Review Article

Asmaa M. El-Shafey*

Carbon dots: Discovery, structure, fluorescent properties, and applications

https://doi.org/10.1515/gps-2021-0006
received June 16, 2020; accepted November 19, 2020

Abstract: Nanotechnology has become one of the most important topics since the beginning of the twenty-first century in numerous fields including drug synthesis and delivery, environmental protection, electronics manufacture, and astronomy due to their nanoscale particles and their properties. The traditional semi-quantum dots are replaced by a new category of fluorescent carbon nanomaterials. Carbon dots (CDs) have been explored in the last few years for their simple synthetic accession, good bio-consonance, and several revelation applications. This review explains the fluorescent properties of CDs in brief, giving also a background on CDs discovery, structure, and composition, as well as on nanocomposites, green synthesis, and their applications. Resources conservation can be achieved by using recycled substances for sustainable development which lead to a new technology. Fluorescent CDs synthesized from food wastes like bananas, orange peel waste, sugarcane bagasse, *Trapa bispinosa* peels, bread, and jaggery have several applications such as sensing, drug delivery, gene transfer, biological imaging, and food safety. In this study, we concentrate on CDs greener methods to prepare effective and biocompatible CDs.

Keywords: C-dots, fluorescence, nanocomposites, green synthesis, bioimaging

1 Introduction

The important environmental matter that occupied our minds is that the world consists of 7.2 billion people and tolerating the waste resulted from food production as well as consumption of this population is considered a big disaster in our universe, a fundamental environmental issue and huge challenge [1–3]. Agriculture and industry outputs in food production increased by science and technology support, but the statistical studies proved a marked increase in food waste by both the consumer and production sides [4]. It was essential to think of a solution to convert wastes into useful materials to achieve the sustainability principle [5], so scientists worked on nanomaterials synthesis from natural sources and products for biological and environmental sensing applications [6–8]. Xu and colleagues were the first team to discover carbon nanodots (CDs) which are a category of photo luminescent nanoparticles (NPs) [9]. CDs and its derivatives have been used for numerous applications which are considered bioconvenient and eco-friendly as CDs can be prepared from any starting material including carbon; therefore, food wastes were reused because of the majority of by-products of the food; food wastes from vegetables, livestock, fruits, and food industry enhance the progress and sustainability of nanotechnology [10–14]. Figure 1 explains sustainable development of CDs technology [15].

New category of fluorescent carbon nanomaterials has size below 10 nm, which means it possesses ultrafine size which is referred to as carbon quantum dots (CDs). The separation and purification of single-walled carbon nanotubes were the main reason for its first discovery in 2004 [9,16]. CDs are perfect for bioimaging [17–19] by shifting the emission wavelength to the red region as CDs emit blue fluorescence under UV excitation and they also have different properties such as excitation-/pH-dependent property, chemical stability, and resistance to photobleaching as well as up-conversion fluorescence so that the CD synthesis and its numerous applications have been studied (Figure 2) [20].

Renewable resources and small molecules are used as precursors with the aid of heating, microwave irradiation, and ultrasound. Depending on the fluorescence changes, different sensing protocols will be achieved especially plenty of sensing strategies have been developed by variations in the CD synthesis methods [21–23].

CDs have several applications [24–26], such as CD probes in food safety [27]. Various types of contaminants, involving pesticides [28], veterinary drugs [29],

* **Corresponding author: Asmaa M. El-Shafey,** Chemistry Department, Faculty of Science and Arts, King Khalid University, Sarat Ebida, Saudi Arabia, e-mail: sommy_28@yahoo.com

Figure 1: Sustainable development of carbon nanodot technology [15].

bacteria [30], and banned additives [31] can be determined by using CD probes beside food analysis application. Therefore, it is fundamental to gather an inclusive literature review to offer great knowledge about the CD discovery, structure, and composition as well as about the green synthesis of CDs, its fluorescent properties, and its several applications. We wish that the review presents worth information and easy induction of CD-based sensing.

2 CDs discovery

Surface defects in single- and multiwalled nanotubes were the provenance of fluorescent carbon observation. Luminescence is promoted by the carbon nanotube surface passivation [32,33], which led to the CD discovery as we mentioned before; the first time of discovery in 2004 was fortuitously through electrophoretic single-walled nanotube purification. Under UV light, different colors have been exhibited by the fluorescent material of the fast moving band. The result of characterization indicated that the material was completely metal free and consisted of carboxyl groups, and the composition determined was C 53.93%, H 2.56%, O 40.33%, and N 1.20% as indicated in Figure 3 [9]. Since then, numerous methods of CDs synthesis have been reported by many groups of researchers.

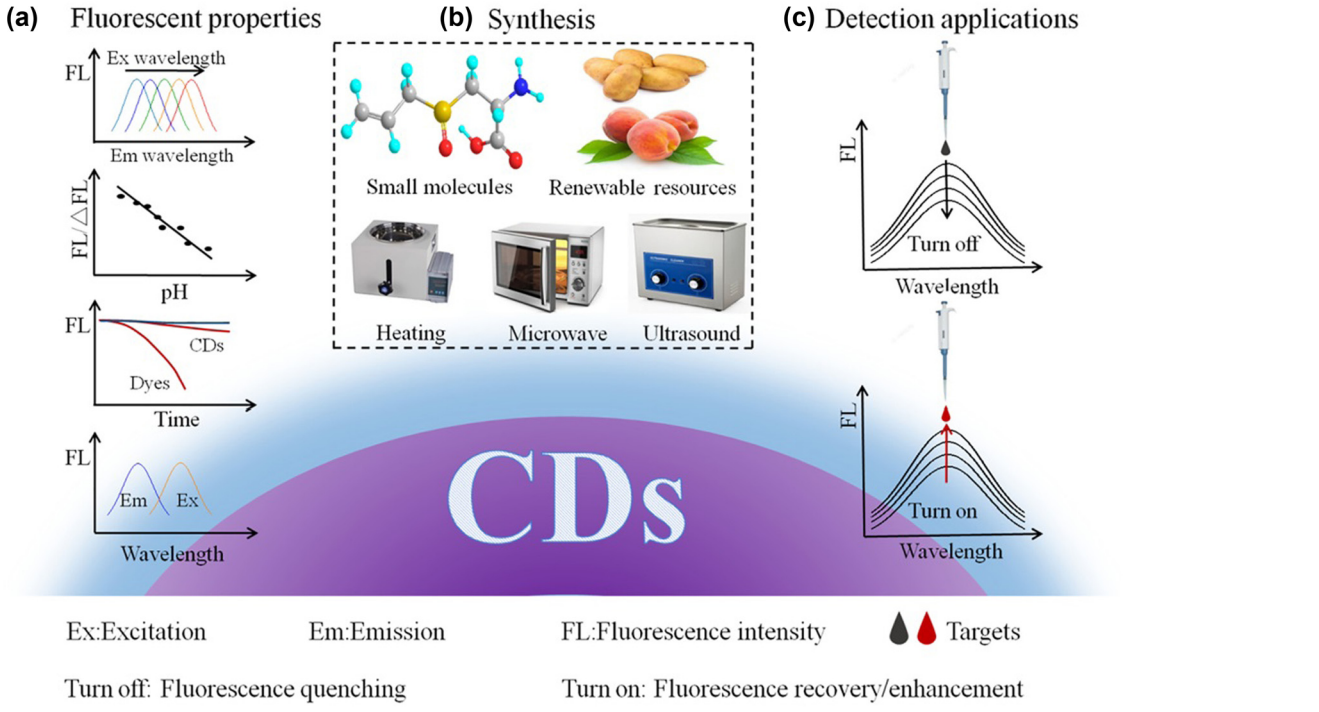

Figure 2: The importance of CDs in fluorescence properties, synthesis, and detection implementations in foods. (a) Fluorescent properties involve excitation-dependent, pH-dependent, antiphotobleaching, and up-conversion fluorescence. (b) Synthetic methods include hydrothermal/solvothermal, microwave-assisted, and ultrasonic-assisted methods. (c) The principles of CD-based biosensor can be divided into two types: fluorescence quenching and fluorescence recovery [20].

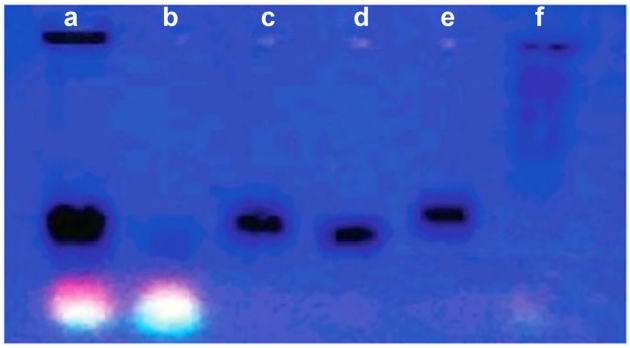

Figure 3: Electrophoretic profile in 1% agarose gel under 365 nm UV light: (a) crude SWNT suspension, (b) fluorescent carbon, (c) short tubular carbon, (d and e) further separation of (c), and (f) cut SWNTs [9].

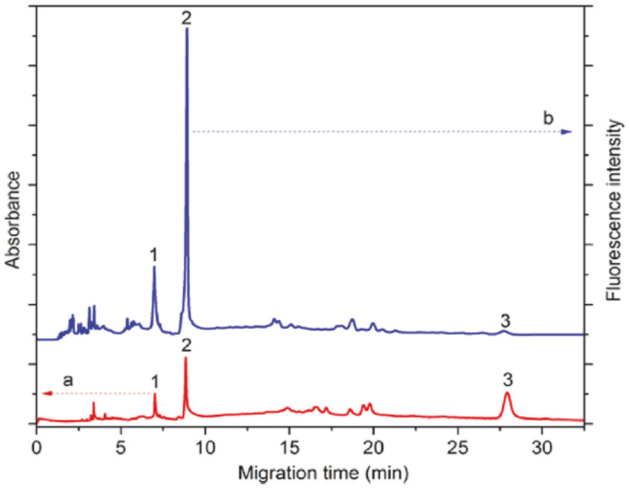

Figure 4: Capillary electrophoretic CD separation monitored at (a) absorption wavelength of 250 nm and (b) laser-induced fluorescence at $\lambda_{ex}/\lambda_{em}$ of 488/550 nm. Peaks (1), (2), and (3) are positively charged, neutral, and negatively charged CDs, respectively [34].

2.1 Capillary zone electrophoresis (CZE)

CZE with featured separation qualification possesses an important speed separation approach for NPs due to their different electrophoretic mobilities (on the basis of charge/size ratio) through an electrolyte solution contained in a fused silica capillary under the impact of an electric field. The CZE utilization in conjunction with a diode array detector (230 nm) for CD separation attained from the flame of an oil lamp. Buffer composition effect tested on the negatively charged CD electropheric pattern by using various pattern types, pH, and concentrations as capillary electrophoresis (CE) is a perfect method convenient to implement favorable separation qualification, the advantages provided by the theoretical plates as high number obtained with CE for CD separation are overshadowed by its UV detection systems, and low sensitivity due to the sample volumes of small injection. To overcome the low-sensitivity limitation of the CDs' analysis accuracy, CDs can be separated by the utilization of CZE apparatus coupled with a diode array detector and a laser-induced fluorescence (LIF) detector. The CD absorption electrograms were obtained at 250 nm and the fluorescence was observed at an excitation wavelength ($\lambda_{ex}/\lambda_{em}$) of 488/550 nm. The separation was achieved using 40.0 cm capillary (50 µm i.d. and 325 µm o.d.) with 30 mM sodium acetate–acetic acid (NaAc–HAc) at pH 3.6 as run buffer and applied voltage of 15 kV. Figure 4 described that the UV (curve (a) and LIF (curve (b)) detection combination detects boosting as well as complex CD mixture supplemental information. For example, positively charged, neutral, and negatively charged CDs gained with two detection processes are the same. While peaks (1) and (2) show intense UV and fluorescence signals, peak (3) exhibits strong absorption but weak emission signals. To explore the reaction time-associated kinetics of CD consistence and identify the functional groups-associated charge states, the CE method was used. Applied CE coupled with UV detection (250 nm) and LIF detection ($\lambda_{ex}/\lambda_{em}$ 488/550 nm) for the separation of hollow CD separation synthesized from glacial acetic acid and diphosphorus pentoxide without external heating. The separation was acheived utilizing 40.0 cm capillary (50 µm i.d. and 325 µm o.d.) with 10 mM sodium dodecyl sulfate and 30 mM phosphate (pH 9.0) as run buffer at an applied voltage of 15 kV. By utilizing UV-Vis spectroscopy, photoluminescence (PL) spectroscopy, and transmission electron microscopy (TEM), the separated fractions were also gathered and analyzed. The CZE is confirmly utilized in identifying the different charge states of CDs species existed in a complex CDs mixture by using individual CE-fractionated. CDs fractions enough amounts collection owing to the low sample injection volume of CZE is time-consumption. The neutral CD species eluted out as one single strong peak, but the charged CDs can only be separated by CE. Isoelectric focusing (IEF) is used for isoelectric point detection of macromolecules and bioparticles. The different sizes of colloidal NPs can selectively be separated by size from their mixture in a homemade miniscale IEF unit as it is a fast, sensitive, and low-cost-effective method [34].

3 CD structure and composition

CDs obtained from different structures may be either graphitic or amorphous. The size of CDs can be tuned by

different nanocomposites. CDs have been studied as a material with a multitude of applications. In terms of analytical attributes (Figure 5), transmission electron microscopy (TEM) and X-ray diffraction (XRD) are commonly utilized to characterize CDs as new material. IR spectroscopy and elementary analysis help in recognizing the surface functional groups which mark CDs' affinity properties and signify chemical mechanisms to be utilized in further expansion. Another attribute of CDs is absorption in UV-Vis spectrum to assess the excitation band for fluorescence spectrum and observe the change in surface properties of CDs because of interaction with another material or derivatization by subordinating fluctuations in the fluorescence intensity of C-dots. CDs' fluorescence emission is used for targets observed under microscope as it makes NPs as label-free probes [11,12].

The reported average size of CDs of less than 10 nm facilitated its use in biological applications. Fluorescence emission can be enhanced by surface passivation of CDs. When CDs were coated by the hydroxyl groups, we noticed the following observations:

1. The reported CD diameter was 3.1 ± 0.5 nm.
2. TEM showed that the particles were uniformly dispersed and spherical in shape as shown in Figure 6.
3. The quantum yield (QY) increased and was about 5.5%.
4. Better fluorescence emission and the particles were photostable [35,36].

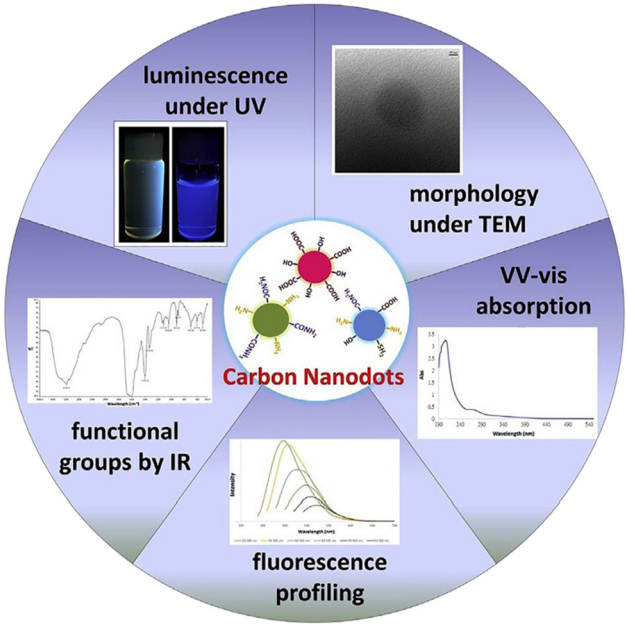

Figure 5: Characterization of C-dots: spectra and images [15].

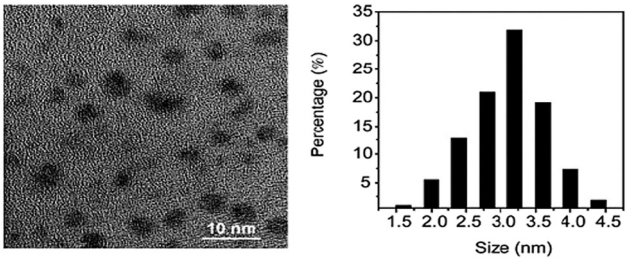

Figure 6: TEM image (left) and size distribution (right) of C-dots [36].

That means if the size of the particle remains under 10 nm even after surface passivation to promote optical properties, CDs would have the best performance in cell imaging.

Another group of CDs prepared from bananas as a starting material had reported a mean size of 3 nm; is spherical in shape; and includes carbon, oxygen, and potassium, though the percentage of potassium is very less and the majority are carbon and oxygen. The interlayer spacing of CDs that involved oxygen-containing groups with sp^3 carbon and hydroxyl connected carbon groups was established to be 0.42 nm which is higher than the graphitic interlayer spacing of 0.33 nm [37], which denotes that CDs are crystalline in nature in comparison to graphite as indicated in Figure 7. The third group of CDs synthesized from food caramels and orange peel waste is amorphous in nature and has no crystalline nature as the XRD displayed a broad amorphous peak [38]. The fourth group of CDs prepared from graphite had a diamond-like structure. The percentage of squares of the ring radius was reported to be 3:8:11:16:19, where the rings correspond to the planes {111}, {220}, {311}, {400}, and {331} that belong to diamond [39]. The fifth group of CDs derived from multiwalled carbon nanotubes by electrochemical oxidation also showed graphitic nature. The high-resolution TEM displayed the lattice spacing to be 3.3°A, which is close to the (002) facet of graphite. The sixth group of CDs attained from candle soot is high in oxygen content and different functional groups such as hydroxyl, carbonyl, carboxyl, and epoxy groups were attached to CDs [40]. The reported structure of soot was C 91.69%, H 1.75%, N 0.12%, and O (calculated) 44.66% [41]. The size distribution of CDs was narrow, i.e., between 2 and 7 nm. CDs have a larger area due to their smaller size, which led to greater absorption to boost CDs' applicability to optoabsorption. CDs also have the susceptibility to allow drug connection to the

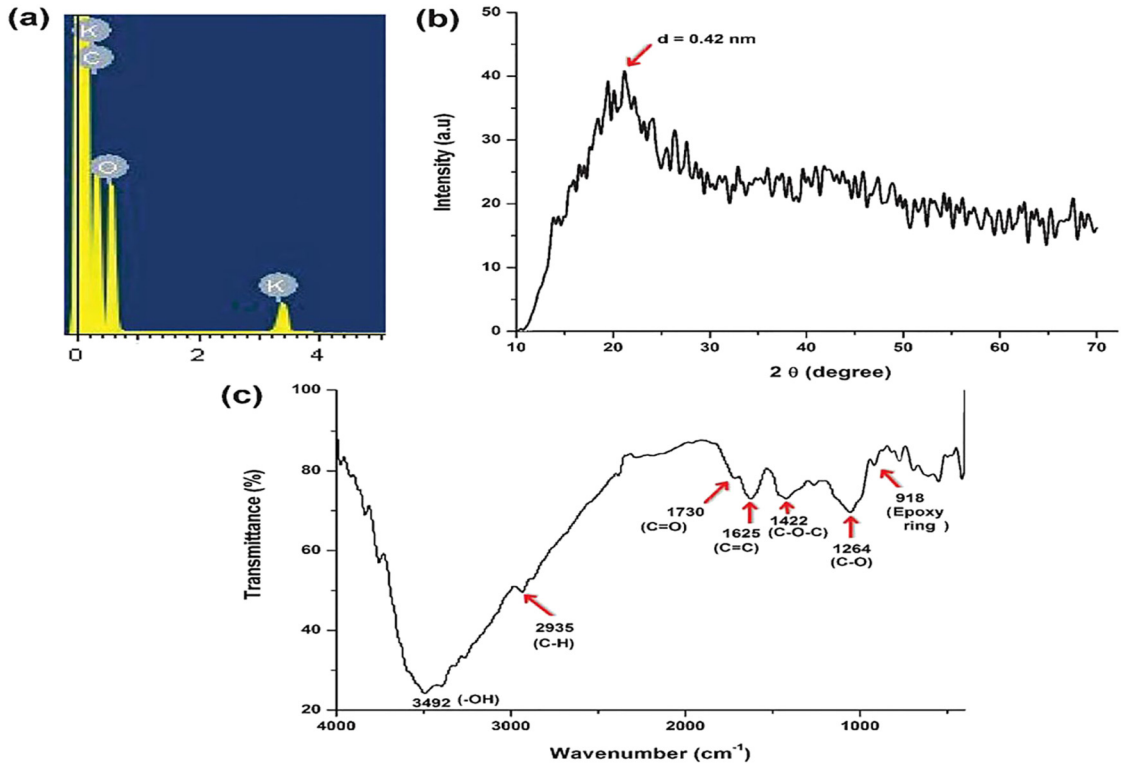

Figure 7: (a) EDX spectrum, (b) XRD pattern, and (c) FTIR spectrum of the carbon dots [37].

surface for drug delivery systems. Finally, the seventh group of CDs, CD/monoclinic bismuth vanadate ($BiVO_4$) nanocomposites, formed two various structures by attaching to nanospherical and nanoplatelet-shaped $BiVO_4$. The complex size increased to 350–400 nm for nanospheres and 500 nm for nanoplatelets [42].

4 Fluorescent properties

CDs' essential optical property is fluorescence emission. However, the mechanism of fluorescence emergence still remains detectable. There are several reported mechanism, including quantum size effect [16,43], surface defect states [44,54], molecular, molecule like states [44–46]. The surface defect states allude to the formed surface defects by oxidation whereas the quantum size effect points to the size effect on radiative recombination of electron–hole pair [47,48]. The CD fluorescence radix in some cases is due to the molecular and molecular-like states, especially for the citric acid-derived CDs [46]. These mechanisms could give explanation for the different fluorescent properties involving excitation- and pH-dependent properties.

4.1 Excitation-/pH-dependent property

By adjusting the excitation wavelength, different fluorescence emissions can be achieved especially when the excitation wavelength changed from 340 to 480 nm, Liu and coworkers observed that the maximum emission wavelength increased from 450 to 550 nm [49] due to the distribution of CDs and the surface states [50–53]. CD fluorescence is affected by pH [54] due to functional group protonation and deprotonation on CDs' surface [55–57]. One of the fluorescence pH sensors has been manufactured by displayed good linearity between fluorescent intensity and pH in the range of 3.5–10.00 [56]. Multicolor imaging, pH sensing, and the fluorescence mechanism are controlled by excitation-/pH-dependent properties which play the main role [58–60].

4.2 Chemical stability, antibleaching, and photobleaching properties

Fluorescence sensing/imaging in detection applications needs stable fluorescence signal and long emission lifetimes. CDs emitted strong fluorescence in aqueous

solution for 6 h [61,62] or even 1 year [63] as CDs are stable when maintained in aqueous solution and high-salinity solutions for long period. By dissolving in 4 NaCl solution as well as in high concentrations (400 μM) of H_2O_2 solution, Liu's group noticed a perfect signal of oxidation impedance when the prepared CDs were quite stable [64]. CDs usually display excellent impedance to photobleaching as CDs have the ability to resist changes in pH over the wide range of 3–12 [65] that is, photobleaching impedance is more important than chemical stability due to the long observation times reported in other essays. For instance, various CDs fluorescent intensity reduced slightly after UV irradiation for 12 h [66] and 24 h [67].

4.3 Up-conversion fluorescence

The emission wavelength is shorter than the excitation wavelength which is referred to as up-conversion fluorescence. Decrease in the background autofluorescence is due to the longer excitation wavelengths and various labeling with different emission wavelengths' sand photon tissue permeation improvement as a result of up-conversion fluorescence, which makes it an essential role in imaging [68]. CDs prepared by ultrasonic treatment has the property of up-conversion fluorescence [62,69,70]. CDs prepared from glucose and ammonium hydroxide displayed an up-conversion emission in the range of 300–600 nm with excitation at 650–1,000 nm [62]. Two photon absorption may generate up-conversion fluorescence [71].

4.4 Long wavelength attributes

When the CDs reported were illuminated with UV light, it emits blue fluorescence [21,72,73]. The biological analysis utilizes blue-emitting CDs which is not veiled since biotissues and cells also emit blue fluorescence, which will lead to spectral interference, so the perfect solution to this problem was to use long wavelength emission to conquer this matter. Numerous treatments such as surface modification [74], size control [75], and pH control [60] were used to prepare CDs with longer wavelength fluorescence. The introduction of heteroatoms such as nitrogen [76] and oxygen [71] led to the red shift in the emission wavelength in spite of the fluorescence from blue to green/yellow. By forming a large conjugated π system, the CDs with red fluorescence have been easily prepared. Preparation of red-fluorescencing CDs with high QY can be executed by using p-phenylenediamine [77] and 1,3-di-hydroxynaphthalene [78] and using the threefold symmetric phloroglucinol as precursor, Yuan et al. [79] worked on expanding the conjugated π system under controlled conditions to prepare highly fluorescent CDs from blue to red to decrease the spectral interference fluorescent signals and protect tissues from potential damage in addition to CDs with longer emission wavelengths' preparation shares in the explanation of the fluorescence mechanism.

4.5 Toxicity

Material toxicity is a significant measure of the material's potential manipulate environment and its denizens in various applications. In the last few years, the toxicity of CDs was discovered. 3-(4,5-Dimethyl thiazol-2-yl)-2,5 diphenyltetrazoliumbromide (MTT) assay is a common *in vitro* toxicity analysis and is assessed by multiple groups. Zhang et al. explored whether the assigned CDs in HeLa cells would have frivolous toxicity in the concentration range of 50–400 μg/mL [80–82]. Sahu and coworkers found that CDs were acceptable at high dose (200 μg/mL) for prolonged incubation time (72 h) and nontoxicity to L929 cell lines when the CD concentration is elevated as 1 mg/mL [83]. Zhou et al. show that the viabilities in MCF-7 cells minimized by 20% [84]. CD toxicity is connected with the surface passivating agents [85] and modulated materials, such as polyethylene glycol (PEG) [80] and polyacrylic acid [86]. The attained results indicated that these CDs are still characterized by the low toxicity *in vitro*. Yang and coworkers estimated the toxicity of CDs in male CD-1 mice even at elevated dosage of 40 mg/kg (CD/body weight) according to the serum biochemistry assays and histopathological analyses [87]. Also, *in vitro* toxicity of CDs and by taking their surface charge into consideration, mouse fibroblasts NH/3T3 cells [88] showed that CDs with negative charge due to the carboxylic groups arrested the G2/M phase of the cell cycle. It is clear that CDs' fabricated reproduction led to higher active oxygen species index without emanating the cell nucleus. Polyethylene glycol (PEG)-modified CDs having neutral charge did not stimulate any abnormalities in cell morphology, neither in intracellular trafficking nor in cell up to a dose of 300 mg/mL. If CDs were coated by polyethylenimine (PEI) with positive charge, they will be the most toxic, being capable of

getting in the nucleus and boosting changes in the G0/G1 phase of the cell cycle at concentration as low as 100 mg/mL. Cytotoxicity profiling CDs from fresh tender ginger juice quelled the growth of human hepatocellularcarcinoma cells with an IC_{50} of 0.35 mg/mL and accompanying 18-fold rise in cellular ROS production [89]. Furthermore, CDs arrested the growth of liver tumors in a BALB/c mouse paradigm, and these CDs were intoxic to MCF-10A cells (noncancerous mammary epithelial cells), FL83B cells (normal liver cells), a 549-cell (human lung cancer), MDA-MB-231 cells (human breast cancer), and HeLa cells (human cervical cancer) [90]. CDs synthesized from spent green tea were water soluble and arrested MCF-7 (IC_{50} = 0.155 mg/mL) and MDA-MB-231 (IC_{50} = 0.072 mg/mL) cell growth with lower toxicity to HeLa, LLC-PKI (renal proximal tubular), and MCF-10A cells. ROS generation occurred in the inhibitory activity. CDs had a little impact on the thrombin activity by fibrinogen conversion to fibrin, thus posing no hazard on blood coagulation. These results showed that CDs with low toxicity can be considered the gold standard in the context of sustainability. According to the CDs' impact in air, rats, and fish [91], many scientists evaluated the low [92] environmental CD toxicity when the CD concentration is not so high.

5 CD nanocomposites

CDs offer an appropriate photo charge carrier flow as it both accepts electron and transports electron, thus boosting the photocatalytic characterization. Semiconductor carbon nanomaterials' preparation led to enhanced catalytic qualification. A lot of reports discussed CDs photocatalytic nature without complex formation as CDs were prepared by using alkali-assisted electrochemical method. C-dot irradiation by near-infrared (NIR) light was used to test the photocatalytic activity led to benzyl alcohol oxidation to form benzaldehyde, which means the photocatalytic activity of CDs has the ability to transform alcohols to their corresponding aldehyde [93]. When ZnO is excited by UV light, electron–hole pair results plus initiation of hydroxyl formation in water [94] making it a stable visible-light-driven photocatalyst [36]. Carbon NPs' union with ZnO aids in enhancing the optical properties. A report explained the solution dispersion method of CDs loaded with ZnO and also naphthol blue black (NBB) azodye was tested using ZnO doped on CDs, as seen in Figure 8. Complete degradation of CDs occurs after 45 min whereas using pure CDs led to the degradation of 4.4% NBB was within the same period [40]. This reflects the fact that photocatalytic nature of CDs makes it useful for harmful dye degradation.

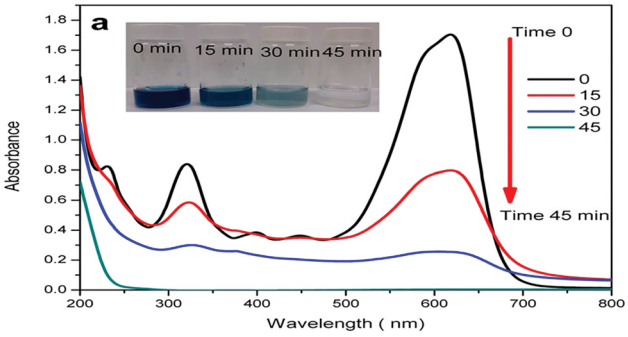

Figure 8: Absorption intensity differentiations of NBB azodye at different irradiation intervals in the existence of CDs/ZnO [40].

Waste water treatment can be executed by using CDs with other photocatalytic materials. Excellent photocatalytic characterization of silver orthophosphate (Ag_3PO_4) was explained by many reports. It can be used to degrade organic contaminants and water oxidation in spite of less tendency to be water soluble. CDs/Ag/Ag_3PO_4 and CDs/Ag_3PO_4 photocatalytic systems were prepared as mentioned by different studies by simple dispersion of CH_3COOAg and polyvinyl pyrrolidone in a CD solution, and Na_2HPO_4 was added drop wise, and the former was stirred at 25°C for 4 h in dark and the resultant material was dried in an oven at 50°C for 12 h [95]. After complex formation, characterization was examined by various techniques – as seen in Figure 9, SEM image detected the rhombic dodecahedral morphology of the complex with a size of 800–900 nm; and the UV-Vis spectroscopy explained that the complex absorbs in the range of 530–1,000 nm led to photocatalytic activity estimation and also its essential role in absorbing sunlight. Under visible light irradiation, methyl orange (MO) photocatalytic activity was shown by CDs/Ag/Ag_3PO_4 complex as MO dye was completely degraded within 10 min, on the contrary to CDs/Ag_3PO_4 complex which needed at least 25 min for degradation while pure Ag_3PO_4 requires 55 min to degrade, which means the prepared complex has the highest photostability and catalytic activity in addition to up-conversion PL exhibition. Photostability improvement, photocatalytic activity, and photocorrosion dodge of metal complex perform as an electron reservoir and take advantage of the entire spectrum of sunlight. By mixing the as-prepared $mSiO_2$ with glycerol and PEG-NH_2 at 230°C for 30 min, a C-dots@miSiO_2-PEG nanocomposite resulted, which was tested for drug delivery as it offered enough space for storing drug molecules, thereby performing as an efficient carrier. For example, controlled drug delivery was prepared using the water-soluble anticancer drug doxorubicin (DOX) was loaded into the

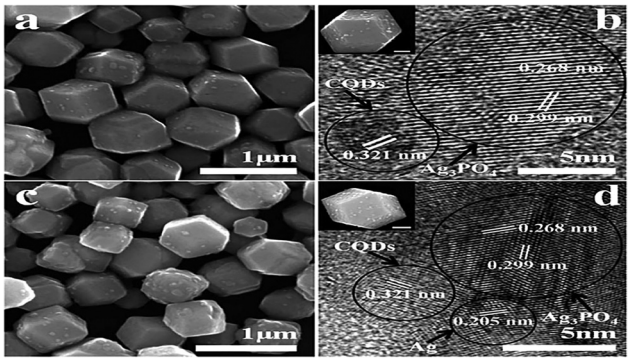

Figure 9: (a) SEM and (b) HRTEM images of CDs/Ag_3PO_4 complex photocatalyst. (c) SEM and (d) HRTEM images of CDs/Ag/Ag_3PO_4 complex photocatalyst [22].

nanocomposite by reducing the drug pre-release before drug absorption by the target cell [96]. $BiVO_4$, a semiconductor material, was used to improve the photocatalytic activity of complex formation with CDs. Degradation of methyl blue dye under visible light at room temperature was used to examine the photocatalytic ability of this complex [42]. Besides, semiconductor complexes considered an important example of photocatalytic activity of CD complexes, especially formation of semiconductor/CD complexes gives the maximum light energy [97]. The essential requirement for photocatalytic systems is improving the power conversion efficiency. Rhodamine B (RhB)/TiO_2 complex was doped on CDs to give an example of CD complex synthesis to perform a semiconductor photoelectric conversion system that led to improved photocurrent density. By CDs' addition to the aqueous RhB solution, there is an increase in the UV-Vis absorption. Due to the presence of oxygen-bearing functional groups, the doped CDs were of greater solubility, and UV-Vis absorption becomes greater when CD was <10 nm. As CDs perform as an electron transfer intermediate, it enhances the charge recombination reduction which means complex system achieved PL quenching. All the previous results led to the knowledge that by using such CDs/dye/semiconductor complex systems, high-efficiency photoelectric systems can be achieved [98]. MO dye degradation can be achieved by N-doped CDs. Harmful chemicals present in water degradation can be achieved by photocatalytic activity of such complexes [99]. CD nanocomposites formed with different materials can be used in many fields such as optoelectronics, drug delivery, waste water treatment, etc. All the previous studies about CD nanocomposites give an idea about the novel composites with NP development to be used in numerous applications.

6 CD green synthesis

New research discussed green synthesis and found good salience. Preparation of value-added products from biodegradable waste is an important topic in the green chemistry field. The affirmation on green chemistry to decrease the use of high-end chemicals due to the toxicity concerns. The materials used in the green synthesis should be eco-friendly and cheap so they are produced from plants to be used as the starting materials. Green synthesis has many advantages, that is, it is biocompatible, non-time-consuming, less toxic, economical, and requires lower temperatures, so it is considered an interesting topic for researchers. Carbon can be extracted by green synthesis as it is available in all organic materials. One of the reports discussed CDs' green synthesis from orange peels by hydrothermal treatment [40], as it is a cheap renewable method to prepare chemical compounds from eco-friendly starting material. Hydrothermal synthesis uses high-pressure and high-temperature conditions, leading to perfect morphology of the structures and considered economic method because of using water as a solvent. First, washing the peels and then exposing it to sunlight for drying followed by oven drying at 150°C for 10 h followed by the addition of H_2SO_4 to wash the carbonized peels rinsed with water, soaked with sodium hypochlorite solution for 4 h, and after that washed with water until the pH of the washed water reached 7; the preheated oxidized orange peels were hydrothermally treated in a Teflon lined autoclave at 180°C for 12 h and then dichloromethane was added to the resulting solution and the separating solution centrifuged at 5,000 rpm for 20 min to obtain a brown solution of an aqueous suspension of CDs as shown in Figure 10. The QY was 12.7% and the resulted particles were 2–7 nm in diameter. Another report displayed a different method for hydrothermal synthesis of CDs from sugarcane bagasse, which contains large amount of carbon and so it is considered a renewable resource as CDs can be easily produced. Bagasse should be soaked in concentrated sulfuric acid for 24 h at room temperature and then washed it in hot water and alcohol until the filtrate become neutral, dried in an oven overnight to obtain carbonaceous blocks, mixed it with NaOH solution, heated for 1 h, and then filtered for elimination of large particles. The solution obtained showed weak fluorescence due to the darkness of the filtrate. Alkaline hydrothermal treatment was implemented on the obtained solution, which gave a bright yellow solution. The QY was about 4.7% [100].

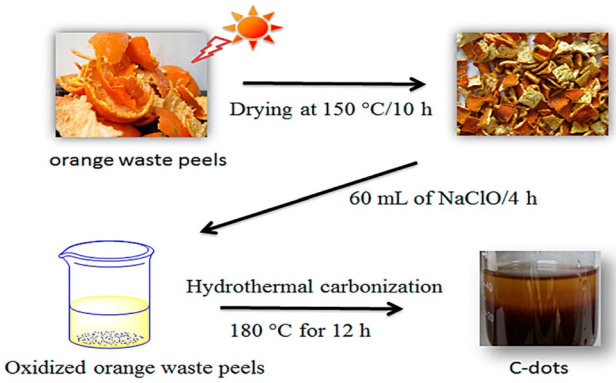

Figure 10: Formation of C-dots by using waste orange peels' hydrothermal treatment [40].

Another group prepared biocompatible CDs from aqueous extracts of *Trapa bispinosa* peels which is considered simple, rapid, and effective method. First, *T. bispinosa* peels were washed in water, soaked in cold water for 30 min, the peels were crushed in distilled water, centrifuged, and suspended in NaOH solution to produce a clear yellow CD suspension [101]. CDs were prepared by centrifugal separation from sugarcane juice; a facile method to prepare crystalline CDs from highly alkaline sugarcane juice. A few milliliters of NaOH solution were added drop wise into the sugarcane juice, which is stirred until a reddish brown solution is obtained, centrifuged at 5,000 rpm for 15 min, and checked under the UV light to have a dark green fluorescence. Sucrose density gradient centrifugation was executed to separate CDs from the mixture. As banana juice contains glucose, sucrose, fructose, and ascorbic acid, some recent study synthesized CDs from banana juice. Banana juice was extracted by crushing banana with a small amount of water, the pulp-free juice was extracted, mixed with ethanol, heated in a glass bottle closed with a cotton cork, then kept in an oven at 150°C for 4 h. When the solution cooled to room temperature, it turned into a dark brown product, which was then mixed with water and filtered to separate the residue. The aqueous solution was mixed with ethanol and centrifuged at 3,000 rpm for 15 min at room temperature, and the ethanol was evaporated completely to obtain the fluorescent CDs whose yield was 600 mg [37]. According to all the previous reports, CDs' green synthesis is of high prominence in the present-day script. These methods have many advantages as it uses very cheap starting materials so it considered cost-effective in addition to high yield of CDs [102]. All the previous methods in the abovementioned reports facilitate the discovery, and many other research of CDs synthesis explained the simple and cost-effective methods. The CDs obtained from eco-friendly starting materials are nontoxic and biocompatible and have fluorescence properties to be applicable in bioimaging technique.

7 CDs synthesis from commercially available food products

The commercial food products consumed in our day-to-day life can be discussed in many recent research. Amorphous CD synthesis is discussed in many recent research. Amorphous CDs are present in different caramel-containing food products like jaggery, sugar, bread, biscuits, and corn flakes; and CDs were extracted from the browner part of the bread, caramelized sugar, and jaggery. The materials were of caramel color under white light and blue fluorescence under UV light as shown in Figure 11. The lowest QY was from jaggery observed at 0.55% and the highest bone was from bread observed at 1.2%. CD morphology was spherical according to TEM images. Bread-extracted CDs possess the highest particle size while those extracted from sugar caramel have the lowest one. The amorphous nature of CDs was obvious by XRD analysis. Due to the presence of carboxyl and alcohol functional groups, the synthesized CDs were hydrophilic in nature [38]. All the pervious perceptions led to the affirmation of CDs' existence in these food products. Coffee grounds can be heated, dried, and separated to synthesize CDs. CDs' preparation from coffee grounds is a simple method as it includes the following four stages: dehydration, polymerization, carbonization, and passivation. As a result of dehydration, polymerization and nucleation occurred in addition to carbonization due to heating. Nuclei growth occurred by solute diffusion toward particle surfaces. Prepared CDs were characterized by using different techniques. The average diameter of the particles was ±2 nm according to TEM results. The existence of carbon atoms was confirmed by XRD as well as EDX data as showed in Figure 12. The amorphous nature of CDs was detected by Raman analysis. The fluorescence emission spectra exhibited a broad range from blue (400 nm) to red (600 nm). The emission peak position shifted to longer wavelengths when the excitation wavelength was increased and the intensity decreased. When excited at 365 nm, the strongest PL of 3.8% occurred at 400 nm and the CDs' fluorescence could only be noticed when they were surface passivated [103]. CD synthesis aids in the management of wastes as the mentioned in the previous reports. CDs can

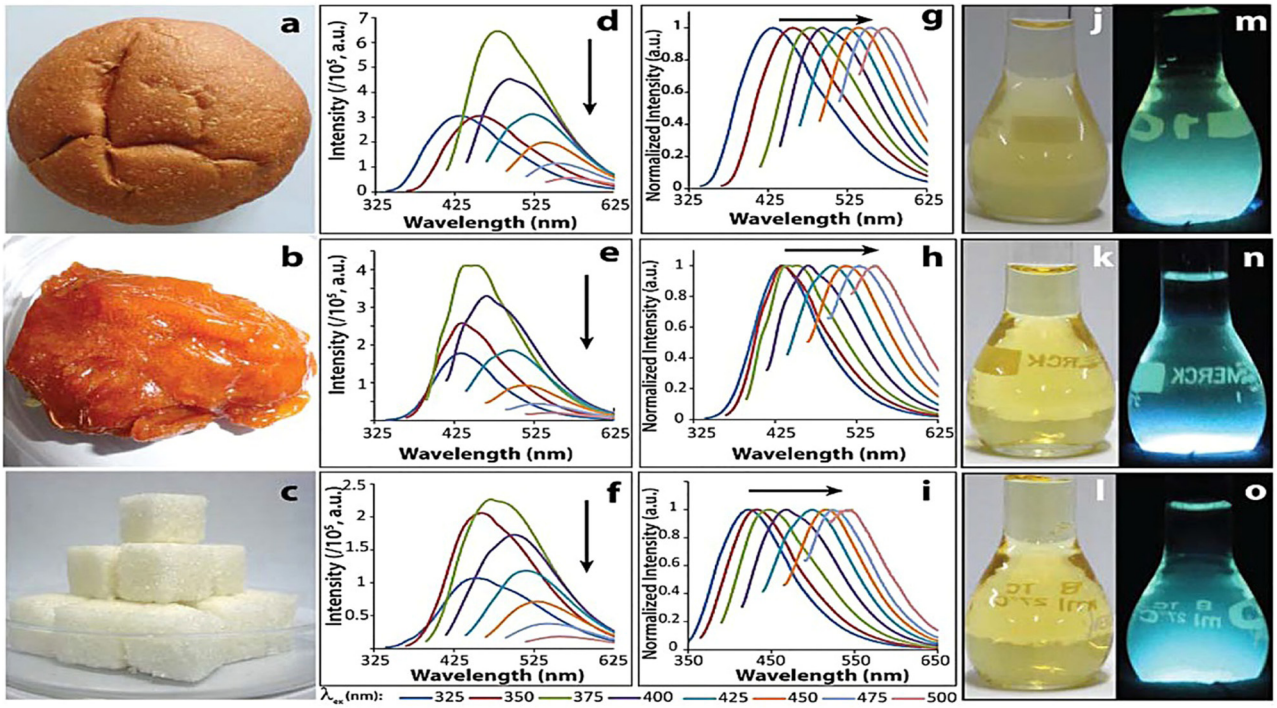

Figure 11: (a–c) Photographs of commercial bread, jaggery, and sugar. (d–i) Excitation-wavelength-dependent emission spectra of CDs from bread, jaggery, and sugar caramel. (j–l) Photographs of CDs dispersion from bread, jaggery, and sugar caramel observed under white light, and (m–o) the same under UV light [38].

be produced from many carbohydrate-rich food products. Waste management participation and green chemistry help in promoting scientific research. Recent improvement in CD synthesis was achieved using greener methods. Green chemistry use compared to the physical methods facilitates the process and offers an eco-friendly synthesis.

8 Applications of C-dots

8.1 Sensing

The most important CD application is the sensing field. On the basis of the fluorescence properties and the surface of CDs' functional groups, such as Hg^{2+} detection and biological thiols (Figure 13a) [104] the electrons and the holes of CDs can be restructured and the fluorescence of CDs can be quenched by Hg^{2+}. The fluorescence of CDs can be restored as Hg^{2+} has strong coordination ability with thiols and recognize the "turn-off" detection of Hg^{2+} and "turn-on" detection of thiols. By using fluorescence quenching from the coordination between CDs' amino group and Cu^{2+}, Dong et al. [105,106] synthesized a branched PEI-modified CDs for Cu^{2+} detection in a river samples with a 6-nM detection limit of 9 (Figure 13b). Quenching effect of Cu^{2+} on the fluorescence CDs enhances image detection of cellular Cu^{2+}, and probing the Cu^{2+} position in cells (Figure 13c) was attained by using AE-TPEA-CDs-CdSe/ZnS nanocomposite [107]. Cellular Cu^{2+} was detected by Vedamalai et al. [108] who used synthesized Cu^{2+}-sensitive CDs. Acetyl choline (ACh), which transformed to choline by acetylcholinesterase by using CDs reduced graphite oxide (CDs@RGO) composites whereas choline could beget H_2O_2 in the existence of choline oxidase (Figure 13d) [109]. The quenching C-dots@RGO fluorescence

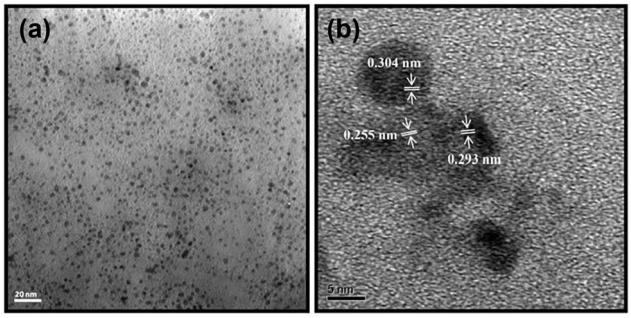

Figure 12: (a) TEM and (b) HRTEM images of CDs [103].

ability of H_2O_2 assists the ACh quantitative detection with 30 PM detection limit. Biological active substances were detected by CDs-Ag/CDs-Au nanocomposite which has another trial in biosensing field [110–112]. The detection limit of glutathinone by using fluorometric/colorimetric bimodal sensor based on CDs-Au composites was 50 nM [111]. In colorimetric method, the detection limit was 0.18 and 1.6 μM for H_2O_2 and glucose, respectively [110]. A boric acid-modified CDs were prepared by Zhang et al. [113] for the glucose detection with the limit of 0.03 nM, taking into consideration the strong affinity between glucose and boric acid (Figure 13e). Glucose was used as a precursor to synthesize a CD via neutralizing the heat process [114]. Because the adjacent hydroxyl groups from glucose remained on the CDs' surface, these CDs exhibited a perfect affinity to boric acid, so CDs had an ability to detect glycoprotein. Chemiluminescence (CL) and electrochemiluminescence (ECL) biosensors were well constructed by using CDs. Lin et al. invented a CD-based CL sensor for nitride detection as they discovered that CDs had CL signal in the presence of nitrous acid peroxide (Figure 13f) [115]. To track Cu^{2+} in the mice brain, Shao et al. [116] utilized CDs and Tri prime and amplification (TPEA), which showed electrochemical response. Cd^{2+} detection with a limit of 13 nM was achieved by Li et al. [117] who constructed a graphene nanodots-based ECL sensor (Figure 13g).

8.2 Drug delivery and gene transfer

One of the interesting fields of CDs application is drug delivery and gene transfer. Recognition of cancer cells can be achieved by using folic acid-modified CDs by amide condensation reaction which offered a good method to improve cell screening and disease diagnosis [118]. PEI-modified CDs have a positive surface potential, so it could absorb the negative DNA to transfer gene [119]. Liu et al. [119] discovered that CDs not only had fluorescence characterization to display the plasmid DNA distribution during the transfer process but also offered detailed information for plasmid DNA physiological function research. After transfection for 3 h, CD DNA composites could enter the cell. During the transport process, different wavelength excitation CDs preserved multicolor fluorescence property.

Lai et al. [120] synthesized a PEG-modified CDs and fulfilled DOX loading and delivery. DOX in cells' release

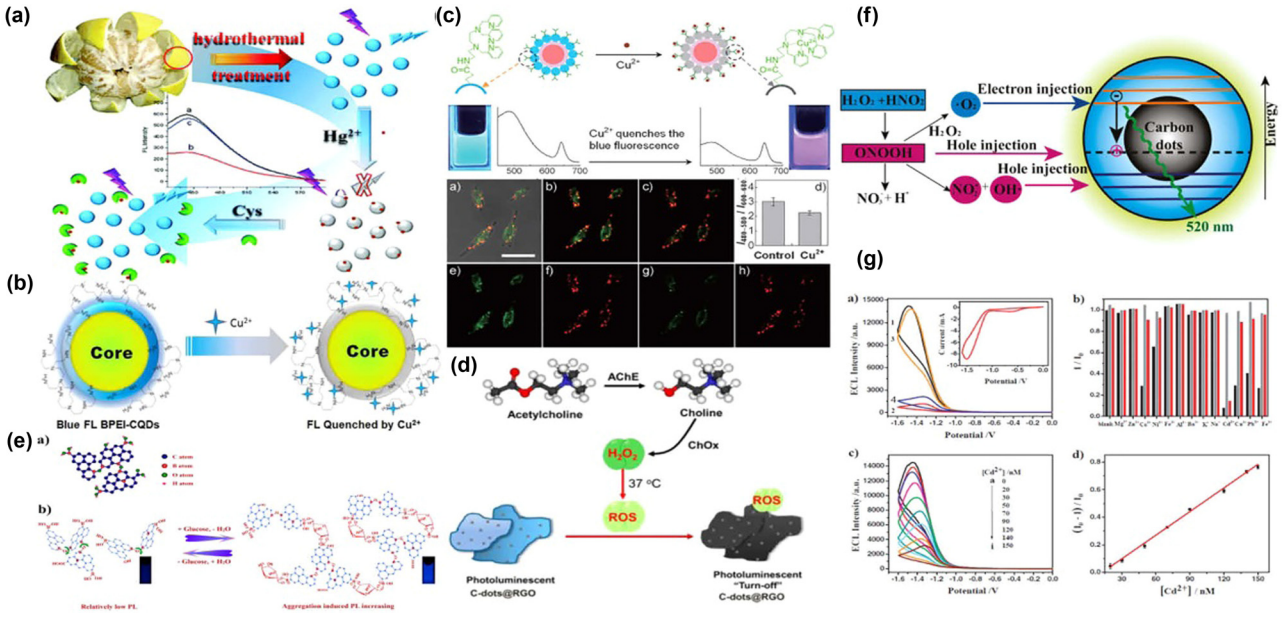

Figure 13: Bio-/chemsensing applications of carbon dots. (a) Schematic representation of an Hg^{2+}/cys (cysteine) biosensor based on CDs prepared from pomelo peel [104]. (b) Schematic representation of a Cu^{2+} biosensor based on CDs-BPEI (branched polyethylenimine) [105]. (c) Fabrication of a ratiometric fluorescent sensor based on a CDs-CdSe/ZnS hybrid material for detection of copper ions, and *in vivo* imaging and monitoring of cellular copper ions [107]. (d) Schematic representation of detection of ACh by C-dots@RGO in a TURN-OFF Strategy [109]. (e) Schematic representation of boron-doped graphene quantum dots, and mechanism for glucose sensing by boron-doped graphene quantum dots [113]. (f) Mechanism for nitrite sensing based on CL of CDs induced by peroxynitrous acid [115]. (g) ECL sensing for Cd^{2+} based on graphene quantum dots [117].

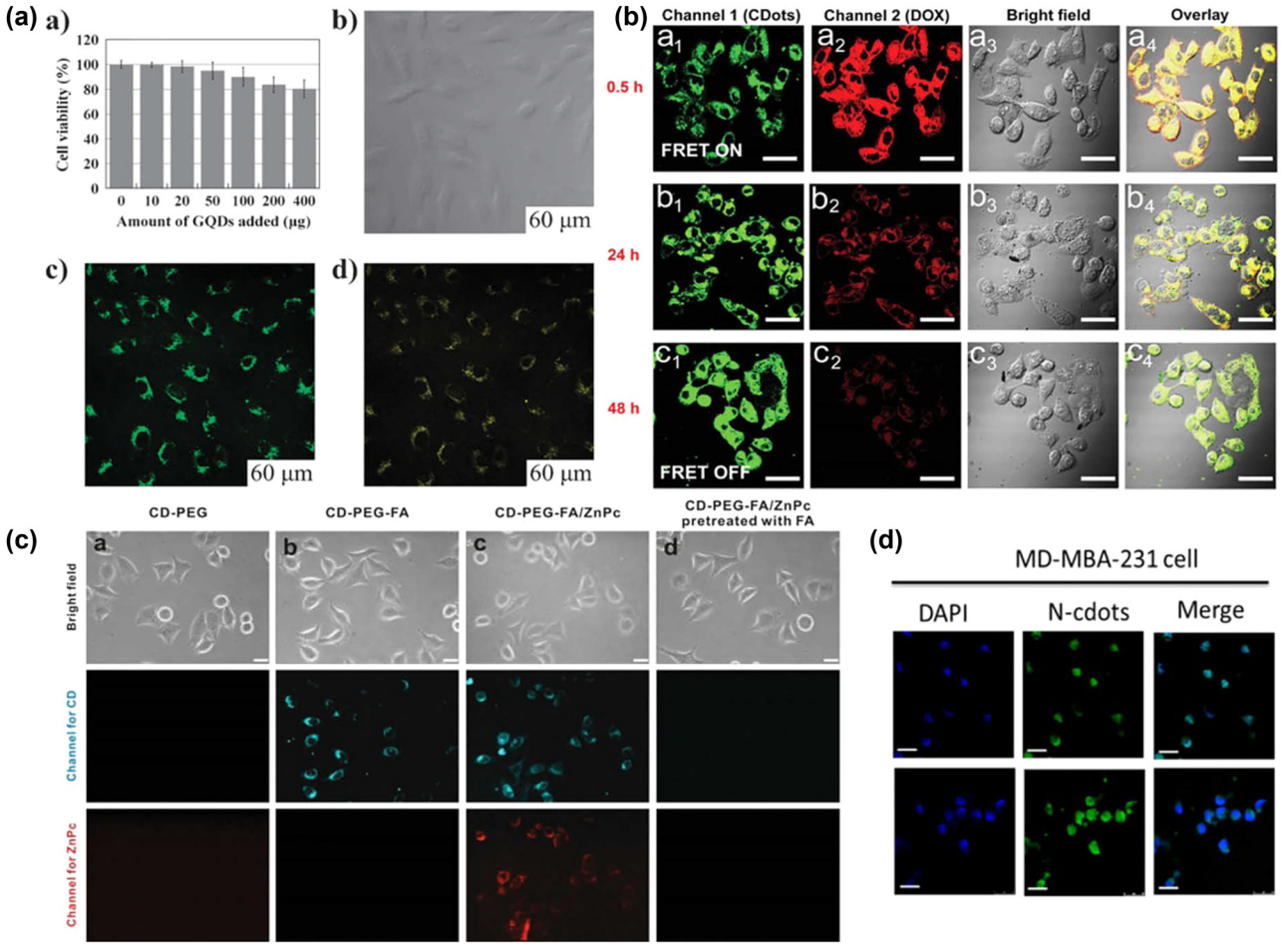

Figure 14: (a) Multicolor images of cells treated with CDs [16]. (b) Fluorescence images of cells treated with CDs-DOX at 0.5, 24, and 48 h [133]. (c) Fluorescence images of (a) CDs-PEG, (b) CDs-PEG-FA, (c) CDs-PEG-FA/ZnPc, and (d) CDs-PEG-FA/ZnPc pretreated with FA [123]. (d) Fluorescence images of MD-MBA-231 cells pretreated with "biomolecule-mimicking" CDs [134].

process is exhibited by fluorescence images. CDs acquired cytoplasm green fluorescence. At the time of treatment, DOX releases into the nucleus after entering the cells, causing the appearance of the red fluorescence. To observe drug delivery, Chowdhuri et al. [121] joined CDs with metal organic frameworks. Wang et al. [122] used the mixture of chitosan, PEG, and CDs to attain a NIR light/pH dual-responsive hybrid gel. All the previously mentioned research indicate CDs' application in drug delivery and gene transfer and corroborate CDs' clinical applications.

8.3 Biological imaging

8.3.1 *In vitro* imaging

In vitro imaging is executed to offer plentiful information on the imaging ability, distribution and cytotoxicity of probes in cells. CDs have many effective uses in cell transfection such as HeLa [123–129], human neutral stem cells [130] 4-T1 [131], NIH-3T3 [132], A549 [108,133], HepG-2 [126], etc. Through endocytosis, CDs enter into the cells and concentrate in the cytoplasm [126]. CDs may enter cell nucleus but only a few reports were discussed this way. Zhu et al. [16] successfully used CDs in cell imaging as they synthesized fluorescent CDs with low cytotoxicity in solvothermal method (Figure 14a). Nitrogen-doped CDs displayed an excitation which was dependent on fluorescence emission for multicolor fluorescence imaging [126] by carbonization extraction. Multifunctional tumor targeting probe preparation can be prepared by CDs' surface modification. Tang et al. [133] discussed cancer cell recognition, drug transport, and fluorescence imaging by using CDs with folic acids and DOX (Figure 14b). Bhunia et al. [129] explained surface modification of CDs with folic acid by preparing a series of CDs with different fluorescence and observed target recognition. To make the tumor abilities obvious and

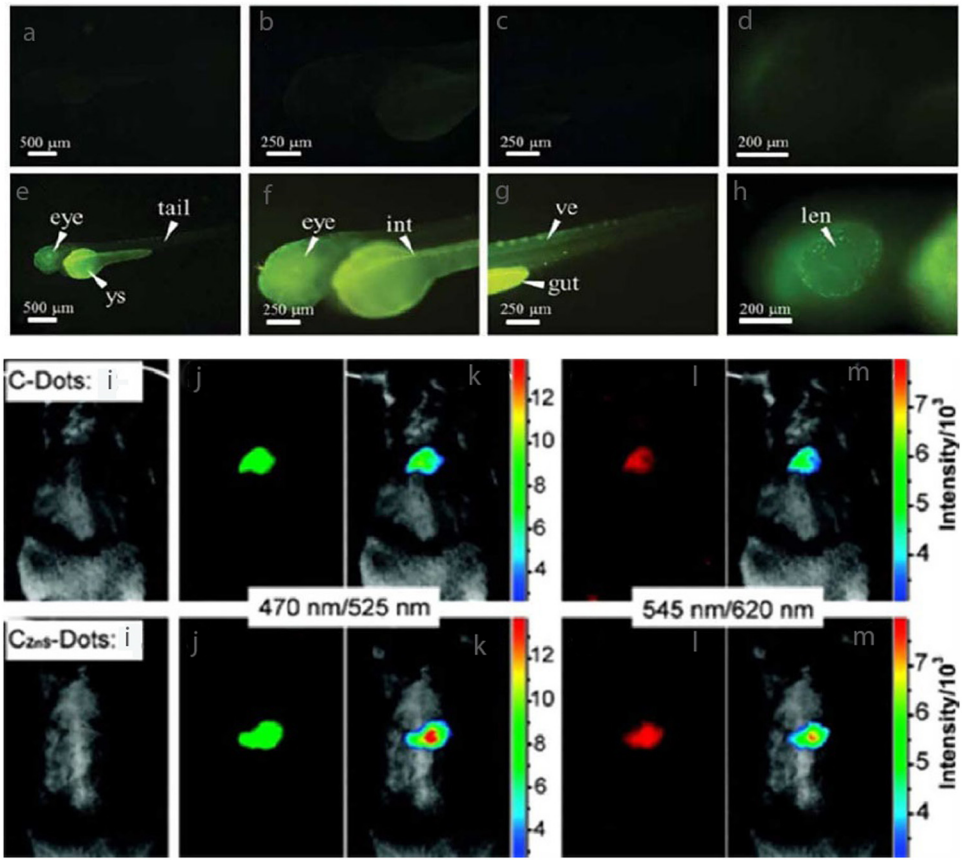

Figure 15: (a–h) Fluorescence image of zebrafish with CDs [139] and (i–m) fluorescence image of rat injected with CDs [87].

execute photothermal therapy (Figure 14c), Choi et al. [123] used CDs' altered with zinc phthalocyanine and folic acid. Dopamine-neutralization heat treatment [134] was used to synthesize a biomolecule mimicking CDs. The dopamine-mimicking CDs could "hoax" nuclear membranes to fulfill nuclear localization and imaging [134] because the functional groups of dopamine were maintained in this CDs (Figure 14d). Elimination of autofluorescence interference can be achieved by CDs' two-photon, cell imaging upon NIR light excitation (800–900 nm) [134]. Under the 880 nm laser excitation, Yang et al. [87] attained green fluorescence images. Cell nucleus two-photon imaging was fulfilled by Zhang et al. [135] who utilized C_3N_4 nanodot as a probe. For living cells and tissue imaging, Kong et al. [136] synthesized pH-sensitive CDs because of its two-photon fluorescence property.

8.3.2 *In vivo* imaging

Many essential medicine science such as disease progression, improved mechanism, and pattern formation were achieved using zebrafish due to its well-defined developmental stages and optical imaging amenability [137]. The fluorescence imaging model was the reason to choose zebrafish; CDs were found to heap up in eyes and yolk sac selectively (Figure 15) [114,138,139]. CDs were preserved over 60 h, so they are suitable for observing the long-term zebrafish developmental stages. PEG-passivated CDs and Zns-doped CDs (CZns-dots-PEG) [80] were used for vivo imaging in spite of their blue and green emission, which were not suitable for *in vivo* imaging. Under different excitations, no apparent toxicity was noticed in tissues and organs [80], green and red emission fluorescence images were obtained. Using CD probes by administering interdermal injection, the lymph of mice was labeled. The metabolism speed of the non-modified CDs was faster than the metabolism speed of PEG-modified CDs. CD fluorescence was seen at the stomach past intravenous injection and heaped up in the bladder after 1 h. Four h post injection, the fluorescence signal decreased and heaped up in the kidney, explaining that CDs are excreted from mice by urine [80]. Under different excitations (455–704 nm), Tao et al. [140] obtained CD *in vivo* images. When CDs were used *in vivo* imaging [141], CDs could enter into brain and appeared blue.

8.4 CDs food safety applications

Chemical contaminations such as metal ions, anions, pesticides, veterinary drugs, and banned additive are the main reasons for many health problems. This demands very effective and actual methods for guaranteeing food safety. In the food quality and safety area, a number of sophisticated CD-based biosensors are required. The main concepts of these CDs-based biosensors can be divided into four kinds:

1. Direct fluorescence quenching (turn-off),
2. Direct fluorescence boost (turn-on),
3. Fluorescence quenching again (off-on), and
4. Fluorescence quenching again (off-in-off).

The fluorescence quenching mechanisms implicate:

1. Dynamic quenching,
2. Static quenching,
3. Fluorescence resonance energy transfer (FRET), and
4. Inner filter effect (IFE) [142].

CDs' excited states return to ground state by collision with quencher and produces energy transfer/charge transfer (ET/CT), which is known as dynamic quenching while the static quenching results when CDs form nonfluorescent ground state complex with quencher. FRET and IFE are on the contrary mechanisms that demand two essential factors, namely, spectrum overlap and the distance between CDs and quencher (receptors). At less than 10 nm distance, FRET occurs while at more than 20 nm distance, IFE takes place. Some targets' quench lead to improve the CDs' fluorescence immediately, permitting merely sensors' design for some targets (metal ions, veterinary drugs, bacteria, and some functional components in foods) [29,56,143,144]. Restoring CDs' fluorescence after supplementing the target into quencher-containing fluorescence quenching system is known as fluorescence quenching (off-on-off) strategy, which depends on quencher, restorer, and target. Where the fluorescence recovers due to the interaction between quencher and restorer and then quench again; to enable the interaction of target and restorer, the "off-on" and "off-on-off" strategies can be utilized to determine other targets (such as anions, pesticides, veterinary drugs, and some functional components in foods) [21,23].

9 Conclusion

This review discussed the discovery, structure, and composition of CDs as well as CDs' nanocomposites and green synthesis and gave a brief summary of the latest research development of CDs in fluorescent properties and their applications that can give explanation of the optical properties among the fluorescent properties. It is obvious that understanding these properties has a long way to go. We focused on the CDs' greener methods which are more economical, less complicated, and less consuming, have lower toxicity, better compatibility, nondestructive nature, and improved optical properties. High QY of CDs by using green synthesis methods is not difficult any more. CDs' research emphasizes on the development of optical properties and discovery of red fluorescence of CDs. Moreover, functional modifications play another essential role in CD improvement: CD fluorescence focuses on blue-green emission and few red-emitting CDs were discussed [145]. Fluorescent CDs can be as follows:

1. CDs' optical properties could be enhanced by tuning carbon sources.
2. Red-emitting CDs can be obtained from phenylenediamines as carbon source as Jiang et al. discussed [146]. Polythiophene as a carbon source exhibited CDs' fluorescence emission shifting to 650–700 nm as Ge et al. explained [147].
3. CDs' fluorescence may be improved by using appropriate passivated agents.
4. The bandgap spacing of CDs' adjusting fluorescence yield and emission range can be done by introducing heteroatoms.
5. Functional molecules can be used to modify carboxyl and amino groups on the surface of CDs by amide condensation [39].
6. CDs' blue shift emission and fluorescence quenching can be achieved by fluorescence resonance energy transfer between CDs and modifications which must be taken into consideration through the following points:
   a. The distance between CDs and modifications could be increased by modified method choice such as choosing appropriate bridging content (such as silicon beads, inorganic clay, etc.) led to resonance energy transfer reduction.
   b. Building novel CDs for multimodal imaging can be executed by multimodal functionalization and multimodal imaging factor introduction.

10 Example

One pot hydrothermal treatment of gadopentetic acid mixture, trihydroxy methyl aminomethane, and betaine

[148] to attain Gd-doped CDs with a size of 3–4 nm was explained by Bourlinos et al. [148,149].

Heteroatom doping [150], large conjugated system formation [78], and change the reaction medium [151] have been executed to enhance QY or red-shift degree. Due to the surface groups (such as carboxylic acids and hydrolysis), most of the synthesized CDs are water soluble. Further surface functionalization of CDs can be achieved by doping with heteroatoms (such as N and S) conferring specific chemical reactivity to CDs permitting CDs to be specific probes/bioconjugates in detection application which is very critical toward surface functionalization [54,152]. Surface groups' significance in linkage with targets is to enhance the CD-based sensors selectivity in food safety applications [153–159]. Toxic elements' detection by CDs depends on energy-transfer capability. CDs can be used in biological sample analyses due to its biocompatible nature. There is still a lot of areas for discovering CDs' functionality with various elements. In the near future, CDs will lighten human lives by slapping the way for more advanced techniques.

11 Future perspectives

11.1 Green chemistry as an essential approach to attain heteromeric superstructures

11.1.1 CDs eco-friendly and sustainable synthesis

Green chemistry is a linkage of important concepts that minimizes or eliminates the implementation or generation of hazardous substances in the design, manufacture, and chemical product implementations. Green chemistry involves using none or less dangerous chemical synthesis, applying safer and nontoxic chemicals, solvents, and processes [160]; for example, biowastes can be utilized as sustainable and cheap carbon sources for CD synthesis. Spherical water-soluble CDs (about 1–3 nm) have been prepared from lemon peel waste, which is the prevailing cost-effective hydrothermal strategy, and the ensuring stable CDs were discovered to be oxygen rich in surface functionalities and displayed the water-soluble and unique PL properties with QY of about 14%. The synthesized CDs were used to design an economic, green, and highly sensitive fluorescent probe for Cr^{6+} ions' detection limit of about 73 nM. Water-soluble CDs considered simple, fast sensitive, and selective Cr^{6+} detection is suitable technique in operations of water purification. TiO_2 – water - soluble CDs composite was inspected utilizing methylene blue dye as a model pollutant because CDs have been immobilized over electrospan. TiO_2 nanofibers and the emanating photocatalytic activity being about 2.5 times more than that of titanium dioxide nanofibers [161]. Water-soluble fluorescent carbon quantum dots (~260–400 nm) were reported via a simple one-step hydrothermal treatment utilizing *Tamarindus indica* leaves. These bioconvenient CDs can be potentially executed in sensing, bioimaging, disease diagnostics, and other analytical implementations [162]. Another fluorescent CD synthesis facile approach requires the hydrothermal treatment of pineapples (*Ananas comosus*) and calamansi (*Citrofortunella microcarpa*) wastes [163]. *Escherichia coli*, fluoresced with CDs as operative probe, has been used for bioimaging applications. Generation of hydrogen bonds between the bacterial cells and CDs eases the quantum dots' attachment onto the bacteria [163]. Greener ozone oxidation of ignite coal was utilized for well-dispersed CDs was utilized for well-dispersed CDs (~2–4 nm) which is copious, cost-effective, and involves oxygen-rich functional groups with suitable water-solubility, optical characteristics, and yield reaching 35% [164]. Synthesized quantum dots utilized for Fe^{3+} detection with remarkable sensitivity and selectivity as well as desirable anti-interference had quenching effects but the CDs' intensity showed clear linear responses to the Fe^{3+} concentrations (10–150 μmol L^{-1}).

With the detection limit of 0.26 μmol L^{-1} [164], in one pot by using cydonia oblonga powder as carbon precursors via microwave irradiation which shows maximum emission at 450 nm if excited at 350 nm with a QY of 85% highly stable and luminescent multi-color CDs would generate. Also CDs were prepared through microwave heating technique in 30 min in comparison to those produced hydrothermally in a Teflon-linen stainless steel body autoclave at 200°C [165]. Fluorescent CDs' greener synthesis by using citrus lemon juice (~2–10 nm) was achieved utilizing hydrothermal approach [166] which showed high PL intensity was obtained at pH of 6 in cell imaging [166]. CDs can be utilized as a fluorescent probe. Amorphous fluorescent CDs can be obtained from orange peel waste by utilizing hydrothermal carbonization approach at mild temperature [40]. Bright green luminescent graphitic carbon nitride doped with oxygen and sulfur were prepared using microwave treatment of citric acid and thiourea. They exhibited excitation wavelength and pH-dependent luminescence behaviors in the visible range. Moreover, the QY of 31.67% shows a strong impedance to the interference of high ionic strength environment, and perfect biocompatability as estimated by the cell viability assay [167]. *Prunus avium* fruit

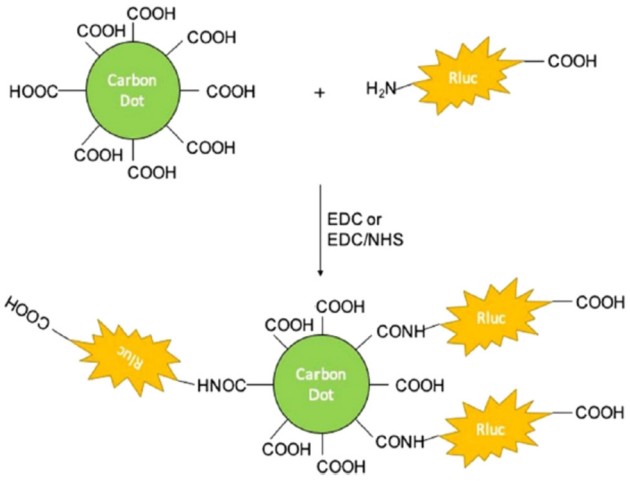

Figure 16: EDC- or EDC/NHS-mediated conjunction of bioluminescent proteins, *Renilla luciferase* (Rluc) to CDs. Both conjunction couples the free surface carboxylic acids on CDs with the amine group on the N-terminal of Rluc. The close proximity between the two molecules allows for bioluminescence resonance energy transfer [186].

extracts were used for fabricating fluorescent nitrogen-doped CDs (~7 nm) which exhibited blue fluorescent characteristics fluorescence. The green CDs were utilized as fluorescent probes for Fe^{3+} ions' biological detection in water with selectivity and sensitivity and for bioimaging of the tested cells [168]. The simple microwave process was entered for fluorescent nitrogen-doped CDs which were hydrothermally synthesized by applying L-ascorbic acid (as the carbon precursor) and β-aniline (perform as nitrogen dopant) with distinct blue fluorescence and low cytotoxicity. These CDs can be utilized as staining probes for confocal cellular imaging [169].

11.1.2 CDs self-illumination by bioluminescence resonance energy transfer

The CDs of the emerging fluorescent NPs (FNPs) display excitation-dependent emission and chemical stability as their identical multicolor PL have magnetized inclusive attention due to the various implementations in photovoltaic devices, bioimaging, etc. [170,171]. Various agents influence CDs' fluorescence:

1. Quantum size effect results from CDs nanoscale size.
2. Surface oxidation degree.
3. Surface functional group like carbonyl and imines [172].

To begin the FNPs excitation, external high-power light source is essential which may generate photocytotoxicity and tissue damage [173]. There are different mechanisms in which fluorescence is executed without external high-power source, for instance, CL resonance energy transfer (CRET) and bioluminescence resonance energy transfer (BRET) as they include a nonradiative energy transfer between a light energy donor and a luminescence acceptor. The donor molecular emission enables covering the acceptor molecular excitation or absorption when the distance between donor and acceptor molecules is close, i.e., <10 nm, so these luminescence resonance energy transfers can occur [174–176]. In order to excite the CRET acceptor molecule, CL reactions in the main reactions in which CRET is relied. While emitting photon to release energy [177], CL reaction causes an electronically excited product followed by electron dropping to ground state [177]. Modern limitations appeared when this successfully removes the external light source requirement. Metallic ions or catalyst enzymes are usually used as catalysts [178] to lower the initial CL reaction activation energy and also cofactors may also be essential for the initial reaction to take place. Biocompatibility may be jeopardized with the use of metallic ions, moreover, the required catalyst and cofactors may not be compatible with microenviroment. Natural bioluminescent molecules exist in firefly, jellyfish, and other organisms, as the light energy donor [179] unlike CRET and BERT. For instance, *Renilla luciferase* (Rluc) enzymatic reaction with its substrate, coelenterazine, can generate luminescence at 480 nm [180]. BERT is more suitable compared to CRET as catalysts and cofactors are not required for the reaction to happen. In bioconjugation of bioluminescent proteins onto nanostructures, e.g. gold NPs, semiconductors' quantum dots have been used in biosensors and bioimaging without the external power supply [181–184]. Compared to the BRET pair containing the acceptor made of organic dye and/or other nanostructures, CDs could be particularly of interest in using for BRET pair, and modify functional groups for further bioconjugation. CDs clearly show better bioconvenient ability than other fluorescence nanostructures, e.g., quantum dots. Some studies debated CDs' self-illuminescence proteins. Herein, explanation of a method for self-illuminated CD synthesis by using BERT technique. Figure 16 explained the bioconjugation of Rluc onto CDs' strategies through carboxyl-to-amine crosslinking. Two essential water-soluble carbodiimide crosslinkers, *N*′-(3-dimethyl aminopropyl)-*N*-ethylcarbodiimide and EDC associated with *N*-hydroxysuccinimide, were investigated. Other different factors including the CD ratio and Rluc and the bioconjunction reaction time are investigated for the successful execution of BERT [185].

Research funding: Author states no funding involved.

Author contributions: Asmaa Mohamed El-Shafey was involved in writing – original draft, writing – review and editing, conception, design, and interpretation of the reported review.

Conflict of interest: Author states no conflict of interest.

Data availability statement: All the data generated or analyzed during this review are included in this published article.

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