delivery

CDs act as efficient non-viral vectors for siRNA. Cationic CDs (eg, PEI-modified) condense siRNA via electrostatic interaction and facilitate endosomal escape via the proton sponge effect. For Examples, Folate-PEI-CDs delivering Survivin siRNA for cancer.[79] In ALI models, CDs-mediated delivery of TNF-α siRNA significantly downregulated protein levels and reduced pulmonary edema, with lower immunogenicity than viral vectors.[80] Interestingly, CDs have even demonstrated the ability to deliver siRNA across rigid plant cell walls, suggesting robust penetration capabilities.[81]

Unlike naked siRNA which degrades within minutes in serum, CD-complexed siRNA utilizes the "proton sponge effect" of surface amines (eg, PEI) to escape endosomes/lysosomes rapidly. This protection extends the functional half-life of siRNA in lung tissue to 24–48 hours, which is sufficient to suppress the peak expression of inflammatory cytokines (TNF-α, IL-6) during the acute phase of ALI.[25,82]

Synergistic Enhancement of Traditional Drugs

Complexing hydrophobic flavonoids (eg, Rutin, Quercetin) with CDs improves their water solubility and bioavailability. The intrinsic antioxidant capacity of CDs works synergistically with the drug to enhance anti-inflammatory efficacy.[12,83] Furthermore, CD conjugation extends the retention time of drugs in tissues, preventing rapid clearance.[84]

Precision Identification

For infection-induced ALI, distinguishing pathogen strains is critical. Silicon-doped CD probes have achieved 100% accuracy in differentiating hypervirulent *Klebsiella pneumoniae* from classic strains in mouse pneumonia models, offering a rapid diagnostic tool.[85]

Bioimaging and Microenvironment Sensing

In vivo Fluorescence Imaging

While traditional blue fluorescence suffers from poor tissue penetration, red and Near-Infrared (NIR) emitting CDs enable clear visualization of drug distribution in the lungs.[24] They allow for the real-time tracking of macrophage migration and accumulation at inflammatory sites, providing a visual assessment of disease severity.[86]

Real-Time Sensing of Inflammation

Nitric Oxide (NO)

A ratiometric probe (NFL-NH2) exhibits a fluorescence blue shift (780 nm to 705 nm) upon reaction with NO, detecting concentrations as low as 0.536 nM in inflammatory models.[26]

Peroxynitrite ($ONOO^-$)

Nitrogen-doped CDs serve as fluorescent probes where fluorescence is selectively quenched by nitrite/peroxynitrite, serving as a biochemical marker for oxidative stress.[87]

pH Sensing

Inflammation creates an acidic microenvironment. pH-sensitive CDs combined with Fluorescence Lifetime Imaging Microscopy (FLIM) can map intracellular pH distribution, aiding the understanding of lysosomal function and metabolic shifts during inflammation.[88,89]

Biosafety and Toxicology

Inhalation Toxicity

Safety is paramount for clinical translation. Unlike Multi-Walled Carbon Nanotubes (MWCNTs), which can cause frustrated phagocytosis and fibrosis due to their high aspect ratio, spherical CDs generally induce only transient, mild inflammation that resolves quickly.[90–95] Cationic CDs (often used for gene delivery) are more cytotoxic, potentially damaging lysosomal integrity and mitochondria. Modifying the surface to be neutral or zwitterionic is a proven strategy to enhance pulmonary safety.[25,86]

Pharmacokinetics

Ultra-small CDs (<6 nm) are rapidly cleared via renal filtration, minimizing long-term accumulation but limiting therapeutic duration.[96] For ALI treatment, enhancing pulmonary retention via liposomal encapsulation or inhalation delivery is often necessary. Systemic administration relies on the "Enhanced Permeability and Retention" (EPR)-like effect caused by vascular leakage in inflamed lungs or active targeting mechanisms.[97,98]

After 4 months of intravenous or intratracheal administration of PEG modified carbon dots into the bloodstream of mice, there were no abnormalities in blood biochemical parameters and histopathological examination, only age-related natural degeneration was observed.[99] Current literature predominantly confirms the safety of neutral CDs over short periods (up to 28 days).[100] However, data regarding chronic exposure (>6 months) and potential fibrogenic responses in large animal models (eg, non-human primates) remain a significant gap. Future studies must rigorously evaluate whether permanent retention of non-degradable carbon cores triggers chronic immune activation or granuloma formation.

Conclusion and Outlook

Recent advancements (2020–2025) confirm that CDs are not merely passive carriers but active therapeutic agents for ALI/ARDS. Their ability to scavenge ROS, protect mitochondria, and modulate the gut-lung axis—combined with mature green synthesis and doping technologies—offers a versatile platform for precision medicine.

However future challenges remain:

Standardization

The heterogeneity of CD structures across laboratories hinders reproducible clinical translation.

Imaging Depth

While red/NIR CDs exist, their quantum yields often lag behind semiconductor QDs. Developing high-brightness NIR-II (1000–1700 nm) CDs is a priority. To address the low quantum yield in the NIR-II window, strategies such as heteroatom co-doping (eg, S, Se) and surface passivation with electron-donating polymers are being developed to suppress non-radiative recombination and enhance brightness.

Long-Term Safety

Chronic immune toxicity and the fate of CDs after long-term pulmonary retention require rigorous evaluation in large animal models.

In conclusion, with standardized synthesis and deepened mechanistic understanding, CD-based nanomedicines possessing high biosafety, smart responsiveness, and multimodal imaging capabilities are poised to become powerful weapons in the clinical management of ALI/ARDS.

Disclosure

The authors report no conflicts of interest in this work.

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