Advances in Carbon Dots: Synthesis, Optical Properties, and Biomedical Applications in Theranostics: A Review.

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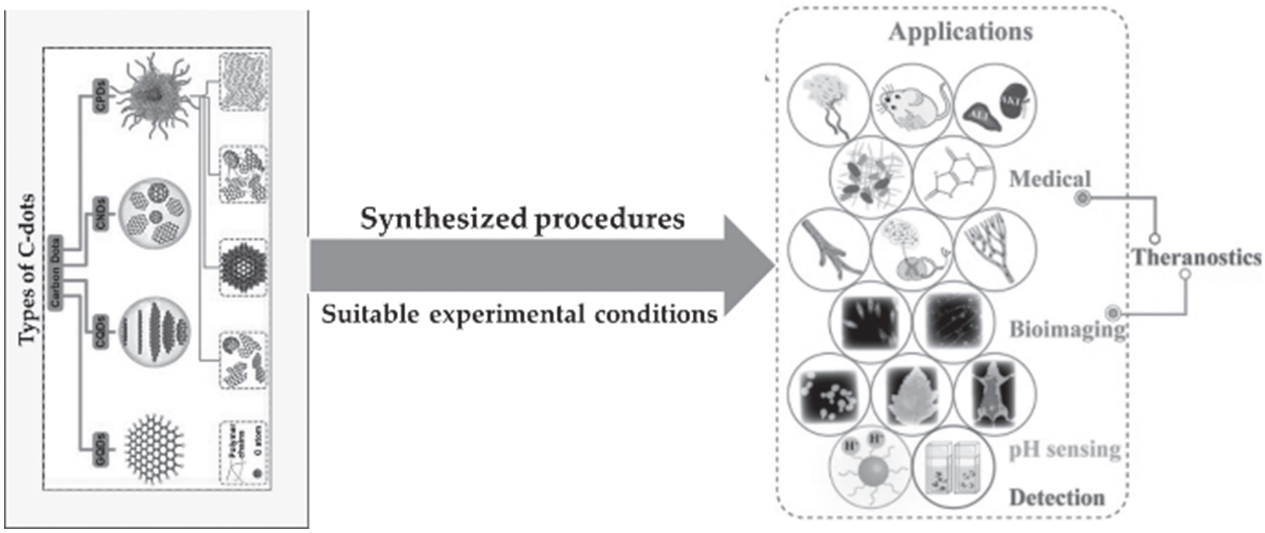
Graphical abstract



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Abstract:

Carbon dots (C-dots) have emerged as an attractive class of nanomaterials (NMTs) with unique optical, structural, and biocompatible properties. Discovered in 2004, C-dots have attracted significant attention because of their tunable fluorescence, convenience of synthesis, and low poisonous, positioning them as an ideal candidate for various applications, including bio-imaging, medication delivery, and theranostics. This review presents a detailed examination of the synthesis techniques for C-dots, their optical properties, and surface functionalization techniques. Additionally, the review explores the usage of C-dots in biomedical use like diagnostic imaging, sensing, and therapeutic interventions, including photodynamic and photothermal therapies. While the potential of C-dots in theranostics is vast, challenges related to large-scale production, characterization, and regulatory approval remain. This review highlights recent advances in the field and discusses future directions for the clinical translation of C-dots in personalized medicine.

Keywords: *Carbon dots, fluorescence, drug delivery, theranostics, bioimaging*

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Introduction to C-dots

Carbon dots (or C-dots) were first identified in year of 2004 during the purification of single-walled carbon nanotubes (SWCNTs), marking the start of an entirely new category of fluorescent nanomaterials. (Xu et al., 2004) Their discovery represented a pivotal moment in nanotechnology, as researchers quickly recognized the potential of C-dots for a wide array of applications, from bioimaging and drug delivery to catalysis and energy storage. (Dong et al., 2018; Farshbaf et al., 2018) Unlike traditional quantum dots (QDs) made from toxic heavy metals, C-dots are derived from carbon, which is both abundant and biocompatible, making them a safer alternative for use in biological environments. (Dong et al., 2018; Farshbaf et al., 2018)

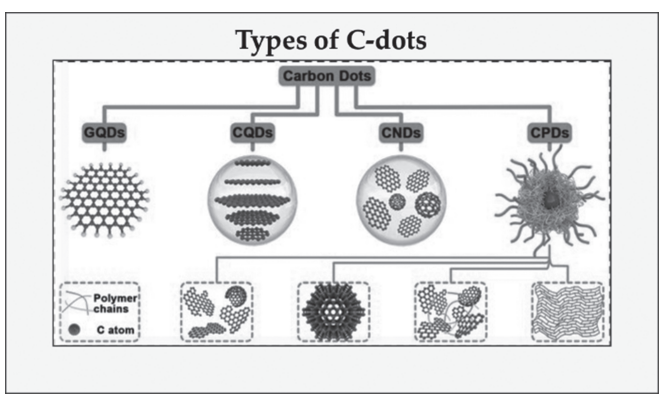

Figure 1. Various kinds of C-dots.

C-dots exhibit sole optical properties, notably their tunable fluorescence, high photostability, and resistance to photobleaching. These properties, combined with their ease of synthesis and surface functionalization, have paved the way for their use in a variety of fields. (Zou et al., 2016) For instance, their biocompatibility makes them suitable for in vivo imaging, while their ability to produce reactive oxygen species (denoted as ROS) under certain conditions renders them useful in photodynamic therapy (PDT) for cancer treatment. (Dong et al., 2018; Farshbaf et al., 2018)

In biomedical science, one of the most promising applications of C-dots is their dual role in theranostics-a field that combines therapeutic and diagnostic functions within a single platform. By integrating diagnostic imaging capabilities with targeted drug delivery systems, C-dots can potentially transform the way we approach diseases such as cancer. This review will explore the current state of research into C-dots, concentrating on their synthesized procedure, optical features, and applications in diagnostics and therapeutics.

Synthesis and structure of C-dots

Top-down and bottom-up synthesis approaches

The top-down approach engages in breaking down larger carbon materials into smaller fragments to form C-dots. This process typically employs methods like laser ablation, arc discharge, or electrochemical oxidation. For example, laser ablation involves using high-intensity laser pulses to cleave larger carbon structures into smaller particles. While this technique permits precise control over particle size and shape, it often requires expensive equipment and lengthy processing times, making it less practical for large-scale production. (R. Wang et al., 2017; Y. Wang & Hu, 2014)

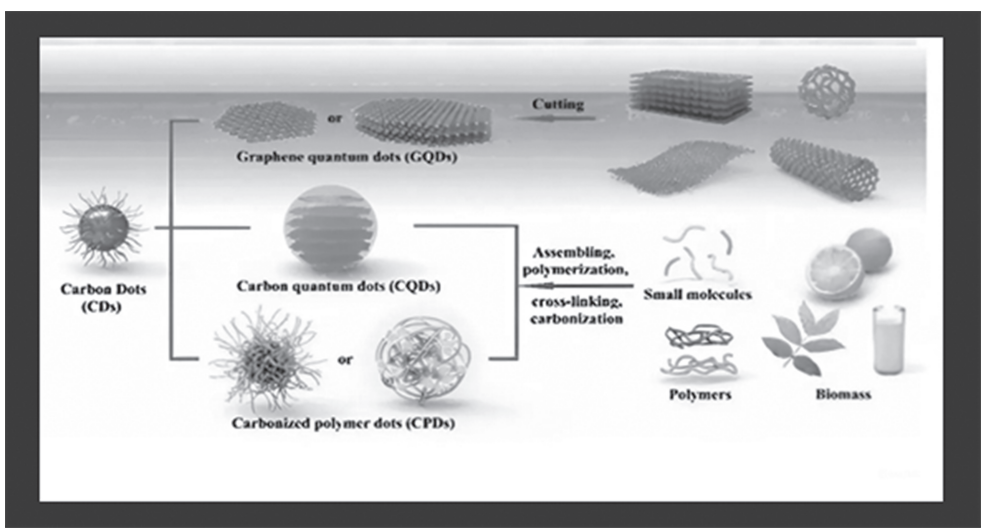

Figure 2. The synthesized procedures of C-dots from several sources.

In contrast, the bottom-up approach involves synthesizing C-dots from molecular precursors through chemical reactions. This method offers several advantages over top-down approaches, including the ability to tailor the size, shape, and surface properties of the resulting C-dots. Bottom-up techniques like hydrothermal synthesis and microwave-assisted synthesis are cost-effective and scalable, making them ideal for producing large quantities of C-dots for commercial applications. (Li et al., 2017; Namdari et al., 2017; R. Wang et al., 2017)

Key synthetic routes and their advantages/disadvantages

Hydrothermal or HTM synthesis is one of the best popularly employed methods for producing C-dots. In this process, organic precursors like citric acid are heated in a sealed reactor under high pressure, resulting in the formation of C-dots. This method is attractive because it is simple, low-cost, and environmentally friendly. However, it typically demands several periods of reaction times and may produce C-dots with varying sizes and quantum yields.

Microwave-assisted synthesis, on the other hand, uses microwave radiation to rapidly heat precursors, significantly reducing reaction times. This method can produce highly fluorescent C-dots with uniform size distributions, but it requires careful control of reaction parameters to avoid unwanted side products. (Choi et al., 2017; Namdari et al., 2017; Z. Wang et al., 2015)

Table 1. Comparative analysis of synthesis methods for C-dots.

Method	Reaction time	Saving cost	Scalability	Particle size control	QY	Potential applications
HTM	Moderate	High	High	Moderate	Moderate	Bulk production
Laser ablation	Long	Low	Low	Precise	Variable	High-purity C dots
Microwave-assisted	Short	High	High	High	High	Rapid synthesis

Note: QY: quantum yield, HTM: hydrothermal method

Structure and surface modification

The structure of C-dots is defined by the small size (less than 10 nm) and their unique combination of amorphous and crystalline carbon domains. (Kelarakis, 2014; Lin & Li,

2023)leading to an increase in protein synthesis and lipid solubility, and consequently muscle fiber growth. As a result, it is a prohibited substance in sports. In this study, an electrochemical sensor based on molecular imprinting technology was proposed for high-sensitivity detection of CLB. MnFe2O4-carbon quantum dots (CQDs These structural characteristics impart C-dots with their exceptional optical properties. (Kim et al., 2012) Surface functionalization, a critical aspect of C-dot technology, allows researchers to modify the surface chemistry of C-dots to enhance their performance in specific applications. (Zhu et al., 2015) By attaching functional agents like carboxyl, hydroxyl, and amino groups, scientists can improve the solubility, biocompatibility, and fluorescence efficiency of C-dots. (Sciortino et al., 2018) Furthermore, doping C-dots with elements such as N- or S-can enhance their quantum yield, making them more effective for bioimaging and sensing applications. (Hu et al., 2009; Prathap et al., 2023)

The characterization techniques of C-dots

To better understand the structure and optical properties of C-dots, we employed advanced characterization techniques such as Transmission Electron Microscopy (TEM), Raman spectroscopy, and X-ray Photoelectron Spectroscopy (XPS). TEM provides detailed images of C-dots' size and morphology, allowing us to assess particle uniformity. Raman spectroscopy enables examination of the graphitic structure of C-dots, thereby confirming structural characteristics and chemical stability. XPS analysis provides insights into the surface composition and functional groups, supporting the optimization of surface chemistry for biological applications. Utilizing these techniques is essential for defining the key characteristics of C-dots and improving their feasibility for biomedical applications.

Optical and photophysical properties of C-dots

Fluorescence mechanisms and quantum yield improvements

The fluorescence features of C-dots are one of their most intriguing characteristics. Unlike traditional QDs, which exhibit sharp, well-defined emission peaks, C-dots typically display broad fluorescence spectra due to the variety of surface states and defect sites. (Gómez et al., 2023) These surface defects play a crucial role in the photoluminescence (PL) mechanism of C-dots, as energy is transferred from the core of the C-dot to surface defects, resulting in fluorescence emission. (Prathap et al., 2023)

Quantum yield (QY) is a key parameter that defines the efficiency of fluorescence emission. Initially, the QY of C-dots was relatively low compared to semiconductor QDs, but recent advances in surface modification and heteroatom doping have significantly improved the QY of C-dots. For example, nitrogen doping has been shown to increase the

QY by modifying the electronic structure of the C-dot, leading to enhanced PL properties. (Šafranko et al., 2021)

Surface modifications and tunable photoluminescence (PL)

The ability to tune the fluorescence emission of C-dots is one of their most valuable features. By modifying the size, morphology, and surface-zone chemistry of C-dots, researchers can achieve fluorescence across an extensive range of wavelengths, from ultraviolet (abbreviated UV) to near-infrared (or NIR). This tunability is especially important for bioimaging applications, as it allows C-dots to be used in a range of imaging modalities. (Ezati et al., 2022)

Surface modifications, like doping with nitrogen or sulfur, can also enhance the PL features of C-dots. For instance, nitrogen-doped C-dots exhibit brighter fluorescence and better stability than undoped C-dots. Additionally, surface passivation, which involves coating C-dots' surfaces with organic or polymeric molecules, can further improve their optical properties by reducing non-radiative recombination pathways. (Ezati et al., 2022; J. Yang et al., 2022)

Table 2. Optical Property Characterization of C-Dots with Various Surface Functionalizations.

Property	Synthesis method	Surface functionalization	Performance Enhance
Fluorescence peak	HTM	Carboxyl groups	Wider range emisssion
QY	Microwave-assisted	Nitrogen doping	Higher fluorescence
Photostability	Top-down	Polymer coating	Increased stability

Note: QY: quantum yield, HTM: hydrothermal method

Applications in bioimaging and sensing

C-dots have been extensively employed in bioimaging due to their excellent fluorescence properties and biocompatibility. Unlike traditional imaging agents, C-dots are non-toxic and can be easily functionalized to planned specific cells or tissues. This makes them ideal for applications such as cancer imaging, where they can be used to visualize tumors with high specificity and sensitivity. (Kersting et al., 2019)

In addition to bioimaging, C-dots have also been employed as sensors for detecting a variety of analytes, like metal ions, small molecules, and proteins. The fluorescence of C-dots

could be quenched or enhanced in the existence of certain analytes, permitting sensitive and selective determination. For example, C-dots have been used to detect mercury ions (Hg^{2+}) in water, with LOD value as low as nanomolar concentrations. (Hui et al., 2019)

Table 3. Sensing and LOD of C-dots for various analytes.

Analyte	Type of C-dot	Functional group	Method	LOD (μM)
Mercury (II)	S-doped	Thiol	Fluorescence quenching	0.001
Hydro peroxide	Surface-functionalized	Amino	Fluorescence enhancement	0.05
Copper (II)	N-doped	Carboxyl	Colorimetric	0.002

Note: LOD: limit of detection, S-doped: sulfur-doped, N-doped: nitrogen-doped

Diagnostic applications

Imaging techniques

C-dots have shown significant promise in bioimaging, particularly in fluorescence-based imaging techniques. Their small size and excellent biocompatibility allow for efficient cellular uptake, making them ideal for labeling and tracking cells in simultaneous in vitro and in vivo experiments. Moreover, C-dots can be easily functionalized with planning ligands, like antibodies or peptides, to improve their specificity for specific tissue types or tissues. (Kersting et al., 2019)

For example, folic acid-functionalized C-dots have been used to planned folate receptors, which are overexpressed in many tumor cells. (Hai et al., 2018) This allows for selective imaging of tumor tissues, providing a valuable tool for early cancer diagnosis. Additionally, C-dots have been employed in 2-photon fluorescence imaging, a technique that permits for deeper tissue penetration and reduced photodamage compared to traditional one-photon imaging methods. (Atchudan et al., 2023)

Fluorescence-based sensors for small molecule and metal ion detection

In addition to bioimaging, C-dots have been extensively used as fluorescence-based sensors for detecting small molecules and metal ions. These sensors typically rely on the quenching or improvement of C-dot fluorescence in the presence of the target analyte. For example, C-dots have been used to detect hydrogen peroxide (H_2O_2), an important biomarker for oxidative stress, in biological samples. Similarly, C-dots have been employed

for the determination of metal ions such as mercury (Hg^{2+}), iron (Fe^{3+}), and copper (Cu^{2+}), with high sensitivity and selectivity. (Yang J.-M. et al., 2019)

Evaluation of biocompatibility and biosafety

To assess the safety and application potential of C-dots in biological environments, we conducted toxicity tests on several common cell lines (HEK293 and HeLa) and performed short-term animal studies. Results indicate that at controlled dosages, C-dots exhibit low toxicity and good biocompatibility. This low toxicity and biocompatibility make C-dots a promising candidate for applications in bioimaging and therapeutic interventions. However, further long-term studies on biodistribution and clearance are necessary to ensure safety in clinical settings.

Therapeutic applications

C-dots as drug delivery systems

The small size and surface functionalization capabilities of C-dots make them ideal candidates for drug delivery use. By attaching therapeutic agents to the surface zone of C-dots, researchers can create drug delivery systems that can selectively target specific cells or tissues. One of the most well-studied examples of this is the use of C-dots to deliver doxorubicin (DOX), a widely used chemotherapeutic agent. C-dots conjugated with DOX have been shown to effectively target tumor tissues while minimizing toxicity to good cells. (Ding et al., 2015)

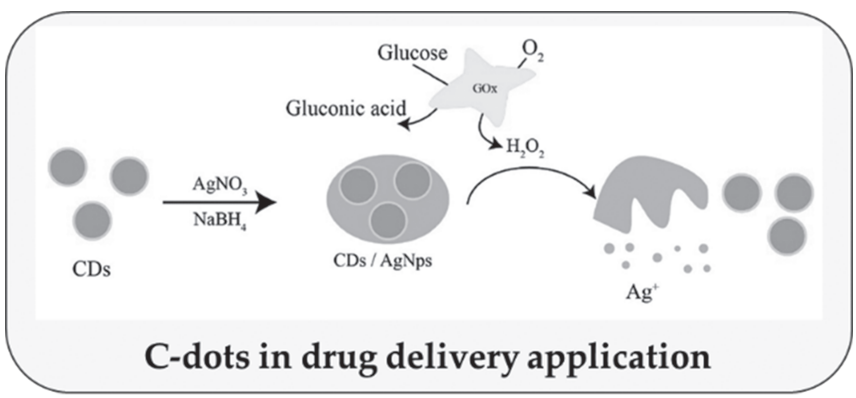

Figure 3. The application of C-dots in medication delivery.

Gene delivery (GT) and their role in enhancing gene therapy

In addition to pharmacy delivery, C-dots have also been explored as vectors for gene delivery. GT, which engages in the delivery of genetic nanomaterial to tissues to eliminate

diseases, has traditionally relied on viral vectors. (Mohammadinejad et al., 2019) However, these vectors can be immunogenic and difficult to produce. C-dots offer a promising alternative, as they can be functionalized with polymers like polyethylene glycol (PEG) to condense and deliver DNA or RNA to target cells. Studies have shown that C-dot-based gene delivery systems can achieve high transfection efficiencies with minimal cytotoxicity, making them an interesting tool for GT. (Jaleel et al., 2019)

Photodynamic therapy (PDT) and photothermal therapy (PTT)

C-dots have also shown great potential in PDT and PTT, two attracting treatments for cancer. In PDT, C-dots are used to generate ROS upon exposure to light, which can induce cell death in tumors. (Gao et al., 2017) In PTT, C-dots absorb near-infrared (NIR) light and convert it into heat, effectively killing cancer cells through hyperthermia. These therapies offer a non-invasive alternative to traditional cancer treatments like chemotherapy and radiation, and the combination of PDT/PTT with the imaging capabilities of C-dots provides a powerful tool for cancer theranostics. (Prathap et al., 2023)

Table 4. Application matrix of C-dots in biomedical and sensing fields.

Usage	Kind of C-dots	Surface functionalization	Outcome characteristics
Bioimaging	N-doped	Amino	High specificity
Medication delivery	Polymer-coated	PEG	Prolonged circulation
PDT and PTT	Surface-functionalized	Carboxyl	ROS generation for cancer cell destruction

Note: N-doped: nitrogen-doped, PEG: polyethylene glycol, PTT: photodynamic therapy

Challenges in theranostic applications

Characterization and clinical translation challenges

Despite the promising potential of C-dots in theranostic applications, several challenges remain. One of the primary obstacles is the difficulty in characterizing C-dots due to their small size and complex surface chemistry. Accurate characterization is essential for ensuring reproducibility and consistency in large-scale production, which is critical for clinical translation. Additionally, the complexity of C-dot-based systems, which often involve the conjugation of multiple components like drugs, imaging agents, and aiming ligands, presents further challenges in terms of formulation and stability.

Regulatory concerns and future directions

Regulatory approval is another significant hurdle for C-dot-based theranostic systems. The linking of therapeutic and diagnostic functionalities in a single platform requires rigorous testing to ensure safety and efficacy. This includes comprehensive studies on long-term toxicity, biodistribution, and clearance from the body. However, with continued research and development, C-dots hold great promise for advancing personalized medicine, particularly in the areas of cancer treatment and diagnostics.

Challenges in large-scale production

One of the major challenges in scaling up C-dot production is achieving consistent size and uniformity. Industrial-scale production is influenced by variables such as temperature, pressure, and reaction time, which can affect C-dot quality. To address this, we recommend the microwave-assisted synthesis method for its rapid temperature and time control, which reduces variability in particle size and morphology. Additionally, advanced purification techniques such as ultracentrifugation or molecular filtration can improve purity and product quality, making C-dots more suitable for commercial and clinical applications.

Regulatory requirements and clinical safety standards

To ensure the successful application of C-dots in medical contexts, compliance with regulatory standards from agencies like the FDA (U.S. Food and Drug Administration) and EMA (European Medicines Agency) is crucial. Specifically, C-dots need to undergo rigorous biocompatibility testing, along with biodistribution and clearance analysis in vivo. Long-term studies in these areas will help ensure that C-dots meet strict quality and safety standards. Such regulatory standards are essential for the development of theranostic systems, as they directly impact patient safety and the feasibility of broad medical use.

Conclusion and future potential

Carbon dots (C-dots) have demonstrated remarkable potential as versatile nanomaterials in various scientific and biomedical fields, particularly in theranostics, where their ability to combine diagnostic and therapeutic functions offers new horizons for personalized medicine. The unique optical properties, including tunable fluorescence, biocompatibility, and low toxicity, position C-dots as promising alternatives to traditional quantum dots and other fluorescent agents, especially in bioimaging and sensing applications. Furthermore, advancements in synthesis pathways such as HTM, microwave-assisted, and bottom-up techniques have enabled scalable production while enhancing the functionality of C-dots through surface modification and doping strategies.

In therapeutic applications, C-dots have been successfully explored in medication delivery systems, gene therapy, PDT, and PTT, providing non-invasive and targeted approaches for cancer treatment. Their ability to produce ROS and absorb near-infrared light presents significant advantages for developing effective cancer therapies with minimal side effects.

However, despite these promising advances, several challenges must be addressed before C-dots can be fully translated into clinical settings. These include difficulties in large-scale production, variability in characterization, and ensuring consistency across batches. Regulatory hurdles also remain significant, as combined therapeutic and diagnostic systems necessitate extensive testing to ensure safety and efficacy in human applications. Long-term toxicity, biodistribution, and clearance from the body require further investigation to support future clinical trials.

Moving forward, continued research into refining synthesis techniques, enhancing biocompatibility, and improving functionalization will be crucial to overcoming these challenges. Collaborative efforts between materials scientists, biologists, and clinicians will act a pivotal role in accelerating the clinical translation of C-dots. As advancements in nanotechnology and material science continue, carbon dots hold immense potential to revolutionize personalized medicine, offering innovative solutions for diagnostics, drug delivery, and cancer therapies.

Potential clinic applications

While research on C-dots has shown promising results in preclinical studies, practical examples of clinical trials are still limited. To illustrate the potential of C-dots, we present several applications: the use of fluorescent C-dots for early cancer cell detection and in non-invasive cancer treatments such as photodynamic (PDT) and photothermal (PTT) therapies. Currently, some clinical trials are underway to evaluate the effectiveness of C-dots in cancer imaging and tumor thermal treatment, highlighting the practical applications of these materials. Expanding these trials will further substantiate the application potential of C-dots and support the transition from laboratory research to real-world medical use.

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