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Review Article

Leveraging the potential of carbon: carbon quantum dots as a versatile probe for cancer diagnosis and treatment

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Abstract

In the global plane, cancer calls for creative strategies for diagnosis and treatment. Carbon quantum dots (CQDs) have emerged as a novel material for the field of cancer theranostics, showing their distinguishing features: biocompatibility, easy surface functionalization, and controllable fluorescence. Compared with semiconductor quantum dots, carbon-based fluorescent nanocrystals, called CQDs typically under 10 nm in size, are easier to synthesize and much less toxic. This paper reviews the synthesis, characterization and applications of CQDs synthesized from biomolecules and medicinal plants, which may be used to treat cancer. Depending on the method, several techniques have been developed for the synthesis of CQDs. Laser ablation, electrochemical oxidation, hydrothermal treatment and microwave synthesis are among the techniques developed for this purpose. Characterization techniques assist in gathering detailed information related to the structural and optical characteristics of CQDs. The review also discusses the challenges of CQDs and their future prospects by underlining the need for further research work to cope with the issues of toxicity, biocompatibility, and delivery specifically to the brain. Overall, the review holds enormous potential to revolutionize cancer treatment through a theranostic approach that combines diagnosis, imaging, and therapy.

Keywords: Carbon quantum dots, cancer, photodynamic therapy

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1. Introduction: Worldwide Rising Burden of Cancer and the Theranostic Potential of Carbon Quantum Dots

The overwhelming global burden of cancer is predicted to cause roughly one in six lives globally by the year 2050[5]. According to the WHO, cancer is either the top or second most common cause of death for people under 70 in the majority of developed nations[6]. This worrying rate emphasizes the essential requirement for better approaches to identify and treat cancer with fewer side effects. Cancer is characterized by uncontrolled growth of abnormal cells, forming tumors that can spread all over the body. This uncontrolled growth of the cells, their high mutation frequency and metastasis of cancer cells make it difficult to detect at early disease stages, and hard to treat with standard methods[6]. Current cancer treatments such as radiotherapy and chemotherapy suffer significant side effects as a result of killing healthy cells as well as lesions and symptoms in the range of the body's worst. This limitation shows that there is an urgent need for a new, more precise approach to cancer diagnosis and treatment. In this context, nanotechnology opens an array of opportunities for the development of innovative and very efficient anticancer therapies. Nanomedicine would become a blessing for the diagnosis and treatment of cancer by providing a new dimension in the application of nanoscale materials for medical purposes. Amongst various kinds of nanomaterials, carbon quantum dots (CQDs) are highly attractive for their unique characteristics within this area.

Carbon quantum dots are carbon-based fluorescent nanocrystals, typically less than 10 nm in size. Because of their special properties, they have proved particularly useful for biomedical applications. These materials are of great interest as they are relatively small, biocompatible and show excellent fluorescence for applications in the diagnosis and treatment of cancer[7]. Biocompatibility: The excellent feature of any compound that is found useful in medicine is biocompatibility. Since CQDs are widely acknowledged to be biocompatible, it is much less likely to cause harmful immune responses inside the body[6]. Fluorescence: One of the characteristics unique to CQDs is their high and tunable fluorescence, which has emerged as particularly useful for bioimaging, or

nanoscale visualization of cells and tissues. Due to this function, CQDs have special applications to activities, such as monitoring therapy response, tracking drug distribution, and improving the accuracy of diagnosis[8]. In comparison to the semiconductor quantum dots (SQDs), CQDs offer advantages in application and usage for bioimaging purposes. These include low toxicity and facile synthesis. Generally, CQDs are less toxic because they lack heavy metal impurities, usually present in SQDs, especially cadmium. Moreover, the synthetic method of the CQDs is facile, simple, and economical. It can also be easily scaled up in case of large-scale production[9].

CQDs are being synthesized for various applications of cancer treatment, including bioimaging, targeted drug delivery, photothermal therapy, and radiosensitizing effects that enhance radiotherapy. Their bright, controllable luminescence qualities make them useful for imaging and following cancer cell migration in early identification and treatment progression. Carbon quantum dots can operate as anticancer medication transporters, delivering anticancer medicines directly to the tumor location while reducing damage to normal tissue and increasing therapy efficacy[10]. CQDs can also be surface-functionalized to cause cancer cell death when activated by light. More importantly, CQDs may increase the radiosensitivity of cancer cells, allowing for lower therapeutic dosages while minimizing damage to normal tissues. Researchers are interested in employing CQDs as adjuvants in other therapies to achieve synergistic anticancer benefits. This paper probes into the prospect of carbon quantum dots (CQDs) in theranostics for cancer; their preparation from natural materials; mechanisms of action in photodynamic therapy and drug delivery; diagnostics and their applications in bioimaging as well as treatment. The paper finally touches on the challenges and possible future applications of CQDs in biomedicine.

2. Carbon quantum dots synthesis

CQDs are a distinct class of carbon nanomaterial made up of carbon nanoparticles with dimensions below 10 nm. Synthesis of CQDs from naturally occurring material has gained great interest in the last decades because not only they show great biocompatibility and nontoxicity but also due to their presence of heteroatoms, fluorescence and surface functionalization. A deeper examination of the natural precursors utilized in CQD synthesis is necessary for a better understanding of CQD synthesis, since their molecular structures and intrinsic functions may have an impact on the physiochemical properties of CQDs. In this review, we particularly emphasis on biomolecules, biopolymers, and medicinal plants as a precursor for the synthesis of CQDs. Since biomolecules (and biopolymers) are great sources of heteroatoms, CQDs orchestrated from these precursors are often doped nitrogen, sulphur, or phosphorous[11]. This doping with nitrogen and phosphorous results in molecular structures and optical properties. On this note, biomass from plants has gained tremendous attention as CQDs of different sizes and emission spectra. In addition, most of medicinal plants have anti-cancer therapeutic properties as well. The surface characteristics and shape of CQDs from distinct plants vary greatly because of the variations in their molecular building block concentration and chemical compositions.

3. Biomolecule-derived Carbon Quantum Dots

The synthesis of CQDs has involved the utilization of a broad variety of biomolecules and biopolymers, including proteins[12], amino acids[13], nucleic acids[14, 15], carbohydrates[16-18], and vitamins[19 20]**.** The selection of precursor is primarily based on the intended utilization since it has an impact on the heteroatoms (doped atoms) and functional group variations inside CQDs, which in turn impacts the CQD's optical and electrical properties. As a result, we first go over the different precursor biomolecules that have been utilized to synthesize CQDs **(fig.2)** in this part, along with their unique characteristics.

3.1 Amino Acids and Proteins

Amino acids are macromolecules made up of two functional groups joined to one carbon atom: amine (-NH2) and carboxylic acid (-COOH). The synthesis of CQDs finds amino acids to be a desirable precursor due to their abundant availability, affordable cost, high solubility, and biocompatibility. Pei et al., for instance, created CQDs through the hydrothermal reactions of amino acids at low temperatures[13]. A thorough examination of material design for the synthesis of CQDs produced from amino acids (AA dots) was recently published by Xu et al[21]. It is discovered that several physiochemical features of CQDs, such as stability, shape, and optical qualities, depend on the functional group (R-group) bonded to the central α-carbon atom. Using a similar approach, Kafra et al. produced high quantum yield CQDs from eight amino acids (arginine, cysteine, glutamic acid, glutamine, aspartic acid, lysine, tyrosine, and methionine) in a different study. Out of all the CQDs, the ones produced from cysteines have demonstrated promising characteristics such as photocatalytic activity, cytocompatibility, and potential uses in cell imaging, sensing, and antibacterial activity. One of the most prevalent macromolecules, protein is well-known for its intricate structure and range of uses. Amino acids are organic chemicals that contain carbon, oxygen, hydrogen, sulphur, and nitrogen. These substances are polymers that makeup proteins. The amide and carboxyl groups they contain make them an important precursor for the synthesis of CQDs. Under specific reaction and environmental circumstances, such as temperature and pH, proteins can readily unfold[22]. The furthermost promising protein for the manufacture of CQDs is albumin because of its superior water solubility, biodegradability, and biocompatibility. Highly fluorescent CQDs have been made using bovine serum albumin (BSA), human serum albumin (HSA), haemoglobin, and gelatin on a large scale. Gelatin-based blue fluorescent CQDs were described by Liang et al[23]. These CQDs have demonstrated up-converted, pH-sensitive, and excitation-dependent PL characteristics. There are many drawbacks to surface passivation, including toxicity, the need for further purification, and difficult production methods.

3.2 Carbohydrates

Carbohydrate is a water-loving (hydrophilic) biomolecule also termed as saccharide made up of carbon, hydrogen, and an oxygen atom. Sugar, starch, and cellulose are also included in this category. The smallest and lowest molecular weight carbohydrates are sugars, often known as monosaccharides. Other classes of these include oligosaccharides and polysaccharides. Carbohydrates show a crucial role in working and regulating numerous processes in living organisms such as energy storage, preventing blood coagulation, immune system, and fertilization. Because of their robust multicolor fluorescence[24, 25] and sustainability[26], carbohydrates have thus been widely employed in the production of carbon-based nanomaterials. For instance, without the need for a surface passivation reagent, Wang et al. described the time-saving synthesis of multicolor photoluminescent (Carbon dots) from carbohydrates such as glycerol, glucose, glycol, and sucrose [27]. In addition to carbs, biomass derived from algae is a significant source of lipids. It would therefore be a fantastic prospective source for the reasonably priced construction of CQDs.

Glucose is inexpensive, non-toxic, and highly soluble in water, it is frequently utilized as a precursor to create carbon quantum dots (CQDs). Nitrogen-doped CQDs (NCDs) were created by Ma et al. using an ultrasonication treatment and a reaction between glucose and ammonium hydroxide[28]. Meanwhile, glucose can cross blood-brain barriers, researchers have started to orchestrate glucose-based CQDs to penetrate the blood-brain barrier for numerous applications linked to brain ailments. For example, Zheng et al. derived CQDs from D-Glucose for imaging cancerous Glioma cells[29]. In addition, other carbohydrates such as fructose, maltose, sucrose, lactose, and their derivatives have been employed as carbon sources. Furthermore, the primary precursors known to generate CQDs include polysaccharides such as cellulose, chitin, and chitosan[30].

3.3 Nucleic Acids

Nucleic acids are the vital class of biomolecules that refers to DNA and RNA. Their typical roles involve encoding and storing data that comes in various chemical forms in order to create proteins. Pentose sugar, a phosphate group, and nitrogenous nucleobases make up nucleic acids. It has been observed that these molecules with various nucleotide sequences serve as the carbon source for the production of CQDs. Guo et al. (2013), for instance, reported the production of blue fluorescent CQDs from DNA of various lengths through self-assembly at 80°C[31]. Ding et al. used hydrothermal treatment at 180°C for 12 hours along with sonication to create CQDs from DNA[32]. Furthermore, most of the covalent bonds found in DNA molecules are said to be preserved in CQDs. Moreover, the interaction of base amino groups with the phosphate groups of neighbouring DNA strands results in dehydration, polymerization, carbonization, and condensation, which in turn forms DNA CQDs. Additionally, Zheng et al. used the hydrothermal approach to create single oxygen-producing CQDs from four basic nucleotides of DNA[33]. Additionally, Luo et al. reported that CQDs were created by heating cytosine, a DNA base, to 160°C[34]. These CQDs are demonstrated to have good photostability and stability over a broad pH range, suggesting possible uses in cell imaging and sensing.

3.4 Additional Molecules

CQDs are also made using other biomolecules, including glutathione, vitamins, and folic acid. For instance, Zeng and colleagues reported a 40% quantum yield of highly water-soluble, vivid blue fluorescent CQDs from L-glutathione[35]. Moreover, using ascorbic acid as the precursor, Gong and colleagues created extremely luminous CQDs[36]. When used to image human breast cancer cells, these incredibly biocompatible CQDs have shown good results (Bcap 37).

4. Medicinal Plant-Based Carbon Quantum Dots

Many plants have been used by humans as medicine since ancient times because of their fascinating qualities, which include the ability to heal themselves[37], be anti-inflammatory[38], be anti-bacterial [39], be anti-venomous[40], be anti-aging [41], and many more[42]. Owing to their innate therapeutic qualities, medicinal plants hold great promise for the identification and management of cancer. It has been demonstrated that some plants possess exceptional anti-cancer qualities, such as the ability to promote cell cytotoxicity [43], induce apoptosis [44], and inhabit tumors [45]. Therefore, CQDS obtained from medicinal plants are finding a novel, fascinating and sustainable approach in the biomedical sector. Moreover, synthesis pathways of CQDs based on medicinal plants and their availability to plants are simple. Therefore, in the last 10 years, medicinal plant based CQDs have gained wide attention. Carbon quantum dots based on medicinal plants have been found to be highly photostable, nontoxic, having a high PL and water soluble [46]. Despite these encouraging developments, to the best of our knowledge, no systemic study has been published on the synthesis of medicinal plant-derived CQDs. In this review, we outline the role and peculiar properties of medicinal plant derived CQDs.

4.1 Precursors for Medicinal Plant-Based Carbon Quantum Dots

Many parts of plants, such as foliage, stems, roots, blossoms, fruits, seeds, and many more, have been used as medicine for a very long time. These components are full of complicated functional groups, metals, nonmetals, and biomolecules. As such, CQDs derived from particular plants have interesting theranostic properties. produced CQDs from ginger juice, for example, and used them precisely as is, without adding any medication [47]. Similar to this, Hsu et al. created extremely photoluminescent and biocompatible CQDs from green tea [48]. When it comes to breast cancer inhabitation, these carbon dots exhibit outstanding efficacy. In order to create CQDs with apoptotic action against breast cancer cells, Arkan et al. produced walnut oil [49]. Furthermore, Meena et al. reported on CQDs derived from plants that are frequently used for therapeutic purposes in Ayurveda, including *Octimum tenuiflorum*, *Azadirachta indica* and *Tridax procumbens*. The root of the plant genus Panax is called

ginseng, and it is widely used as a medical and functional food. It is widely used as a medication for neurological conditions and anti-cancer activities because of its extremely beneficial properties, which include anti-inflammatory and antioxidant properties [50]. Ginsenoside Re, ginseng's active component, was transformed into CQDs by Yao et al. through a one-pot hydrothermal procedure [51].

5. Synthetic Synthesis of Carbon Quantum Dots

To create nanomaterials with the correct size, shape, and orientation, researchers have investigated a range of methods. According to [52] and [53], these technical techniques can be categorized as top-down and bottom-up respectively. Carbon quantum dots are usually produced in a top-down manner using bulk materials such as carbon powder. This method is inexpensive and doesn't call for a lot of harsh chemicals or complicated experimental setups. Nevertheless, it generates a significant quantity of waste and is challenging to regulate the morphology and size of CQDs, which affects their physiochemical characteristics. Using a bottom-up method is an alternative that may be more economically viable because it produces less trash. Building material atom by atom, molecule by molecule, or cluster by cluster is known as the bottom-up approach. A few of these methods are either in the early stages of development or have just started to be employed in commercial manufacturing. In the synthesis of CQDs, the bottom-up strategy is preferred over the top-down approach because of its numerous advantages, which include less flaws, more uniform chemical composition, and a more organized structure. Additionally, it is stated that the primary variables to take into account for CQD synthesis in the bottom-up method include kinetics, thermodynamic equilibrium, and Gibbs free energy [54]. Here, we go over a few popular methods for creating CQDs.

A. Top-down approaches

a) Laser ablation[10]

Recently, laser ablation has been widely employed to manufacture CQDs because it can synthesize various nanostructures with readily controlled morphology[55-57]. Sun et al. used argon as a carrier gas to create CQDs from a cement and graphite powder mixture[58]. Afterward, it was discovered that CQDs had the advantage of having size-controllable laser pulses, which had an impact on the formation and expansion of CQDs[57]. The interaction of the laser beam with the graphite produced an instantaneous high temperature and a high-pressure steam/plasma plume at the interface between the graphite and the surrounding liquid medium. The laser plume in the laser generated the bubbles because of the liquid's limitations. The formation of nuclei occurred when the laser pulse width was too great because the pressure caused the foam to contract and the inner region to cool. Moreover, by varying the laser pulse width, bubbles with various cluster densities were created, which led to the production of CQDs in various sizes.

b) Electrochemical oxidation

The process of creating CQDs by oxidizing a carbon source electrode electrochemically is commonly referred to as the electrochemical oxidation method. Reports from the present mostly concentrate on the synthesis of CQDs using graphite, carbon black, and multi-wall carbon nanotubes as working electrodes, demonstrating the benefits of a high yield, gentle reaction conditions, and controlled size[59-63].

Using an electrochemical process, Zhou et al. synthesized the first fluorescent CQDs from multi-walled carbon nanotubes[61]. Later, Kang et al. published an electrochemical technique that produced CQDs with superior optical and electrical properties with the help of alkali, offering a fresh approach to high-quality preparation. This was accomplished by electrochemically oxidizing graphite honeycomb to produce ultra-fine particles, from which CQDs of different sizes were produced. In this instance, the control group demonstrated that the synthesis of CQDs required an alkaline environment. Additionally, it was reported on the synthesis of extremely crystalline CQDs using graphite electrodes and electrochemical oxidation in an alkaline environment[62]. It's interesting to note that the colourless aqueous solution of CQDs eventually turned brilliant yellow when kept at room temperature. This could be related to the surface species gradually becoming oxygenated over time.

c) Chemical oxidation

Chemical oxidation is a high-efficiency and convenient way of generating carbon quantum dots (CQDs) by using strong oxidants to cut and oxidize macromolecular carbon compounds [63-66]. Lately, a lot of work has been done to create CQDs through chemical oxidation using a variety of carbon sources. Huo et al. used activated carbon as the carbon source and created a straightforward, mass-producible method for creating photoluminescent CQDs. Specifically, nitric acid treatment of the raw materials made them easily etched into individual CQDs, and amine-terminated compounds were then carried out through a passivation procedure.

d) Ultrasonication synthesis

In liquids, ultrasonic waves can produce alternating waves that cause vacuum bubbles to form and rupture. Strong fluid shear force, depolymerization, and high-velocity impinging fluid jets are all caused by these cavitations[63, 67, 68]. This means that macroscopic carbon materials can be chopped into nanosized CQDs using the ultrasonic energy produced during this procedure. Later, it was revealed that an H2O2-assisted ultrasonic technique was used to synthesize CQDs. Interestingly, after six months of storage, there was no evidence of nanoparticle precipitation[63]. Furthermore, Park et al. created green CQDs by ultrasonic treatment of leftover food, and the TEM results showed that the CQDs' average size was smaller than 4.6 nm.

B. Bottom-up approaches

a) Microwave synthesis

Using microwave radiation to break bindings with electromagnetic energy is an eco-friendly and effective way. This method can produce consistent and synchronous heating, which will produce a consistent CQD size distribution [25, 69-71]. Surprisingly, CQDs with excellent dispersion in an aqueous solution were first produced using a microwave technique, and they displayed stable and strong photoluminescence (PL) [25]. To be precise, varying concentrations of sugar and PEG200 were added to deionized water to create a clear solution, which was subsequently heated for 2–10 min in a 500 W microwave; as the reaction duration rose, the colorless aqueous solution turned brown, confirming the synthesis of CQDs. Liu et al. created highly fluorescent CQDs by simply heating citric acid, L-cysteine, and dextrin as basic materials in a microwave. The produced CQDs had an average particle size of 2.61 nm, and they were utilized in Cu2+ detection[72].

b) Thermal decomposition

Previous reports on the synthesis of various magnetic nanomaterials and semiconductors have mentioned thermal breakdown. Prior research has demonstrated that heat from the outside significantly accelerates the carbonization and dehydration of organic materials, turning it into CQDs[71, 73, 74]. Having the low cost and mass production benefits, as well as the customized qualities of CQDs due to the degree of decomposition control. It was claimed that nitrogen-doped graphite QDs were synthesized at a carbonization temperature of 260–280°C utilizing ethylene-diamine tetra acetic acid (EDTA) as carbon sources[73]. The selectivity created by EDTA decarboxylation may gradually merge together in the solid-phase process. High temperatures won't harm the system's nitrogen, which can also be converted into nitrides. Robert used derivatives of citric acid as carbon sources to create CQDs through thermal breakdown, and he used a TEM to determine the average particle size of the CQDs. The size of the CQDs was 5–15 nm after 0.5 hours of the reaction; 2 hours later, the size of the CQDs rose to roughly 30 nm and had a wide distribution[75].

c) Hydrothermal treatment

One common technique for creating CQDs from raw sugar or biomass is hydrothermal treatment, which has the benefits of being inexpensive and easy to use[76, 77]. Following hydrothermal treatment at 180 °C for varying periods of time, the lignin and H_2O_2 combination was filtered, dialyzed, and freeze-dried to produce CQDs with particle sizes ranging from 2 to 10 nm[78]. Furthermore, Hua et al. created fluorescent CQDs using ethylenediamine, dimercaptosuccinic acid, and chitosan. These might be utilized for PDT targeted at the mitochondria and mitochondrial imaging without requiring the modification of additional ligands[79]. Sun and colleagues created CQDs using polyethyleneimine and citric acid using a straightforward one-pot solvothermal technique (160°C 4h). After that, the artificial CQDs self-assembled with PSs (Ce6) and were decorated with Cu2+ to create Cu/CC NPs, which were then used to create a stimuli-responsive tumor microenvironment (TME)[80]. More specifically, at neutral conditions—that is, the environment found in the human body—the nanocomposite demonstrated fluorescence quench. Due to the decreased pH and over-expressed GSH and H2O2 stimulation of TME, the FL imaging, PDT, and chemical dynamic treatment capabilities of Cu/CC NPs were only selectively active in tumors. This resulted in increased phototherapy to further destroy tumors and lessen adverse effects.

d) Templated methods

Because the template approach can produce a wide range of nanomaterials with high QY and a uniform size distribution, it has been widely used in the synthesis of CQDs recently. Using well-ordered mesoporous silica (OMS) SBA-15 as the hard template and the copolymer Pluronic P123 as the soft template, Yang et al. demonstrated an unprecedented softhard template technique toward photoluminescent CQDs from organic molecules. In this research, the target CQDs were generated via carbonization templating and passivation, and the organic precursors were enwrapped into the P123 micelles in an embryo mesostructured silica by a modified synthesis of 3D SBA-15[81]. It's interesting that this method made it simple to modify the size and degree of graphitization of CQDs by choosing various antecedents.

6. Mechanism of working of CQDs

6.1 Photodynamic therapy

The name "PDT" was first used by von Tappeiner, who described it as a site-specific theranostic treatment for cancer. The three main elements of this process are oxygen, light (at the right wavelength), and photosensitizer (PS). When QDs are exposed to laser light as a light source, reactive oxygen species (ROS) are produced as a result of their interaction with oxygen molecules in the tumor environment (damaging DNA and activating the immune response) [82-89]. Due to its minimally intrusive nature, less light dispersion, cost-effectiveness, selectivity, fewer side effects, and the ability to deliver many doses at the same location without going over the dosage limit, PDT offers significant advantages over conventional treatments. Additionally, it has drawbacks such as poor solubility, a near-infrared (NIR) excitation wavelength, the inability to cure malignant tumors because it is a localized treatment [90], and the burning sensation it causes in nearby healthy tissue [91, 92].

In 1903, Tappeiner and Jesionek used eosin as a photoactive PS to present the first PDT results on skin cancer [85]. PDT's clinical application has expanded significantly over time. Numerous research institutes have been looking at the potential use of PDT in cardiovascular therapy, including the treatment of atherosclerosis and the prevention of restenosis following inflatable angioplasty [93-97]. Basal cell carcinomas, psoriasis, bone cancers, ocular melanoma, rheumatoid arthritis, ovarian, prostate, dysplasia, papilloma, and pancreatic cancers are among the conditions for which PDT is currently used [98-100]. PS can

be used in PDT applications in both synthetic and natural forms. 5-ALA, zinc phthalocyanine, tin etiopurpurin, foscan, and MAOP (methyl amino levulinate) are PSs that have recently been created [101].

6.2 Photosensitization

This mechanism is described **in Fig. 3.** In the presence of oxygen (O_2), a process known as photosensitization occurs when PS and visible light combine to create toxic reactive oxygen species (ROS) [102]. Hence, cytotoxicity is started when PS absorbs a specific light source wavelength. For the production of ROS, PDT required two stages: (i) PS administration and (ii) PS activation [103]. Upon exposure to light, PS converts photon energy to the oxygen in the surrounding environment, producing free radicals (superoxide anions, hydrogen peroxides) and reactive oxygen species (ROS) [104].

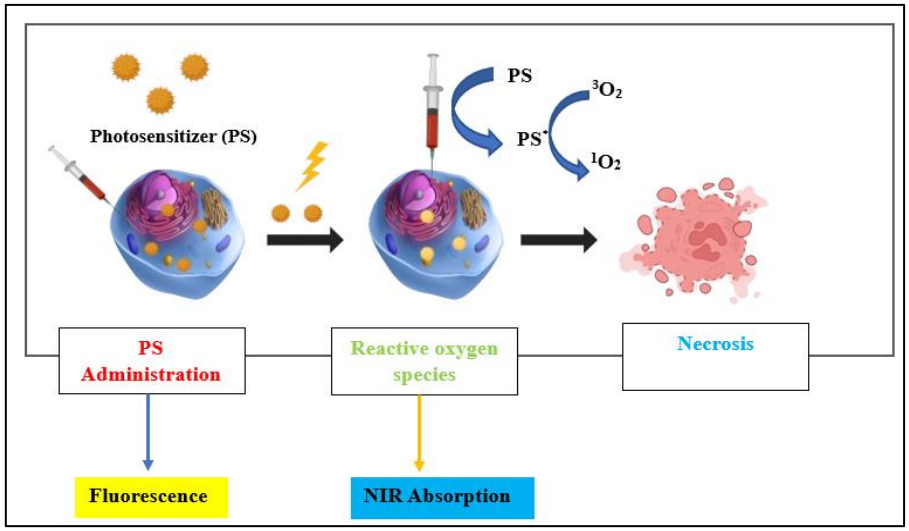

Figure 3: Mechanism of PS (Photosensitizer)

The PS releases at the targeted location upon exposure to an external stimulus, such as an external light source [105]. PS then produces ROS by two distinct processes, type I and type II, after excitation from the singlet excited state to the triplet excited state[106]. O_2 molecules are necessary for both procedures. Through the absorption of certain photons generated by radiation, the PS transitions from the ground state to the singlet excited state [107, 108].

i) Type I mechanism of PDT (charge transfer)

Type I PDT (charge transfer) mechanism: Free radicals such hydrogen peroxide, hydroxyl radicals, and superoxide anion are produced by electron transfer between the cancerous cell and PS [109, 110].

ii) Type II mechanism of PDT (energy transfer)

Due to their identical spins, the PS's energy is instantly transferred to the O_2 molecules (PSO_2) in the type II process [109, 111]. Instead of damaging the cell structure, the excited PS only interacts with O_2 species, which results in oxidative stress-induced cell death [112, 113]. The most crucial phase of PDT is thought to be the type II mechanism. Proteins and other materials are seriously harmed by ROS. Necrosis is the process by which the impact results in the death of cancerous cells [114] **(fig.4).**

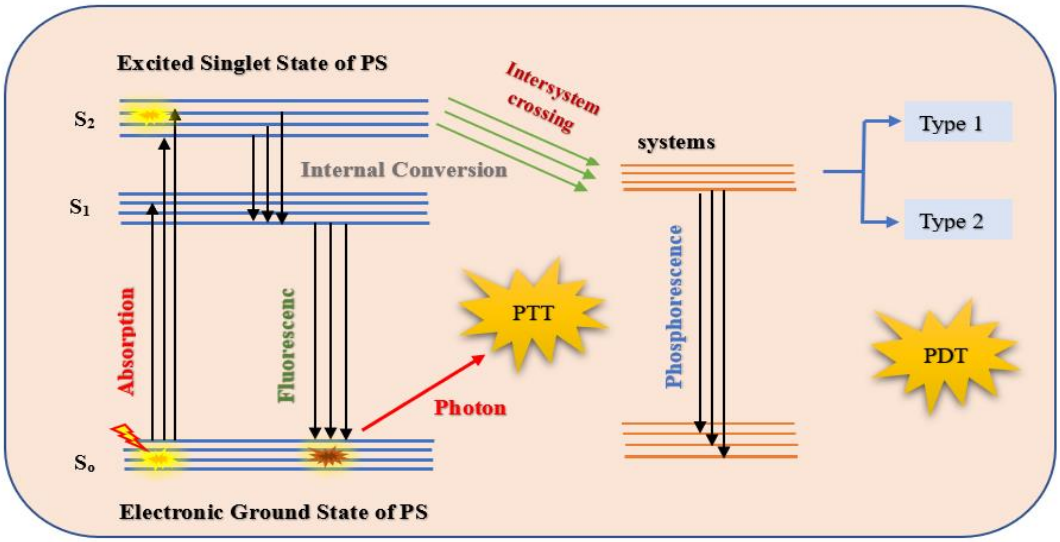

Figure 4: Jablonski diagram explaining the energy levels and transition happening in the PS.

6.3 Quantum dots as a photosensitizer

For the PDT effect, an optimal PS might produce more singlet oxygen species, and for fluorescence detection, it might produce a significantly high fluorescence quantum yield (QY) [102]. Sadly, even well-known PSs like Tookad® and Photolon® have a lower QY than conventional fluorescent dyes, which restricts their theranostic uses for PDT and simultaneous fluorescence detection. In order to address this problem, QDs were employed for improved fluorescence detection and PDT using two different excitation pathways: direct via triplet energy transfer (TET) mechanisms and indirect via fluorescence resonance energy transfer (FRET) processes **(fig. 5).**

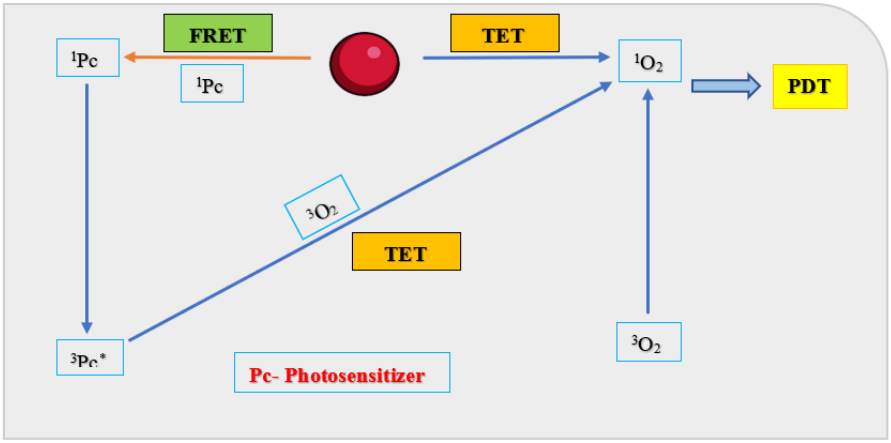

Figure 5: The excitation pathways; FRET and TET mechanism of PDT

FRET: The QDs are perfect for FRET experiments because they have highly adjustable emission properties and are resistant to photobleaching [115-117]. Two light-sensitive molecules exchange energy through this non-radiative process. They might give traditional photosensitizers vitality. For instance, an excitation wavelength between 550 and 650 nm will instantly activate phthalocyanine-based PS phthalocyanine 4 (Pc4). If QDs operate as principal energy donors—that is, if they transfer their energy to Pc4 rather of producing light—then excitation wavelengths between 400 and 500 nm are necessary. Therefore, the FRET process based on QDs is an indirect way to produce singlet oxygen species ($^1O_2$) [115, 118].

TET: Through an energy transfer process, TET directly interacts with oxygen molecules to produce $^1O_2$, which is used in therapies and treatments, without the need for a mediating photosensitizer [111, 119]. To proceed through the TET process, the QDs must interact with the ground state triplet oxygen molecule ($^3O_2$) to produce $^1O_2$. Lysosomes, mitochondria, and other cell organelles sustain irreversible damage from the oxygen species generated [120], leading to changes [118].

6.4 Carbon quantum dots as targeted nano-carriers

By transporting drugs straight to the affected area, nanocarriers often improve the delivery of the API in the tumor while reducing exposure to healthy tissues. This lessens the harm done to the surrounding tissues and the dosage needed for the treatment [121, 122]. High stability, robust mechanical strength, biocompatibility, controlled API release, and easy conjugation with bioactive chemicals are all desirable properties of a DDS material. As drug delivery nanocargos, QDs represent a new paradigm in the healthcare industry due to their exceptional qualities, which include their small size, surface chemistry, optical properties, functionalization, photoluminescence, and—above all—their systematic drug release profile at the cellular level [123-127]. Additionally, they give chemotherapy medications like doxorubicin (DOX) [128, 129], methotrexate (MTX), 5-fluorouracil (5-FU), paclitaxel (PTX), cisplatin, boldine[130], flutamide [131], and lisinopril a greater surface area[132]. Unfortunately, these chemicals assault normal cells out of desperation and have detrimental repercussions. The decreased and harmful dispersion of anti-cancer medications is therefore one of the most significant issues related to chemotherapy. The durability, better water solubility, reduced toxicity, and target specificity of the QD may all be enhanced by a surface coating [133, 134]. CQDs enlarge to enhance cellular absorption, enhance biocompatibility, and solubilize insoluble medications [135]. Only the fluorescent QDs exhibit additional features, such as cold discharge, biocompatibility, additional drug cargo, and manifold imaging capabilities [136].

7. Characterization:

Several techniques were used in the characterization of synthesized CQDs, namely ultraviolet-visible spectroscopy, Fourier transform infrared radiation, X-ray photon spectroscopy, photoluminescence spectroscopy, nuclear magnetic resonance spectrum, transmission electron microscope, and Raman spectroscopy to evaluate photostability.

7.1 Ultraviolet-visible spectroscopy:

Carbon quantum dots (CQDs) are amorphous carbon structures with surface functional groups through the carbonization and polymerization of organic compounds. Because they comprise a core of sp2 carbon and surface states, they exhibit unique absorption properties. These dots' predominant photoelectric absorption was in the

UV-Vis region of 280-380 nm, with extremely small Stokes shifts upon stimulation. The fundamental absorption peaks result from π-π* transitions of the sp2 domains and n-π* transitions of functional groups such as carboxyl, hydroxyl, and amine. For example, in **fig. 6** researchers ascribed the occurrence of absorption peaks at 285 nm and 380 nm to surface states responsible for the extremely strong fluorescence emitted by nitrogen-doped CQDs [2]. Overall, UV-Vis spectroscopy information proves highly useful for describing the optical properties, functionalities, and structural features of CQDs, which are quite helpful in their characterization and prospective application development.

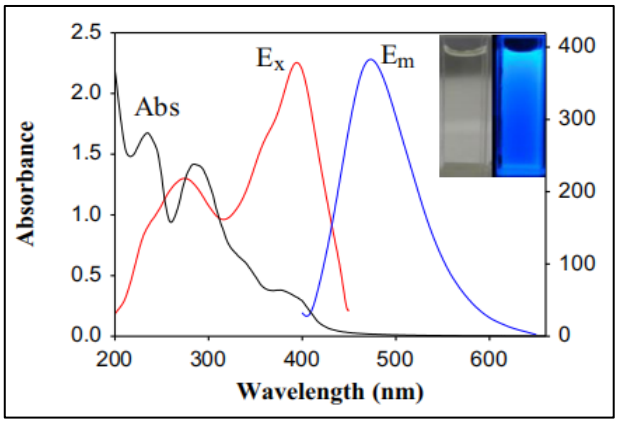

Figure 6: Spectra of N-CQDs dissolved in aqueous solutions demonstrate UV-vis absorption, photoluminescence excitation and emission at mg mL^{-1} [2]

7.2 Photoluminescence (PL):

Carbon nano-dots possess quite interesting PL properties resulting from quantum confinement. For bare CQDs, the photoluminescence QY drops to below 10% owing to the effect of surface emissive traps. Passivation and modification of the surface can significantly improve QY [137]. CQDs have emission spectra ranging from visible to near-infrared, with wavelength-dependent excitation. It generally exhibits an apparent red shift along with emission as the excitation wavelength increases. Aside from that, the emission spectra are determined by the size, functional groups, and presence of heteroatoms[6]. Lin et al. used a solvothermal approach to create CDs from three distinct phenylenediamine isomers (PDs). The resulting CDs can produce numerous fluorescence colors when activated at a single wavelength. The study found that the variance in PL emission between CDs is caused by changes in particle size and nitrogen concentration. Yang's study examined the impact of hydrothermal treatment temperature on PL QY utilizing ultrafast spectroscopy [138].

7.3 X-Ray Diffraction (XRD):

Carbon-based QD characterization and additional information, including particle size, phase purity, and crystal structure, are primarily done using XRD. This method identified the crystalline phases of carbon-based QDs. XRD analysis reveals a considerable degree of disorder on the surface of CQDs, as evidenced by the broad peak. Yang et al. employed this technique to investigate the surface properties of carbon quantum dots**.** Changing the crystalline peak of chitosan from 2θ= 20 to 23° resulted in the formation of CQDs while it exposed an amorphous carbon phase [139]. While XRD profile of DPBI-based CQDs is depicted in **Fig. 7** showing a high peak at 25.8°, which corresponds to the (002) reflection planes, indicating the thinness and disorder stacking of the CQDs [3].

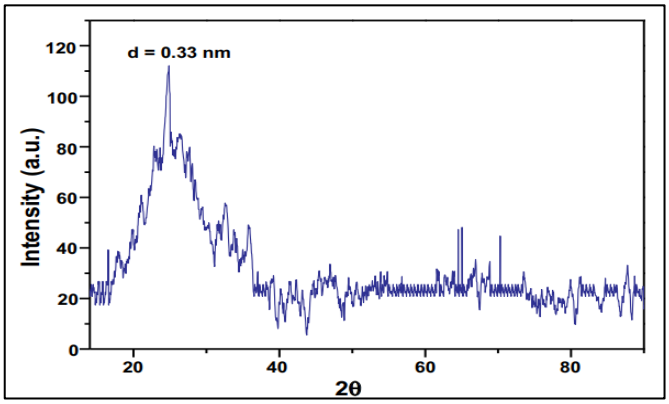

Figure 7: XRD patterns show that DPBI-based CQDs have high crystallinity at 2θ = 25.8° corresponding to the (002) reflection plane [3]

7.4 Raman Spectroscopy:

Raman spectroscopy is a rapid, nondestructive, and very high-resolution tool that relates to the lattice structure and electronic, optical, and phonon properties of carbon materials, such as 3D diamond and graphite, 2D graphene, 1D carbon nanotubes, 0D fullerenes, and carbon-based QDs [140]. CQDs typically exhibit two Raman spectral bands: D band and G band. Li X *et al*. in their work during the investigation of cancer cells using CQDs observed band D at 1346 cm^{-1} and G at 1580 cm^{-1} [141]. Similarly, Fahmi et al. prepared CQDs from bamboo leaves and showed a D band approximately at 1332 cm-1, confirming the highly disordered sp3 hybridized carbon atoms on the surface. They also were able to identify the peak approximately at 1582 cm-1 which pointed to the sp2 hybridized carbon atoms presence on CQDs **(fig. 8)** [4].

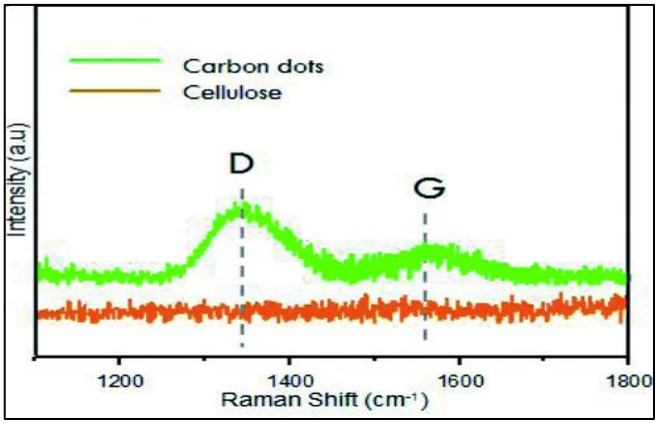

Figure 8: Raman Spectra of raw cellulose and CDs. The Inset presents a photo image of CDs and water against the background of a UV lamp illuminator 365 nm) [4]

7.5 Fourier transform infrared radiation (FTIR):

FTIR spectroscopy is an appropriate analytical technique for the identification and characterization of different carbon compounds. It provides researchers with essential details regarding their composition, structure, and functionalities, which eventually emerge as a crucial tool in understanding and developing new applications. Bangda Yin et al. synthesized CQDS from sweet pepper using a one-pot carbonization technique. They performed an FT-IR spectroscopy study to investigate the surface functions of CQDs. The study found an intense peak associated with the hydroxyl group, which is prone to oxidization. They exploited their understanding to develop hypochlorite ion sensing, a widely used oxidizing agent in chemical synthesis [142].

7.6 Nuclear Magnetic Resonance (NMR):

The hybrid carbon atom in crystalline lattices is identified by the interaction of nuclear magnetic resonance. It also provides a structural perspective of carbon-based QDs. Algarra et al. prepared CQDs using a green variation of the Hummers method from graphite. A ss-NMR study characterized the chemical structure of CQDs. The direct ^{13}C polarization spectrum of CQDs has signals only from the graphitic portion of sp^2 at 128.3 ppm in a magnetic field of 7 T. However, at 14 T the spectrum revealed some other signals at 113.7 and 164.7 ppm, resulting from carbons of the lactol type with 5 or 6-membered lactol rings, ester carbonyl carbons, or carboxylic acid groupings (-CO-O-R or $-CO_2H$) [143].

7.7 X-ray Photoelectron Spectroscopy (XPS)

An important tool in the study of the structural properties of carbon quantum dots is x-ray photoelectron spectroscopy. It depends on a phenomenon called the photoelectric effect, which is very important for the determination of electronic structure, elemental composition and even oxidation states of elements in a material. XPS can reveal the types of surface functionalization, core/shell architectures, and all the components of CQDs. For example, it can be applied to confirm the successful doping of elements such as nitrogen, sulphur, or iodine besides metals like manganese, ytterbium, and ruthenium in CQDs. XPS data provide clues about the chemical composition and bonding patterns involved in CQDs; hence, the researchers can understand its unique features and probable applications [144].

7.8 Photostability (PL):

CQDs exhibit photostability and photobleaching characteristics, so they are highly suitable for applications in bioimaging, photosensing, and energy conversion. Wei et al. found that hydrothermally prepared N, S-doped CQDs through the mixing of mphenylenediamine with L-cysteine exhibited a photobleaching with a photostability to a certain level. The fluorescence stability of the yielded CQDs was investigated in three mediums 0.9% NaCl, PBS (pH = 7) and DI water, which shows that there is a small fluorescence-enhancing effect resulting from the ions. The fluorescence intensity was measured in NaCl at different concentrations between 0.00 and 0.45 mol.L-1, with a maximum value obtained at 0.15 mol.L-1. Prolonged illumination exhibits less than 10% variation in fluorescence intensity with pronounced anti-photobleaching properties [145].

7.9 Transmission Electron Spectroscopy (TEM):

TEM is an electron beam microscopy technique. The ultra-thin material will interact with the sample as it passes through. Electrons in a sample are caused to interact in such a way that they build up an image, which is then magnified and focussed on an imaging device such as a fluorescent screen or sensor. In nanotechnology, due to its resolution of up to 1 nm, TEM is applied very widely for studies of shape and size distribution. For example, Singh H et al. synthesized CQDs presented in **Fig. 9** showed that the CQDs were quasi-spherical in shape and monodispersed structures well separated from each other. The average size distribution was determined to be around 2–4 nm [1].

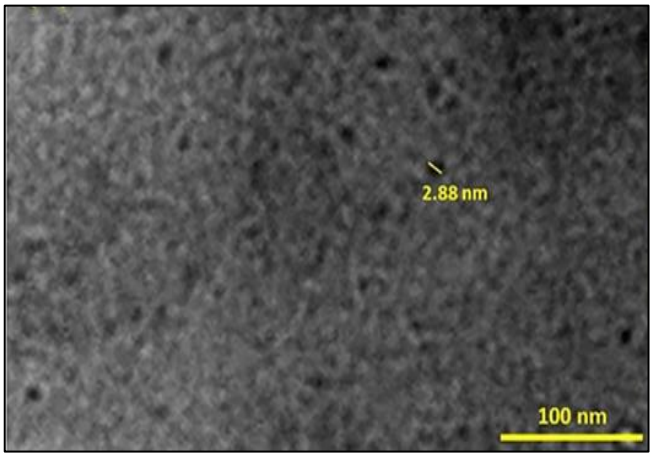

Figure 9: TEM images of CQDs [1]

8. Application of CQDs in cancer treatment systems:

Carbon quantum dots are presently interesting materials in cancer theranostics due to their unique attributes including biocompatibility, photoluminescence, and ease of surface functionalization. It has been demonstrated that CQDs can be very useful for a wide variety of applications, ranging from diagnostics and bioimaging to drug delivery, photoinduced therapy, and sensing.

8.1 Diagnosis:

CQDs can be applied for the diagnosis of cancer via various techniques including fluorescence resonance energy transfer (FRET) and biosensor design. For instance, the diagnosis of breast cancer was performed with CQDs prepared from citric acid and ethylenediamine based on FRET [146]. Analogously, there is another work consisting of tumor cell diagnosis by using CQDs prepared from carbon powders based on the FRET concept. Another promising application of CQDs is in the biosensing identification of cancer biomarkers. Citrus lemon-derived CQDs are found to be efficient for detecting the cytokeratin19 fragment (CYFRA 21-1), a biomarker of lung cancer [147].

8.2 Bioimaging:

The excellent PL properties, water solubility, and biocompatibility make CQDs very promising for bioimaging. Because of their small size, CQDs can easily penetrate the cell membrane and penetrate into the cell, ensuring efficient fluorescent labeling. Scientists have demonstrated the successful application of CQDs synthesized from different sources for bioimaging. CQDs made from wheat straw (WS) have been used in optical *in vivo* bioimaging experiments with animals implanted with tumors [148]. The other example is the application of CQDs in the form of ginseng-derived as an imaging probe [51].

8.3 Drug Delivery:

CQDs can be operated as efficient drug delivery carriers, due to their huge surface area to volume ratio and their ability to interact with many biomolecules, such as antibodies, genes, and antigens, which makes it possible to deliver chemotherapeutic medications into tumor cells via a targeted drug delivery process. For example, CQDs were used to deliver the anticancer drug doxorubicin (DOX) towards the cancerous cells [129]. Another example is the dual-responsive complex consisting of a combination of CQDs, RGD peptide, MPEG, and cisplatin. In this complex, RGD peptide binds with integrin v3 receptors, which are overexpressed in tumor cells [149].

8.4 Photoinduced Therapy:

CQDs have great prospects in photoinduced therapy, particularly with photothermal therapy and photodynamic therapy. Their dark color makes them the ideal candidate for PTT, but optimizations of raw materials and synthetic processes can enhance their photothermal conversion efficiency. In PDT core conjugation, photosensitizers are integrated so that under the irradiation of light, it could generate reactive oxygen species (ROS) preferably leading to preferential killing of tumor cells [150].

8.5 Other applications:

Carbon quantum dots (CQDs) hold more promise for applications beyond their current purpose. They can be used as carriers of drugs to deliver therapeutic genes, which can greatly enhance techniques in gene therapy. The CQDs also show antibacterial properties that help immunocompromised people avoid infections, as observed when derived from Henna leaves [6]. There is the possibility of tissue repair by CQDs, which is useful during the post-surgical healing phase and decreases the damage induced by cancer treatment. Therefore, the anti-inflammatory properties of compounds of this type might provide the basis for the reduction of tumor-associated inflammation and enhancement of other treatments. These applications need to be further researched to determine clinical feasibility.

9. Challenges, future perspective and conclusion of CQDs:

This paper discusses a critical review on recent progress in carbon quantum dots (CQDs) for cancer theranostic application toward cell imaging, drug delivery, photoinduced therapy, and sensing of drugs. While CQDs may have developed rapidly, issues of toxicity and biocompatibility still persist; therefore, more ecological and decomposable synthesis routes must be identified. Genotoxicity concerns also demand a deep investigation to improve anti-tumor therapies effectively. There is also a need for non-toxic CQDs responsive to the biological window of transparency, that is, in the range 650–950 nm where light is better absorbed for photoinduced therapy. Still challenging to target and inhibit cancer tumors of the brain is for reasons attributed to the presence of the blood-brain barrier, which prevents most CQDs from crossing into the central nervous system. Penetration of the blood-brain barriers requires CQDs to be highly specialized. Strategic improvements in bulk industrial production and cost-effective synthesis are some of the biggest challenges in need of immediate attention.

In addition to the difficulties highlighted above, structural design and biomolecule interaction should be studied to gain a better understanding of how self-assembly generates more functional and controllable CQDs. Deforestation is causing the loss of medicinally valuable plant species. The rare medicinal plant and herb species must be preserved and protected to create more opportunities for research in the future about CQDs with anti-cancer properties.

This review has comprehensively elaborated the distinguishing features, synthesis techniques, characterization techniques and applications for targeting cancer with biomolecules and medicinal plant derived CQDs. Since it is non-invasive, with tunability of optical properties and solubility in water, biomedical applications of CQDs must be developed by the teamwork of scientists, industry and health sector for clinical applications. Although these challenges persist, it can be said safely that with long-term intensity in the pursuit of research coupled with growing health awareness in society over time, CQDs are going to become ubiquitous in their biomedical applications in the not-too-distant future.

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