Review Paper:

Carbon Dots in Cancer Therapeutics: Advancements in Drug Delivery and Imaging Technologies

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Abstract
Carbon dots are emerging as versatile nanomaterials in cancer therapeutics due to their unique physio-chemical and optical properties. Their synthesis via top-down and bottom-up methods allows for precise control over chemical structures and functionalization, enabling the production of CDs having superior optical qualities, minimal toxicity and high biocompatibility. Recent research highlights the quantum-confined properties of CDs, making them efficient photocatalysts and enhancing their use in biological applications such as cellular bioimaging, biomarker detection and pharmacological sensing. CDs have demonstrated tremendous potential in delivering drugs and bioimaging for cancer treatment. Photoactive near-infrared CDs are notable for deep tissue penetration and superior imaging in photodynamic therapy. CDs integrated into mesoporous silica nanoparticles demonstrate potent anticancer activity through apoptosis-mediated cell death while their unique optical properties support precise tumor imaging and treatment strategies.

Green synthesis methods further align CDs with sustainable nanotechnology, producing biocompatible and effective CDs for applications such as metal ion sensing and microbial bioimaging. Surface functionalization techniques have improved CDs solubility, biocompatibility and photoluminescence, expanding their applications across imaging, treatment and diagnostics for cancer. Their synthesis from renewable sources, combined with their tunable properties and biocompatibility, underscores their potential to advance cancer treatment strategies while promoting sustainable practices towards sustainable cancer treatment.

Keywords: Carbon Dots, Cancer Therapeutics, Drug Delivery, Imaging Technologies, Nanomedicine.

Introduction
Carbon dots (CDs) are a group of nanoparticles based on carbon. Because of their special qualities and extensive range of applications, it has been a major focus of research. Easy one-pot production methods can be applied to control the tunable optical, chemical and physical characteristics of these nanoparticles. Top-down and bottom-up approaches can be used to synthesize CDs which enable the creation of certain chemical compositions with required band gaps, hetero-atom doping and chemical functionality[87]. CDs represent a new class of nano-luminescent materials due to their superior optical characteristics, minimal toxicity and exceptional biocompatibility[103]. Synthesis of CDs from sources such as carbohydrates, biomass and bio-waste highlights the move towards sustainable and environment-friendly production methods[14].

Carbon-based nanoparticles because of their special qualities and extensive range of applications, have been a major focus of research. Easy one-pot production methods can be used to control the optical, chemical and physical properties of these nanoparticles. Top-down and bottom-up strategies can be used to synthesize CDs which enable the creation of certain chemical structures with required band gaps. Hetero-atom doping and chemical functionalities in CDs research have focused on exploring their quantum-confined properties, which endow them with special optical, photochemical, semiconductor and catalytic properties[44]. Within the domain of energy conversion, CDs have been recognized as very promoting metal-free photocatalysts because of their excellent charge transfer capacity, adjustable energy-level design and robust UV–vis optical absorption[129].

The doping of CDs with heteroatoms has been a reliable strategy to improve their photoluminescence (PL), electrical and structural characteristics, opening new avenues for use in cellular bioimaging, biomarker detection and pharmaco-sensing applications[70]. Numerous studies have been conducted on the physicochemical and optical characteristics of CDs including their high quantum yield, PL and excitation-dependent emission behavior. These characteristics are affected by the quasi-spherical nanoparticles of sp^2/sp^3 hybridization found in the CDs[97]. The development of "green" CDs from renewable biomass through hydrothermal and microwave processes represents a crucial advancement towards environmentally friendly synthesis methods[17].

Applications for CDs can be found in numerous fields including energy technology, optics and biomedicine, due to their specificity, scalability and biocompatibility[30]. Recent studies have particularly focused on the green fabrication of CDs and their uses in pathogenic control, microbial bioimaging and metal ion sensing[54]. This comprehensive exploration of CDs underscores their potential as versatile nanomaterials for future technological advancements. Recent advances in carbon dots (CDs) have significantly impacted cancer therapeutics, demonstrating their promise as an adaptable cancer cure.

Owing to their special attributes, such as excellent photostability, biocompatibility and fluorescence emission, carbon dots have become a viable option for drug delivery and bioimaging in the treatment of cancer[106]. The study of nanomaterials has been ongoing for their applications in cancer diagnosis and therapy, offering new avenues for treating various disorders[15]. Specifically, photoactive near-infrared CDs (PNCDs) have gained attention for their deep therapeutic tissue reach and advanced imaging performance in photodynamic therapy (PDT)[100]. The development of heteroatom metal ion-doped CDs has opened new possibilities in cancer therapies, enhancing the physio-biochemical properties of CDs for multimodal-visualization with image-guided PDT[53].

Moreover, the incorporation of CDs for targeted cancer therapy and fluorescent imaging into mesoporous silica nanoparticles has demonstrated potent and selective anticancer activity, highlighting the CDs' role in apoptosis-mediated cell death[48]. CDs' effectiveness in targeted bioimaging and therapy has been acknowledged with their unique structure and optical properties enabling precise tumor imaging and treatment strategies[102]. The fluorescent CDs further emphasize the role of CDs in cancer diagnosis through tunable fluorescence properties, facilitating tumor imaging[60].

Additionally, CDs have been explored as photosensitizers, vaccines and immunoadjuvants in tumor immunotherapy, indicating their potential to enhance the immune function of patients[18,49].

Investigating potential biomass precursors for CD synthesis has contributed to the sustainability and eco-friendliness of these nanomaterials, with its use in targeted drug administration, bio-imaging and phototherapy for the treatment of cancer being especially notable[73]. The advances underscore the significant role of CDs in the evolving landscape of cancer therapies, offering promising strategies for diagnosis, imaging and treatment. The potential utilization of CDs in cancer therapy is promising because of their numerous uses and versatile properties.

CDs have shown effectiveness in tumor immunotherapy by serving as photosensitizers, vaccines and immunoadjuvants[78]. Additionally, CDs have been utilized in PDT for cancer treatment, with PNCDs demonstrating excellent photoactivity and tissue penetration capabilities[18].

Furthermore, CDs have been explored for their theranostic properties in pediatric brain tumors, offering a modifiable platform for drug conjugation and tumor-specific targeting to enhance treatment efficacy and reduce toxicity[109]. The integration of CDs with targeted therapeutic moieties presents a promising avenue for developing patient-tailored immunotherapy, monitoring treatment efficacy and identifying alternative strategies for non-responders[106].

Synthesis and Functionalization of Carbon Dots

Chemical Method: The synthesis of carbon dots and their functionalization have seen significant advancements, primarily through chemical methods which have been pivotal in tailoring their properties for various applications. Top-down and bottom-up techniques are the two major categories into which the synthesis approaches for CDs fall, each enabling the generation of CDs with specific chemical structures, band gaps, hetero-atom doping and chemical functionalities[87]. The electrochemical synthesis, a subset of these methods, has been highlighted for its green, practical and efficient production of more effective CDs, with the added benefit of fine-tuning properties by altering operational parameters[10].

Improving the solubility, biocompatibility and PL of CDs requires functionalization. Extensive surface functionalization, achieved through chemical methods, endows CDs with water solubility and allows for further bio-conjugation, making them superior to traditional semiconductor-based quantum dots[129]. This surface modification can be achieved post-synthesis, enabling the fine-tuning of supramolecular interactions for targeted functions, such as sensing, bio-imaging and drug administration[99]. The formulation of CDs has also been the focus of recent research from various carbon sources including biomasses and organic waste, promoting sustainable processes within the circular economy framework[45]. The advancement of quantum dots (QDs) based on carbon, covering graphene QDs and graphitic carbon nitride QDs, through chemical synthesis methods, has been instrumental in advancing their applications in energy storage, conversion and bio-applications[130].

Moreover, the utilization of CDs in bone tissue engineering (BTE) underscores the importance of their biocompatibility and unique optical properties, further enhanced by chemical functionalization to support osteogenesis, fluorescence tracing, phototherapy and antibacterial activity[133]. The versatility of CDs, facilitated by chemical synthesis and functionalization, continues to open new avenues in bioimaging, biosensing, catalysis and beyond, addressing existing challenges and exploring future directions in research and application[8,119,127].

Green Synthesis Approaches: The synthesis and functionalization of CDs using green synthesis approaches have marked a significant stride toward environmentally harmless and sustainable nanotechnology. CDs, known for their exceptional PL, biocompatibility and versatile applications, have been synthesized through various green methods, emphasizing the use of renewable resources and minimizing environmental impact[87]. The green synthesis of CDs often employs plant-based materials, agro-waste, or other organic biomaterials, offering an economical and superior alternative to traditional physicochemical methods due to their simplicity, high stability and eco-benign nature[6]. Synthesis of carbon nanoparticles from plant sources has been demonstrated in figure 1. One innovative approach includes the utilization of plant-associated bacteria for the synthesis of nitrogen–phosphorus–sulfur-codoped CDs hydrothermally, showcasing a graphene-like structure and promising bactericidal activities[42]. Similarly, the production of CDs from *Azadirachta indica* leaves using a one-pot sand bath approach has demonstrated concentration-dependent biocompatibility and potential for bioimaging, antioxidants and antimicrobial agents[10].

Another noteworthy method is the rapid toasting of bread slices which provides a simple and economical method to produce CDs suitable for bioimaging applications[88]. Biogenic carbon dots, synthesized from naturally derived materials, have shown distinct features such as good aqueous solubility and fluorescence tunability, making them suitable for a range of applications, such as drug administration, bioimaging and biosensors[32]. It has been highlighted that electrochemical synthesis is a practical, economical and eco-friendly method of producing superior CDs with precisely adjustable properties[52]. Moreover, the green synthesis of CDs via microwave-assisted method, doped with nitrogen and sulfur from simple and cheap sources like sucrose and thiourea has been developed, showcasing excellent optical and electronic properties[39]. Various methods of CD synthesis, precursors used, conditions, key features and applications have been discussed in table 1.

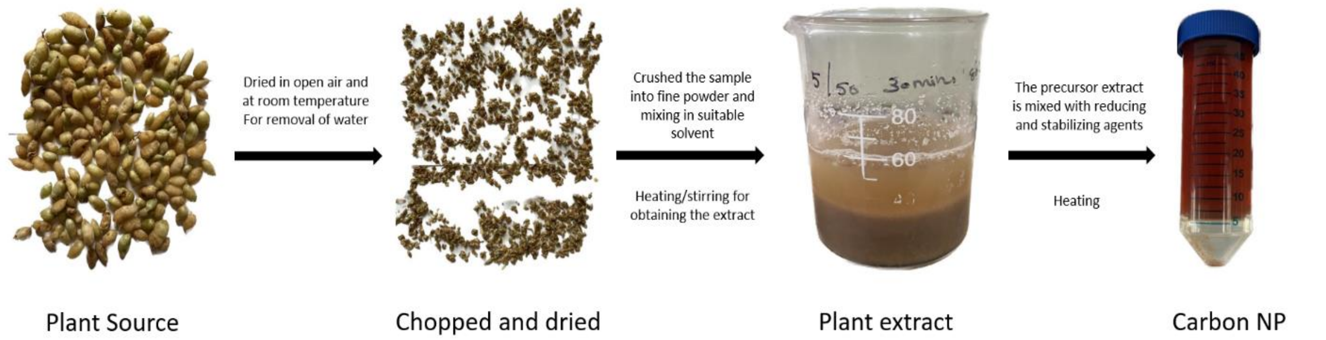

Fig. 1: Synthesis of Carbon nanoparticle from plant source

Table 1
The synthesis methods of CDs, their method, precursors, conditions, key features and applications

Method	Precursors	Conditions	Key Features	Applications
Hydrothermal	Organic compounds, biomass	High temperature, high pressure	Uniform size, high quantum yield	Bioimaging, Drug Delivery[124]
Microwave	Organic acids, carbohydrate	Microwave irradiation	Rapid synthesis, uniform particle size	Sensing, Photocatalysis[31]
Electrochemical	Graphite rods, carbon sources	Electrochemical reaction	Green synthesis, tunable properties	Bioimaging, Energy Storage[69]
Top-Down	Graphite, carbon fibers	Chemical oxidation, sonication	Controlled size, surface passivation	Optoelectronics, Photovoltaics[43]
Bottom-Up	Organic molecules, polymers	Pyrolysis, solvothermal	High photoluminescence, diverse functional groups	Bioimaging, Drug Delivery[80]
Hydrothermal, Solvothermal	Biomass, organic solvents	High temperature, solvothermal	High stability, high quantum yield	Catalysis, Bioimaging[85]
Microwave	Citric acid, urea	Microwave heating	Fast production, high quantum efficiency	Sensing, Imaging[77]
Green Synthesis	Natural resources, biomass	Mild conditions, low temperature	Environmentally friendly, biocompatible	Bioimaging, Environmental Monitoring[74]
Electrochemical	Graphite electrodes	Electrochemical exfoliation	High purity, controlled particle size	Energy Storage, Sensing[55]
Solvothermal	Organic amines, solvents	High temperature, solvothermal	Doped CDs, enhanced photoluminescence	Bioimaging, Photocatalysis[63]

Surface Functionalization Strategies: The synthesis and functionalization of CDs have seen significant advancements, leveraging surface functionalization strategies to improve their characteristics and to broaden their uses. CDs, a novel form of nanocarbon, have drawn notice for their outstanding PL, biocompatibility and eco-friendly synthesis methods, among other advantages[125]. Some of the functionalization techniques along with their impacts and applications have been listed in table 2. Surface functionalization is a critical step in enhancing the dispersion, PL quantum yield and compatibility of CDs with various matrices[10].

This is achieved through methods such as the modification of CDs with trifluoroacetic acid to enhance their affinity with fluoropolymer films[93] and the attachment of functional groups like N-ethylcarbazole via radical addition to improve structural stability[36].

Surface functionalization strategies include the use of wet and dry oxidation methods to introduce functional groups onto the carbon surface, which can significantly alter the surface properties while retaining the bulk characteristics of the material[119]. Additionally, sp^3-type surface functionalization with groups such as O, OH, or F has been shown to dramatically increase fluorescence intensity, supporting the advancement of fluorescence sensors[66]. The incorporation of heteroatoms or the modification of edge structures further tailors the optical properties of CDs, enabling precise control over their emission characteristics[51,60]. Recent innovations have also explored the use of supramolecular strategies to achieve room-temperature phosphorescence in CDs without the need for a polymeric or inorganic matrix, opening new avenues for their use in information encryption and anti-counterfeiting techniques[135].

The versatility of CDs is further highlighted by their potential for medication administration and bioimaging and even energy applications such as photovoltaics and electrochemistry, facilitated by their tunable optical properties and ease of functionalization[71]. Surface functionalization technologies have greatly increased the synthesis and functionalization of CDs, improved their optical properties and increased their potential uses in energy conversion, environmental sensing and medicinal imaging, among other domains.

Characterization Techniques of Carbon Dots

Structural Characterization: The synthesis of CDs often results in a diverse set of materials with different properties, necessitating comprehensive characterization techniques to elucidate their structure-property relationships. Atomic Force Microscopy (AFM) and Transmission Electron Microscopy (TEM) are pivotal in determining the morphological and structural characteristics of CDs, providing information about their crystallinity, size and shape[75]. Various characterization techniques are depicted in figure 2 and listed in table 3 along with their advantage and disadvantages. These techniques are complemented by Energy Dispersive X-ray Spectroscopy for elemental analysis and Fourier Transform Infrared Spectroscopy (FTIR) for identifying functional groups on the CD surface, which are essential for understanding their chemical composition and potential for surface modification[92].

Table 2
Surface functionalization strategies for Carbon Dots (CDs), detailing various techniques, the functional groups introduced, their impact on properties and their applications

Functionalization Technique	Functional Groups used	Impact on Properties	Applications
Wet Oxidation	Carboxyl, Hydroxyl	Improved water solubility, enhanced fluorescence	Bioimaging, Drug Delivery[3]
Dry Oxidation	Epoxy, Carbonyl	Increased thermal stability, modified electronic properties	Catalysis, Optoelectronic Devices[114]
Heteroatom Doping	Amino, Pyrrolic, Pyridinic	Enhanced quantum yield, improved photostability	Fluorescent Probes, Sensing[134]
Heteroatom Doping	Thiol, Sulfonic Acid	Modified band gap, enhanced charge transfer capabilities	Bioimaging[89]
Heteroatom Doping	Phosphate, Phosphonic Acid	Improved biocompatibility, enhanced cell uptake	Bioimaging, Drug Delivery[13]
Functional Group Addition	Carboxyl	Increased specificity, improved drug loading capacity	Targeted Drug Delivery, Biosensors[120]
Functional Group Addition	Hydroxyl	Increased hydrophilicity, enhanced dispersion in aqueous solutions	Medical Diagnostics, Sensing[38]
Functional Group Addition	Amino	Enhanced interaction with analytes, increased sensitivity	Chemical Sensors, Biosensors[98]
Polymer Coating	Polymer Groups	Enhanced stability, reduced cytotoxicity	Multimodal Imaging, Drug Delivery[16]

Table 3
Characterization techniques for Carbon Dots (CDs), including their structural, optical and biocompatibility properties

Characterization Technique	Purpose	Key Parameters Measured	Advantages	Limitations
Transmission Electron Microscopy	Structural Analysis	Particle size, morphology	High-resolution, detailed structure	Expensive and requires extensive sample prep[40]
UV-Vis Spectroscopy	Optical Property Analysis	Absorption spectra, optical bandgap	Simple, quick measurement	Limited to optical properties[101]
Fluorescence Spectroscopy	Optical Property Analysis	Emission spectra, quantum yield	High sensitivity, non-destructive	May require fluorescent labeling[68]
Fourier Transform Infrared Spectroscopy	Surface Chemistry Analysis	Functional groups, chemical bonding	Provides detailed chemical information	Less effective for metals and small molecules[67]
Cytotoxicity Assay	Biocompatibility Testing	Cell viability, toxicity levels	Directly measures biocompatibility	Time-consuming, requires cell cultures[4]
Raman Spectroscopy	Structural and Optical Analysis	Raman shifts, molecular vibrations	Non-destructive, high specificity	Fluorescence can interfere[29]
X-ray Diffraction	Crystallographic Analysis	Crystal structure, phase identification	Provides detailed crystal structure	Requires crystalline samples[79]
Dynamic Light Scattering	Size Distribution Analysis	Distribution of particle sizes and zeta potential	Fast and simple size measurement	Less effective for non-spherical particles[22]

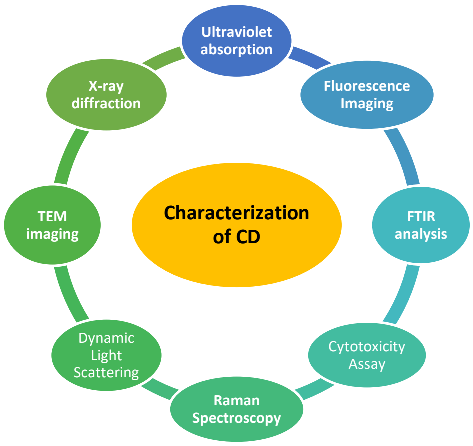

Fig. 2: Characterization of CD

PL and Electron Paramagnetic Resonance (EPR) spectroscopy are also integral for studying the characteristics of optical and electronic structures of CDs respectively. PL can reveal information about the quantum yield and emission properties which are influenced by the size, surface states and doping of CDs[24,135].

EPR provides valuable data on the unpaired electrons and defects within CDs, which can affect their catalytic and electronic properties[70]. Synchrotron near-edge X-ray absorption fine structure testing has been used recently and it provides an effective technique for investigating the relationship between the structural characteristics, photo-physics and emission performance of CDs[72]. This technique, along with transient photo-induced voltage/current measurements, has opened new avenues to comprehend the kinetics of charge transfer as well as the behavior of electron separation and transfer in photo and electro catalysts[59]. Many separation procedures have been utilized to isolate discrete fluorescent components inside CDs including solvent extraction, column chromatography, gel electrophoresis and dialysis, further aiding in the detailed structural and optical characterization[12,34].

Optical properties: The characterization of CDs and their optical properties has seen significant advancements as evidenced by recent research. TEM and potentiometric titration are among the primary techniques used to characterize the nanoparticles, providing insights into their structure and chemical properties[91]. Additionally, FTIR spectroscopy, fluorescence and ultraviolet-visible spectroscopy have been employed to research the optical

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characteristics of CDs, demonstrating their superior optical and physicochemical qualities and their possible applications in numerous domains[75,129]. The importance of CDs in photocatalytic applications has also been underlined by recent research, which credits their efficacy for their strong UV–vis optical absorption, adjustable energy-level configuration and improved charge transfer capacity[117].

The unique optical, antibacterial and anticancer properties of CDs, along with their biocompatibility, have been explored using a range of characterization methods including AFM, energy-dispersive X-ray spectroscopy (EDS) and PL[116]. Dynamic light scattering has been utilized to estimate the size distribution of CDs. To thoroughly examine their optical characteristics, fluorescence lifetimes have been studied[135]. The luminescent properties of CDs synthesized through hydrothermal treatment have been characterized, showing intense blue PL and a significant quantum yield[37]. Research into the fabrication methods of CDs, including surface modification and heteroatom doping, has provided insights into their properties relevant to photo and electro-catalysis[103].

The CDs' optical and structural characteristics synthesized from various precursors have been investigated using SEM, AFM and TEM, revealing their shape, size and the influence of functional groups on their luminescence[59]. Potential uses in bioimaging, sensing and anti-counterfeiting have been made possible by research into the luminous mechanism, synthetic approaches and property modulation of CDs' persistent luminescence. The present study provides a systematic analysis of the synthesis procedures, doping effects, surface engineering and CDs' optical characteristics, with a focus on their potential applications for enhancing the white light-emitting diode and photovoltaic systems' efficiency. The optical properties of CDs have been better understood because of these characterization technique developments, opening up new applications for CDs across a variety of industries.

Biocompatibility and Toxicity Assessment: Advances in the characterization techniques of CDs have significantly contributed in understanding their biocompatibility and toxicity which are crucial for their application in biomedicine and environmental safety. The synthesis of CDs, particularly through green methods using natural resources, has been highlighted for its capacity to produce CDs with exceptional biological application efficacy, such as tailored therapy for human tumors that is non-invasive and does not damage healthy cells[104]. Except for some cell types, *in vitro* and *in vivo* investigations have evaluated the biocompatibility and bio-interactions of nano CDs, indicating their promise as effective optical nanoprobes for cell tracking and biomedical labeling[23]. Further, the toxicity and biodistribution of boron-doped amine-functionalized CDs have been explored, showing their biocompatibility and efficacy as fluorescent imaging agents[115]. Problems including large-scale synthesis, difficult purification and low quantum yield have been overcome and the structure-property correlations of CDs have been better understood. It has been demonstrated that the type of precursors utilized in CD synthesis and the degree of functionalization determine CD cytocompatibility and cellular uptake[92]. Aquatic toxicity assessments have indicated that CDs possess low toxicity and lack bioaccumulation in zebrafish, suggesting their safety for environmental applications[90]. Graphene quantum dots (GQDs) have been synthesized from bio precursors utilizing environmentally friendly processes. The effects of various processing factors on the characteristics of GQDs have been investigated[28].

Optical properties, comprising PL and near-infrared fluorescence, have been correlated with CDs' structure, aiding in their application in biosensing and bioimaging[112]. Lastly, the therapeutic potential of CDs has been recognized for their ability to increase drug solubility, target specific sites and to facilitate drug passage across impermeable membranes, with their intrinsic fluorescence valuable for diagnostic applications[132]. The usage of CDs in a variety of applications is now safer and more efficient due to these developments in characterization techniques.

Enhanced Drug Solubility and Stability: Two major issues in the field of oncology have been addressed by the application of CDs for cancer therapy delivery. Drug solubility and stability have been greatly improved. With a particle size of less than 10 nm, CDs are potential nanomaterial because of their outstanding chemical inertness, biocompatibility and environmental friendliness. This makes them useful as nanocarriers for pharmaceuticals with several functions[57]. Their wide specific surface area is particularly beneficial for anti-inflammatory, antibacterial and anticancer drugs[94]. A novel approach involving CDs-biolabeled heat-inactivated *Lactiplantibacillus plantarum* hybrid has shown that CDs can enhance the anticancer activity of drugs like prodigiosin, offering improved stability and controlled drug release[1].

Similarly, chalcone-loaded CDs have demonstrated enhanced bioimaging and antitumor activity, with a higher toxicity value against cancer cells compared to bare CDs, indicating an efficient drug delivery model[41]. The development of PNCDs for PDT further highlights the role of CDs in enhancing the therapeutic efficacy of cancer treatments through high ROS generation efficiency[106]. Research on green biomass-derived CDs underscores the importance of developing high-quality CDs for the precise and traceable delivery of anti-cancer medications, aiming to minimize the side effects of chemotherapy by ensuring site-specific drug delivery[81].

Functionalized carbon nanomaterials, including CDs, have shown promise in diagnostics, drug delivery systems (DDSs) and stem cell therapy, providing a high loading capacity and regulated release for challenging medicinal compounds[111]. The fluorescence emission, good

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photostability and ease in surface functionalization of CDs facilitate simultaneous bioimaging and drug delivery, enhancing the solubility and stability of anticancer drugs[48]. Targeted nanocarrier systems like CDC-H have demonstrated pH-dependent drug release and specific binding to tumor cells, reducing the cytotoxicity of chemotherapeutic agents[121].

The development of DDSs based on carbon nanomaterials including CDs has been instrumental in achieving better therapeutic outcomes and reducing malignancy side effects through controlled drug delivery[62].

Targeted Drug Delivery Systems: CDs have significantly propelled the field of cancer-targeted DDSs, offering innovative strategies for diagnosis, treatment and real-time monitoring of cancer. CDs are celebrated for their biocompatibility, eco-friendliness and excellent chemical inertness, making them ideal nanocarriers for multifunctional drugs including those aimed at cancer therapy[57].

Table 4
Applications of CDs in photodynamic therapy, drug delivery, bioimaging and theranostics in the treatment of cancer

Application	Mechanism	Benefits	Challenges
Drug Delivery	CDs are functionalized to carry anticancer drugs, targeting specific cancer cells and releasing the drugs intracellularly.	Increased drug solubility and stability, targeted delivery and reduced side effects.	Potential toxicity, ensuring targeted delivery without affecting healthy cells[19].
Bioimaging	CDs exhibit strong fluorescence, enabling high-resolution imaging of cancer cells and tissues.	High sensitivity and specificity, non-invasive imaging and real-time monitoring.	Fluorescence quenching, potential interference with biological processes[102].
Photodynamic Therapy (PDT)	When exposed to light, CDs produce reactive oxygen species (ROS), which kill cancer cells	Minimally invasive, targeted treatment, can be combined with other therapies.	Depth of light penetration, potential damage to surrounding tissues[110].
Theranostics	Integrating therapeutic and diagnostic features into a single CD platform to detect and treat cancer at the same time.	Integrated diagnosis and treatment, personalized therapy and real-time monitoring.	The complexity of design ensures the effectiveness of both diagnostic and therapeutic functions[26].
Drug Delivery	CDs enhance the efficacy of chemotherapeutic agents by improving their delivery to cancer cells and overcoming multidrug resistance.	Enhanced drug efficacy, overcoming resistance and reduced side effects.	Potential toxicity, ensuring compatibility with chemotherapeutic agents[27].
Bioimaging	Real-time tracking of therapeutic progress through their fluorescent properties, providing immediate feedback on treatment effectiveness.	Immediate feedback, improved treatment outcomes and non-invasive monitoring.	Fluorescence stability, ensuring accuracy over prolonged periods[11].
Photodynamic Therapy (PDT)	CDs target cancer cells specifically, ensuring that ROS generation and subsequent cell destruction occur in malignant tissues.	Increased specificity, reduced collateral damage, effective at lower doses.	Targeting efficiency, potential off-target effects[106].
Theranostics	CDs are used for multimodal imaging combined with therapeutic capabilities, offering a comprehensive approach to cancer management.	Versatile imaging and therapy, improved diagnostic accuracy, effective treatment.	Integration complexity, ensuring compatibility of multiple modalities[50].
Drug Delivery or Radiotherapy	CDs enhance the effects of radiotherapy by increasing the radiosensitivity of cancer cells, leading to more effective treatment outcomes.	Improved treatment efficacy, potential dose reduction and minimized side effects.	Radiosensitivity variability, ensuring selective targeting[46].
Drug Delivery or Immunotherapy	CDs deliver immuno-therapeutic agents directly to tumor sites, enhancing the immune response against cancer cells.	Enhanced immune response, targeted delivery and potential for combination with other therapies.	Immunogenicity, ensuring the stability and bioavailability of immunotherapeutic agents[33].

Their superior drug delivery capabilities are attributed to their enhanced cellular uptake and absorption which facilitate the binding of medications more efficiently than traditional methods[94]. A unique strategy has been the production of a theranostic nanoplatform using CDs for fluorescence imaging and targeted cancer therapy, eliminating the need for conventional chemotherapeutic anticancer drugs[53].

In addition, sustainable materials such as green biomass are utilized in the production of CDs, promoting waste reduction and cost-effectiveness, crucial for the scalable production of these nanomaterials[81]. Innovatively, hyaluronic acid and carboxymethyl chitosan have been utilized to create targeted nanocarrier CDs, demonstrating enhanced tumor therapy and bioimaging capabilities[121]. The intersection of nanoscience and oncology has led to the development of DDSs based on CDs, aiming for targeted, controlled release to minimize toxicity and side effects[62]. The potential of CDs in cancer diagnosis and therapy is further highlighted by their application in bio-imaging and PDT, offering new avenues for treating various disorders[15]. Recent designs include chalcone-loaded CDs for enhanced bioimaging and antitumor activity, demonstrating the adaptability of CDs in drug delivery and cancer cell targeting[41].

Moreover, CDs have shown promise as materials for concurrent delivery of drugs and bioimaging, capable of overcoming challenges associated with cancer chemotherapy through targeted and multifunctional approaches[48]. The synthesis of folate CDs for tumor-targeting and the creation of a tumor microenvironment responsive nanoplatform exemplify the advances in synergistic cancer therapy, combining photodynamic and chemo-dynamic therapies for improved outcomes[113]. Collectively, these advancements underscore the significant potential of CDs in revolutionizing cancer-targeted DDSs. A few Applications of CDs in photodynamic therapy, drug delivery, bioimaging and theranostics in the treatment of cancer and their mechanism, benefits and challenges have been listed in table 4.

Stimuli-Responsive Drug Release: CDs have significantly contributed to the development of stimuli-responsive drug release mechanisms in cancer medication, offering promising strategies for targeted therapy with minimal side effects. CDs are renowned for their excellent biocompatibility, large capacity for drug loading and ability to facilitate regulated drug distribution, which are crucial attributes for effective cancer treatment[94]. The integration of nitrogen-doped CDs with polyethylene glycol has been shown to enhance biocompatibility and to enable more effective drug release at acidic pH, typical of cancerous tissues, thus reducing toxicity to normal cells[56]. This pH-responsive behavior is pivotal for targeted cancer therapy, ensuring that drugs are released more efficiently in the acidic tumor microenvironment[57]. Moreover, CDs have been utilized in co-delivery systems for siRNA and chemotherapeutics, demonstrating a significant potential to overcome chemoresistance in lung cancer by facilitating synchronized drug release within cells in an acid-triggered manner[84,128]. This approach not only increases drug accumulation in tumors but also enhances the therapeutic efficacy by silencing drug resistance mechanisms[128]. The development of CDs loaded with metal-organic frameworks has introduced a novel pH and temperature-responsive platform for neuroblastoma imaging and therapy, showcasing the versatility of CDs in creating multifunctional nanocarriers[96]. Additionally, the intrinsic enzyme like properties of CDs have been exploited to oxidize glutathione, increasing reactive oxygen species (ROS) in tumor cells and thereby enhancing the cytotoxic effect of co-delivered drugs[5,25].

Recent studies have also explored the integration of CDs with stimuli-responsive poly(N-isopropylacrylamide) hybrid nano gels, which effectively accumulate at tumor sites and facilitate deep tissue penetration and enhanced cellular internalization through photothermal and PDT effects triggered by external stimuli[131]. This multifaceted approach not only improves tumor targeting but also promotes rapid clearance of the nanocarriers from the body, addressing key challenges in nano-theranostic agent design for cancer therapy. CDs for stimuli-responsive drug release in cancer medication highlight their potential to enhance the specificity, efficacy and safety of cancer therapy, offering new avenues for clinical applications.

Imaging Technologies utilizing Carbon Dots

Fluorescence Imaging: CDs have significantly enhanced cancer therapys diagnostic and therapeutic capabilities. Carbon dots owing to their distinct qualities like enhanced photostability, variable photoluminescence and excellent biocompatibility, have turned into a main attraction in cancer diagnosis and curing[86]. These nanomaterials, often synthesized through green methodologies, exhibit low toxicity and superior chemical stability, making them appropriate for applications involving medication delivery and bioimaging[53]. Innovative strategies have been developed to exploit the tumor microenvironment for activating fluorescence imaging and chemo-dynamic therapy (CDT) with CDs. For instance, vanadium-doped CDs have been designed to remain inactive in normal tissues but to remain active in the tumor microenvironment for precise imaging and treatment, showcasing a promising approach to minimize systemic toxicity[61].

Similarly, mesoporous silica nanoparticles loaded with anticancer CDs have been functionalized for targeted cancer therapy, demonstrating potent and selective anticancer activity alongside fluorescence imaging capabilities[35]. Furthermore, advancements in PDT using PNCDs have shown great promise due to their exceptional imaging capabilities and deep tissue penetration, marking a significant step forward in non-invasive cancer treatments[106]. The development of fluorescent CDs from biologically active sources has also been explored, highlighting their selective cytotoxic nature towards cancer cells and potential as alternatives to conventional chemotherapy[3].

Recent research has highlighted carbon quantum dots relevance in simultaneous bioimaging and drug delivery, emphasizing their simplicity of surface functionalization and low toxicity[48]. Additionally, the exploration of heteroatom or metal ion-doped CDs has opened new avenues for multimodal imaging and photodynamic therapies, offering enhanced therapeutic outcomes[83,100]. These developments, coupled with ongoing research into the emissive processes and surface engineering of CDs, continue to push the bounds of their applicability in live cell bioimaging and cancer therapy[65].

Photoacoustic Imaging: Photoacoustic imaging (PAI) using CDs for cancer medication has shown promising developments in both the imaging and therapeutic domains. CDs, because of their excellent optical qualities, abundant raw materials, low toxicity and favorable biocompatibility, have emerged as a new generation of nano-luminescent materials, gaining widespread research for their potential in bio-imaging and therapy[106]. Particularly, because PAI efficiently integrates the advantages of ultrasound and fluorescence imaging while reducing each technology disadvantages using a light-in and ultrasound-out strategy, their implementation in PAI is gaining a lot of interest. Because of CDs broad absorption, superior biocompatibility, variety of imaging properties and photostability, their integration with PAI for cancer therapy is especially beneficial[105]. Because of these characteristics, CDs are very effective imaging agents for photoluminescence bioimaging of tumor cells, which improves the accuracy of targeted bioimaging and treatment[136].

Furthermore, PNCDs have deep therapeutic tissue penetration, great imaging performance, outstanding photoactivity and photostability all of which are necessary for successful cancer PDT. The creation of PNCDs has drawn growing attention[107]. It has been suggested that combining PAI with sonodynamic therapy (SDT), in which sonosensitizers produce ROS when ultrasound is present, is a promising method of treating cancer[95,103]. By monitoring time-dependent variations in tumor oxygen saturation, PAI can guide therapy and can improve the therapeutic efficacy of SDT. Nevertheless, there are still issues with using nanomaterial-based contrast agents for PAI-guided SDT, such as the requirement for straightforward designs, in-depth pharmacokinetic research and a decrease in expensive manufacturing[102].

Furthermore, the recent exploration of CDs in multimodal imaging and phototherapy treatments highlights the ongoing research efforts to overcome clinical application challenges[92]. Despite obstacles like low quantum yield and difficulty in extensive synthesis, the advancements in CD characterization, production, modification and application show substantial progress in the field[122]. Furthermore, the investigation of diketopyrrolopyrrole (DPP) dyes due to their simple functionalization, variable photophysical properties, high thermal and photochemical stability and effective creation of ROS and thermal impacts, further enriches the landscape of imaging-mediated cancer theranostics. The recent advances in PAI using CDs for cancer medication are marked by significant progress in the development of efficient imaging agents, exploration of novel therapeutic approaches like PDT and SDT and the overcoming of existing challenges through integrated research efforts.

Magnetic Resonance Imaging (MRI) Contrast Agents: CDs as MRI contrast compounds have demonstrated encouraging outcomes in cancer bioimaging research, leveraging their unique properties for enhanced diagnostic capabilities. The development of novel T1 nano-contrast agents using graphene quantum dots functionalized with poly(ethylene glycol) bis(amine) for MRI has demonstrated significantly higher longitudinal proton relaxivity compared to commercial agents, indicating superior performance in MR imaging[64]. This innovation aligns with the broader exploration of CDs in cancer diagnosis and therapy where their luminescence, biocompatibility and photoactivity are leveraged for bioimaging and PDT[15,106].

The development of gadolinium-doped carbon dots as multipurpose probes for fluorescence and magnetic resonance imaging is another example of this field's progress. These probes have shown good biocompatibility, cell permeability and the ability to enhance MRI signals *in vivo*, highlighting their potential for dual-modality imaging[20]. The exploration of CDs in biomedical research, particularly for biosensing, bioimaging and cancer therapy, underscores the growing interest in their capabilities and the need to overcome technical challenges for their practical application[118]. Additionally, the production of extremely amorphous carbon structures with remarkable magnetic resonance imaging capabilities from starch by the synthesis of passivated gadolinium-doped carbon quantum dots has promise for applications in brain mapping and biological diagnosis[61].

The advancements in heteroatom metal ion-doped CDs have also been recognized for their potential in cancer theranostics, offering new avenues for image-guided PDT[82]. These developments are part of a broader effort to design efficient nanoscale contrast agents for MRI with improved relaxivity, specificity and biocompatibility, addressing the limitations of current Gd-based agents and commercial materials. The multifunctionality of CDs, including their application in simultaneous bioimaging and drug delivery, positions them as a promising nanomaterial in the evolving landscape of cancer nano-theranostics and targeted drug delivery[100]. Collectively, these advances highlight the significant potential of CDs in enhancing MRI contrast agents for bioimaging in cancer studies, promising to improve diagnostic accuracy and therapeutic outcomes.

Multimodal Imaging and Therapeutic Platforms

Combined Drug Delivery and Imaging Systems: CDs have shown great chemical inertness and less toxicity than other nanocarriers, making them a potential option for the efficient delivery of multifunctional medications which are crucial for cancer treatment applications[57]. Their large specific surface area and excellent biocompatibility promote cellular uptake and absorption, making them excellent vehicles for delivering anti-inflammatory, antibacterial and anticancer drugs[94]. Innovative designs, such as chalcone-loaded CDs, were developed to deliver drugs straight to cancerous cells. while enhancing bioimaging and antitumor activity. These designs utilize the unique optical abilities of CDs for both targeting and imaging cancer cells, demonstrating their potential in theranostics, the combination of therapeutic and diagnostic functions[41].

Moreover, CDs have been modified to contain inherent enzyme like characteristics, which allow them to function as co-delivery vehicles for siRNA and chemotherapeutics, defeating chemoresistance in the treatment of lung cancer by inhibiting particular genes linked to resistance[128]. Nitrogen-doped CDs, synthesized through green methodologies, have demonstrated potential in pH-responsive medication delivery systems and bioimaging, highlighting their role in efficient anticancer activity and imaging[35]. The versatility of CDs extends to their application in cancer diagnosis and therapy where they have been utilized for targeted gene delivery, bio-sensing and PDT, underscoring their potential to revolutionize cancer treatment[15].

Recent developments have concentrated on producing premium CDs from sustainable raw materials or green biomass to enable the targeted and traceable delivery of anticancer drugs, thereby addressing the fundamental challenge of drug distribution in chemotherapy[81]. Hybrid quantum dots including carbon-based and graphene-based ones have been explored for their theranostic capabilities in cancer, offering a new era of targeted delivery and treatment strategies[2]. Lastly, CDs have been applied as photosensitizers in cancer theranostics, combining imaging and drug delivery to boost the drug delivery system's efficacy[21].

Theranostic Applications of Carbon Dots: CDs are now a potentially useful nanomaterial for cancer theranostics, offering unique applications in diagnosis, imaging and therapy. They are perfect for medication administration and fluorescence detection in the healthcare industry because of their large surface area, adjustable fluorescence and biocompatibility. CDs can act as photosensitizers, producing ROS under light for PDT, or convert light energy to heat for photothermal therapy of cancer, highlighting their versatility in treatment modalities[47]. Through the co-delivery of siRNA and chemotherapeutics, the intrinsic enzyme-like characteristics of CDs, such as glutathione oxidase or peroxidase activities, further boost their therapeutic potential and help to overcome chemoresistance in the treatment of lung cancer[9].

Moreover, CDs have been utilized in tumor immunotherapy, serving as photosensitizers, vaccines and immunoadjuvants due to their unique structure and properties. This application highlights the potential applications of CDs to modulate the immune system, offering a new avenue for cancer treatment[76,109]. CDs' capacity to break through the blood-brain barrier also creates opportunities for the treatment of brain illnesses and neurodegenerative diseases. expanding their therapeutic scope beyond cancer[18]. Recent advancements have aimed to enhance the photochemical aspects of CDs for improved photo-theranostic performance, including absorption, fluorescence and photothermal conversion, which are crucial for efficient cancer treatment[128].

Additionally, the development of a theranostic nanoplatform using CDs for fluorescence imaging and tailored cancer treatment without conventional chemotherapeutics demonstrates the innovative application of CDs in theranostics[123]. The cytotoxic nature of CDs that are specific to cancer cell lines, potentially through apoptosis via the mitochondrial pathway, further supports their role as an alternative in cancer chemotherapy[53]. These exceptional and distinctive uses of CDs in the treatment of cancer highlight their promise as a flexible and powerful theranostic instrument[2,3].

Integration with other Nanomaterials for Synergistic Effects: The synergistic effects of CDs when integrated with other nanomaterials for cancer treatment, have proved to enhance therapeutic outcomes. CDs, known for their excellent biocompatibility and drug delivery capabilities, have been effectively used in combination therapies for cancer treatment, offering a multifaceted approach to combat the disease[94]. For instance, the integration of red CD-doped Cu-metal-organic framework nanoparticles has been designed to enhance PDT and CDT effects by amplifying ROS levels in cells, thereby improving systemic anti-tumor immunotherapy[108]. Additionally, folate-based CDs have been created for tumor targeting; when combined with photosensitizers, they offer a nanoplatform that responds to the tumor microenvironment and can be used in conjunction with PDT and CDT to give synergistic cancer therapy[113].

The PNCDs represent another innovative approach, offering deep therapeutic tissue penetration and superior imaging performance, which are crucial for effective cancer PDT[106]. The intrinsic enzyme-like properties of CDs have also been exploited for co-delivery systems that carry siRNA and chemotherapeutics, simultaneously releasing them in a controlled manner to overcome chemoresistance in lung cancer treatment[128]. Inspired by natural systems, Fe-decorated CDs have been constructed to efficiently convert

H_2O_2 to OH, demonstrating light-regulated cytotoxicity against cancer cells[126].

Moreover, CDs have shown potential in targeting tumor-associated macrophages within the tumor microenvironment, offering new avenues for immunotherapy[78]. Further validation has been provided for their use in targeted bioimaging and therapy, with CDs and their derivatives serving as highly efficient imaging agents[102]. Lastly, the development of heteroatom elements/metal ion-doped CDs has opened new possibilities for image-guided photodynamic therapies, highlighting the adaptability and potential of CDs in cancer theranostics[100].

Discussion

CDs significantly enhance drug solubility, stability and targeted delivery, addressing critical challenges in oncology. Studies demonstrate that CDs that are smaller than 10 nm, are biocompatible and chemically inert, making them effective nanocarriers. For instance, chalcone-loaded CDs have shown improved stability and controlled drug release, enhancing anticancer activity. Moreover, CDs synthesized from green biomass promote sustainable and targeted drug administration, minimizing chemotherapy side effects. Heteroatom-doped CDs exhibit enhanced physicochemical and biological properties for multimodal imaging and PDT. These doped CDs, when integrated into mesoporous silica nanoparticles, demonstrate potent and selective anticancer activity through apoptosis-mediated cell death. Such integrations underline the importance of CDs in precise tumor imaging and targeted drug delivery.

CDs' excellent optical properties and biocompatibility make them ideal for various imaging technologies. Their high photostability and fluorescence emission facilitate effective bioimaging, crucial for cancer diagnostics and therapy. For example, PNCDs provide deep tissue penetration and superior imaging for PDT. Additionally, mesoporous silica nanoparticles loaded with anticancer CDs target cancer cells effectively, combining potent anticancer activity with fluorescence imaging. Recent advancements in photoacoustic imaging highlight CDs' potential in cancer therapy. CDs' optical properties and biocompatibility enhance the precision of PAI, which combines ultrasound and fluorescence imaging. Moreover, studies on CDs used in MRI contrast agents show promising results with gadolinium-doped CDs demonstrating good biocompatibility and enhanced MRI signals *in vivo*.

CDs offer significant potential in theranostic applications, combining diagnostic and therapeutic functionalities. They are ideal for PDT, drug administration and fluorescence sensing due to their tiny size, large surface area and programmable fluorescence. CDs can act as photosensitizers for PDT or convert light to heat for photothermal therapy. Nitrogen-doped CDs synthesized through green methods have shown promise in pH-responsive drug delivery and efficient anticancer activity. Moreover, the co-delivery of siRNA and chemotherapeutics is made possible by CDs' enzyme-like characteristics, which help treat cancer patients who are resistant to chemoresistance. The selective cytotoxicity of biologically active CDs towards cancer cells also supports their potential as alternatives to traditional chemotherapy.

Conclusion

Combining CDs with other nanomaterials enhances their therapeutic outcomes. For example, by increasing ROS, red carbon dot-doped Cu-metal-organic framework nanoparticles enhance photodynamic and CDT. Folate-based CDs, modified with photosensitizers, provide tumor-targeting nanoplatforms for synergistic cancer therapy. These integrations underscore CDs' versatility in enhancing multimodal imaging and therapeutic efficacy. While CDs offer numerous benefits in cancer therapeutics, several challenges remain. One significant challenge is the reproducibility and scalability of CD synthesis, especially for clinical applications. Although green synthesis methods from renewable biomass present eco-friendly alternatives, achieving consistent quality and functionality remains a hurdle.

Furthermore, the low quantum yield and potential toxicity of CDs, despite their generally low toxicity, need thorough investigation and optimization for safe biomedical applications. The stability and biocompatibility of CDs in physiological conditions are also critical factors that require further exploration to ensure their effectiveness and safety *in vivo*. Another challenge is the precise control over CD's surface functionalization which is crucial for their targeted applications. While surface functionalization strategies have significantly enhanced CD's properties, achieving consistent and specific functionalization for desired applications remains complex.

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