Carbon Nanodots-Based Nano-Biosensors

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Semiconductor quantum dots (QDs) were a modern form of nanostructure that demonstrated excellent qualities for diagnosis and therapy. Controlling QDs size and distribution made it simple to adjust their electrical and optical characteristics. Yet, since certain semiconductor QDs include hazardous substances such as, cadmium, arsenic, selenium, and mercury, they have several disadvantages. One such disadvantage is cytotoxicity. As a result, these QDs are neither environmentally friendly nor biodegradable. On the other hand, since their inception in 2004, carbon nanodots (CNDs) have been recognized as a strong contender to replace the extremely dangerous metallic semiconductor class of quantum dots. This is partly because the characteristics of carbon quantum dots are widely acknowledged to include their nanoscale size, roughly flat or spherical morphologies, great water solubility, broad absorption in the UV-visible light spectrum, and vibrant fluorescence. CNDs have an amorphous or nanocrystalline center, mainly sp^2 carbon, graphite grid spacing, and outside oxygenic functional groups, allowing for water solubility and subsequent complexation.

biomarkers carbon nanodots miRNAs

1. Synthesis of Carbon Nanodots

Both “bottom–up” and “top–down” strategies may be used to create semiconductors based on CNDs. Bottom–up strategies encompass thermal decomposition, electrochemical carbonization, microwave irradiation synthesis, and hydrothermal/solvothermal treatment. Top–down methods include laser ablation, ultrasonication, arc discharge and electrochemical oxidation. For both these processes, a strict reaction environment is frequently needed, including high-grade carbon substrates, extreme heat, powerful alkali/acid solutions, and hazardous organic solvents.[1]

1.1. Top–Down Approach

Due to their simplified preparation procedures, top–down approaches are appropriate for the mass manufacturing of CNDs nanomaterials. The top–down approach “cuts” carbon particles including CNTs and graphite into CNDs via an arc discharge, laser ablation, or chemical oxidation. Arc discharge and laser ablation are the most commonly used top–down methods for producing CNDs. Gonçalves et al. used laser ablation in water solution, N-acetyl-l-cysteine, and NH2-polyethylene glycol (PEG200) to create passivated CNDs. Chemical oxidation involves introducing oxygen-containing hydrophilic functional groups into carbon nanostructure complexes by oxidizing them with a potent acid. The carbon nanostructures become water-soluble, which facilitates their discharge into the fluid. Scientists have also produced CNDs by hydrothermally slicing graphene sheets.[2] Wang et al. used graphene oxide as the precursor to creating C-dots using the hydrothermal process with microwave assistance. Carbon dots that are hydrophilic, hydrophobic, or even amphiphilic can be made using microwave-assisted synthesis. A simple one-step microwave-assisted synthesis of hydrophobic C-dots was described by Mitra et al. Using glucose as a starting material, Ma et al. reported the ultrasonic synthesis of N-doped C-dots (**Figure 1**).[3]

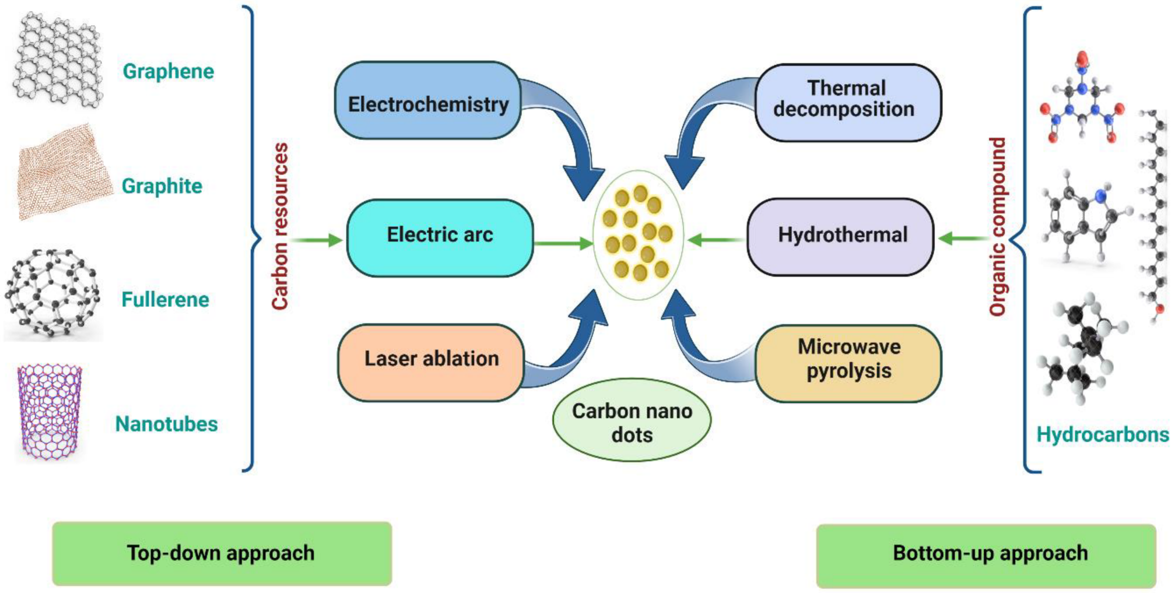

Figure 1. Top–down and bottom–up approaches for the synthesis of CNDs by using hydrothermal, microwave pyrolysis, thermal decomposition, laser ablation and other different synthesis methods.

1.2. Bottom–Up Approach

In a "bottom–up" approach, CNDs are synthesized from small carbon molecules using microwave, hydrothermal, and pyrolysis methods. Basic principles involve burning and heating carbon precursors. CNDs can be prepared very efficiently through a bottom–up approach using a plethora of starting materials, and the choice of reactants determines their properties, especially in surface coating. Much more important is the fact that the roots of the carbon substrate can have a massive effect on the CNDs' characteristics, including their sensing capabilities. Another advantage of the bottom–up approach is the easy addition of heteroatoms and other dopants. Sucrose, citric acid, amino acids, and food waste are carbon sources.[4]

Direct pyrolysis, the pyrolytic technique, or the carbonization of precursor materials at high temperatures are standard methods for producing carbon dots. Zhu et al. were the first to employ microwave pyrolysis as a synthesis mode, using a dissolved saccharide and PEG-200. The size of CNDs increased with reaction time as this solution was heated in a 500 W microwave. The yield of CNDs increases, and side reactions are reduced during microwave pyrolysis. Many CNDs variants have been created through direct thermal decomposition, in which precursors are heated in an inert environment until they are carbonized. Solvents are then used to extract them. The carbonization of small molecular precursors is used in the bottom–up synthesis of CND. One of the most common bottom–up synthesis approaches produces CND from a mixture of citric acid and a nitrogen-containing molecule such as urea.[5] When these molecular precursors are pyrolyzed by microwaves or in an autoclave, the synthesis readily produces a black nanopowder of CNDs, which is highly dispersible in water and displays remarkable fluorescent properties. Depending on the conditions, these CNDs can display blue, green, or red emissions, although extensive purification is often needed to isolate CNDs from molecular intermediates produced during the synthesis. Bottom–up methods were efficient routes to produce fluorescent CNDs on a large scale. For example, small molecules and polymers can undergo dehydration and further carbonization to form CNDs.[6]

1.3. Preparation of CNDs Using Green Approach

CNDs synthesized from biological sources play a significant role in biomedical and environmental applications, including bioimaging, biosensing, metal ions detection and electrocatalytic oxidations. Green synthesis has attracted the interest of scientists because it is cost-effective, less hazardous, eco-friendly, less time-consuming, and requires lower temperatures (**Table 1**). The production of CNDs from mostly reusable substrates includes naturally available raw materials that are relatively cheap and simple to make. CNDs made from natural sources can be used to transform low-value biomass waste into rich and valuable products. The low manufacturing cost and constant availability of raw ingredients for CNDs synthesis have made it a viable procedure for the industry also. Additionally, no dangerous organic solvents are required; instead, an aqueous solution may be used, increasing the CND's water solubility (**Figure 2**).[7]

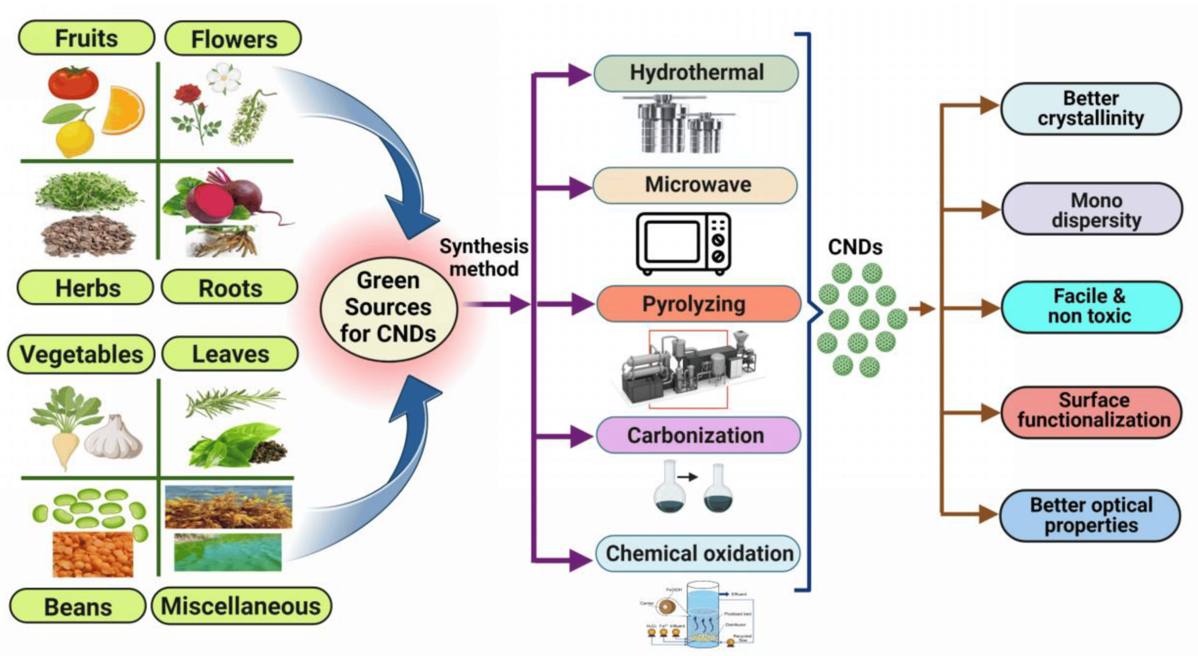

Figure 2. Various natural precursors for the synthesis of CNDs by using hydrothermal, microwave, pyrolysis chemical oxidation and carbonization as green approaches.

Recently, Hashemi et al. manufactured CNDs using a low-cost, simple, and green one-step hydrothermal process, producing luminous CNDs with high quantum yield from red beetroot as an organic source. According to the paper, red beetroot was sliced into small pieces and mixed with deionized water, continuously swirling for 20 min before being sonicated for an hour. The mixture was then placed in a Teflon-lined autoclave and heated in the oven (180° for 10 h). It was then centrifuged (1000 rpm for 30 min) and filtered to obtain the CNDs solution. To obtain a pure

CNDs solution, the mixture was dialyzed for three days to remove contaminants.[8] As a result, in the current context, the green synthesis approach of C-dots produces high C-dot yields at a cheap cost because of low-cost raw materials. The simple procedure adopted, as well as the fluorescence qualities found in C-dots derived from environmentally sourced materials, open the way for harmless and biocompatible C-dots to be used in sensing approaches. The study describes a single-step hydrothermal strategy to synthesize colored CNDs from maple leaves to specifically capture cesium ions. The CNDs made emit blue fluorescence and varied in size from 1 to 10 nm. Based on the electron transfer method, these CNDs were successfully employed in glycerol electro-oxidation catalysts and cesium-detecting probes.[9] Arumugham et al. made CNDs using catharanthus roseus (white) leaves as the carbon source without the addition of an oxidizing agent or an encapsulant. These CNDs have excellent antioxidant activity and bioimaging potential against MCF-7 cells as well as strong fluorescence (FL) emission, high water solubility, stability, and non-toxicity, among other properties.[10]

Table 1. List of Various Natural Sources Used in the Preparation of Carbon Nanodots Using Different Green Synthesis Methods.

S. No.	Source	Method of Synthesis	Size	Percentage Yield	Detection Limit	Inference	References
1	Banana peel	Microwave treatment	5 to 15 nm	16.0%	1.82 × 10–17/mol	CNDs are fabricated by the microwave treatment of banana peels in a single pot for the determination of colitoxin DNA in human serum.	[11]
2	Sargassum fluitans	Hydrothermal	2–8 nm	18.2%	-	A hydrothermal method is used to produce CNDs from waste seaweed sargassum fluitans (*S. fluitans*) to detect DNA.	[12]
3	Tomato juice	Hydrothermal	1.3–3.7 nm	13.9%	0.3 ng/mL	CNDs are synthesized by hydrothermal treatment of tomato juice for the sensing of carcinoembryonic antigen.	[13]
4	Limes	Pyrolyzing	5-10 nm	-	-	The pyrolyzing process is used to	[14]

S. No.	Source	Method of Synthesis	Size	Percentage Yield	Detection Limit	Inference	References
						synthesize CNDs for the detection of hepatitis B virus DNA.	
5	Lemon juice	Carbonization	6–9 nm	-	0.23 mM	Carbonization of lemon juice is performed to form CNDs for the detection of l-tyrosine.	[15]
6	Lemon	Pyrolyzing	10 nm	-	0.0049 µM	Synthesis of CNDs from a lemon by the process of pyrolysis for the detection of doxorubicin hydrochloride in human plasma.	[16]
7	Syringa oblata lindl	Hydrothermal	1.0–5.0 nm	12.4%,	0.11 µM	A hydrothermal method is used to fabricate CNDs from syringa oblata lindl for sensors and cell imaging.	[17]
8	Grapefruit	Hydrothermal	>30 nm	20%	-	Grapefruit is used to create CNDs using a hydrothermal process for the detection of *E. coli bacteria.*	[18]
9	Alfalfa and garlic	Hydrothermal	1.3–6.9 nm	10%	86 nM	A hydrothermal method is used to form CNDs from alfalfa and garlic as a fluorescent probe for cysteine, glutathione, and homocysteine.	[19]
10	Catharanthus roseus (white flowering plant)	Hydrothermal carbonization	-	-	-	Catharanthus roseus (white flowering plant) is hydrothermally carbonized to	[10]

S. No.	Source	Method of Synthesis	Size	Percentage Yield	Detection Limit	Inference	References
						create CNDs to detect the Al^{3+} and Fe^{3+} ions.	
11	Lemon juice	Hydrothermal	-	-	-	The one-pot facile hydrothermal approach was used to create highly luminous carbon dots (C-dots) from lemon juice.	[20]
12	Daucus carota	Hydrothermal	-	7.60%	-	A hydrothermal method is used to produce CNDs from Daucus carota to detect mitomycin.	[21]
13	Natural polymer starch	Hydrothermal	2.25–3.50 nm	-	-	Hydrothermal treatment of natural polymer starch is performed to produce CNDs.	[22]
14	*P. acidus*	Hydrothermal	5 nm	12.5%	-	CNDs are produced by a hydrothermal process from *P. Acidus* for live cell imaging.	[23]
15	Citrus peel powder	Sand bath heat-assisted method	4.6 ± 0.28nm	-	-	The sand bath heat-assisted method is utilized to form CNDs from citrus peel powder for free radical scavenging and cell imaging.	[24]
16	Lentil	Hydrothermal	7 ± 4 µm	10%	3.0 µg	A hydrothermal method is used to form CNDs from lentils for the colorimetric determination of thioridazine hydrochloride.	[25]

S. No.	Source	Method of Synthesis	Size	Percentage Yield	Detection Limit	Inference	References
17	Rose flowers	Hydrothermal	1.0–5.0 nm	-	0.02–10 μM	CNDs are produced by a hydrothermal process from rose flowers for the determination of diazinon.	[26]
18	Saffron	Hydrothermal	>20 nm	23.6%	1.8 n/mol	A hydrothermal method is used to produce CNDs from saffron for the sensing of prilocaine.	[27]
19	Valerian root	Hydrothermal	>10 nm	14%	0.6 ng/mL	Valerian root has been used to make CNDs using a hydrothermal process for the determination of imipramine.	[28]
20	Rosemary leaves	Hydrothermal	Approx. 5 nm.	18%	8 ng/mL	Rosemary leaves have been used to make CNDs using a hydrothermal process for the determination of thiabendazole in juices.	[29]
21	Beetroot	Microwave	5 & 8 nm	6% & 5%	-	CNDs made from aqueous beetroot extract by the process of a microwave for in vivo live animal imaging applications.	[30]
22	Eutrophic algal blooms	Chemical oxidation	Approx. 8 nm	13%	-	Eutrophic algal blooms have been used to make CNDs using chemical oxidation for in vitro imaging.	[31]
23	Green tea leaf	Pyrolyzation	2 nm	14.8%	-	Synthesis of CNDs from green tea leaf	[32]

...hemicals. ...opy. The hydrothermal technique used for this research is a reactive technique that produces CNDs of good yield and high quality. In a recent article, Saleem et al. present a one-step flexible approach to produce fluorescent CNDs utilizing carrot root species. The synthesized CNDs worked as nano-vehicles for the mitomycin medication delivery. By

S. No.	Source	Method of Synthesis	Size	Percentage Yield	Detection Limit	Inference	References
						[36] by the process of pyrolysis for the sensing of gefitinib.	
24	Waste tea residue	Chemical oxidation	3.2 nm	2.47%	Be 0.04 μg /mL	Waste tea residue has been used to make CNDs using chemical oxidation for the quantification of tetracycline.	[33]
25	Palm shell powder	Chemical oxidation	4–10 nm	6.8%	0.079 μM	CNDs are synthesized by the chemical oxidation method from palm shell powder for the sensing of nitrophenol.	[34]
26	Soybeans	Ultrasonic-assisted method	2.4 nm	16.7%	0.9μM	[38] An ultrasonic-assisted method is used to produce CNDs from soybeans to detect Fe^{3+} ions.	[35]

Abbreviations: nanometer (nm), millimeter (mm), micrometer (μm), carcinoembryonic antigen (CEA), *Escherichia coli* (*E. coli*), *Phyllanthus acidus* (*P. acidus*), nanograms (ng).

ed CNDs ... n content ... YO) were ... NDs that ... ion (EYO ... animals in ... tivate the ... apacity to ... dicine.[37] ... ly amino- ... ization of ... ntails two ... (RCG). A ... rids was ... The entire ... l CS, the GR/CNTs/CS hybrid was created and might be used to trap organophosphate pesticides. In another study, a simple, cost-effective, and environmentally friendly method for producing ternary nanocomposites of carbon, polydopamine, and gold was demonstrated. The technique did not employ harsh reaction conditions such as those found in hydrothermal or high-temperature techniques. The excellent electrocatalytic activity was demonstrated by the CNTs/PDA/AuNPs modified electrode to oxidize chloramphenicol.[39] One more research study covered a synthesis of multiwall carbon nanotube/Cu_2O-CuO ball-like composite (MWCNTs/Cu_2O-CuO) adopting a green hydrothermal approach which had been investigated as a novel sorbent for the solid-phase extraction of uranium utilizing inductively coupled plasma mass spectrometry.[40]

2. Carbon Nanodots in Biosensing of microRNAs

Macromolecules and circulating analytes in biological systems must be detected in a way that is efficient, reliable, and inexpensive. Recent developments in the field of biosensors have aided the development of functionalized nanosensors that have the potential to provide a cost-effective, efficient, and quick diagnostic approach for the detection of circulating miRNAs. Along with this, some unique properties—such as biocompatibility, high stability and water dispersibility, and accessible green synthesis, surface functionalization of C-dots that creates a strong interaction between CNDs and biological processes—all make them significant for sensing circulating analytes.[41] Fluorescent, colorimetric, chemiluminescent, and surface plasmon resonance are the most common sensing systems used to detect circulating miRNAs.[42] This is due to the relative ease of making fluorescent CNDs and their photostability, which can be used as low-cost alternatives for sensing significant biomarkers (**Table 2**).

Fluorescence-based analytical approaches allow for the accurate, efficient, and reproducible detection of biomarkers and nucleic acids. Furthermore, changes in fluorescent signals caused by biological events such as nucleic acid probe hybridization are detectable. Thus, fluorescence-based detection technologies have become increasingly popular due to these benefits.[43]

Table 2. List of Various Carbon Nanodots Used in Biosensing of Cell-Free Circulating MiRNAs Using Along with Synthesis Sources, Conjugation Chemistry, Analytical Methods, Target miRNAs, and Detection Limit.

S. No.	Carbon Nanomaterial	Source and Synthesis	Conjugation Chemistry	Biomolecule (Analyte)	Analytical Method	Detection Limit	Inference	References
1	Carbon nanodots (CNDs)	O-phenylene diamine, 2-amino terephthalic acid by solvothermal method	EDC-NHS	miRNA-21	Fluorescent biosensor	0.03 fM	CNDs are synthesized and conjugated via EDC-NHS chemistry to detect miRNA-21.	[44]
2	PEI-Carbon dots	Polyethyleneimine (PEI) by hydrothermal method	-	miRNA-21	Fluorescence biosensor	-	The synthesized CNDs is employed to detect miRNA-21 by fluorescence biosensor.	[45]
3	CNDs/AO	Citric acid in formamide	π-π conjugation	miRNA-92a-3p	Fluorometric assay (FRET)	0.14 nM	To detect miRNA-92a-3p, CNDs are fabricated and conjugated using π–π conjugation.	[46]
4	CNDs–DNA walker	Citric acid and urea by microwave-assisted method	EDC-NHS	miRNA-21 miRNA-155	Electrochemiluminescence biosensor	33 fM for miRNA-21. 33 aM for miRNA-155	CNDs are created and conjugated via EDC-NHS chemistry to discover miRNA-21 and miRNA-155.	[47]
5	CNDs	Oxidized maple leaf by a pyrolytic method	EDC-NHS	miRNA-21	Electrochemiluminescence biosensor	21 aM	CNDs are synthesized and conjugated via EDC-NHS chemistry to detect miRNA-21 associated with breast cancer.	[43]
6	CNDs	Tiger nut milk by carbonization	-	miRNA-21	Chemiluminescence biosensor	0.721 fM	Synthesized CNDs are used to detect miRNA-21 associated with	[48]

S. No.	Carbon Nanomaterial	Source and Synthesis	Conjugation Chemistry	Biomolecule (Analyte)	Analytical Method	Detection Limit	Inference	References
							cardiovascular disease.	
7	CNDs	Glutaraldehyde, nitro benzaldehyde by solvothermal method	-	miRNA-21	Fluorescence sensor	0.03 fM	An miRNA-21 associated with breast cancer is identified using a fluorescence sensor that is based on carbon dots.	[49]
8	CNDs	Malic acid centrifugation	EDC-NHS	miRNAs	Fluorescence	0.03 pM	The synthesized CNDs is conjugated via EDC NHS chemistry and used to detect miRNA.	[50]
9	CNDs	Citric acid by microwave method	π-π stacking	miRNAs	Fluorescence biosensor	2.78 fM	CNDs were synthesized and employed to detect miRNAs by fluorescence biosensor.	[51]
10	CNDs	Tree leaves by hydrothermal method	EDC-NHS	miRNA-155	Fluorescence biosensor FRET	0.3 aM	CNDs were synthesized and conjugated via EDC-NHS chemistry and were used to detect miRNA-155 by fluorescence biosensor.	[52]
11	CNDs/BHQ 2	Ethane diamine, p-benzoquinone	Maleimide-thiol	miRNA-141	FRET	16.5 pM	miRNA-14 is conjugated with synthesized CNDs via maleimide–thiol conjugation chemistry and detected by a fluorimetry test.	[53]
12	Carbon nanotubes (CNTs)	Hydrogen tetrachloroaurate trihydrate	EDC-NHS	miRNA-21	Fluorescence biosensor	36 pM	A synthesized CNT is conjugated via EDC-NHS chemistry to detect intracellularly miRNAs-21.	[54]

When a target interacts with a recognition element, a fluorescent biosensor translates information quantitatively or semi-quantitatively. After hybridizing complementary nucleic acid with its target miRNA, fluorescent-based nucleic acid detection can be generally achieved via signal-on (signal production) and signal-off (signal quenching). For DNA hybridization and tumor marker detection, carbon nanomaterial biosensors based on the FRET mechanism have practical utility in research and clinical practice. A FRET sensing platform for sensitive miRNAs detection

S. No.	Carbon Nanomaterial	Source and Synthesis	Conjugation Chemistry	Biomolecule (Analyte)	Analytical Method	Detection Limit	Inference	References
13	CNDs	Pyrolysis synthesis	Amine-amine conjugation	miRNA-21	Ratiometric fluorescence	1 pM	Synthesized CNDs were used to detect miRNA-21 associated with gastrointestinal cancer.	[55]
14	CNDs	Citric acid ethylene diamine/carbonization	Amine - glutaraldehyde	miRNA-155	FRET	0.1 aM	Fabricated CNDs are used to identify miRNA-155 present in cancer cells.	[56]
15	CNTs (MWCNT/AuNCs)	Carboxylic acid-ultrasonic cell disruption	Thiol conjugation	miRNA-155	FRET	33.4 fM	CNTs are synthesized and used to detect miRNA-155.	[57]
16	CNDs	Citric acid–hydrothermal	π-π stacking	micro-RNA	Fluorescence		A CNDs is used to detect miRNA by fluorescence method.	[58]
17	CNTs	-		miRNA-21	Electrochemical biosensor	1.95 fM	miRNA-21 is detected by a carbon nanotube-based electrochemical biosensor.	[59]
18s	Carbon nanofibers/SPE	-	Amine-carboxylic acid conjugation	miRNA-34a	Electrochemical biosensor	54 pM	The electrochemical biosensor is utilized to detect miRNA-34a using carbon nanofibers.	[60]
19	DNA-CNDs/CNTs	-	π-π stacking	miRNA-7f	Photoelectrochemical biosensor	34 fM	A CNTs is used to detect miRNA-7f by a photoelectrochemical method.	[61]
20	Carbon nanoparticles/ssDNA probe	Graphite electrode by an electro-oxidation method	π-π stacking	miRNA let-7a	Fluorescence	0.35 pM	Synthesized carbon nano-particles conjugated via π–π stacking are used to detect miRNA let-7a.	[62]

free fluorescent scheme based on strand displacement amplification (SDA) to detect miRNA with extreme sensitivity utilizing CNDs functionalized with sulfydryl (CDs-SH) as the probe. Based on the catalytic oxidation of -SH into -S-S- by hemin/G-quadruplex, CDs-SH demonstrated an outstanding response to G-quadruplex DNA against other DNAs.[49] In a study using on CNDs, a sensor for miRNA 9-1 recognition was created. On excellent fluorescence QY, water dissolvable, and low-toxicity CNDs, single-strand DNA with the FAM tag was immobilized. As a physical attribute for sensing, the fluorescent quenching of CNDs caused by the transfer of energy of fluorescence resonance among CNDs and FAM was utilized.[58] Jiang et al. proposed a self-assembled tetrahedral DNA nanostructure coupled with gold nanoparticles (AuNPs) and CNDs. The constructed nanostructure enables double fluorescence channels for the parallel estimation of miRNA and telomerase function, which is also easily transported within live cells for in situ scanning by adding an iRGD peptide sequence afterward.[63] Using single-walled carbon nanotubes, a derivative of CNDs that have been sensitized with DNA-CdS emiconductor quantum dots (QDs), a flexible photoelectrochemical biosensors platform has been created. A practical, accurate, and focused biosensor for the direct detection of miRNAs was developed by integrating with cyclic enzymatic multiplication, offering a unique method for miRNA detection.[61] In another study, they presented the selective and sensitive detection of exosomal miRNAs using a ratiometric fluorescent bio-probe based on DNA-labeled carbon dots (DNA-CNDs) and 5,7-dinitro-2-sulfo-acridone coupling with the target-catalyzing signal amplification, in which high FRET between CNDs and DSA boosted the assay's sensitivity of the bio probe.[68] Similarly, a new strategy

Abbreviations: Forster resonance energy transfer (FRET), Single-stranded DNA (ssDNA), Ethyl(dimethylaminopropyl)carbodiimide/N-hydroxysuccinimide (EDC-NHS), Screen-printed electrodes (SPEs), Black hole quencher 2 (BHQ-2), Multiwalled carbon nanotube (MWCNT), Gold nanocomposites (AuNCs), Polyethylenimine (PEI), Acridine orange (AO), Femtomolar (fM), Nanomolar (nM), Attomolar (aM), Picomolar (pM).

was developed for the construction of a dual-emission fluorescent sensor using a new ratiometric nanohybrid fluorescent probe for the detection of miRNA-21 with dual-colored CNDs (blue CNDs and yellow CNDs) as they are provided with the same excitation wavelength (360 nm), two distinct and steady emission signals (409 and 543 nm) were produced as fluorophores and then their applications for ratiometric miRNA-21 sensing and the bioimaging of cancer cells in a microfluidic device were confirmed.[44] The strong and precise binding of DNA probe functionalized B-CNDs to the complementary miRNA-21 target caused probe structural perturbations and changed fluorescence intensity in both wavelengths as miRNA-21 concentration increased. Thus, because of its rapid reaction, high sensitivity, and technical simplicity, the proposed fluorescent nano-biosensor has become a reliable analytical sensing tool.[69] The great sensitivity (because of CNDs' high brightness), multiplex capability (due to CNDs' color tunability), and homogeneous assay formats are all key advantages of CND's performance in fluorescence biosensors for the detection of circulating nucleic acids.[70] Using CNDs as photosensitizers, TiO_2 was grown on the edges of gold nanorods (AuNRs) to form dumbbell-shaped structures (AuNRs@end-TiO_2), which were then hydrophobically attached to fluorine tin oxide (TiO). FTO was bonded to the electrode surface. As a result, a compact photoelectrochemical miRNA-21 was created. Hairpin probes (HPs) were used to bind to the TiO_2-modified FTO electrode surface, while CNDs-modified homologous DNA (CNDs-cDNA) served as the photosensitive label. When targets were present, the miRNA hybridized with the HP, which caused a double-stranded specific nuclease to associate with the miRNA to the homologous segment of the HP. This released the miRNA, potentially starting a new cycle that would result in signal acquisition.[71] Gold nanoparticles conjugated with CNDs have also demonstrated excellent sensing capability. In a study, gold nanoparticles conjugated with CNDs have also shown excellent sensing capabilities. Photo-assisted biofuel cell-based self-powered biosensors (PBFC-SPBs) is also used in biosensing to identify miRNA. The coupling of PBFC-SPBs for miRNA monitoring with a Cu^{2+}/carbon nanotube (Cu^{2+}/CNTs) cathode with laccase-mimicking activity made this possible. When the target was identified, the matched miRNA with the same sequence eluted DNA2/CdS from the electrode, resulting in a weak signal. The method does not require the use of an external power source[72]. CNDs have been also widely used for the fluorescent analysis of various targets, including small molecules such as ions, H_2O_2, and biomolecules, due to their excellent PL properties. Aptamers were also recognized using CNDs. Aptamers are artificial single-stranded DNA or RNA that have a high affinity for different analytes. Xu et al. created an aptasensor for thrombin detection; it has several aptamer binding sites. Two thrombin aptamers with amino groups were created. They were modified separately on silica nanoparticles and CNDs, and both are capable of recognizing thrombin by forming an intramolecular G-quadruplex.[73]

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