

# Red Carbon Dots as Theranostic Nanoplatforms for Cancer: Synthesis, Functionalization, Imaging, and Therapeutic Applications

Sadia Sarmin Tania<sup>1</sup>, Md Shadin Hosen<sup>2\*</sup>, Tanzia Islam Shorna<sup>3</sup>

<sup>1</sup>Master's Student, School of Chemistry and Chemical Engineering, Shanxi University, Taiyuan 030006, P. R. China

<sup>2</sup>Master's Student, School of Chemistry and Chemical Engineering, Shanxi University, Taiyuan 030006, P.R. China

<sup>3</sup>Graduate Student, Department of Pharmacy, School of Biological & Food Engineering, Changzhou University, Wujin District 213164, Changzhou City, Jiangsu Province, P.R. China

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## ABSTRACT

The tunable optical features, high photostability, and water-dispersibility, along with the rich surface functional groups, of red carbon dots have made them promising theranostic nanoplatforms for cancer diagnosis and therapy. The red and NIR emissive carbon dots have great potential in biomedical applications, as they have several advantages over conventional blue and green emissive carbon dots, such as reduced tissue autofluorescence, enhanced in vivo imaging contrast, deeper tissue penetration, and reduced tissue photodamage. They are excellent candidates for fluorescence imaging, image-guided therapy, and light-responsive cancer therapy. In this review, recent progress in red carbon dots as nano-platforms with multifunctionality for cancer theranostics, focusing on their synthesis, functionalization, imaging performance, and therapeutic applications, is summarized. The major synthetic strategies such as hydrothermal, solvothermal, microwave-assisted, and precursor-engineered approaches are discussed with respect to their impact on particle size, surface chemistry, quantum yield, red-shifted emission, and their photothermal and/or photodynamic efficacy. Significant emphasis is on surface functionalization strategies to enhance the properties of colloidal stability, biocompatibility, tumor targeting, cellular uptake, loading, and stimuli-responsive release. The review also emphasizes the potential applications of red carbon dots in cancer imaging, targeted drug delivery, photodynamic therapy (PDT), photothermal therapy (PTT), chemodynamic therapy (CDT), sonodynamic therapy (SDT), and synergistic cancer therapy. Although significant advances have been made, there are several challenges to address, such as the definition of emission mechanisms, batch-to-batch variability, lack of long-term biosafety data, and difficulties in clinical translation and evaluation of pharmacokinetics. In summary, red carbon dots are an intriguing and promising family of carbon nanomaterials in precision oncology. They will need to understand these structure–property–function relationships in-depth to facilitate the design of safer, reproducible, and clinically applicable theranostic systems.

**Keywords:** Red carbon dots; theranostic nanoplatforms; cancer imaging; photodynamic therapy; photothermal therapy; nanomedicine.

## INTRODUCTION

Cancer remains one of the most challenging diseases to treat, given its complexity, variability between patients, and resistance to treatment. While treatments like surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy have advanced cancer care, there are still a number of limitations. A lot of the anti-cancer medications are known to cause severe side effects and also do not penetrate the tumor to an adequate level. Research is thus increasingly focused on the development of smarter treatment systems that can target cancer cells more effectively, as well as enable doctors to monitor the treatment process. Theranostics nanoplatforms

are one type of platform that are playing a significant role in the ongoing research of modern cancer for diagnostic and therapeutic purposes in cancer. In other words, the same material may be used for the detection, delivery, and monitoring of therapeutic response. Carbon dots are among the nanomaterials that have gained tremendous interest because of their very small size, water dispersion, fluorescent property, photostability, and relative biocompatibility. They also have numerous functional groups that allow the drug, polymers, targeting molecules or imaging agents to be attached to their surface<sup>[1-3]</sup>. In particular, red carbon dots are of significant interest for cancer theranostic applications. Red and NIR emissive carbon dots are more ideal for biological applications for imaging than blue or green carbon dots due to their ability to avoid background autofluorescence, increase imaging contrast, and penetrate deeper into tissues. In addition to imaging, red carbon dots can play a role in cancer therapy via photodynamic therapy, photothermal therapy, targeted drug delivery, and combinations of these therapies<sup>[4-6]</sup>. A second crucial benefit of red carbon dots is their capability to be functionalized on the surface. They can be modified on their surfaces to enhance their level of stability, their ability to target tumors, their ability to be taken up by cells, and their ability to release the drug in a controlled manner. Carbon dots can be doped with anticancer agents like doxorubicin and docetaxel via electrostatic interactions,  $\pi$ - $\pi$  stacking, hydrogen bonding and covalent bonding. These systems release the drug when tumor-related conditions are fulfilled (acidic pH, high level of glutathione, presence of certain enzymes, or light irradiation)<sup>[1, 2, 7, 8]</sup>.

Hence, the focus of this review is on red carbon dots as theranostic nanoplatforms for cancer. It covers their synthesis, surface functionalization, imaging performance, drug delivery capability, and therapeutic applications, based on the structure of the suggested review paper.

### Synthesis of Red-Emissive Carbon Dots

The major bottom-up carbonization methods for the preparation of red-emissive carbon dots (RCDs) involve dehydration, condensation, polymerization, aromatization, carbonization, and surface passivation reactions of small organic molecules into nanoscale carbon structures with red-shifted fluorescence. The major synthetic strategies are the hydrothermal/solvothermal, microwave-assisted, and precursor-engineered strategies, as shown in Fig. 1, which offer different degrees of control over the particle size, carbonization degree, surface chemistry, conjugated domain, and optical properties<sup>[9-16]</sup>.

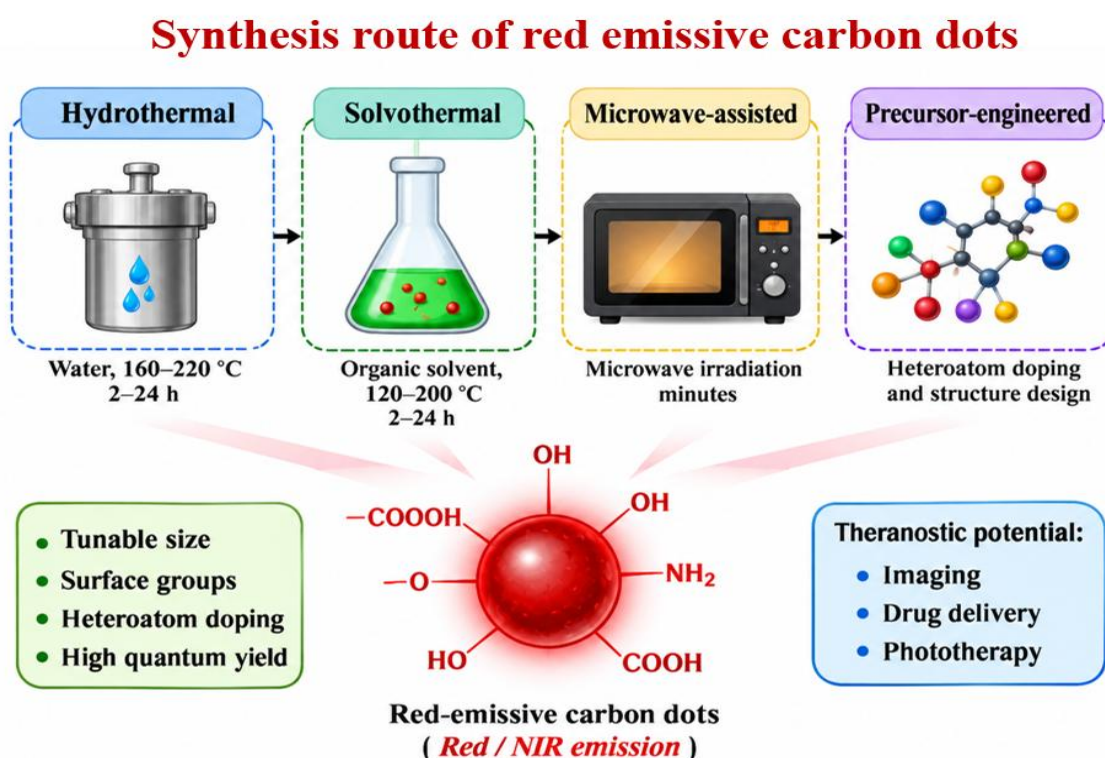


Fig.1 Schematic overview of major synthesis routes for red-emissive carbon dots.

One of the most popular methods is hydrothermal synthesis, which is simple and inexpensive and can be used for precursor systems containing water. The hydrothermal process transforms the organic precursors into carbonaceous nanoparticles with abundant oxygen/nitrogen or other heteroatom groups on the surfaces, which greatly affect both the surface-state emission and the fluorescence properties of the nanoparticles <sup>[13, 14]</sup>. The carbonization mechanism of solvothermal synthesis is similar, but the use of organic solvents provides better control over the solubility of the precursor, the reaction rate, surface passivation, and extended  $\pi$ -conjugated structure, which is very valuable for the realization of red and near-infrared emission <sup>[14-16]</sup>. The microwave-assisted synthesis can be conceived as a fast alternative as it involves efficient volumetric heating and speeds up the nucleation and carbonization reactions, cutting down the reaction times from hours to minutes. The optical properties obtained depend on the microwave power, irradiation time, solvent, and composition of the precursors, which affect the conjugated carbon domain and emissive surface states generated <sup>[13-16]</sup>. One of these methods is precursor engineering, which has gained significant importance in the design of RCDs with predictable optical properties. Aromatic and highly conjugated precursors can facilitate the creation of larger  $sp^2$  carbon domains, while precursors containing nitrogen, sulphur, phosphorus, and other heteroatoms can provide extra electronic states, reduce the band gap, and shift the emission to the red or near-infrared. Aromatic and highly conjugated precursors can help to create larger  $sp^2$  carbon domains, while precursors containing nitrogen, sulphur, phosphorus, and other heteroatoms can introduce additional electronic states, reduce the band gap, and shift the emission into the red or near-infrared <sup>[9, 12]</sup>. Controlled graphitization and surface functionalization were proven to be effective methods to tune the emission wavelength of carbon-dots, and the molecular fluorophores produced during carbon-dot synthesis may also play a role in red emission via a molecular-state emission mechanism <sup>[9, 10]</sup>. Further, the electronic structure, surface defects, charge transfer properties, and the efficiency of the photoluminescence of RCDs can be further tuned by heteroatom doping and conjugation engineering <sup>[12, 14]</sup>. Hence, the production of red-emissive carbon dots is not just a carbonization process but rather a well-regulated procedure that involves the selection of precursor materials, reaction conditions, carbon core formation, and surface-state manipulation. The particle size, emission wavelength, quantum yield, water dispersibility, and biological performance of RCDs are critical parameters that are determined by these factors for the application of RCDs in cancer imaging, drug delivery, and theranostic therapy <sup>[9-16]</sup>.

## Photophysical Properties and Emission Mechanisms

The photophysical properties of red carbon dots (RCDs) play a key role in their application as theranostic nanoplateforms in cancer imaging and therapy. In comparison with carbon dots emitting blue and green, RCDs exhibit longer-wavelength emission, less tissue autofluorescence, higher imaging contrast, greater tissue penetration, and minimal photodamage, making them very attractive for various applications in the field of fluorescence imaging and in image-guided therapy, photodynamic therapy, and photothermal therapy. They have optical properties predominantly governed by the carbon core structure, particle size, surface states, heteroatom doping, molecular fluorophores, solvent effects, and surface functional groups. Typically, RCDs have absorption bands associated with  $\pi$ - $\pi$  transitions of  $sp^2$  carbon domains, further bands associated with  $n$ - $\pi$  transitions of oxygen- and/or nitrogen-containing sites, and possible shifts of the absorption and emission colors towards the red or near-infrared region due to extended conjugation and/or heteroatom doping <sup>[17-20]</sup>. If there are two or more surface defects (or emissive traps), their fluorescence may be excitation-dependent; if the uniform emissive centers dominate, the fluorescence may be excitation-independent. The mechanisms of emission of RCDs are generally attributed to the emission from the carbon core-state, surface-state emission, molecular-state emission, heteroatom-doping-induced emission, and aggregation-related emission. Of these, surface-state and molecular-state mechanisms are particularly relevant, as functional groups, surface oxidation, passivation, and fluorescent molecular intermediates can have a significant effect on the emission wavelength, quantum yield, and photostability. Long-term cancer cell imaging and in vivo tracking require high quantum yields and excellent photostability; high visible or near-infrared absorption is desirable for light-triggered therapy for the generation of reactive oxygen species and photothermal conversion. The precise nature of the emission is more complicated, though, as multiple mechanisms may be at play depending on the composition of the precursors, the synthesis method, the reaction temperature, the solvent used, and the post-synthetic modification. Hence, better knowledge of the structure-property relationship of RCDs is crucial to enhance the efficiency, reproducibility, biosafety, and therapeutic efficacy of the application in cancer theranostics <sup>[21-23]</sup>.

This section is meant to cover your uploaded review outline under the section photophysical properties and emission mechanisms.

Table 1. Summary of photophysical properties and emission mechanisms of red carbon dots

| Property Mechanism           | Main Origin                                                 | Effect on Optical Behavior                                            | Importance in Cancer Theranostics                                         | Reference    |
|------------------------------|-------------------------------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------------|--------------|
| $\pi$ - $\pi^*$ transition   | Sp <sup>2</sup> carbon domains                              | Produces UV absorption and contributes to core electronic transitions | Supports basic optical absorption behavior of CDs                         | [9, 10]      |
| n- $\pi^*$ transition        | C=O, C=N, C-N, and other surface groups                     | Produces longer-wavelength absorption and red-shifted emission        | Helps improve visible-light excitation and bioimaging performance         | [9-11]       |
| Surface-state emission       | Surface defects and functional groups                       | Produces tunable fluorescence emission                                | Useful for cancer cell imaging, sensing, and image-guided therapy         | [10, 11, 19] |
| Molecular-state emission     | Fluorescent molecular intermediates formed during synthesis | Gives bright and sometimes excitation-independent emission            | Improves imaging stability and fluorescence intensity                     | [11, 17, 18] |
| Heteroatom doping            | N, S, P, B, or metal dopants                                | Narrows band gap and shifts emission toward red/NIR region            | Enhances fluorescence imaging, PDT, and PTT performance                   | [11, 12]     |
| Core-state emission          | Conjugated carbon core                                      | Causes red-shifted fluorescence by reducing the energy gap            | Important for long-wavelength emission and deep-tissue imaging            | [9, 10, 17]  |
| Aggregation-related emission | Interparticle interaction or restricted molecular motion    | May cause red-shifted or enhanced emission in some CD systems         | Useful for tumor-activated imaging probes, but requires stability control | [12, 18]     |
| Photostability               | Stable carbon framework and surface passivation             | Reduces photobleaching under continuous irradiation                   | Allows long-term cell tracking and image-guided cancer therapy            | [9, 10, 19]  |

## Surface Functionalization Strategies

Surface functionalization refers to the process of changing the surface of the red carbon dots without destroying the fluorescent carbon core of the dots. Carboxyl, hydroxyl, and amino groups are present in the naturally occurring red carbon dots. These groups enable the covalent coupling of polymers, targeting ligands, drugs, photosensitizers, or imaging agents via electrostatic interactions, hydrogen bonding, and  $\pi$ - $\pi$  stacking [9, 24]. The water dispersibility, aggregation, and stability of polymers in biological fluids are often enhanced by polyethylene glycol, polyethyleneimine, and chitosan. PEGylation can also extend the circulation in the blood, whereas positively charged coatings can increase cellular uptake. But nonspecific interactions and toxic effects can be increased by strongly positive surfaces, so the surface charge has to be precisely controlled [24, 25]. Red carbon dots can also be conjugated with folic acid, hyaluronic acid, RGD peptides, aptamers, or antibodies for active tumor targeting. These ligands bind to receptors that are overexpressed in certain cancers, including folate receptors, CD44, integrins, HER2, and EGFR. Groups can thus, if effective, provide more efficient cellular uptake and less exposure to normal tissues, but this can differ between tumour types and be influenced by protein corona formation in the bloodstream [25-28]. Controlled release of a drug may also be obtained through functionalization. Anticancer drugs may be linked by acid-sensitive bonds that are cleaved in the acidic tumor environment or by disulfide bonds that are cleaved due to high levels of glutathione in the cell. Other types of linkers, such as enzyme- and heat- or light-sensitive ones, can be used instead. For instance, the conjugates of carbon dots and doxorubicin have been demonstrated to have a dual pH- and redox-responsive drug release [8]. In summary, surface functionalization enables the co-assembly into one platform of tumor

targeting, imaging, drug delivery and light-responsive therapy using red carbon dots. The thickness of the coating, the density of the ligands, the surface charge and the particle size, however, can affect the fluorescence, biodistribution, cellular uptake and toxicity. These properties should thus be carefully investigated prior to biological evaluation.

## Drug Loading and Controlled Release

Table 2: Drug Loading Capacity, Efficiency, and Release Profiles of RNCD-Based Drug Delivery Systems

| RNCD System                                 | Drug      | Loading Method                           | Release Trigger       | Key Outcome                                                                               | Reference |
|---------------------------------------------|-----------|------------------------------------------|-----------------------|-------------------------------------------------------------------------------------------|-----------|
| Porphyrin-CDs + DOX                         | DOX       | $\pi$ - $\pi$ stacking / Electrostatic   | pH-responsive         | Enhanced cytotoxicity in MCF-7/MDA-MB-231                                                 | [1]       |
| HPRCD@DTX (HER2 aptamer)                    | Docetaxel | Covalent                                 | pH-responsive         | 96.13% release at pH 6.5 (72 h); apoptosis $\uparrow$ 8.39 $\rightarrow$ 24.61%           | [2]       |
| Sucrose-CDs + DOX                           | DOX       | Electrostatic / H-bonding                | pH-responsive         | Improved anticancer effects; renal clearance                                              | [3]       |
| HA-targeted DOX/CGFH                        | DOX       | Self-assembly                            | pH/GSH/HAase/NIR      | Multi-stimuli; CI=0.77 (synergy); PCE 29.7%                                               | [5]       |
| CDs/CS-FA + DOX                             | DOX       | Electrostatic                            | pH-responsive         | 90% release at pH 5.0 (30h); 52% at pH 7.4; FA-mediated uptake                            | [6]       |
| Gadolinium-functionalized carbon dot system | DOX       | Drug loading on nucleus-targeting Gd-CDs | Intracellular release | Combined fluorescence/MRI imaging and nucleus-targeted chemotherapy                       | [4]       |
| cRGD-HA-CDU@DTX                             | Docetaxel | -                                        | pH-responsive         | 90% release at pH 5.0 (48 h); 3-fold $\uparrow$ apoptosis; 64.12% tumor reduction in vivo | [7]       |
| C-dots-S-S-dox                              | DOX       | Covalent (disulfide)                     | Redox + pH            | Redox-triggered release with DTT; faster release at acidic pH                             | [8]       |

## Targeting and Cellular Uptake

Targeting and cellular uptake are crucial factors that determine the diagnostic and therapeutic efficacy of nanoplatforms in cancer theranostics based on red carbon dots. This section should follow the Drug Loading and Controlled Release section and precede the Therapeutic Applications section in your review structure. In systemic administration, red carbon dots may be delivered to the tumor by passive targeting, primarily due to the poor lymphatic drainage and leaky tumour blood vessels, but this targeting has also been shown to be heterogeneous and sometimes inadequate to ensure sufficient delivery to the tumour [29, 30]. Active targeting ligands like folic acid, hyaluronic acid, peptides, aptamers, antibodies, or other receptor-specific molecules can be surface-modified onto the red carbon dots to achieve tumour selectivity [25, 26, 31]. In addition to their ability to bind to receptors in normal cells, these ligands can bind to receptors that are present in excess in cancer cells, including folate receptor, CD44, integrin  $\alpha\beta$ 3, HER2 and EGFR, leading to enhanced receptor-mediated binding and cellular uptake [26, 29, 31]. The ligand-functionalized red carbon dots have the potential to increase the drug concentration in tumor cells, improve imaging contrast, and lower the toxicity to normal tissues as compared to non-targeted systems [24, 25]. After binding to the cancer cell membrane, the red carbon dots can be internalized by various endocytic pathways such as clathrin-mediated endocytosis, caveolae-mediated endocytosis, macropinocytosis, and ligand-receptor-mediated internalization [27, 32, 33]. The dominant uptake pathway is dependent on the size of nanoparticles, surface charge, hydrophilicity, density of ligands, type of

cancer cells, and biomolecular corona formed in biological fluids <sup>[27, 28]</sup>. One of the main reasons to consider protein corona formation is that the adsorbed proteins can alter the surface identity of red carbon dots, which influence the surface recognition by receptors, circulation time, immune clearance, and cellular internalization <sup>[13, 27]</sup>. Upon internalization, red carbon dots are primarily delivered to early endosomes, late endosomes, and lysosomes, and acidic pH in these organelles can facilitate drug release and/or trigger pH-dependent therapeutic function <sup>[32, 33]</sup>. Controlled release or activation of phototherapy can be achieved in cancer cells using the acidic pH, glutathione concentration, specific enzymes, and near-infrared light, in addition to the acidic pH. Intracellular trafficking can also be further engineered towards the specific organelles for advanced cancer theranostics, such as lysosomes, mitochondria, and the nucleus, to increase imaging accuracy and therapeutic effects <sup>[27, 32]</sup>. Systems targeted to the mitochondria could augment the effects of oxidative stress-based therapies, and systems targeted to the nucleus could boost the delivery of chemotherapies or the effects of DNA damage-based therapies <sup>[25, 32]</sup>. Enhanced targeting is, however, difficult due to the biological heterogeneity of tumors, patient-specific differences in receptor expression, and the extracellular matrix, which may impede the penetration of nanoparticles <sup>[29, 30]</sup>. Other significant issues for clinical translation are also off-target liver, spleen, and kidney accumulation, etc. <sup>[25, 30]</sup>. For this reason, the ideal future red carbon dot nanoplatfrom should possess passive tumor accumulation, active recognition via a ligand, controlled endocytic uptake, stimuli-responsive release, and organelle-specific trafficking and real-time imaging guidance for safer and more precise cancer diagnosis and therapy <sup>[13-16, 24, 27, 28, 32-35]</sup>.

## Therapeutic Applications

### Photodynamic Therapy

Photodynamic therapy (PDT) is a treatment of cancer using light energy, a special type of light, and a substance that becomes activated by the light to kill the cancer cells. Absorbed light raises the energy of the photosensitizer and gives electrons or energy to nearby oxygen molecules to create reactive oxygen species (ROS) such as singlet oxygen and free radicals. These are highly reactive molecules that are able to attack the cellular membrane, proteins, mitochondria, and DNA, which eventually results in the death of cancer cells <sup>[34, 35]</sup>. The combination of fluorescence imaging and light-induced ROS production makes red carbon dots especially appealing PDT agents. Their optical properties with red or near-infrared emission have better tissue penetration and imaging contrast than blue or green-emitting carbon dots, and lower tissue autofluorescence. It can also be seen that the ability to form ROS in the treatment is also enhanced by the strong visible or near-infrared absorption. Depending on the electronic structure, the red carbon dots could generate ROS directly by Type I electron-transfer reactions or by Type II energy-transfer reactions. In recent years, carbon-based quantum dots have demonstrated their effectiveness in producing singlet oxygen and in destroying cancer cells in light-dependent processes <sup>[36]</sup>. Conventional photosensitizers (e.g., porphyrins or chlorin e6) can also be attached to red carbon dots. They can be functionalized with folic acid, hyaluronic acid, peptides, or aptamers to enhance targeting and cellular uptake for tumors. The multifunctional design enables the same nanoplatfrom to find the tumor using fluorescence imaging and to destroy cancer cells after light irradiation <sup>[24, 36]</sup>. Poor light penetration and the typical low oxygen concentration in solid tumors can, however, limit the effectiveness of PDT. The high brightness of the fluorescence does not always correlate with high production of ROS. Future studies should therefore provide information on the quantum yield of ROS, irradiation conditions, dark toxicity, biodistribution, and therapeutic performance in hypoxia. Overall, the red carbon dots are promising candidates for image-guided PDT, but more in vivo safety and clinical studies are needed.

### Photothermal Therapy

Photothermal therapy (PTT) is an optical therapy that utilizes a light-absorbing material that absorbs the light and then transforms it into heat. The local rise in temperature causes damage to cancer cells through the disruption of cell membranes, denaturing of proteins, and the effect on mitochondrial function. The light can be focused on the tumor; thus, heating can only occur in the treated area and not in surrounding healthy tissue <sup>[37]</sup>. Carbon dots are potential near-infrared photothermal agents, which can absorb the long-wavelength light and dissipate some of the absorbed light energy as heat. Meanwhile, the fluorescent characteristics can facilitate the detection of the tumor and the monitoring of the distribution of the nanoplatfrom. Ge et al. created red emissive

carbon dots that enabled both fluorescence and photoacoustic imaging besides photothermal treatment of tumors in mice <sup>[38]</sup>. Likewise, Bao et al. reported almost NIR-emitting carbon dots which, after intravenous injection, accumulated in a tumor and provided effective PTT upon laser irradiation <sup>[39]</sup>. Surfaces of red carbon dots can also be functionalized with targeting ligands or anticancer drugs. This enables PTT to be used alongside chemotherapy and/or photodynamic therapy. The heat from the carbon dots could enhance the release of drugs and render cancer cells more vulnerable. The photothermal performance is still affected by the absorption wavelength, the photothermal conversion efficiency of carbon dots, their concentration, the laser power, and irradiation time. Lack of light penetration and potential overheating of healthy tissues are still significant challenges. Thus, further research is warranted to investigate the biodistribution, temperature changes, long-term toxicity, and treatment efficiency in vivo.

## Chemodynamic Therapy

Chemodynamic Therapy (CDT) is a therapeutic approach that relies on chemical reactions within the tumour to generate extremely reactive oxygen species (ROS) that are toxic to the tumour. The acidic environment and high level of hydrogen peroxide in the tumour lead to metal ions ( $\text{Fe}^{2+}$ ,  $\text{Cu}^+$ , or  $\text{Mn}^{2+}$ ) catalyzing Fenton or Fenton-like reactions, creating hydroxyl radicals ( $\bullet\text{OH}$ ). These radicals can attack proteins, cell membranes, mitochondria, and DNA and ultimately lead to the death of cancer cells <sup>[40, 41]</sup>. In the systems based on carbon dots, the carbon dots are usually used as the carriers or supporting platforms of catalytic metal ions/metal nanoparticles. They can be modified with surface functional groups that bind to iron, copper, manganese, or any other catalytic components, and the red fluorescence can track the nanoplatform inside the tumor. Surface modification may also render it tumor-targeting and release catalytic ions under acidic conditions. CDT does not require the presence of light or molecular oxygen, unlike PDT; this could make it potentially useful for poorly oxygenated tumors <sup>[40, 42]</sup>. However, the efficiency of CDT can be limited because of the lack of hydrogen peroxide, the low acidity of the tumors, and the high level of glutathione, which neutralizes the radicals. Thus, the strategy of red-carbon-dot nanoplatforms can be developed to boost the production of hydrogen peroxide, deplete the level of glutathione, or integrate with photothermal therapy, PDT, or chemotherapy <sup>[42, 43]</sup>. While most promising, these CDT systems are still in the laboratory or animal testing phase, and the toxicity, biodistribution, clearance, and long-term safety profile of these systems in the context of metals still needs to be investigated.

## Sonodynamic Therapy

Sonodynamic therapy (SDT) is a non-invasive therapy that involves the activation of a sonosensitizer within the tumor using ultrasound. This activation leads to the formation of Reactive Oxygen Species, such as Singlet Oxygen and Free Radicals, that create damage in the cellular membranes, proteins, mitochondria, and DNA. In addition, ultrasound can have mechanical effects, including acoustic cavitation, which also helps to destroy cancer cells <sup>[44, 45]</sup>. In comparison with light-based therapy, ultrasound is capable of reaching deeper tissues and is thus an appealing alternative for tumors that cannot be reached by photodynamic therapy. In red-carbon-dot-based systems, the dots can serve as sonosensitizers that can generate ROS or as fluorophores for other sonosensitizers. Their water dispersibility and tunable surfaces may enhance the targeting, cellular uptake, and imaging guidance for tumors. The red carbon dots can also be used for enhanced antitumor effects with photothermal therapy, chemotherapy, and chemodynamic therapy <sup>[45, 46]</sup>. But the direct evidence of the free carbon dots in SDT is still limited, and a number of reported systems have employed carbon dots as part of hybrid nanocomposites. Tumor hypoxia, low ROS production, and antioxidant molecules like glutathione can decrease the effectiveness of SDT. The sensitivity of the treatment also relies on the frequency, intensity, duration of irradiation, and the concentration of the sensitizer. Hence, more in-depth research is required to fully understand the sonodynamic action, treatment conditions, as well as safety and clearance of the red-carbon-dot-based systems in the long term.

## Synergistic Therapies

Synergistic therapy is a combination of two or more treatment modalities, the effect of which is greater than the sum of its parts when each is used alone. This is because the surface of a red carbon dot is also fluorescent,

allowing modification with drugs, targeting molecules, photosensitizers or catalytic agents, and it also facilitates light-based treatment <sup>[24]</sup>. One of the widely used approaches is to use photothermal therapy and PDT together. The heat generated by red carbon dots can weaken the cancer cells and enhance blood circulation, and when reactive oxygen species are created during photodynamic therapy, they lead to oxidative damage in cancer cells. Laser-induced heating can also be used in combination with chemotherapy, which can induce the release of the drugs by the red carbon dots and enhance the sensitivity of cancer cells to the anti-cancer drugs <sup>[24, 38, 39]</sup>. Other combination therapies could be chemodynamic–photothermal or photodynamic–chemotherapy. The systems are multifunctional, which could decrease the amount of drug or laser needed, and can overcome treatment resistance. But a greater effect is not necessarily a true synergy. Each treatment needs to be compared with the combined treatment, and proper quantitative methods, like the combination index, should be used. The long-term toxicity, biodistribution, the time for treatment, and any potential damage to healthy tissues should also be carefully considered. However, specific evidence of synergic therapies based on red-emissive carbon dots in vivo is still limited.

### Theranostic Imaging Integration

The use of a single nanopatform for cancer imaging and treatment is known as theranostic imaging integration. In particular, red or near-infrared fluorescent carbon dots could help track tumor location, track the uptake of nanoparticles, and the timing of the treatment. Once the carbon dots arrive at the tumor, they can produce heat or ROS, which can be used for photothermal or photodynamic therapy. This simultaneous method enables researchers to watch the path of the therapeutic material and determine the location of the therapeutic effect when it is activated <sup>[38, 39]</sup>. Fluorescence imaging is the most widely employed imaging technique in the case of red carbon dots due to its sensitivity, simplicity, and applicability to cell and small animal imaging. Red or near-infrared emission results in less background autofluorescence and can result in improved tissue imaging. Carbon dots that have either near-infrared excitation or multiphoton fluorescence properties might also be less damaging and can penetrate deeper <sup>[11]</sup>. But the depth and spatial resolution of fluorescence imaging are only satisfactory for smaller-sized tissues. These drawbacks can be overcome by combining red carbon dots with other imaging techniques. Ge et al. synthesized red emissive carbon dots that were able to do both fluorescence imaging and photoacoustic imaging and photothermal therapy in mice <sup>[38]</sup>. The photoacoustic imaging detects sound waves generated by light absorption and can achieve deeper imaging than fluorescence. Likewise, Bao et al. reported near-infrared emitting carbon dots which enabled tumor imaging and PTT upon intravenous administration <sup>[39]</sup>. Carbon dots can also be fused with a magnetic or catalytic material to be used as multimodal systems. For instance, magnetofluorescent assemblies of carbon dots have been utilized in fluorescence imaging, magnetic resonance imaging, and for the generation of oxygen as an aid to photodynamic therapy of hypoxic tumors <sup>[47]</sup>. Carbon dots are used in these hybrid systems for their fluorescent and surface functional group properties, and the additional components for their magnetic, photoacoustic, or catalytic properties. Improved diagnostic accuracy may be achieved by multimodal imaging because each technique could deliver a different piece of information regarding tumor location, tissue structure, and nanoparticle distribution <sup>[15, 24]</sup>. Theranostic integration can also be useful to assess therapeutic efficacy. The fluorescence, photoacoustic signal, tumor size, or temperature before and after treatment can be monitored. However, the intensity of imaging does not always directly correlate to the intensity of the therapeutic dose to the tumor. Interpretation may be affected by signal loss, photobleaching, tissue absorption, degradation of the nanoparticles, and off-target accumulation. Future studies should therefore enable imaging signals to be linked to biodistribution, drug concentration, generation of heat, production of reactive oxygen species, and therapeutic effects. In general, red carbon dots are a promising platform for image-guided cancer therapies; however, there remains a need for enhanced imaging depth, quantitative monitoring, pharmacokinetic evaluation, and long-term safety studies.

### Challenges and Future Outlook

Although red carbon dots have great potential as multi-functional theranostic nanopatforms for cancer imaging and therapy, they still have some problems to be addressed for clinical translation. The second major constraint is the uncertainty of the origin of the red/NIR fluorescence, which could be from the carbon core states, surface defects, molecular fluorophores, heteroatom doping, or aggregation-related effects, and this makes it difficult

to design materials with predicted optical properties. Further, batch-to-batch variability is a significant issue, with the particle quality varying with shifts in precursor type, solvent, temperature, reaction time, pH, and purification process, which can have a substantial impact on particle size, surface chemistry, quantum yield, drug-loading capacity, and biological efficacy. Overall, it is thought that these red carbon dots are biocompatible, but long-term biosafety studies are needed, such as chronic toxicity, immunogenicity, organ accumulation, metabolism, pharmacokinetics, biodistribution, and clearance pathways. Additionally, tumor targeting is challenging because nanoplateforms need to pass through biological barriers including protein corona formation, immune clearance, heterogeneous tumor vascular tissue, inadequate penetration into tissue, endosomal trapping, and off-target accumulation. In addition, the key challenges to translate red carbon dots from the research lab to clinical application include their large-scale production, purification, stability in storage, and regulatory standardization. Mechanism elucidation, standard synthesis, green and scalable production, higher red/NIR quantum yield, renal clearance or biodegradable design, precise in vivo tracking, and multifunctional platforms with fluorescence imaging, drug delivery, PDT, PTT, and multimodal imaging-guided treatment should therefore be the focus of future research. The improved control of structure–property–function relationships could enable red carbon dots to be used as safer, more reproducible, and effective nanomaterials for precision cancer diagnosis and therapy <sup>[13-16]</sup>.

## CONCLUSION

The excellent optical properties along with good biocompatibility, water dispersibility, and easy surface modification make red carbon dots (RCDs) one of the most promising carbon-based nanomaterials for cancer theranostics. Compared with the traditional blue/green carbon dots, RCDs have several significant advantages, such as deeper tissue penetration, less tissue autofluorescence, increased imaging contrast, and less photodamage. They are very useful for fluorescence imaging and image-guided cancer therapy.

This review has summarized the recent advances in the synthesis, photophysical properties, surface functionalization, drug delivery, targeting, imaging, and therapeutic applications of RCDs. The use of different synthesis methods and precursor designs has led to the development of RCDs with tunable optical properties and enhanced therapeutic performance. Moreover, their biomedical applications have been significantly broadened by controlling their drug delivery, cellular uptake, tumor targeting, and stability with surface functionalization. Therefore, RCDs have exhibited significant application potential in fluorescence imaging, PDT, PTT, CDT, SDT, and combination therapy, paving the way for simultaneous cancer diagnosis and therapy in a single nanoplateform.

While these promising developments are promising, there are a number of problems that must be addressed before RCDs can be implemented in clinical practice. These mechanisms are not yet fully understood, and it is challenging to design materials that have predictable optical properties in the red and near-infrared. The variability of the synthesis conditions also causes batch-to-batch variations, impacting reproducibility and performance. Also, longer-term biosafety, pharmacokinetics, biodegradation, biodistribution, immune responses, and clearance studies are needed for more comprehensive studies. Other challenges such as protein corona formation, heterogeneous tumor microenvironments, and off-target accumulation also hinder efficient tumor targeting.

Further work is needed to develop reliable and scalable synthetic approaches, optimize the efficiency of red/NIR fluorescence, and establish a structure-to-fluorescent/biological performance relationship for RCDs. There is also a need for more standardized characterization methods and systematic studies in vivo to assess their safety and therapeutic efficacy. Furthermore, integrating RCDs with multimodal imaging, smart drug delivery systems, and other cutting-edge therapeutic approaches could enhance their efficacy in precision oncology.

In summary, red carbon dots are a highly promising and emerging nanoplateform for cancer theranostics. As the materials develop and biological evaluation and clinical research progress further, it is believed that RCDs are expected to be safe, effective, and clinically relevant in the early diagnosis of cancer, image-guided therapy, and personalized cancer treatment.

## ABBREVIATIONS

ATP, Adenosine Triphosphate;  
 CD44, Cluster of Differentiation 44;  
 CDs, Carbon Dots;  
 CDT, Chemodynamic Therapy;  
 CI, Combination Index;  
 DOX, Doxorubicin;  
 DTX, Docetaxel;  
 DLE, Drug Loading Efficiency;  
 EGFR, Epidermal Growth Factor Receptor;  
 EPR, Enhanced Permeability and Retention;  
 FA, Folic Acid;  
 GSH, Glutathione;  
 HA, Hyaluronic Acid;  
 HAase, Hyaluronidase;  
 HER2, Human Epidermal Growth Factor Receptor 2;  
 HCC, Hepatocellular Carcinoma;  
 H<sub>2</sub>O<sub>2</sub>, Hydrogen Peroxide;  
 MRI, Magnetic Resonance Imaging;  
 NIR, Near-Infrared;  
 PCE, Photothermal Conversion Efficiency;  
 PDT, Photodynamic Therapy;  
 PEG, Polyethylene Glycol;  
 PEI, Polyethyleneimine;  
 PTT, Photothermal Therapy;  
 RCDs, Red Carbon Dots;  
 RGD, Arginine–Glycine–Aspartic Acid Peptide;  
 RNCDs, Red/Near-Infrared Carbon Dots;  
 ROS, Reactive Oxygen Species;  
 SDT, Sonodynamic Therapy;  
 sp<sup>2</sup>, -Hybridized Carbon;  
 UV, Ultraviolet.

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