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Review

Carbon Dots: New Rising Stars in the Carbon Family for Diagnosis and Biomedical Applications

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Abstract: Carbon dots (CDs) are a class of carbon-based nanomaterials undergoing rapid development with broad potential applications across diverse biomedical fields. These materials are highly attractive for diagnostics, therapeutics, and nanomedicine due to their remarkable optical and physicochemical properties, including photoluminescence, biocompatibility, and aqueous dispersibility. CDs can be synthesized using various techniques, ranging from top-down to bottom-up approaches. Among these, biogenic synthesis, utilizing natural sources and waste materials, presents an eco-friendly and sustainable alternative. CDs have exhibited considerable promise in diagnostics, especially with bioimaging and biosensing, providing both high sensitivity and precise identification. CDs are presently being investigated in the pharmaceutical sector for their potential applications in cancer and infection treatment, as well as in photodynamic and thermal therapies. The advancement of CD composites, through enhanced functionality and broader application, facilitates novel research in nanomedicine. This article highlights the advantages of CDs, focusing on their structural properties, classification, and versatility in synthesis methods. Furthermore, the safety and toxicity profiles of CDs are critically analyzed. In conclusion, the innocuity, adaptability, and multifunctionality of CDs position them as a cornerstone in the advancement of nanotechnology and biomedical applications. With their broad applicability and promising potential, CDs stand poised to drive significant innovation across diagnostics, therapeutics, and other domains, heralding a new era in nanomedicine and sustainable material development.

Keywords: carbon nanodots; chemistry; synthesis of CDs; carbon-based nanomaterials

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1. Introduction

Due to recent breakthroughs in nanotechnology, various carbon nanomaterials (CNMs) are currently accessible. Before the 1980s, naturally occurring forms of carbon were limited to graphite, diamond, and amorphous carbon. Over the past three decades, researchers have discovered and characterized numerous new forms of carbon, such as fullerene

(C60) [1,2], carbon nanotubes (CNTs) [2,3], carbon nanohorns (CNHs) [4,5], carbon nano-onions (CNOs) [6,7], graphene derivatives [8,9], nanodiamonds (NDs) [10], and carbon dots (CDs) [11,12], as shown in Figure 1. Due to their appealing thermal, chemical, and mechanical properties, CNMs have garnered considerable interest in biomedical applications since their discovery [10,11]. CNMs are comparable in size to proteins (1–100 nm) and DNA strands (2–3 nm), making them promising carriers for the intracellular delivery of targeted genes and drugs in vivo. Their small size and capacity to incorporate various functional groups on their surfaces make them ideal for these applications [11–14].

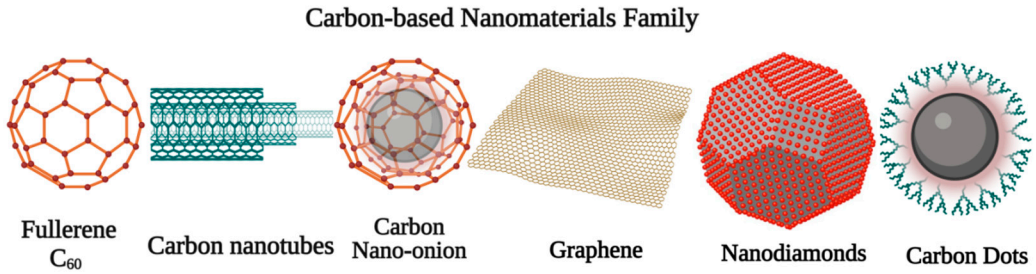

Figure 1. Carbon-based nanomaterial family.

CDs are among the most recently developed carbon-based nanomaterials [15,16]. These photoluminescent nanocarbons are typically smaller than 10 nm in diameter. However, multiple studies have provided evidence that CDs can attain a maximum size of 60 nm [15]. These nanomaterials comprise an intricate molecular assembly comprising sp2 and sp3 carbon atoms and various polymer chains and functional groups attached to their outer surfaces [17]. Scientists have devoted considerable attention to CDs for their innumerable advantageous qualities including the high quantum yield (QY) of photoluminescent [18] light, fluorescence characteristics, resistance to photodecomposition, tunable excitation and emission properties, enhanced electrocatalytic activity, favorable solubility in aqueous solutions, superior biocompatibility, and chemical stability over extended periods [15,19]. These properties have made CDs a promising candidate for diverse applications, including medicine, catalysis, and optoelectronics [20], owing to their remarkable and manipulable characteristics. Graphene oxide exhibits striking similarities in its chemical composition and physical characteristics to carbon quantum dots (CDs) or graphene quantum dots (GQDs). These particles have a smaller diameter of less than 10 nanometers, differentiating them from graphene oxide [21].

In recent years, carbon dot composites, which integrate carbon dots with various polymeric materials, have emerged as a transformative option in nanotechnology [22]. These composites possess unique optical characteristics, biocompatibility, and customizable functionality, rendering them suitable for biomedical applications. They provide a safer, more environmentally sustainable alternative to conventional nanodots, which often depend on heavy metals [15,23,24]. CD/PEG and chitosan composites are extensively utilized in pH-sensitive fluorescent biosensing, CD/polyurethane composites in bone tissue engineering, and CD/poly(N-isopropylacrylamide) composites in thermo-responsive drug delivery and bioimaging [25]. CD/polymer composites possess significant adsorption, separation, and electrochemical characteristics that render them valuable for analytical detection; yet, further investigation is required to establish straightforward, economical, and eco-friendly synthesis methods to fully exploit their capabilities [24,26].

Furthermore, there are many other uses of CDs, including biological, physiological, and chemical ones. Their low cytotoxicity has been reported in many cell lines, including 293T [12] and HepG2 cells [13], and their biocompatibility has been demonstrated in developing the zebrafish (*Danio rerio*) model [14]. CDs are potent imaging agents that may

photograph particular cells, tissues, organs, or combinations thereof in real time, essential for correctly detecting cancer and other disorders. In addition to being effective nanocarriers for gene and drug delivery, they are potent therapeutic agents for light-based therapies such as photodynamic and photothermal therapy [6,21]. Due to the abovementioned properties, CDs have excellent foundations for application in various diagnostic and therapeutic contexts [21]. In addition, quantum dots (QDs) were utilized to label CNTs fluorescently. Researchers inserted CDs/ZnS QDs into single-walled carbon nanotubes (SWCNTs) to study their absorption by cells and their subsequent intracellular localization [27]. This article discusses the arrangement of carbon dots (CDs), their ideal qualities, broad synthesis techniques, and fundamental characterization methods. In addition, it highlights the most recent advancements in the use of CDs in medical applications, emphasizing their significant and emerging roles in electrochemical and bioimaging, optical biosensing, drug delivery, as well as photodynamic (PDT) and photothermal therapies (PTT).

2. The Advantages of CDs

- As a member of the nanocarbon family, affordable CDs are gaining popularity due to their low price and excellent availability [28];
- Due to their composition and stability, CDs offer superior photostability compared to organic dyes and conventionally synthesized CDs that are prepared using common carbon precursors like sucrose and glucose. Other types of CDs are synthesized using different carbon precursors and varied surface passivation methods (e.g., nitrogen-doped and silica-coated CDs) which may lead to lower photostability [29,30];
- CDs have a shorter emission peak and a larger excitation spectrum, linked to organic dyes and other cadmium-based CDs;
- CDs have unique biological properties that make them useful in biosensors, drug delivery, and bioimaging. These properties include hydrophilicity, low toxicity, chemical stability, and good biocompatibility [31,32];
- Enhanced light emission relative to other CDs;
- Due to their excellent electrical capabilities as electron donors and acceptors, carbon-based CDs create electrochemical luminescence and chemiluminescence, providing considerable applicability in optoelectronics, catalysis, and sensing [30];
- The chemical stability of CDs is superior to that of conventional or metallic CDs [28,31].

3. The Structures and Chemistry of CDs

Most CDs contain graphitic in-plane spacings of 0.18 to 0.24 nm and graphitic interlayer lattice spacings of 0.32 nm. CDs are formed of carbon crystalline cores comparable to sp2 carbon and amorphous clusters; however, their precise structure can vary depending on the raw ingredients and synthetic process (Figure 2) [33–35]. CDs are often less crystalline than graphene quantum dots (GQDs), and some CDs contain sp3 carbon, similar to diamonds [36]. These observations are supported by Raman spectroscopy, which typically exhibits two peaks at 1350 and 1600 cm^{-1}, indicative of disordered sp2 carbon and crystalline graphitic carbon, respectively [35]. Surface passivation, or functionalization [37], is generally used to introduce various functional groups to shield the surface and improve the fluorescence of CDs.

A coating of organic ligand stabilizes the inorganic atoms of the carbon dots (CDs), potentially making them a new class of fluorophore. CDs are better than organic dyes because they (a) have broad absorption spectra, (b) have very narrow emission spectra, (c) have longer fluorescence lifetimes, and (d) are very stable under light. These properties make them useful in many medical, biological, technical, and analytical processes. Atoms from groups II (alkyl) and VI (organic salts) (Se, S, and Te) synthesize CDs. CDs must

be water-soluble to be helpful in bio-applications and analytical chemistry [38,39]. In semiconductors, electrons and holes are usually considered electrical conductors [40]. Excitons are photo-generated electron-hole pairs that, following recombination, produce the fluorescence emission of CDs [41]. As a result, surface or defective states determine the mixture's fluorescence efficiency and ligand type [42]. Chemical bonding between the surface atoms and a material with a large band gap eliminates energy levels within the band gap [42,43].

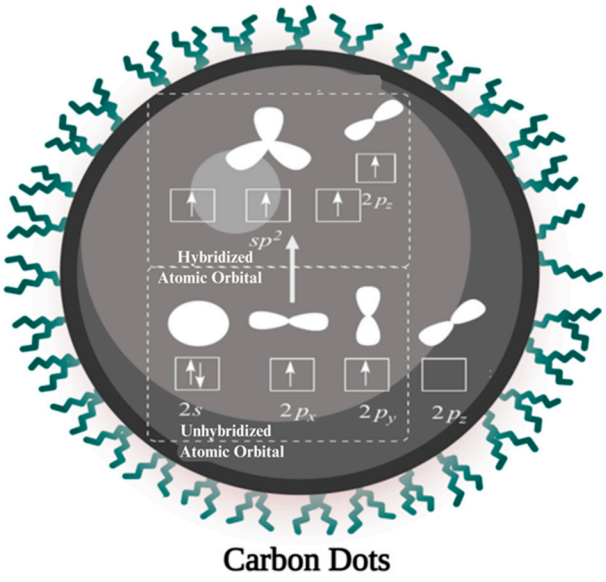

Figure 2. Illustration of CDs with cores containing sp2 hybridized carbon.

Semiconducting metallic CDs lack support in biocompatibility, hemocompatibility, and toxicity, and the chemistry of interaction with metabolites and live cells restricts their practical applications in several areas. CDs synthesized using green synthetic techniques and environmentally acceptable raw materials are highly sought after due to their low toxicity [44]. In recent years, eggshells, oranges, spinach, sugarcane, papayas, pomegranates, ginger, rose petals, and rice have all been extensively studied for the green synthesis of nanomaterials. Bhartiyaa et al. also studied the synthesis of CDs from a diversity of starting materials via hydrothermal, solvothermal, and microwave treatment, as well as their characteristics and potential applications in numerous scientific fields [40].

4. The Classification of CDs

CDs are classified based on their carbon nuclei structure and exterior functional groups [17,45]. These are graphene quantum dots (GQD), carbon quantum dots (CDs), carbon nanodots (CND), and carbonized polymer dots (CPD) (Figure 3). Due to the presence of chemical groups, nanocrystalline quantum dots (CDs) exhibit the CD's intrinsic state luminescence and quantum confinement effect [46]. GQDs are small, anisotropic graphene fragments that create mono- or multiple layers of graphene sheets connected by a graphene network in their most fundamental form. GQDs can display quantum confinement and edge effects due to chemical functionalities at their edges or inside interlayer faults. CNDs demonstrate intense carbonization and edge effects while maintaining their non-exposure to crystalline or polymeric structures. In addition, the phenomenon of quantum confinement is not observed in CNDs [15,47,48]. CPDs comprise a carbonized core surrounded by polymeric chains and various functional groups [15,49].

Figure 3. Classification of carbon dots: graphene quantum dots (GQDs), carbon quantum dots (CQDs), carbon dots (CDs), and carbonized polymer dots (CPDs).

5. The Synthesis of CDs

Two synthetic methodologies for CDs are bottom-up and top-down approaches, which mainly comprise chemical, electrochemical, and physical systems [50]. Top-down techniques include arc discharge, electron beam lithography, laser ablation, reactive ion etching, and electrochemical processes for reducing carbon matter to CNPs. Bottom-up techniques comprise micro-emulsion, hot solution decomposition, pyrolysis process, sol-gel [51], the reverse micelle method, microwaves, and the oxidation of substances [52]. CDs must be modified to provide desirable surface qualities essential for solubility and applications [28,53]. CDs are also produced from carbon precursors such as coffee grounds, tea leaves, grass, and fine sediment. These precursors are abundant and economical for CD production [49]. In addition, wool (a natural and harmless resource) can be employed in an eco-friendly, one-step synthesis of fluorescent CDs for glyphosate detection [28,54]. Figure 4 has a summary of the numerous synthetic processes. Additionally, Table 1 represents the advantages and disadvantages of the different methods of CD synthesis.

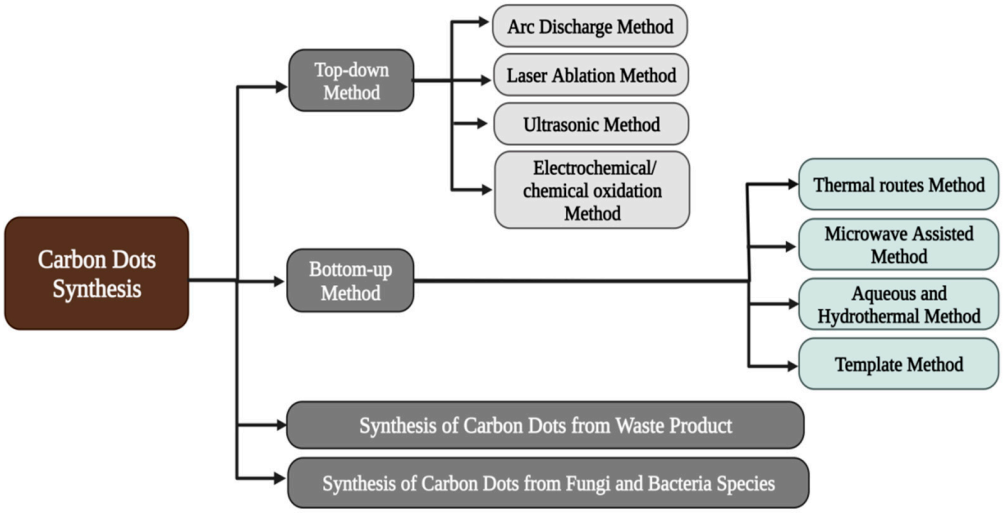

Figure 4. Synthesis of carbon dots by different approaches.

5.1. Top-Down Approaches

5.1.1. Arc Discharge

This approach uses soot from crude carbon nanotubes to make CDs (sediment). The silt is oxidized by introducing carboxyl groups with 3.3 M HNO_3; the resulting substance can be extracted using a NaOH/pH 8.4 basic solution, and the resulting suspension will be stable and dark in color. Gel electrophoresis is utilized to purify the isolated material [50]. The photoluminescent NPs are made by combining undamaged carbon nanotubes with those treated with nitric acid, the latter produced by an electric arc (Figure 5). Fluorescent nanoparticles made from pure carbon nanotubes are hydrophobic and fluorescence localized. However, the fluorescent NPs of oxidized carbon nanotubes display a more extensive division and can collect in water due to their external interaction between oxygen and a thin carbon coating. Arc discharge soot technique CNPs have a limited yield, and the process consists of several composite segments. Nonetheless, it is not easy to purify these sub-segments [52].

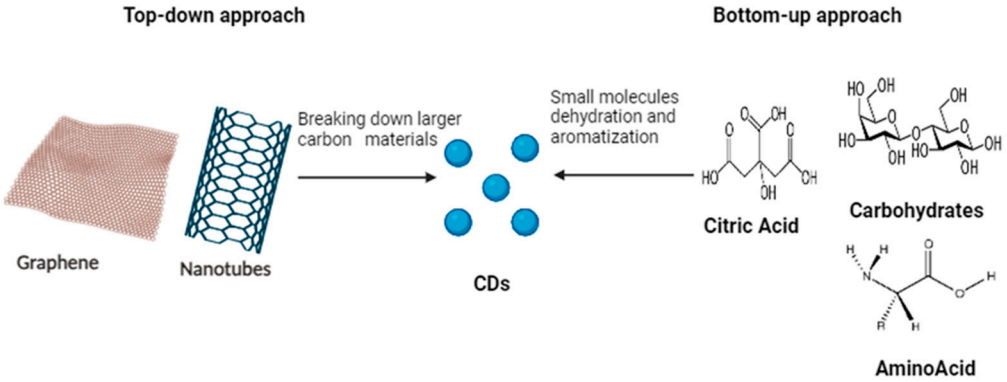

Figure 5. Schematic depiction of the top-down and bottom-up synthetic methods for the groundwork of CDs.

5.1.2. Laser Ablation

The CD mixture, which contains small carbon-based nanoparticles with unique optical properties, undergoes laser ablation [45]. CDs have gained noteworthy consideration in recent years due to their probable applications in countless fields, including bioimaging, drug delivery, sensors, and photoluminescent materials [55]. Laser ablation is one of the techniques employed to produce CDs. This method produces fluorescent CDs by irradiating a C-target with a laser [55]. Cement and graphite powder are burned to generate a carbon target, which is then utilized to create carbon nanoparticles (CNPs) by laser ablation/or removal in an argon gas stream, including water vapor at 900 °C and 75 kPa. The aggregation procedure produces nanoscale carbon particles of various sizes and photoluminescence (PL) [56]. After 12 h of refluxing in an aqueous HNO_3 (nitric acid) solution, the sample reacts with polyethylene glycol (PEG1500N) or poly-propionyl ethyleneimine-co-ethyleneimine, and the resulting passivated CDs are strongly photoluminescent and approximately 5 nm in size. These C-dots emit fluorescence with a quantum yield (QY) of 4–10% after being stimulated at 400 nm [52]. Doping CDs with inorganic salts such as zinc acetate and Na2S or NaOH enhances the QY further, indicating that the dopants (e.g., ZnO and ZnS) aid as a passivating mediator to stabilize the CDs. Doped CDs activated at 450 nm demonstrate robust PL (QY 45%). The organic particles work as a passivation ligand, allowing different-colored PL CDs to be made in organic and aqueous conditions [50]. Laser ablation has numerous benefits, including its simplicity. While this process enables the creation of a diverse array of nanostructures, it necessitates a significant quantity of carbon material to generate targets. Laser irradiation produces CNPs of various sizes; large

particles are easily removed by centrifugation, so the yield of the resulting CNPs is low, and the usage efficiency of carbon matter is low [52].

5.1.3. Electrochemical Method

For this method, Lu et al. used high-purity and pyrolytic graphite rods as the anode buried deep in the ground. The counter electrode was a 2-cm platinum wire partition [57]. The exfoliation of the carbon materials began with static potential. Anionic intercalation after the ionic fluid and anodic oxidative water cleavage were essential to exfoliation. The exfoliating possessions were cleaned with water and ethanol until the pH reached a neutral level. CDs were produced with a QY range of 2.8% to 5.2% after parting by filtration and ultracentrifugation at 15,000 rpm and 20 °C. In the center of the electrolyzer, Yao et al. used a spectrum-pure graphite ring as the anode and a titanium tube as the cathode. An O-ring separated the cathode or anode for insulating purposes [58]. The electrolyte medium consisted of sterile water. By concurrently applying ultrasonic power and electrolytic voltage, pure blue luminous CDs of only 2–3 nm in size were created fast and efficiently. The CDs obtained had a QY of 8.9%. The resultant CDs demonstrated exceptional thermodynamic stability in water and a brilliant fluorescence effect [52]. Reducing the current density makes it possible to create larger CDs with a longer emission wavelength [50]. Using the electrochemical shocking of multi-walled carbon nanotubes, 3 nm photoluminescent CDs are produced [59]. Another technique for producing water-soluble CDs is through the chemical oxidation of flour [60].

5.2. Bottom-Up Approaches

5.2.1. Thermal Routes

Initially, CDs were created from candle-burning residue. Applying oxidants to sediments, such as HNO_3 or H_2O_2/AcOH, created CDs. Using polyacrylamide gel electrophoresis to isolate CDs indicated that more adaptable CDs have PL at shorter emission wavelengths [28]. The range of CD QY forecasts was between 0.8% and 1.9%. The remains from natural gas were treated through HNO_3 and subsequently neutralized with $NaHCO_3$; the final refinement, made possible by dialysis, led to the discovery of photo-luminous CDs. The separate additions of metal salts such as $AgNO_3$, Cu $(NO_3)_2$, and $PdCl_2$ to a C-dots solution containing a reducing agent (ascorbic acid) led to the production of metal nanostructures on the CD surface [28]. Soot-based techniques are straightforward and simple [28,61]. However, the fluorescent CNPs' QY is substantially smaller (0.1%), rendering them useless. An enhanced soot-based approach has been devised to produce fluorescent CNP with a size range of 2 to 6 nm and a QY in the 3% range. Three key enhancements are included in the updated method. First, a fundamental technique for separating a tiny fluorescent molecule after a heterogeneous particle mixture must be established [28]. This method can synthesize these elements (on a milligram scale). The second technique reveals that massive particles are less luminous than small ones; hence, filtering out the negligible molecules increases the QY (by 0.1% to 3%). The third method focuses on the fact that tiny particles can penetrate cells without functionalization and that the fluorescence possessions of the molecules can be employed for fluorescence-based cell imaging [61]. Because of this, isolating the various colored particles produced by soot-based technologies via gel electrophoresis is difficult [28,61].

5.2.2. Microwave-Assisted Method

Guan et al. considered using folic acid molecules as nitrogen and carbon together to produce luminous CDs [62]. First, a combination was created by dissolving 15 mg of folic acid in 3 mL of diethylene glycol; then, it was cooked in a 750-watt home microwave oven for 40 s, and three days of dialysis against clean water produced a reddish-brown

suspension. After additional processing, carbon nitride nanoparticles stayed extremely luminous through a mean size of 4.51 nm. After further-down activation at 360 nm, the carbon nitride NPs' QY was 18.9%. Excitation at varied wavelengths (320 nm to 420 nm) had a negligible effect on the location of the release peak (at 460 nm). Wang et al. created water-soluble CDs containing phosphorus by employing a simple one-step microwave-assisted process [63]. This technique involves combining 2 milliliters (mL) of 70% phytic acid with 1 milliliter (mL) of ethylenediamine in 25 milliliters (mL) of ultrapure water, and then heating the resulting turbid mixture in a microwave oven for approximately 8 min at 700 watts (W). After the material was purified, phosphorus dots with aromatic structures and phosphorus groups covalently connected to them were produced. Activation at longer wavelengths produced a single peak at 525 nm (green fluorescence) for the NPs, but activation at shorter wavelengths produced two peaks for the phosphorus-containing CDs (360–460 nm). The QY for consequent CBD-containing phosphorus was 21.65% [52]. The microwave-assisted technique is more practical because the carbon precursors can be heated quickly. This approach significantly simplifies the synthesis process, making it possible to create CDs with increased QY in a couple of minutes [28,52]. Under this procedure, CDs can also be produced by microwaving a clear aqueous solution of PEG200 and saccharides for 2–10 min at 500 W. Excited by light with a wavelength range of 330 to 460 nm, the resultant CDs display fascinating ex-subordinate PL features. The CDs' quarterly growth rate jumped from 3.1% to 6.3% [28,52].

Similarly, CDs were produced by the ultrasonication of glucose with an alkaline (or acidic) solution for 4 h. PL emission from the CDs covered the full visible-to-near-infrared (NIR) range. The CDs displayed up-change PL characteristics when activated between 700 and 1000 nm, implying outflow between 450 and 750 nm [28].

5.2.3. Aqueous and Hydrothermal Methods

Hydrothermal treatment was applied to coffee beans to make PL CDs. Before being processed into powder, recycled coffee beans were dried in an oven [50]. After autoclaving, they were calcined in the air at 300 °C for 2 h. Four processes comprised the CD preparation procedure [28]: dehydration, polymerization, carbonization, and passivation. CDs were created by heating recycled green tea leaves at 300 degrees Celsius for two hours using a similarly eco-friendly process. The resulting black carbonized powder was resuspended in sterile water, and CDs were purified by dialysis [64]. The copious catechins found in green tea likely played a vital role in the production and passivation of the CDs. Four distinct compounds, cadaverine, glycine, ethylene diamine-tetra acetic acid (EDTA), and 2-amino-2-hydroxymethyl-propane-1,3-diol (TRIS), were calcined hydrothermally in an aqueous solution for two hours [28,64]. For highly water-diffusible and photoluminescent CDs, agents containing both carboxyl and amino groups were advantageous [28]. For two hours, CDs were produced by heating EDTA to 400 °F in a nitrogen environment. Some EDTA precursors were not destroyed and were employed to create CDs with enhanced hydrophilicity [65]. This was accomplished in an aqueous solution by calcining EDTA with a carboxylic and amino group for two hours at 300 °C. Highly water-dispersible, photoluminescent CDs that were produced required carboxyl and amino precursors [28].

Organosilane-functionalized CDs were produced using (3-aminopropyl) trimethoxy silane as a precursor at 300 °C for two hours without a passivating mediator [28]. CDs were also created using 4-amino antipyrine and ammonium citrate as carbon precursors in the air at 300 °C for two hours. Different organic ammonium species were covalently bound to the surface [28,50], which altered the hydrophilicity. Sucrose, glucose, and starch were employed as starting materials alongside strong acids such as H_2SO_4 to synthesize CDs. By treating these solutions with nitric acid and attaching a carboxyl group to their

exteriors, a family of carbon nanostructures, including CDs, was created. Passivating their surfaces with organic compounds and polymers was essential to improving their PL intensity further [50]. Using glucose as a precursor in manufacturing CDs is a basic hydrothermal process [66]. Ethylene diamine can be utilized as a passivated mediator to enhance fluorescence emission.

Table 1. Different methods of synthesis: advantages and disadvantages.

Strategies	Fabrication Method	Carbon Source	Size	Yield (%)	Luminescence Wavelength (nm)	Advantages	Disadvantages	Ref.
Bottom-up	Thermal Decomposition	Sucrose	1.84	21.4	365	Less time-consuming, easy to operate, low-cost, large-scale production	Broad size distribution	[67]
	Hydrothermal treatment	Citric acid	2.69, 3.10	71, 78	420–520	Cheap, eco-friendly, lack of toxicity, low cost	Low yield	[68]
	Microwave synthesis	Glucose	2.75, 365	6.3, 3.1	330	Fast, low-cost, ecofriendly	Poor size control	[69]
Top-Down	Electrochemical/ Chemical Oxidation	Acetonitrile	2.8	6.4	365	High yield, high purity, low cost, control over size	A few small molecule precursors	[70]
	Arc Discharge	Arc soot	18.0	-	365	Fabricate carbon NPs in a variety of gases	Required more purification	[71]
	Laser ablation					Easy control over size and photolumi-nescent property	High-cost and sophisticated process	[72]
	Ultrasonic Treatment	Waste food	4.6	2.85	>400	Convenient to break large carbon materials, well dispersed, low crystallinity	High energy cost	[73]

5.2.4. Template Method

Nanoscale CDs have also been created using this technology. First, CDs are formed by calcination in a suitable mesoporous silicon sphere or template, and then, in a second step, the supports are removed and nano-sized CDs are formed by etching [28]. Zong et al. suggested a technique for using mesoporous spherical silica as stiff molds. These silica balls were immersed in a citric acid and complex salt solution. The mono-dispersion and photo-stability of the CDs generated after the mesoporous supports were calcinated and removed, demonstrating their exceptional luminosity [74]. An efficient method for producing consis-

tently morphologic PL CDs using a soft-hard template method has been reported [28,75]. As carbon sources, this approach utilized organic compounds such as diamine benzene and 1, 3,5-trimethylbenzene, while the copolymer Pluronic P123 functioned as a soft template. After template removal, passivation, and carbonization, additional high stability qualities, up-conversion PL, and PL efficiencies as high as 3.3–5.7% were achieved from the CDs due to their compositions, adjustable sizes, and crystalline degrees [75]. This soft-hard template method alleviated the difficulties of aggregate formation, enabling the generation of CDs in a narrow size spread due to confinement [75]. Lai et al. developed CDs in mesoporous silica nanoparticles to manage the particle size distribution (NPs). In this study, mesoporous silica nanoparticles ($mSiO_2$) were initially synthesized; these $mSiO_2$ NPs were mixed with PEG-NH_2 and glycerol, then heated at 230 °C for 30 min [28,76]. The rough materials were removed using centrifugation to obtain scratch-free CD nanocomposites. When PEG was simultaneously capped onto the surface of $mSiO_2$, the QY, biocompatibility, and colloidal stability were further enhanced in the CDs. As creating mesoporous silica was difficult, a corrosive acid or base was anticipated to etch the template during the CD synthesis process [76]. This approach was extremely time-consuming and expensive [76]. In addition, the high-temperature pyrolysis of the template made it impossible to eradicate it, the parting and refinement procedure was arduous, and the QY was low [28,52].

5.3. The Biogenic Synthesis of CDs from Fungi and Bacteria Species

The creation of carbonaceous nanoparticles, for example, by the fermentation of certain fungal and bacterial species, has contributed to long-term development. Carbon sources in the past have included algae [77], yoghurt [78], enokitake mushrooms [79], microalgae charcoal [80], mushrooms [81], agarose waste [82], and *Shewanella oneidensis* [79]. Pacquiao et al. found that passivating with tetra-ethylene pentamine in the presence of 5% v/v sulfuric acid increased the quantum yield from 11 to 39% [79]. The CD synthesis methods are summarized in Table 2.

Table 2. Biogenic synthesis of CDs from fungal and bacterial species.

Precursor		Technique	Properties			Year	Ref.
Carbon Source	Passivation/Solvent		Particle Size	Fluorescence	Quantum Yield (%)		
Algal Blooms	Phosphoric acid	Microwave	TEM-8.5 nm	438 nm 360 nm	13	2016	[65]
Yogurt	Hydrochloric acid	Pyrolysis	TEM-3.5 nm	420 nm 320 nm	2.4	2018	[74]
Enokitake mushroom	Sulfuric acid Sulfuric acid and Tetraethylene pentamine	Hydrothermal	TEM-3.5 nm	470 nm 360 nm	11 39	2018	[75]
Microalgae Biochar	Potassium permanganate	Oxidizing agent and autoclave	TEM-4 nm	398 nm 280 nm	-	2019	[76]
Mushroom	Ultrapure water	Hydrothermal	AFM-68 nm	440 nm 360 nm	11.5	2020	[77]
Agarose waste	-	Thermal treatment	TEM-5.8 nm	420 nm 300 nm	62	2021	[77]
Shewanella oneidensis	Luria Bertani	Hydrothermal	HRTEM-2–10 nm	410 nm 320 nm	7	2022	[78]

5.4. The Synthesis of Carbon Dots from Waste Products

There are initiatives to enhance photoluminescence, lower production costs, and safeguard the environment. One of the most popular areas of research for the creation of CDs right now is the recycling of various plants and fungi from waste products, including used cooking oil, polystyrene, biocrude oil, tea powder, spoiled milk, coal powder, used papers, polyolefin, polypropylene plastic waste, bike soot, etc. Heavy oil products and plastic waste now have a QY of above 60%, making them feasible precursors [83]. Out of all the plastic waste sources, CDs made from disposable cups had the highest quantum yield value at 310 nm (65%), followed by bottles (64%) and poly bags (64%). The presence of NH_2 is implied by the high QY of the CDs, which is significantly correlated with their carbonyl groups. The emission peak of each of the three CDs was also slightly redshifted concerning the excitation wavelength. The observed alterations in behavior were mainly caused by the hydroxyl and epoxy functional groups on the CDs made from plastic waste [83].

Recent studies show CD synthesis is more suited to precursors due to its higher molecular weights, heteroatoms, and aromatic structures. The fluorescence QY of CDs made from asphalt, heavy oil, light deasphalted oil (LDAO), and heavy deasphalted oil (HDAO) was investigated by Ma et al. in 2021 [84]. Due to their higher-than-usual aromatic carbon to naphthenic carbon to alkyl carbon ratios, the CDs recovered from asphalt were preferred. Asphalt has a higher carbon-to-hydrogen ratio, oxygen-to-nitrogen ratio, and sulfur content than the other precursors. The double-peak and (002) peaks existed in the asphalt X-ray diffraction pattern [83].

6. The Diagnostic Application of CDs

CDs are utilized in various biological applications due to their peculiar optical features, vast surface area, and adjustable surface functionalization. Although there are still some biosafety concerns regarding CDs, in vitro cytotoxicity investigations of several cell line series have not revealed acute toxicity or morphological abnormalities [85]. Recent in-vivo experiments established that CDs are safe and biocompatible. Below are a few examples of CD applications in the field of diagnosis [85].

6.1. Bioimaging

CDs are superior to traditional organic dyes and semiconductor quantum dots (QDs) because of their unique qualities, such as their multicolor emission profile, small size, low cytotoxicity, strong biocompatibility, and excellent photostability [86]. CDs are advantageous alternatives to traditional probes for investigating living organisms due to their distinctive features [87]. Fluorescent-core CDs were produced by carbonizing ammonium citrate via dry heating [88]. In solid-state reactions with mannose and folic acid, the CDs were dehydrated to form CDs functionalized with mannose and CDs functionalized with folic acid, respectively. Other researchers have produced and evaluated CDs for imaging a cervical cancer cell line [89]. Pan et al. and Hu et al., respectively, employed thermal reduction of monolayer graphene oxide sheets with H_2SO_4 and HNO_3 and hydrothermal treatment of graphene oxide in the presence of ammonia to synthesize CDs [90,91]. These CDs were predominantly restricted to the cytoplasm and exhibited no discernible toxicity to the cells. Ge et al. utilized polythiophene phenyl propionic acid to make red-emitting CDs with broad absorbance from 400 to 750 nm [68]. When animals harboring the HeLa tumor were injected intravenously with the CDs, they gathered primarily within the tumor [88]. Consistent with the prior examples of cell imaging, CDs are primarily seen in the cytoplasm and the cell membrane. How a substance will be absorbed into a cell is mainly determined by its size and charge [92]. CDs are rapidly internalized into the cytoplasm due to their small size (10 nm) [93]. However, due to the abundance of carboxylate groups

on the surface, CDs are predominantly negatively charged which hinders their ability to penetrate the cell nucleus. The cell nucleus is indispensable for metabolic functions, genetic transmission, and cell division [94]. Thus, staining the nucleus is the first step in understanding nuclear morphology and function. Consequently, nuclear localization of the fluorescent agent is a highly desirable result [95].

However, recent advancements have demonstrated that the surface functionalization of CDs can resolve this issue. A recent study conducted by Guangmei Han and colleagues showed that by modifying the surface of the CDs such as via cationic stabilization, the charge distribution is altered to make them more positively charged, ultimately facilitating their delivery within the nucleus [96]. These modified CDs showed an enhanced ability to enter the nucleus, making them more valuable for cellular imaging and other biological applications as well. Further research conducted has also demonstrated that CDs functionalized with a quaternary ammonium (betaine) precursor have significantly improved nucleus uptake. For instance, Datta et al. were among the first researchers to announce that CDs had entered the cell nucleus [97]. They produced CDs that penetrated the nucleus due to their significant positive charge from the quaternary ammonium (betaine) precursor and their small size. In their research, Kanget et al. utilized dopamine and neutralized it with heat to produce nitrogen-doped CDs that resemble biomolecules. They also observed a similar charge effect. The efficiency of these CDs as a nucleus stain was demonstrated using four distinct cancer cell types [98]. The study utilized A549, HepG2, rat pheochromocytoma (PC12), and breast cancer (MD-MBA-231) cell lines [88]. Hydrothermal treatment of p-phenylenediamine (pPDA) with a variety of metal ions led to the creation of fluorescent CDs with emission wavelengths up to 700 nm, but the CDs retained the metal, which acted as a "catalyst" [99]. Nickel coupled with CDs created biocompatible CDs, enabling real-time, wash-free, high-resolution imaging of the cell nuclei and high-contrast imaging of mice and zebrafish with tumors [100–103].

CDs have been utilized in two-photon fluorescence imaging. This technique avoids harmful UV or blue excitations and enables the visualization of living tissue at depths not attainable with traditional (one-photon) fluorescence or confocal imaging [104]. Since Cao et al. initially demonstrated this technique, two-photon luminescence microscopy has been utilized to observe cells utilizing CDs. They demonstrated the two-photon absorption cross-section of amine-polymer-passivated CDs and compared it to the best-performing core-shell quantum dots [105]. A receptor molecule was covalently bonded to the CD's surface to achieve these pH-sensitive reactions. The fluorescence intensity increased as the acidity of the CD system decreased. With an excitation wavelength of 800 nm and an emission wavelength of 490 nm, this system proved effective in live tissues at depths between 65 and 185 mm [88].

6.2. Bio/Chemical Sensing

Researchers have utilized CDs as a bio- and chemical-sensing material due to their excitation-dependent emission, excellent photostability, reduced cytotoxicity, and water solubility [106]. Fluorescence property changes caused by resonance energy transfer, the inner filter effect, and photo-induced electron and charge transfer are typically responsible for sensing. CDs can detect many biological molecules and intracellular metal ions, including hydrogen peroxide (H_2O_2), iron (Fe^{3+}), glucose, vitamin B12, L-cysteine, galactose, etc. Wu et al. were the first to use L-glutamic acid-derived CDs to detect hydrogen peroxide (H_2O_2). These CDs could detect H_2O_2 with a limit of detection [18] of 20 mM, whereas Qian et al. employed hydroquinone and $SiCl_4$-derived CDs as sensors for H_2O_2, Fe^{3+} and melamine, respectively. Si-doped CDs were used to detect H_2O_2 by an electron transfer process, while Fe^{3+} was detected through electron and energy transfer methods. After adding melamine,

H_2O_2 formed a stable adduct with the amine, which recovered fluorescence and served as a sensitive amine detector [107]. Last, Shan et al. used boron-doped CDs to selectively detect H_2O_2 with a detection limit of 8.0 mM. In conjunction with these CDs, glucose oxidase, the enzyme responsible for forming H_2O_2 from glucose, could be employed to detect glucose [108].

It has been discovered that human urine contains trace amounts of biological substances such as folic acid and galactose. Chen et al. created CDs for detecting folic acid by heating lactose and NaOH [109]. They discovered that attaching folic acid to the preparation CDs decreased the dots' fluorescence. Using CDs functionalized with boronic acid, Yang et al. could quench galactose. The boronic acid group on the CDs surface reacted with the galactose cis-diol units to produce cyclic boronate esters [110]. Lan et al. employed hydroxyl and carboxyl groups to passivate fullerene (C60)-generated CDs for the detection of biological iron (Fe^{3+}). These groups inhibit fluorescence due to their interactions with Fe^{3+} [88].

7. Biomedical Applications of CDs

7.1. CDs as a Nanomedicine

CDs demonstrate a variety of therapeutic behaviors like antibacterial activity, anticancer activity, antiviral activity, and antioxidant activity in addition to serving as drug delivery vectors [20,111]. By retaining pharmacophores in their structures and by creating new active structures, carbon-based polymer dots (CPDs) prepared from drug molecules (such as metronidazole, gentamicin sulfate, or glycyrrhizic acid) typically exhibit therapeutic routines that are comparable to or even higher to those of pure drugs [111,112]. Recent studies highlight their ability to enhance therapeutic efficacy while improving biocompatibility, water solubility, and fluorescence for theranostic applications. For instance, Yang's group generated Met-CPDs via hydrothermal treatment of broad-spectrum antibiotics effective against obligate anaerobes [111]. Met-CPDs have higher water solubility and biocompatibility than metronidazole due to the synthesis of additional functional groups, such as carboxyl, hydroxyl, and amino groups. In agreement with the principal mode of action of metronidazole [20], experimental biological data revealed that Met-CPDs exhibited outstanding selective antibacterial activity against obligatory anaerobes due to the presence of the pharmacophore nitro group. Similarly, curcumin base carbon-based polymer dots (Cur-CPDs), which are derived from curcumin, exhibited notable antiviral activity against enterovirus 71 (EV71) infection in RD cells in comparison to raw curcumin [113]. Due to the unique pyrolytic curcumin polymers on the CPDs, Cur-CPDs exhibit outstanding aqueous solubility, antiviral activity against EV71, and biocompatibility. Although it has been demonstrated that these drug-CPDs are effective against germs, tumors, and viruses, additional study is necessary to establish the precise biochemical process underlying these actions [114].

7.2. CDs in Microorganism Therapy

Using CDs in microorganism therapy has gained significant potential for combating various infections including infections like bacterial keratitis. Bacterial keratitis [115] is an example of an infectious condition for which carbon quantum dots (CQDs) therapy has been demonstrated. The direct pyrolysis of spermidine tri-hydrochloride powder (Spd) produced super-cationic CQDs (CQDSpds) were effective against Gram-positive and Gram-negative bacteria and multidrug-resistant pathogens such as MRSA [116]. A highly positive charge (about 45 mV z-potential) has been hypothesized as the antibacterial mechanism of CQDSpds [88]. Huang's team further demonstrated the antiviral potential of CDs [113]. Polymer-like curcumin and somewhat degraded (pyrolytic) curcumin polymers

or molecules ornamented the surfaces of the curcumin CDs (Cur-CDs), generated by simple dry heating. In RD cells, Infectious Vesicle enterovirus 71 (EV71) was suppressed by Cur-CDs (human rhabdomyoma sarcoma). Cur-CDs are capable of preventing the attachment of EV71 to the cell membrane of RD cells by inhibiting the translation of EV71, EV71-induced eIF4G cleavage, and the production of phosphorylated p38 kinase. The administration of Cur-CDs during in-vivo animal research protected newborn mice from EV71 infection. Folic acid-derived carbon dots (FA-CDs) have emerged as a pH-responsive smart antimicrobial system. FA-CDs exhibit significant antibacterial activity under acidic conditions while inhibiting bacterial superoxide dismutase. This helps in the effective killing of Gram-positive *S. aureus* and the disruption of mature biofilms. FA-CDs exhibit excellent biocompatibility and therapeutic efficacy for *S. aureus*-infected wounds, highlighting their potential for therapeutic applications [117]. Using CDs to differentiate and classify bacterial species is another exciting field [118]. Consequently, Gram-type bacteria may be recognized rapidly and eliminated selectively. Yang et al. demonstrated eloquently that the adsorption of their CDs onto Gram-positive bacteria rendered them inactive [118,119]. Lin et al. comprehensively described the latest developments of CDs for sensing and killing microorganisms, including bacteria, fungi, and viruses [120].

7.3. Cancer Therapy

CDs provide significant advantages over conventional drug delivery systems, including fluorescence emission, small size (which allows them to enter cells quickly), less toxicity, chemical inertness, and water solubility. Despite their simple functionalization, they offer significant potential as drug carriers. Several scientists have utilized CDs in drug-delivery devices [121,122]. Doxorubicin (DOX) is one example of an anticancer medicine. The CDs conjugated with DOX enable targeted drug delivery, as described by Tang et al. The high fluorescence resonance energy transfer (FRET) efficiency phenomena were characterized by a drop in the CDs' fluorescence and an increase in the DOX fluorescence [123]. CDs conjugated with DOX enable real-time monitoring of the drug release profile by FRET and two-photon imaging. The separation of DOX and CDs enhances the fluorescence intensity because the FRET phenomenon between DOX and CDs is diminished. Yang et al. produced DOX-containing CDs, which were then passivated with polyamine-containing organosilane molecules. Due to the hydroxyl groups on their surface, these CDs were water-soluble while being able to carry a significant amount of medicine (62.8%) [124].

These substances were taken up by human breast cancer cells (MCF-7) and carried into their cytoplasm, where the DOX could progressively detach from the surface of the CDs and reach the cell nucleus. CDs are advantageous for drug delivery, fluorescence imaging, and magnetic resonance imaging (MRI). Fluorescence imaging simplifies microscopic tissue analysis, while MRI's greater tissue penetration and spatial resolution make this a potent combination [88]. CDs have been synthesized using Eu^{3+}, Mn^{2+}, and Gd^{3+} ions. Zou and colleagues developed Gd^{3+}-doped CDs to treat tumors utilizing MRI. Gd-doped CDs demonstrated efficient in vivo bio-dispersion and passive tumor targeting with a 6 h circulation period. A dose increase with the Gd-doped CDs directly resulted in effective tumor suppression with radio-sensitized radiotherapy, as demonstrated by the first findings in an in vivo tumor xenograft model [88].

7.4. Photodynamic/Thermal Therapy

In addition to their usage in transporting medicines and genetic materials, theranostic CDs have been engineered for photodynamic therapy (PDT) and photothermal therapy (PTT) [125]. In these unique therapeutic methods, different types of laser light with varying laser power and intensities have been employed. For PTT to function, the photo-absorber

CDs must be highly efficient at converting NIR light into thermal energy to induce thermal ablation and cell death in targeted cells. Showcasing advantages such as non-invasiveness, high selectivity, and high temporal selectivity and resolution [125,126], PTT has distinct benefits over conventional cancer treatment methods, such as invasive surgery, chemotherapy, and radiation. In recent years, numerous laboratories have examined PTT's potential as a cancer treatment. PTT can kill cancer cells at the primary tumor site or in adjacent lymph nodes to battle the initial stage of cancer spread. In the presence of photothermal agents, particularly nano-dimensional compounds, the therapeutic efficacy of PTT depends heavily on the conversion of light to heat. Also, it is believed that the strong electron–electron interactions and the weak electron–phonon interactions result from the CD structure's features, such as the high number of p electrons. It proposes that most captured light can be altered to heat via non-radiative mechanisms [126].

In addition to PTT, CD-based PDT has gained substantial interest. PDT comprises three essential components: a photosensitizer, a light source, and ROS. Typically, a laser excites the photosensitizer, creating radicals or ROS. Extremely cytotoxic to cells, species such as $^1O_2$, O^{2-}, and -OH destroy sick tissue. CDs have been widely employed to transfer photosensitizer chemicals to sick tissue owing to their ease of synthesis, surface functionalization, high-carrying capacity, and excellent biocompatibility [127]. He et al. utilized chitosan and diketo-pyrrole to generate the release of singlet oxygen species when subjected to a single laser ($^1O_2$) [128].

The hydrophilicity and biocompatibility of the CDs they created were established by both in vitro and in vivo studies. The results demonstrated that concentrations of the produced CDs up to 200 μg/mL were non-toxic to HepG2 cells without laser irradiation, whereas 100 μg/mL values were sufficient to kill 50% of the cells. Hua et al. [129] further demonstrate this notion; they generated CDs by hydrothermally treating chitosan, ethylenediamine, and mercaptosuccinic acid in a single step. By conjugating these CDs with the photosensitizer Rose Bengal (RB), they could synthesize CDs that entered cells quickly and accumulated in mitochondria, paving the door for mitochondrial-targeted photodynamic treatment [129].

8. CD-Based Nanocomposites

Although classical nanodots, including metal nanoparticles and quantum dots, demonstrate efficacy in numerous applications, carbon dot composites are gaining traction [25]. These composites, which integrate various polymeric materials with CDs, exhibit distinctive optical properties, biocompatibility, and customizable functionality, making them beneficial for biomedical applications [25]. CDs are mostly carbon-based and may be synthesized from several precursors, making them a safer and more environmentally sustainable alternative to traditional nanodots, which frequently contain heavy metals or other toxic substances. The shift to carbon-based materials improves the safety of the nanomaterials and promotes the development of cutting-edge biosensing, bioimaging, and drug delivery methods [25].

The CD/PEG and chitosan composite are recognized uses of carbon dot composites with considerable potential in pH-sensitive fluorescent biosensing devices. The non-invasive analysis of acidic microenvironments in problematic tissues using these materials enhances the early detection and treatment of diseases like cancer [130]. CD/polyurethane composites are functional scaffolds in bone tissue engineering due to their remarkable bioactivity and mechanical properties, which promote bone repair [131]. CD/poly(N-isopropylacrylamide) (PNIPAM) composites have bioimaging and thermoresponsive drug delivery capabilities. The unique properties of PNIPAM enable the regulated release of

pharmaceuticals in reaction to temperature variations, improving therapeutic effectiveness and advancing research on real-time drug delivery mechanisms [132].

The broad adsorption, separation, photoelectronic, and electrochemical capabilities of CD/polymer composites have generated attention in this field due to their capacity to enable rapid and reliable analytical detection. Further investigation is necessary to determine straightforward, economical techniques for fabricating environmentally beneficial CD/polymer composites intended for biosensors, drug delivery, bioimaging, and other applications (Table 3). This discovery is crucial for the complete realization of the promise of carbon dot composites and the demonstration of their adaptability as a tool in modern nanotechnology [25].

Table 3. Applications of carbon dot/polymer composites.

Carbon Dot/ Polymer Composites	Applications	Ref.
CD/polyethyleneimine [133]	Drug delivery with bioimaging	[134]
CD/poly (N-isopropyl acrylamide-acrylamide vinyl phenylboronic acid)	Glucose detection and measurement with hydrogel technology	[135]
CD/polyamidoamine and gold nanocrystal	Immune detection of alpha-fetoprotein biosensor	[136]
CD/DNA	Nano-biohybrid biosensor for fluorometric detection of histones	[137]
CD/starch	Tissue scaffold for tissue engineering	[46]
CD/Chitosan/Polyurethane composite	Engineering of bone tissue and pH-sensitive biosensing	[138]
CD/poly(N-isopropyl acrylamide) (PNIPAM) composite	Bioimaging with thermosensitive drug delivery	[139]
CD/polyurethane composite	Scaffold for bone repair and regenerative medicine	[140]
CD/PEG composite	pH-sensitive fluorescent biosensing in acidic microenvironment for early disease detection	[141]

9. The Toxicity of CDs and Their Safety

CDs are valuable for biomedical applications because they are biocompatible and generally effective cytotoxic agents. Although CDs are widely used in photodynamic antimicrobial chemotherapy (PACT) applications, their influence on host cells, potential medical problems, and toxicity [142] must be thoroughly investigated. Because light sensitizers must contact mammalian cells or tissues during PACT applications, CD toxicity is of the utmost concern. Another safety challenge is the risk of light sensitizers moving into living organisms from the surface. Studies on the cytotoxicity of CDs in mammalian cells have produced encouraging findings; at the appropriate dosages, CDs are non-toxic in vitro and in vivo [143,144]. Since characteristics vary widely between precursors and synthesis methods, the cytotoxicity of CDs cannot be ignored. CDs manufactured from "biosafe" precursors, such as glucose, are widely assumed to be non-toxic.

Nevertheless, in certain instances, CDs can only keep their low cytotoxicity in the dark, whereas cytotoxic chemicals are created when exposed to light [145]. Consequently, comprehensive research is required to assess the potential toxicity of CDs in people. Concentration has a significant effect on the toxicity of CDs [142]. CDs are neurotoxic at concentrations sufficient to harm the brain and spinal cord. According to toxicity reports, most studies suggest the safe usage of GQDs, but this may differ depending on the concentration and testing method used in the synthesis technology [145]. Studies have demonstrated that negatively charged CDs are more cytotoxic to mammalian cells [146] and that compact CDs are more hazardous than large CDs [145]. ROS generation plays a role in cell death in addition to its role in CD sterilization. Promoting safe and controllable CD synthesis strategies and application methods is essential for addressing the issues mentioned above,

and a comprehensive investigation of the potentially toxic side effects and complications of using CDs in handling infectious diseases is essential [142,145].

10. Conclusions and Future Perspective

CDs have emerged as multifaceted and promising nanomaterials with diverse applications. In recent years, CD-based nanomaterials have progressed enormously in the biomedical field, showcasing their unique properties and multifunctionality, ultimately making them the ideal candidate for diagnostics and therapeutic intervention. This article examined the benefits, frameworks, chemistry, and several synthesis techniques of CDs, encompassing both top-down and bottom-up methodologies. Applications like bioimaging and biosensing underscore the potential of CDs in the medical diagnostic field. Furthermore, CDs have considerable potential in therapeutic applications, encompassing their utilization as nanomedicines, in microbial therapy, and oncological treatments using photodynamic and photothermal modalities. The synthesis of carbon dots from waste materials and biogenic sources such as fungi and bacteria offer an environmentally sustainable method, enhancing sustainability in nanotechnology. Moreover, the advancement of CD composites establishes new horizons in nanoparticle research, augmenting their usefulness and range of applications. Although CDs have multiple advantages, their toxicological profiles and safety must be meticulously assessed to guarantee their secure deployment across diverse contexts. Future research should concentrate on refining synthetic techniques to generate carbon dots (CDs) with exact shapes and chemical compositions, capitalizing on their distinctive optical and redox characteristics. This will facilitate their wider utilization in diagnostics, treatments, and other areas.

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