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Review

Nanotheranostic Carbon Dots as an Emerging Platform for Cancer Therapy

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Abstract: Cancer remains one of the most deadly diseases globally, but carbon-based nanomaterials have the potential to revolutionize cancer diagnosis and therapy. Advances in nanotechnology and a better understanding of tumor microenvironments have contributed to novel nanotargeting routes that may bring new hope to cancer patients. Several low-dimensional carbon-based nanomaterials have shown promising preclinical results; as such, low-dimensional carbon dots (CDs) and their derivatives are considered up-and-coming candidates for cancer treatment. The unique properties of carbon-based nanomaterials are high surface area to volume ratio, chemical inertness, biocompatibility, and low cytotoxicity. It makes them well suited for delivering chemotherapeutics in cancer treatment and diagnosis. Recent studies have shown that the CDs are potential applicants in biomedical sciences, both as nanocarriers and nanotransducers. This review covers the most commonly used CD nanoparticles in nanomedicines intended for the early diagnosis and therapy of cancer.

Keywords: carbon nanoparticles; CDs; bioimaging; drug delivery system; theranostic

1. Introduction

Low-dimensional carbon dots (CDs) are known as carbon nanodots, carbon nanoparticles, carbon quantum dots, carbogenic quantum dots, or fluorescent carbon nanoparticles (FCNs). The ideal size of these quasispherical CDs is usually less than 20 nm (nanometers) or even 1 nm. The main component of CDs is carbon, so the sources for synthesis are easily obtainable. The CDs are sp^2- and sp^3-type hybridized carbon, commonly known as the "D" (diamond) and "G" (graphene) band carbon. Moreover, CDs decorated with surface functional groups such as –COOH, –OH, –CHO, and $–NH_2$ are sufficiently soluble in water, which is the prerequisite for drug loading and thus a drug carrier. CDs can increase photoluminescence (PL) when polymer chains are attached to the uncovered surface, making a bioimaging probe for cancer diagnosis [1–6]. At the same time, CDs offer the development of theranostic (therapeutic and diagnostic) nanoparticles for combined cancer imaging and therapy.

The fascinating photoluminescence (PL) property of CDs can be used in different biomedical fields, especially in cancer diagnosis and therapy. Typically, the CDs show a full absorption spectrum in the ultraviolet (UV) region, owing to the extensive π-conjugated electrons in a sp^2 carbon skeleton. Attributed to them are π–π* transition for the C=C bonds and n–π* transition for the C=O bonds or other connected groups. Additionally, CDs with different sizes, composition, structure, or surface passivation effect can change their light absorption spectrum [7–9].

The emission spectrum of CDs is excitation-dependent and ranging from UV to the visible or near-infrared (NIR) region. Therefore, they are highly promising for multicolor bioimaging applications.

Although the mechanism of PL emission is still a controversial issue with regard to CDs, it is an essential tool for biomedical use (Figure 1). There are two proposed mechanisms: the quantum confinement effect (QCE) mechanism based on the band gap of the conjugated π-electron, and the edge effect mechanism based on the surface defect states of both sp^3 and sp^2 hybridized carbons. This effect increases the localization of electrons on CDs and contributes to multicolor fluorescence emissions (Figure 1b,c). Furthermore, their inherent photostability and introduced surface passivation properties could amplify the fluorescent properties and empower their biological application in different ways. In the case of surface passivation, the increased densities of the π-electrons facilitate the radiative combination and the quantum confinement of electron–holes (e/h) pairs have improved the fluorescent properties of raw CDs [7,10–12].

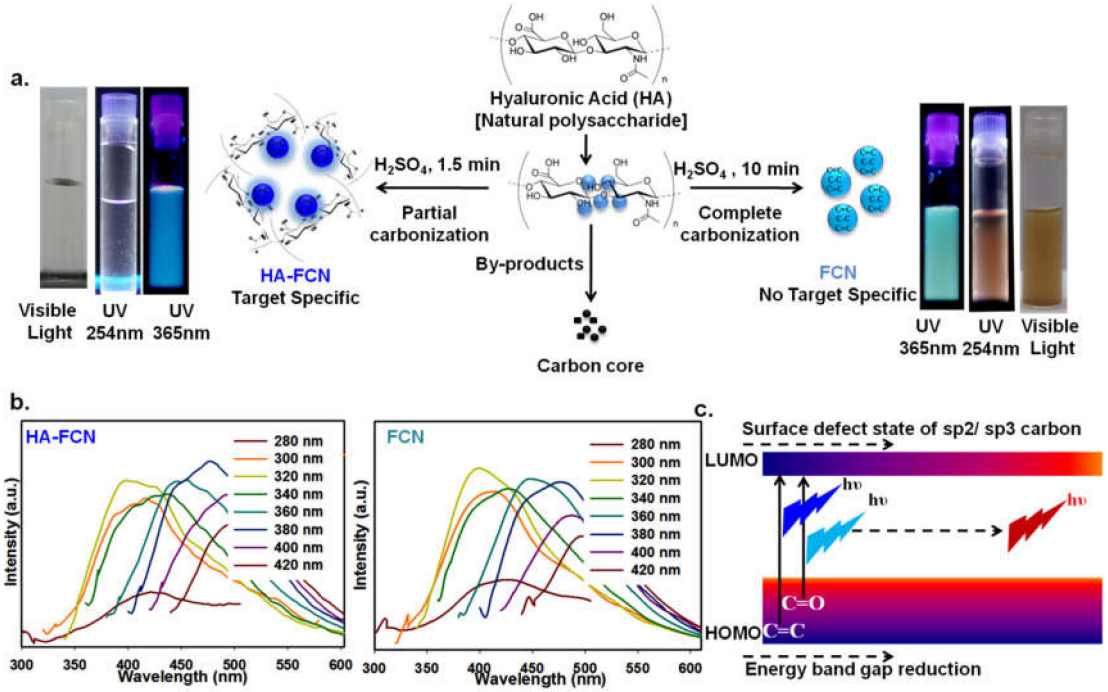

Figure 1. (**a**) Scheme of synthesis of carbon dots (CDs) from hyaluronic acid (HA) and illuminated photograph of aqueous solutions of HA-derived HA–FCN (hyaluronic acid–fluorescent carbon nanoparticles) and FCN under visible light, and 254 nm and 365 nm UV lamps. (**b**) The excitation wavelength-dependent fluorescence emission spectra of HA–FCN and FCN. (**c**) The graphical representation of the typical fluorescence emission mechanism of CDs. © The Royal Society of Chemistry [13].

FCNs (fluorescent carbon nanoparticles), a type of CDs, are considered excellent luminescence probes for bioimaging due to their unique optical properties, size tuning capacity, surface functionalization capacity, and reduced photo blinking and photobleaching characteristics. Although the surface functionalization of CDs is a complicated engineering method, the resultant fabricated and functionalized CDs can exhibit multiple functions. They can work as a unique drug carrier system and a gene delivering aid. Furthermore, the modified CDs are excellent phototherapeutic agents and sensor probes for various therapeutic and diagnostic purposes, possibly due to their maximum drug-loading capacity [13,14]. Numerous in vitro and in vivo studies have shown CDs have low toxicity or are nontoxic compared to other fluorescent nanomaterials. Moreover, the ease of administration of CDs via different routes, such as oral, nasal, and parenteral, makes them better and more convenient forms of drug delivery systems to deliver therapeutic substances.

Cancer therapy and diagnosis remain among the most challenging tasks throughout the world. The cancer treatments used against diseases are chemotherapy, radiation, and surgery. Each of these

treatments has some merits and demerits, and one treatment pathway cannot address all the types of cancer. In this context, chemotherapeutic delivery and diagnosis based on nanoparticles (NPs) such as CDs could be considered to be potential candidates and have shown promising results recently. CDs can work in the nano–bio interface, where the light induces specific photochemical or photophysical reactions allowing diagnosis and chemotherapeutic delivery. They can also be used in cytotoxic cancer therapy, such as photodynamic therapy (PDT) and photothermal therapy (PTT) [7,15–20].

The competitors of CDs are quantum dots (QDs), which are semiconductors in nature and have been used as excellent fluorescent probes in biomedicine, optoelectronic devices, and biological identification. The typical QDs contain heavy metals such as Cd (cadmium) or Hg (mercury) that cause many health and environmental hazards; however, green and environmentally friendly QDs have demonstrated a wide variety of therapeutic applications [19,20]. In contrast, CDs do not carry such heavy materials, which make them safe to use, and this is a significant difference between them. The QDs have lower quantum yield and narrower size distribution than CDs. However, QDs are small in size and have a wide surface area, so multiple conjugations are possible, which might not be possible with CDs. Moreover, compared to classic organic (fluorescence) dyes, the CDs show extraordinary attributes; for instance, higher photostability, brighter fluorescence, better biocompatibility, high quantum yield, and less photobleaching. The typical organic dyes may agglomerate within the cell, or interaction with other dyes might cause quenching of those dyes and ultimately show toxicity [21–24]. Therefore, this review focuses on the recent development of CDs, emphasizing the source and methods for synthesis and their surface engineering. The review article also includes different diagnosis results, drug delivery systems (DDS), and biomedical uses for therapeutic purposes.

2. Existing Sources and Technologies for the Synthesis of Carbon Dots (CDs)

Until now, two different strategies, namely "top-down" and "bottom-up", have been used to synthesize carbon nanoparticles or CDs from various carbon precursors (Table 1). In the case of top-down strategies, large carbon structures are broken to form carbonaceous nanoparticles or CDs. Laser ablation, arc discharge, and electrochemical oxidation have been used in this regard. The bottom-up approach leads to several CDs from carbon sources subjected to thermal combustion, acidic oxidation, hydrothermal oxidation, and microwave methods (Figure 1a) [14]. After synthesis, both top-down and bottom-up approaches use centrifugation, dialysis, or electrophoresis to separate and purify CDs [25]. However, these processes only produce small-scale products due to low yield, complicated processes, and critical synthetic conditions. Consequently, researchers are still searching for better options to make large-scale and more effective components and methods to synthesize CDs [26].

Table 1. Source and synthesis of carbon dots (CDs).

Source	Example	Reference
CDs from natural products	1. Watermelon peel	[27]
	2. Mango fruit	[28]
	3. Food caramels	[29]
	4. Egg yolk	[30]
	5. Orange peel	[31]
	6. *Trapa bispinosa* peel	[32]
	7. Tapioca sago	[33]
	8. Banana	[34]
	9. Linseed	[35]
	10. Schizonepetae herba carbonisata	[36]
	11. Milk	[37]

Table 1. *Cont.*

Source	Example	Reference
CDs from biomaterials	1. Melanin granules	[38]
	2. Chitosan	[39]
	3. Dopamine–melanin	[40]
	4. Polydopamine	[41]
	5. Folic acid	[42]
	6. Hair fiber	[43]
	7. Bovine serum albumin	[44]
CDs from carbon precursors	1. Silica spheres	[45]
	2. Kerosene	[46]
	3. Carbon soot	[47]
	4. Graphite powders	[48]
	5. Candle soot	[49]
	6. Active carbon	[50]
	7. Graphite	[51]
	8. Silane	[52]
	9. Activated carbon fiber	[53]
	10. Frying oil	[54]
CDs from carbohydrates	1. Sucrose	[55]
	2. Saccharide	[56]
	3. Glucose	[57]
	4. Carbohydrate	[58]
	5. Flour	[59]
CDs from chemical materials	1. Poly-(*N*-isopropyl-acryl-amide)	[60]
	2. Poly-(dimethyl-aminoethyl-methacrylate)	[61]
	3. Succinic acid and *tris*-(2-aminoethyl)amine	[62]
	4. Polyacrylamide	[63]
	5. Lauryl-gallate	[64]
	6. L-ascorbic acid	[65]
	7. EDTA	[66]
	8. Pluronic® F-127	[67]
	9. Resorcinol and formaldehyde	[68]
	10. Aromatic compounds	[69]
	11. Sodium citrate	[70]
	12. Polyamine	[71]
	13. Polystyrene	[72]
	14. Peroxynitrous acid	[73]
	15. Xylan	[74]

Modification and fabrication of the surface and carbogenic core of CDs are possible with various engineering methods so that the required physicochemical and optical properties can be achieved. Depending on the intended use of the CDs, the fabrication and modification method will vary and give rise to the desired properties for optimum use. Recently, various types of doped CDs have been produced by doping hetero atoms, such as boron (B), fluorine (F), nitrogen (N), sulfur (S), and phosphorous (P), into the basic structure (C, H, and O) to prepare B-/F-/N-/P-/S-doped CDs [75]. Among them, the fluorinated CDs exhibit high transfection efficiency for nucleic acid delivery. Besides, N- and S-codoped CDs have been found to present a unique quenching mechanism for detecting the anticancer drug methotrexate via fluorescence resonance energy transfer (FRET) between codoped CDs and the drug itself, which is highly beneficial for cancer theranostics [76].

Recent studies have revealed CDs modified for fluorescence intensity, wavelength, and lifetime showing high sensitivity and linearity depending on the temperature. This property is considered highly beneficial for various biomedical uses, such as the release of drugs at body temperature (Figure 2) [60,77–79]. In one study, multiband wavelength active carbon dots (CDs) as the sensitizers in 3D (three-dimensional) porous zinc oxide (ZnO) microspheres showed superior optical and

photoelectrical properties compared to bare ZnO. The modified CDs can work as highly active photocatalysts in various biological processes [80,81].

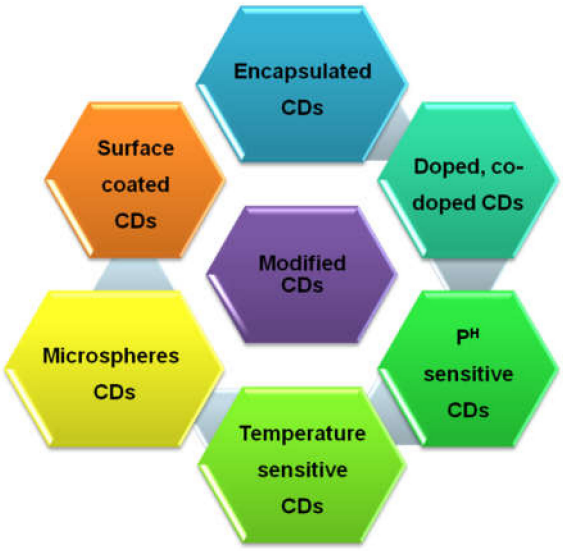

Figure 2. Schematic diagram of different types of CDs obtained through different synthesis strategies.

3. Common Methodology for the Surface Engineering of CDs

CDs having the desired functionality for the intended application can be obtained through surface functionalization, commonly known as surface passivation [82–86]. Specific chemical interactions, such as covalent bonding, electrostatic interaction, or pi–pi conjugation, are used for surface functionalization of CDs. For example, in previous research, carbodiimide covalent crosslinking utilized the surface carboxylic group (–COOH) following reaction with an amine group to covalently conjugate CDs with a therapeutic agent. The available –COOH group on CDs allows this type of zero-length carboxyl-to-amine crosslink covalent bonding to occur. In this case, the conjugation protocol using 1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide (NHS) reagents is a general method of practice in experiments. In this regard, protein-based therapeutics and small-molecule drugs that have a free amine group are favorable for this kind of conjugation. At the end of the reaction, the resultant conjugated products were dialyzed for purification and freeze-dried for storage and further study [87,88].

Moreover, the weak chemical interaction, including pi–pi stacking and electrostatic interaction, can empower the functionalization process. For example, the sp^2 hybridized C=C pi (π) bond of CDs is able to undergo pi–pi conjugation with a desired molecule having similar pi bonds. For instance, the anticancer doxorubicin (DOX) can be combined with CDs. This type of strategy also enables the conjugation of other small-molecule dyes with CDs. Moreover, the negative surface charges of CDs have a potential role in electrostatic interaction with positively charged therapeutic agents. The positive charges of folic acid (FA) and polyethyleneimine (PEI) are a few such examples. Their weak interactions with different bioactive agents allow controlled release from the CDs' surface at a predetermined rate (Figure 3) [89].

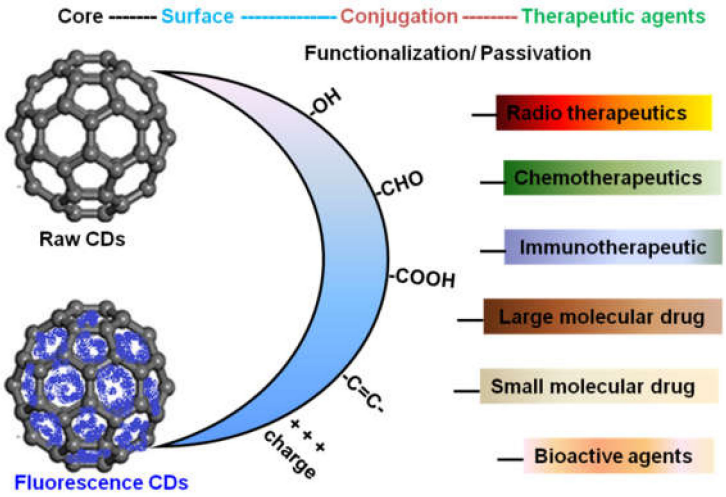

Figure 3. The surface-engineered CDs for the functionalization of therapeutic and diagnostic applications.

4. Unique Properties of Surface-Functionalized CDs

The CD surface has been altered by complex engineering with small organic molecules, metallic nanoparticles, polymeric materials, and so on, which are conjugated via covalent, hydrogen, and ionic bonds to enhance water solubility and photoluminescence properties [87]. Surface-engineered CDs exhibit more targeted drug delivery, diagnostic imaging, and target-modulated sensing (Figure 3) [88]. The improved genre of CDs is produced via various surface passivation and fabrication methods, giving them better luminescent properties than the unmodified ones. The final quantum yields (%) of the produced CDs vary depending on the initial source materials that have been used. With advanced surface functionalization, the upgraded version of CDs can be generated for diverse theranostic purposes [90–92].

5. Results of CDs in Diagnosis and Drug Delivery

5.1. In Vitro Study

Carbon dots (CDs) are considered as excellent luminescence probes for bioimaging due to their unique optical properties, size tuning capacity, surface functionalization capacity, and reduced photo blinking and photobleaching characteristics. CDs have shown a range of colors from blue to red, and even NIR emissions, based on different synthesis approaches. Various in vitro studies have shown low toxicity or nontoxicity of CDs compared to other fluorescent nanomaterials [87]. Many in vitro studies confirmed the internalization of CDs not only in the cytoplasm, but also in mitochondria. Recent studies demonstrated that CDs could also penetrate in vitro within two hours of incubation through a nonendocytosis pathway due to their smaller size and being organic in nature [88]. The quantitative cellular accumulation of bare CDs and CDs with attached targeting ligand on healthy (MDCK) and cancerous (MDAMB and A-549) cells previously demonstrated more efficient uptake in cancerous cells than in healthy cells. The considerable amount of ligand-attached CDs taken up by the cancer cells showed target selectively via receptor-mediated endocytosis. At the same time, the enhanced permeability and retention effect (EPR) could play a significant role in the uptake of nanosized CDs inside the tumor [14,93–122]. The in vitro studies' reports on the cell tracking and biological processing of CDs are a key indicator of predicting the success in vivo of any therapeutic material.

5.2. In Vivo Study

Fluorescent materials in the short-wavelength region are not a preferable choice because in vivo bioimaging needed deeper light penetration into the tissue sample. However, most of the existing CDs

emit a blue color and are excited by shorter wavelengths. The CDs' fluorescence emissions in the red to NIR wavelength for in vivo bioimaging are still most challenging. Several studies conducted on tuning CDs fluorescence emissions in the visible to NIR window are very promising. Otherwise, CDs are very promising mainly due to their small sizes, which confer an enhanced permeability and retention (EPR) effect to target the malignant tumors. CDs can be readily excreted by the urinary system to limit in vivo toxicity (Figure 4). Moreover, CDs are very promising as a carrier system that can deliver different therapeutic agents. CDs conjugated with therapeutic agents attempt to serve a theranostic function in the delivery of chemotherapy, photodynamic therapy (PDT), photothermal therapy (PTT), gene therapy, and radiation therapy [7,123–127].

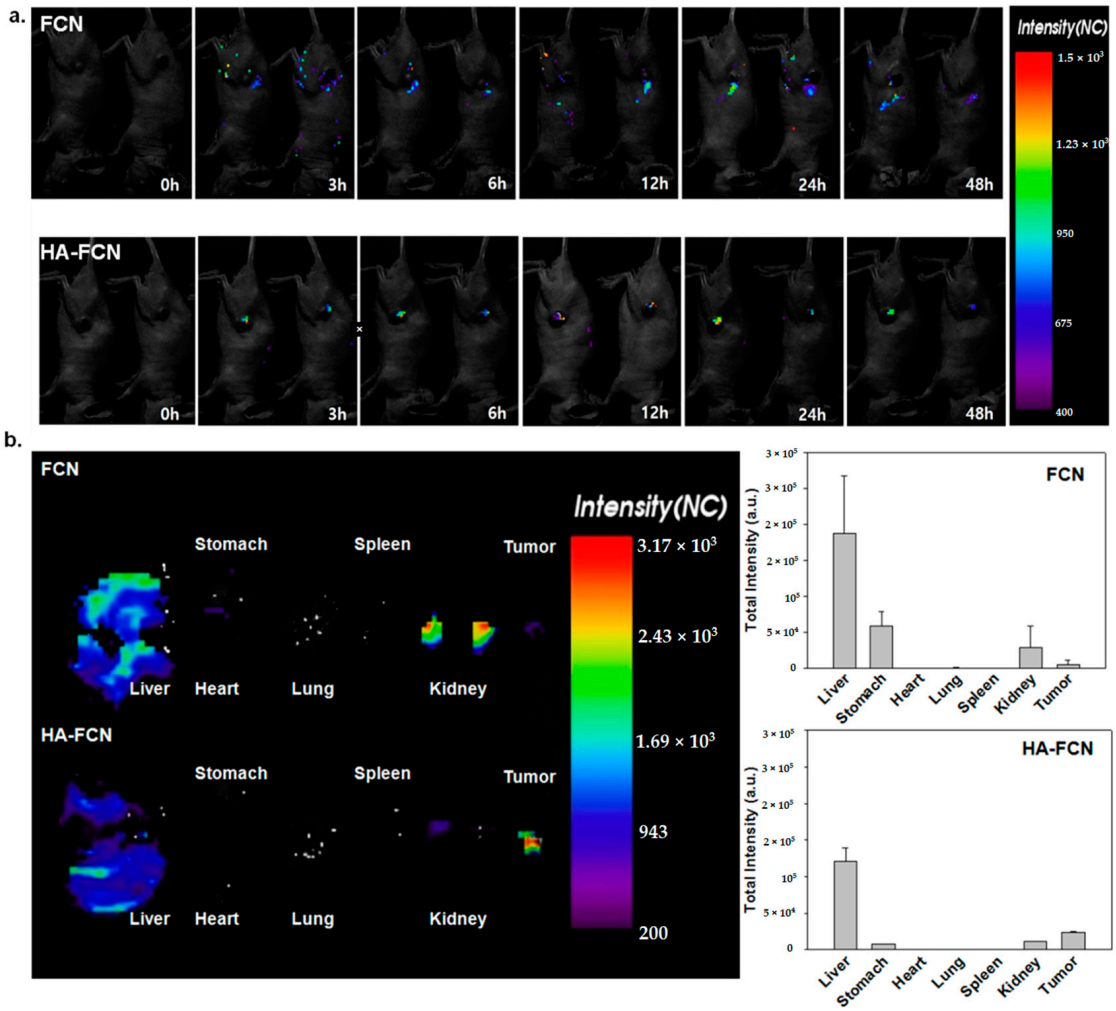

Figure 4. (**a**) In vivo biodistribution and corresponding intensities of CDs from FCN and HA–FCN of tumor-bearing nude nice at 0 h, 3 h, 6 h, 12 h, and 24 h. after administration (**b**) The ex vivo biodistribution and corresponding intensities of FCN and HA–FCN from the liver, heart, lung, spleen, kidney and tumor, respectively, after dissection, with the normalized intensity from dissected organs. © The Royal Society of Chemistry [13].

The bioimaging and tracking of stem cells by CDs is another branch that remains almost unexplored. A small number of promising studies have revealed that CDs can penetrate inside stem cells through endocytosis and remain in the cytoplasm. The presence of CDs did not affect cell differentiation and expression of the cell-specific marker. Furthermore, the study of cancer stem cells allows us to predict the tumor area's heterogeneous nature. In this context, the pancreatic cancer stem cells labeled by CDs–rhodamine confirmed internalization and allowed the evaluation of cellular morphology and

detection of Fe^{3+} ions. The internalization of CDs might be due to the nanosize, physicochemical properties, and surface charge of the nanoparticles. The scope of CDs' rational design is expected to complement the existing typical fluorescent probes for biomedical applications [7,128,129].

Moreover, the irradiation of photoactive CDs with nanosecond pulse laser light leads to the generation of heat and acoustic waves that can be employed for photoacoustic (PA) imaging. CDs are an emerging noninvasive class of imaging materials that provides high-resolution images in deep tissues due to a laser-induced photoacoustic effect [71,130]. High detection sensitivity, quantifiability, and increased penetration capacity of single-photon emission computed tomography (SPECT), positron–electron tomography (PET), and magnetic resonance imaging (MRI) combined with the multifunctional and tunable characteristics of CDs offer massive opportunities in early detection of the tumor. CDs can also offer individualized treatment monitoring, patient screening, and dose optimization, which might provide guidance in overcoming particular crucial challenges in medical and pharmaceutical science (Figure 5) [131,132].

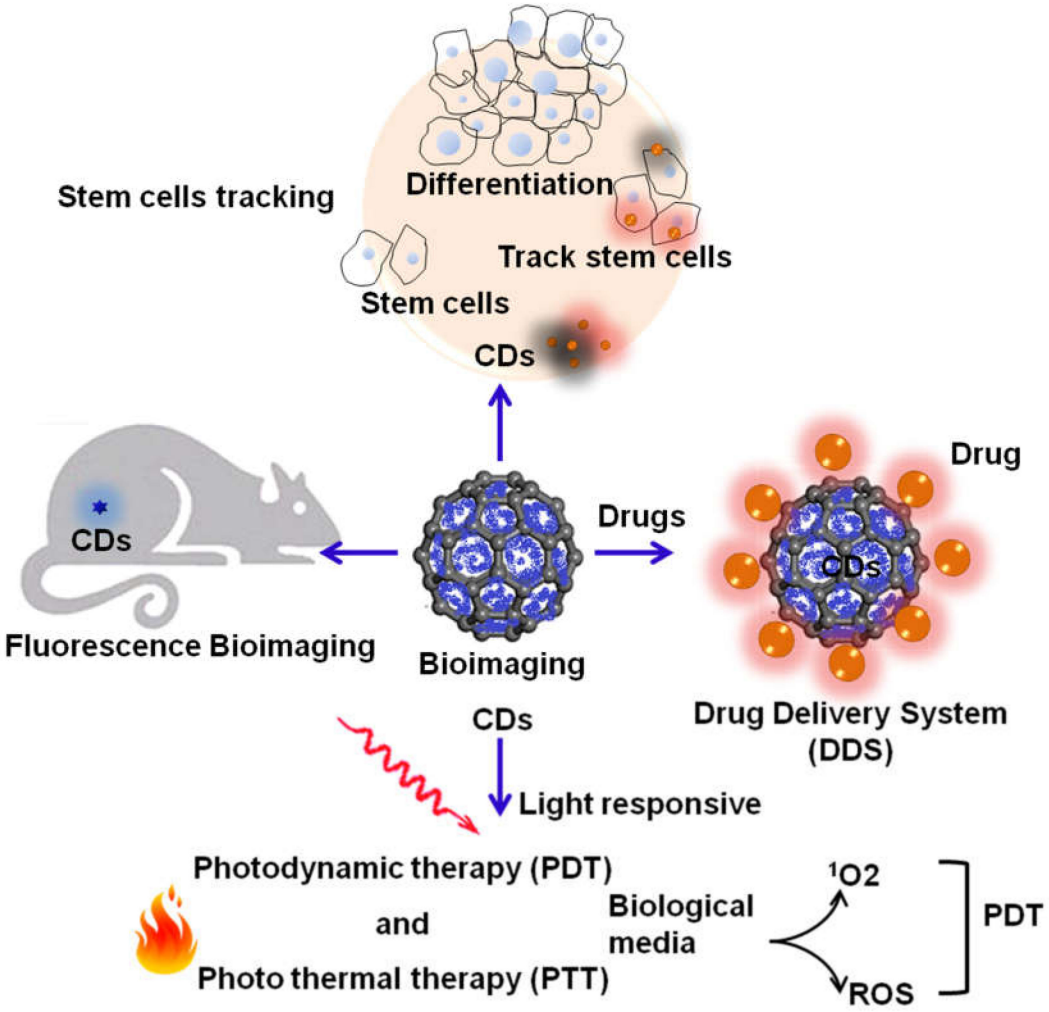

Figure 5. The application scope for carbon dots (CDs) as multipurpose theranostic agents.

The specific chemical bonding, pi–pi stacking, and hydrophobic interaction or nonspecific surface absorptions have allowed different anticancer molecules to be covalently conjugated to CDs. Furthermore, the anticancer drug-conjugated CDs can increase the aqueous solubility of doxorubicin (DOX), paclitaxel (PTX), oxaliplatin (OXA), and other hydrophobic drugs [8,133]. This is an up-and-coming technique for the enhanced permeability and retention (EPR)-based passive targeting of tumors. Furthermore, the introduction of a targeting ligand with a CDs drug delivery system

also offers an active targeting strategy. The active targeting goal can be achieved by chemical conjugation of folic acid (FA), hyaluronic acid (HA), aptamers, RGD (Arginine-Glycine-Aspartate) peptide, and antibodies [13]. Like anticancer drug delivery, CDs can also be used in the field of gene delivery. In one study, the positive surface charge of polyethyleneimine (PEI)-fabricated CDs was conjugated with negatively charge DNA. These electrostatically bonded CDs–DNA could transfer genes inside the cells within three hours of transfection. In both drug and gene delivery, CDs can maintain fluorescence properties under different excitation wavelengths, demonstrating their potential in the development of advanced diagnostic tools [14].

Moreover, light-triggered photosensitizing properties of CDs, alone or in combination with photosensitizing agents, can generate reactive oxygen species (ROS) in tumor cells. This is another branch of cancer therapy, commonly known as near-infrared (NIR) light-irradiated photodynamic therapy (PDT) (Figure 5) [134–141]. For example, PEG (polyethylene glycol)-functionalized CDs with the photosensitizer chlorin (Ce6), protoporphyrin, or zinc phthalocyanine (ZnPc) generated ROS under the excitation of CDs for targeted PDT [142,143].

Furthermore, it has been observed that high levels of nitric oxide (NO) can be cytostatic or cytotoxic for tumor cells. However, the short half-life (t1/2) of NO and bioactivities in other tissues have limited its profound therapeutic implications. In this context, CDs with photoresponsive 4-nitro-3-(trifluoromethyl) aniline attached have shown phototriggered NO release inside the cancer cells [144].

Like PDT, the NIR-responsive photothermal therapies (PTT) can hyperthermally kill the targeted cancer cells. Different carbon-based nanomaterials can absorb NIR light in the electromagnetic spectrum and convert it into heat to thermally destroy the malignant cells (Figure 5). For example, carbonized polydopamine (pDa) has demonstrated NIR-responsive photothermal conversion and multicolored fluorescence emission under different excitation wavelengths [41,145–147]. Moreover, a CD-based hybrid system can simultaneously perform PDT, PTT, and pH- or NIR-responsive drug release. Such a multifunctional smart delivery system enables synergistic cancer therapy [148]. For example, CDs nanogels with integrated PEG–chitosan have shown dual pH- and NIR light-responsive drug release and PTT against tumor cells. In another attempt, carbonized fluorescence hyaluronic acid (HA–FCN)-conjugated boronic acid (BA) decorated with β-cyclodextrin showed promise as a multiresponsive paclitaxel (PTX) DDS (drug delivery system) (Figure 6). This kind of DDS exploits an acidic pH-dependent and remote external NIR-responsive on-demand cooperative controlling strategy [13]. Development of such collaborative stimulus-responsive DDSs having bioimaging potentiality is a promising method for chemotherapeutic release that can be adjusted according to physiological needs [149].

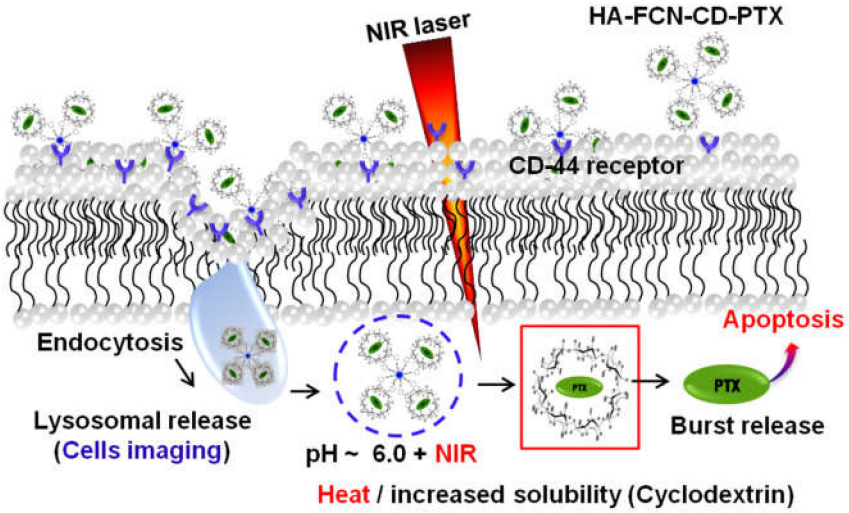

Figure 6. The schematic illustration of multistimulus-responsive carbonized fluorescence hyaluronic acid (HA–FCN) conjugated boronic acid (BA) decorated with β-cyclodextrin used for the delivery of paclitaxel (PTX). © The Royal Society of Chemistry [14].

The unique photoluminescence properties, suitable size, excellent DNA/RNA condensation capacity, and extraordinary biocompatibility of CDs mean they are considered as remarkable aids for delivering nucleic acids. Moreover, doping of CDs with various heteroatoms and surface-modified cationic CDs can make them capable of acting as image trackable nucleic acid nanocarriers. This property can possess high transfection efficiency and has been utilized for plasmid DNA and siRNA (small interfering RNA) delivery, thus bringing revolutionary changes in gene therapy (Figure 7) [150].

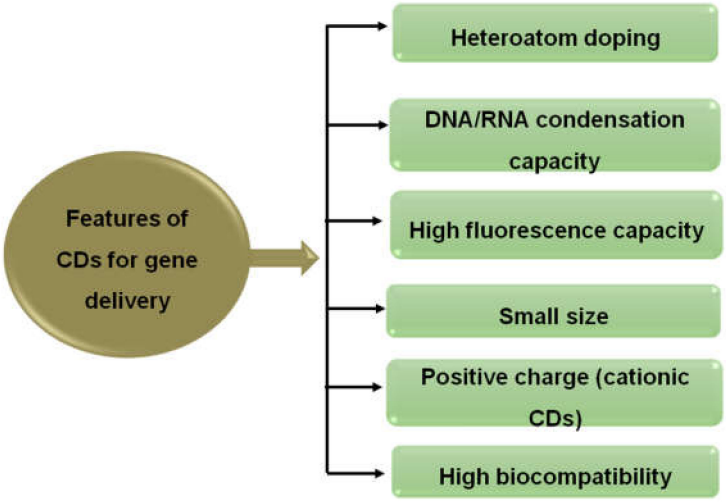

Figure 7. Essential features of CDs necessary for the gene delivery system.

6. Challenges and Limitations of the Usage of CDs in Cancer Therapy

Although huge numbers of CD applications have been possible to establish to date, there are some in vivo limitations that need to be overcome. The mechanism of CDs is debatable due to change in synthetic routes, initial synthetic materials used, surface functional groups, and wide range of size distribution. Some factors, such as toxicity, blood compatibility, rapid excretion from the body, suitable hydrodynamic diameter, and the lowest possible adsorption of proteins, must be taken into account while designing CDs [151,152]. The clinical feasibility studies have reported the concentration-dependent in vivo effects of CDs on the blood components. The concentration of CDs

above 0.1 mg/mL shows disruptions and lysis of (red blood cells) RBC, activation of the complement system, and triggering of the platelet-activated coagulation function [153–156].

Therefore, the prospect of CD synthesis and fabrication methods should be explored more so that the highest quantum yield (%) of CDs can be produced for the proper use of therapeutic carriers. Besides, most CDs have an absorption band in the short wavelength region (green and blue), which is unsuitable for in vivo imaging; hence, synthesis of CDs which emit light in the longer wavelength region is desirable [157–162]. More research studies should be carried out upon doped and codoped CDs with multicolor emissive properties. They can exhibit higher photoluminescence effects and can be utilized in different bioimaging and therapeutic applications [163–194]. Furthermore, the fundamental mechanism of how CDs interact with low-energy photons should be explored more in order to facilitate improvement in their optical properties related to image resolution and contrast.

7. Conclusions

A collective effort from nanotechnology has required the development of cancer therapeutics to overcome the hurdle of translating CD-based nanomaterials. The preliminary works of CDs are promising because of their small sizes, functionalization potentiality, and the ability to introduce multiple therapeutic agents on their surfaces. Moreover, the photoluminescence properties of CDs play an additional advantage for the bioimaging and diagnosis of tumors. Agents with combined therapeutic and diagnostic functionality are termed theranostic; this captures the main potential of CDs to address the challenges of cancer therapy. It can be a paradigm shift in the way that we treat cancer. Although CD-based cancer therapeutics are in the midst of development, they have the technical capability to develop a brand new DDS that can bring new hope for diagnosing, treating, and preventing cancer soon.

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