Chapter-1

INTRODUCTION

According to the National Nanotechnology Initiative, nanotechnology is the understanding and generation of matters having dimensions ranging between 1-100nm leading to their novel applications. It is considered to be multidisciplinary as it covers the fields of surface engineering, bio-engineering, materials science, synthetic chemistry, and phytomedicine and thus has proved a boon for emerging advanced nanotechnologies. Nanomaterials can be synthesized either by top-down or bottom-up approach wherein under specialized ablations, bulk precursors are reduced to the nanoscale, and nanomaterials *are formed via self-assembly* [Keat *et al*., 2015, Abou El-Nour *et al*., 2010]. According to a few forecasts, the global market for nanomachines and nanodevices is expected to increase to $2.7 billion in 2028 from $736.1 million in 2018 [McWilliams *et al*., 2018].

1.2 Amalgamation of nanotechnology with natural products

Natural products (NPs) are an invaluable source for new drug discovery. They are a group of chemical constituents with wide bioactivities and have been extensively exploited to treat multifaceted diseases [Newman *et al.,* 2020]. Reverting to nature for unresolved answers is a viable means of discovering drugs that can treat refractory diseases; for example, vincristine, taxol, vancomycin, and artemisinin are all naturally derived. The interdisciplinary amalgamation of nanomaterial science and NPs chemistry leads to the better management of cancer and other diseases. Nanomaterials can be either inorganic based such as metals and metal oxide particles, organic based, such as cyclodextrin, liposome, micelle and dendrimers, carbon based single-walled carbon nanotube, multiwalled carbon nanotube, an activated carbon graphene, carbon black and fullerene or composite based such as metal-organic frameworks. CNDs have been reported for various other health and environmental applications including optoelectronic devices [Ren et al., 2022], catalysis [Lopez-Cantu *et al*., 2022], bio functional materials [Fu *et al*., 2022], theranostics [Ray *et al.,* 2022], etc.

Expensive and hazardous precursors used during synthesis processes and time-consuming reactions justify the use of NPs' in CNDs synthesis. Though crude NPs are effective in inducing cancer cell inhibition, several studies have reported that nanotechnological modifications of NPs may help to improve their bioactivities [Majidzadeh *et al.,* 2020, Jafari *et al.,* 2019]. Out of various nanoparticles such as metal nanoparticles, polymeric nanoparticles, ceramic nanoparticles, and silica nanoparticles, carbon nanomaterials have emerged as potential nanomedicine having comprehensive utility in various domains. Compared to other carbon-based nanostructures, such as carbon nanotubes, graphene, and fullerenes, carbon nanodots (CNDs) possess unique photophysical and physicochemical properties. In 2004, CNDs were discovered in arc-discharge carbon soot [Xu *et al*., 2004], and in 2006, photoluminescence emission of CNDs was improved by polymer surface passivation [Sun *et al*., 2006]. In 2010, size-dependent fluorescence was depicted by well crystalline, purified CNDs. Unique properties of CNDs such as tunable fluorescence, low toxicity, dispersibility, biodegradation, biocompatibility, low-cost precursors, and eco-friendly nature favor the broad utility of CNDs. The easy availability, one-pot synthetic routes, and cost-effective large-scale preparation have made CNDs popular among research fraternities. Incorporation of CNDs onto a suitable scaffold could lead to the development of sensing-based devices that will be suitable for rapid and onsite colorimetric detection and quantification of various analytes in biological and well as environmental samples. The Bhasmas are vital Ayurvedic formulation which are considered to be parallel to recently emerging carbon nanodots [Sreelakshmi *et al.*, 2021, Pal *et al.*, 2014]. However certain parameters such as methods of preparation, size, principle differentiate bhasmas from CNDs as shown in Table **1.1**. The bhasmas which are told in Ayurveda can be considered as parallel to green synthesized nanoparticle in modern science.

Table 1.1. Comparison of CNDs and Bhasmas.

Parameters	**Carbon nanodots (CNDs)**	**Bhasmas**
Methods of preparation	Usually One -pot mechanism by employing hydrothermal, laser ablation, arc-discharge, methods. Requires 1-10 h heating.	Involves several procedures, such as parpati, rasayoga, sindora from purification to incineration. Requires high heat energy for longer time.
Characterizations	Characterized for hybridization, surface defects, morphology, functional groups using Fourier-transform infrared	Characterized for Permeance, irreversibility, tastelessness, lightness to float in water, fineness to enter finger ridges,

	spectroscopy (FT-IR), X - ray Photoelectron S pectroscopy (XPS), X-ray powder diffraction (XRD)	
Description	Carbon nanodots are referred to zero-dimensional carbon nanomaterials as carbon forming the main core	Bhasma is referred to an ash obtained through incineration of feathers, horns, metallic and nonmetallic minerals, shells, etc. Herbo-mineral-metallic compounds having mixture of micro or nano particles
Size	In nano dimension (1-10 nm)	Micro to nano dimension (Usually 1-2 µm)
Principle	Bio-organic compounds are employed as a reducing agents which can be termed as Bottom-up approach.	During Bhasmikaran, metal is converted to higher oxidation state from its zerovalent state which can be termed as top-down approach (Bulk particles to nanoparticles). During this process minerals/metals are

		subjected to different step-wise procedures which involves purification and repeated incineration.
Precursors	Main precursors are carbon containing biomasses	Main precursors are metals/ metal oxides and organics such as plant extracts are used as catalysts.
Toxicity	No major toxicity to body and environment	Do not show toxic effects while internally applied and do not lead to environment contamination.
Therapeutic efficacy	Good therapeutic value	Good therapeutic value
Cost to scale up	Less costly	Less costly

1.3 Synthesis and properties of carbon nanodots (CNDs)

The CNDs can be synthesized by either top-down or bottom-up approaches [Doring *et al.,* 2022]. Several precursors, such as organic products, biomass, polymers, carbohydrates, and bio-products have been incorporated to fabricate CNDs via solvothermal methods, thermal decomposition, or microwave treatments [Wang *et al.,* 2022]; however, due to harsh reaction conditions employed in these methods, makes their reaction mechanisms too complicated to be understood. In contrast, reaction temperature, time, solvents, and surface passivating agents are the critical parameters in the "bottom-up" approach-led synthesis of CNDs. Figure **1.1** shows various synthesis methods of CNDs.

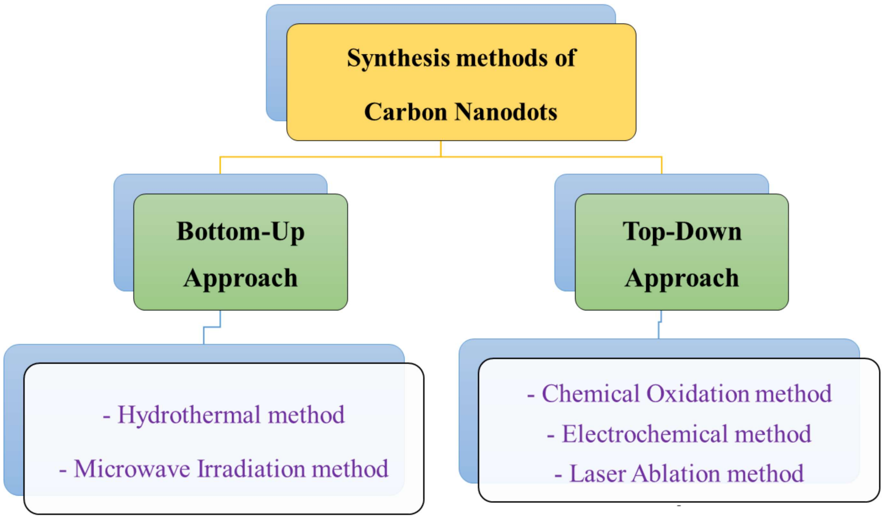

Figure 1.1. Various synthesis methods of CNDs.

Initially, CNDs were synthesized using carbonaceous natural precursors. Later, with the aim of increasing their quantum yield (QY) and enhancing their photoluminescent properties, researchers began to manufacture CNDs using synthetic precursors and passivating agents. However, these synthetic precursors can have long-term harmful effects on humans and the environment. There is, therefore, a need to focus on developing eco-friendly and economical CNDs. Plant parts such as leaves, fruits, stems, bulbs, roots, bark, seeds, and flowers can be used as precursors of CNDs [Mohapatra *et al.,* 2021, Mohapatra *et al*., 2022]. Among various synthetic approaches (top-down and bottom-up), the bottom-up approaches are more popular due to their simplicity of synthesis, cost-effectiveness, and ecofriendly nature. They can be synthesized by various methods such as hydrothermal, pyrolysis, microwave irradiation, carbonization, and simple heating, or by a combination of two methods, such as hydrothermal carbonization. Using arc-discharge, electrochemical etching, laser ablation, or acidic exfoliation, bulk carbon materials such as graphite and carbon nanotubes can be cut into CNDs [Zheng *et al.,* 2009]. Microwave synthesis enables selective and direct heating of precursor mixtures within a short time; however, a requirement of specialized equipment makes its usage limited. However, electrochemical carbonization and laser ablation methods are not helpful for synthesizing CNDs due to their high energy requirement and tedious procedures [Naik *et al.,* 2021, Mohapatra *et al.,* 2022]. A brief overview of the developmental pathway of CNDs is illustrated in Figure **1.2.**

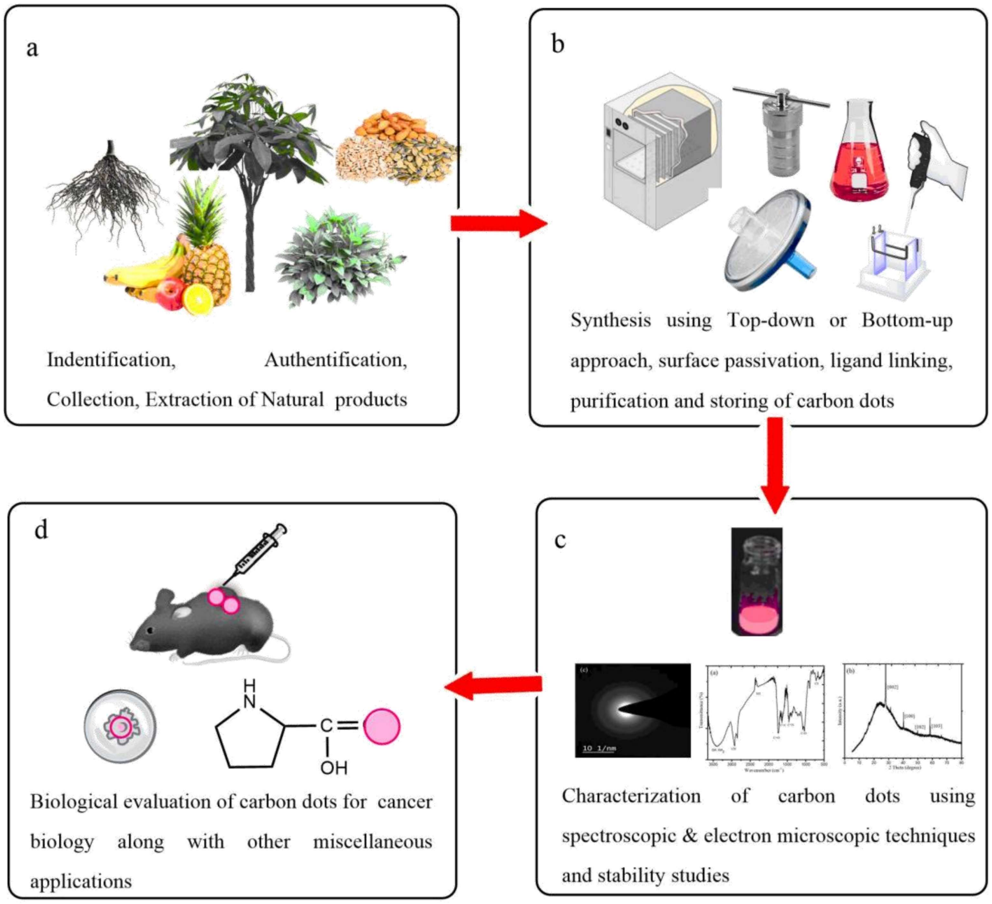

Figure 1.2. Development of natural product-derived carbon nanodots. A general overview of the development of carbon nanodots derived from natural products involving [a] extraction of natural products [b] synthesis of CNDs [c] characterization of CNDs and [d] evaluations of CNDs for biological activities. Reprinted with permission from Naik *et al.,* 2020.

The fabricated CNDs need to be devoid of any significant toxicity and should be chemically stable. Furthermore, for this, green-chemistry-based methods such as hydrothermal method has been useful. Table **1.2** shows merits and demerits of synthesis methods for CNDs. Hydrothermal method-driven synthesis of CNDs involves employing non-toxic solvents and renewable precursors that are safe and easily affective. Due to its cost-effective and easy operability, a hydrothermal method is the most widely used approach for CNDs synthesis, which requires, teflon-lined autoclaves, controlled temperature, time, and pressure. It is the widely exploited to prepare CNDs simply with a narrow particle size distribution. The hydrothermal method supports the usage of water or mild organic solvents such as ethanol. In some instances, precursors such as Tender coconut water [Nugroho *et al.,* 2022] and essential oils [Rimal *et al.,* 2021] act as carbon sources and solvents. During the CNDs, synthesis, other small side-products are also generated, which can be eliminated via gel filtration, dialysis, high-performance liquid chromatography, etc. [Zhang *et al.,* 2015, Li *et al.,* 2017].

The surface of CNDs is decorated with crucial functional groups such as carbonyl, carboxylic, hydroxyl, amine, and epoxy. Depending upon the precursors and solvents used in the process, the CNDs can be either crystalline or amorphous. Surface passivation and heteroatom doping are employed to tune the surface properties, molecular interactions, and electronic properties of CNDs [Li *et al.,* 2018, Ma *et al.*, 2012]. This leads to the regulation of band gaps of CNDS and improvises the fluorescence emission. Figure **1.3** depicts the significant advantages of CNDs.

Table 1.2. Merits and demerits of synthesis methods for CNDs.

Synthesis method	**Merits**	**Demerits**
Chemical ablation	Most-accessible method, Various starting materials	Drastic processes, variable sizes
Laser ablation	Rapid process, effective, cost-effective	Poor size control, low QY
Arc discharge method	Fabricate NPs in a variety of glass	Requires further purification of CNDs

Electrochemical carbonization	High QY, good control over fabrication technique, Cost-effective	Few small-molecule precursors
Microwave irradiation	Rapid process, consumes less time	Poor control of size, Non-uniformity in size
Hydrothermal method	Environment friendly, cost-effective and easy operability, comparative better QY	Poor control of size,

The structure of CNDs consists of sp^2/sp^3 carbon hybridization and hetero-atom-based functional groups [Schneider *et al.,* 2017, Tepliakov *et al.,* 2019]. The size and shape of the CNDs are influenced by both the carbon source and their fabrication method. They exhibit significant Stokes shifts and display a broad emission peak, imparting distinctive optical properties compared with synthetic dyes [Yan *et al.,* 2019]. Also, if the particle size is too small to be compared with an electron wavelength, then the quantum confinement effect is observed [Suresh *et al.,* 2013]. The quantum confinement effect is mainly responsible for tunable photoluminescence. CNDs are generally spherical shaped and are either amorphous or crystalline.

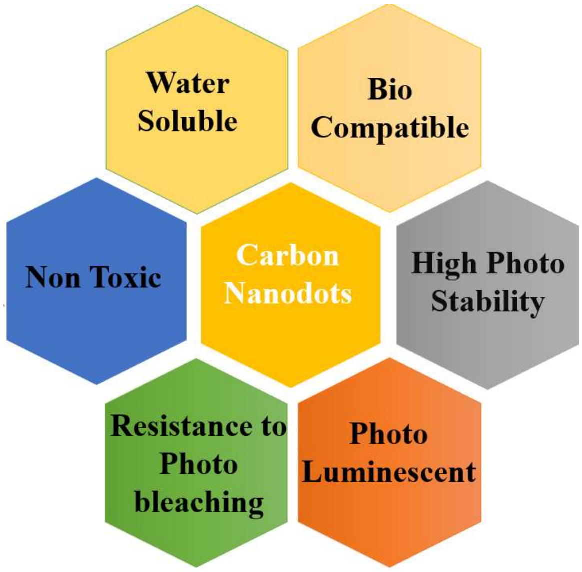

Figure 1.3. Advantages of CNDs.

However, Yuan *et al.,* 2018, synthesized triangular CNDs which exhibited extraordinary narrow bandwidth emission for multicolored LEDs. The critical factors responsible for high color purity are the weak electron-photon interactions, molecular purity, crystalline perfection, and unique rigid triangular structure. Apart from size and morphology, surface charges of CNDs are crucial for evaluating cancer therapeutics and toxicities. Reactive oxygen species (ROS) generated by carbon nanomaterials such as CNDs may affect cell signaling pathways, thereby promoting cancer in some instances. CNDs with smaller sizes can easily penetrate cells; however, they can sometimes be more toxic. Small particle size and large surface area may contribute to higher levels of ROS [Fu *et al.,* 2014].

Few studies are available related to the fate of CNDs upon penetration into cancerous cells. This might be due to the hurdles faced while accessing authentic analytical methods for intracellular quantification. Based on their physicochemical properties and consequent interactions, cells take up CNDs, but there is still a research gap addressing their fate upon penetration into the cells. Generally, the translocation of nanomaterials is restricted by the tight blood endothelial tissue. However, endothelial fenestration is induced by the cancerous tissue, which facilitates the nanomaterials to permeate cancerous cells [Dudley *et al.,* 2012]. Upon internalization by cells, nanomaterials are, in due course, transported via endocytic vesicles to the lysosome, which leads to the degradation of ingested nanomaterials or triggered drug release. Nuclear membrane pores restrict the entry of nanoparticles larger than 9 nm, which becomes a key barrier for nucleus targeting [Macara *et al.,* 2001]. The nanomaterials uptake by mammalian cells occurs primarily through endocytotic pathways [Doherty *et al.,* 2009].

Biodistribution and metabolism of CNDs are essential parameters to determine the in vivo circulation time. The mononuclear phagocyte system (MPS) and reticuloendothelial system (RES) are two crucial systems that eliminate nanoparticles from the body within a few hours. The size and shape of CNDs would be essential attributes for considering biodistribution. Because of their small size and surface charge, CNDs have a short circulation time. It was found that when the charge of CNDs was positive at a slightly acidic tumor microenvironment (TME) with a cell membrane exhibiting a negative charge, it facilitated the smooth penetration of nanomaterials into the tumor cells. This feature considerably enhanced the internalization efficiency. As the size of CNDs increases from 5 to 35 nm, its shape changes from circular and elliptical with armchair, zigzag edges to hexagonal and rectangular types showing armchair edges. The fate of CNDs upon their penetration into cancerous cells is influenced by their size and shape [Naik *et al.,* 2021, Nurunnabi *et al.,* 2013].

Fluorescence plays a vital role in biosensing applications as it can be used to reveal the presence, absence, or release of chemotherapeutic drugs and ions. The mechanisms responsible for the luminescent properties of CNDs are surface state emission [Zhu *et al.,* 2018], quantum confinement effect [Yan *et al.,* 2013], and molecular fluorescence [Essner *et al.,* 2018]. When there are many oxygen-containing functional groups on the surface of the CNDs, the surface defect increases, leading to excitons trapping and red-shifted emission [Sun *et al.,* 2017, Sun *et al.,* 2018]. The surface defect refers to a spherical shell or a boundary region different from the carbon core region. Surface oxidation is responsible for generating the surface defects and can act as a capture center for excitons. Ground state radiation relaxation from the excited state leads to surface defects fluorescence [Du *et al.,* 2016, Sachdev *et al.,* 2014].

1.4 Toxicity issues of carbon nanodots

The type of CNDs precursor, size, fabrication methods, passivating agents, surface morphology, concentration range, and functional groups on the surface of CNDs are some key parameters that determine their toxicity and bioactivity. Hence, various strategies have been employed to facilitate hetero-atom doping of CNDs to alter their surface functional groups, thereby altering optical and chemical properties [Xu et al., 2015, [Tu *et al*., 2020]. Accumulating CNDs in the organs and tissues at specific concentrations contributes to their toxicity [Tedesse *et al.,* 2020]. Atchudan *et al.,* employed *Piper betel* leaves as a source of carbon and nitrogen in synthesizing fluorescent CNDs without the need for passivating reagents. They exhibited multi emissions at different excitation wavelengths, and their cytotoxicity was evaluated using human colon cancer (HCT-116) cells as a model. A 95% viability of CNDs post 24 h was observed at a 200 µg/mL dose, which suggested their biocompatibility. Blue, green, and red emissions were observed in CNDs treated cells at 405nm, 488nm, and 555nm, respectively, while non-treated cells did not exhibit any fluorescence. Also, no morphological damages were observed in cells upon incubation [Atchudan *et al.,* 2019]. The carbonaceous CNDs are considered to be more biocompatible as compared with inorganic quantum dots, as carbon constitutes the backbone of all organic bio-molecules. Hence its excellent and excitation-dependent fluorescence is utilized in bioimaging. CNDs have also exhibited negligible cytotoxicity in several other cell lines [Atchudan *et al.,* 2019, Tedesse *et al.,* 2020]. It is reported that CNDs functionalized with polyethyleneglycol with a neutral charge exhibit significant potential for biomedical applications as they do not affect the cell cycle and cell morphology up to a concentration of 300 µg/mL. However, CNDs functionalized with positively charged polyethyleneimine and pristine CNDs with negative charge induce most cytotoxicity and higher oxidative stress, respectively [Havrdova *et al.,* 2016]. Thus, the toxicity of CNDs can be reduced by the incorporation of biocompatible polymers, such as PEG, etc. [Chen *et al.,* 2018].

1.5 Applications of carbon nanodots

Over the years, the applicability of CNDs has expanded from multi-photon bioimaging [Cao *et al*., 2007] to photocatalysis [Aggarwal *et al*., 2020], multi-ion sensing [Arumugham *et al*., 2020], nano-drug delivery [Hettiarachchi *et al*., 2019], dual-functional modifiers [Guo *et al*., 2019] and so on. Properties such as photoluminescence, inert chemical nature, biocompatibility, low toxicity, versatile surface engineering properties, superior electron transfer ability, photo-bleaching resistance, photo-stability, and simple functionalization make CNDs promising candidates for the carbon nanomaterials family for comprehensive healthcare and energy applications. In recent times, CNDs had been explored for various biomedical, environmental, and energy applications. Figure **1.4** depicts critical applications of natural product-derived carbon nanodots.

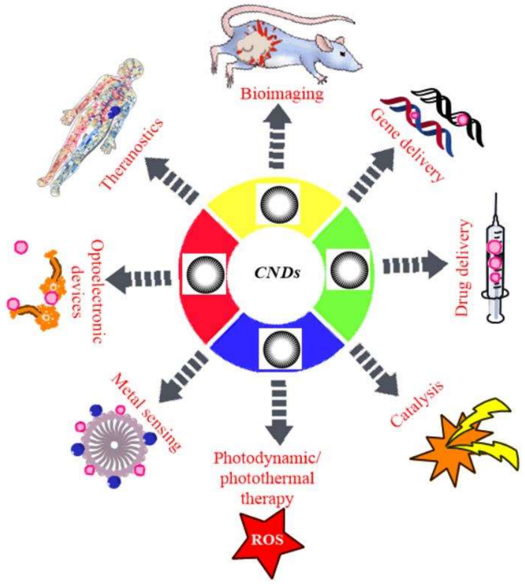

Figure 1.4. Key applications of natural product-derived carbon nanodots (CNDs). ROS: Reactive oxygen species.

Due to the unique properties such as tunable fluorescence, significant biocompatibility, penetration capabilities, excellent photostability, CNDs demonstrated outstanding potential in probing biological systems, especially for imaging-guided applications. The expression of different proteins and structures of affected and normal cells leads to selective imaging of the cells [Geng *et al.,* 2018]. Imaging of organelles such as mitochondria, nucleus, endoplasmic reticulum could provide important information on organelle-related diseases [Datta *et al.,* 2014]. The currently available *in-vitro/in-vivo* techniques and agents such as synthetic dyes, bio-assays are costly, time consuming and require trained professional and sometimes prove to be harmful to the normal cells as well. Hence there has been increased scope of investigating CNDs for developing imaging-probes as an alternative to synthetic organic/inorganic dyes.

Selective imaging of cancerous cells is crucial in cancer biology studies [Urano *et al.*, 2009] as it provides a precise indication of cancer progression and assists in deciding the courses of cancer therapy. In order to diagnose cancer, a probe should be able to distinguish between healthy and cancerous cells [Zhang *et al.,* 2021]. An ideal probe does not only exhibit full-color emission but also demonstrates high selectivity and accumulation in cancerous cells without the need for further conjugation with targeting molecules. The mean fluorescence intensity of cancerous cells after treatment with CNDs is superior to that of normal cells, indicating selectivity and more uptake of CNDs toward cancerous cells. In some cases, various receptors present abundantly on the cancerous cells facilitate the targeting effect of CNDs. For example, the nucleus-targeting ability is attributed to folate receptor-mediated internalization [Zheng *et al.*, 2015]. Folic acid is greatly attracted by the extracellular membrane of the cancerous cell due to folate receptors on the membrane. In another case, glucose transporter (GLUT-1) is found abundantly in the blood-brain barrier and brain tumors, which impart brain tumor-targeting properties via glucose metabolism by the glucose transporters [Noguchi *et al.*, 2000].

Several efforts have been made to modulate the surfaces of CNDs with specific ligands and biomolecules that will allow cell surface receptors to achieve cell target ability and curtail toxicity. Folate receptors are widely applied as a targeting agent since they are minimally distributed in normal cells compared to cancerous cells [Wang *et al.,* 2020, Li *et al*., 2020]]. Unlike other nanomaterials such as inorganic molecules, liposomes, polymeric nanoparticles, macromolecular scaffolds, micelles, nucleic acid-based nanoparticles, and dendrimers, whose optical-chemical properties are primarily governed by the presence of fluorophores, the photoluminescence of CNDs results from quantum confinement effects related to their size as we have discussed in previous sections. Consequently, the fluorescence emission of CNDs can be tailored by inducing changes in the size of their monolayers. However, the tunable optical-chemical properties, easy functionalization, resistance to photo-bleaching, broad applicability, and less toxicity make them a desirable candidate for drug delivery compared to other diversified nanomaterials.

Currently used detection techniques such Inductively coupled plasma mass spectrometry (ICP-MS), atomic fluorescence spectrometry, atomic absorption spectroscopy immunoassays, HPLC (High-performance liquid Chromatography), LC-MS-MS (Liquid Chromatography-Mass spectrometry), GC (Gas Chromatography), GC-MS (Gas Chromatography-Mass spectrometry), immunochemical, electrochemical, capillary electrophoresis, chiral pressure liquid chromatography for sensing of heavy metals, biochemical, drugs, and DNA require complex methodology, long operational time, sophisticated instruments, and more highly-trained personnel, which are not feasible for rapid on-site detection. Therefore, a simple and rapid technique with high sensitivity detection of heavy metals would be quite essential. To overcome above mentioned issues, CNDs can be considered as a potential sensing probe. Based on sensing ability CNDs may have other applications, such as enhancing latent fingerprints, detecting biological compounds, molecular sensing, explosives, drugs, heavy metals, pesticides and poisonous substances. Also, fabricating a robust device using CNDs for an operational, quick, on-site, and accurate colorimetric sensing of such analytes is essential. Mechanisms, such as the inner filter effect, photo-induced electron transfer, photo-induced charge transfer, and resonance energy transfer are responsible for inducing fluorescence changes in CNDs; hence they can be employed in metal sensing and other analytes sensing applications. Fluorescent carbon nanodot-based sensors work either by direct interactions with analytes leading to changes in fluorescence signals, post-surface modifications, or integration of CNDs with fluorescence quenchers or fluorophores [Liu *et al*., 2019, Zhang *et al*., 2019].

ROS such as hydroxyl radical, peroxides, singlet oxygen, α-oxygen, peroxides are chemically reactive oxygen containing chemical species. Free radicals are sometimes interchangeably used in place of ROS, however free radicals are short-lived highly reactive entities with an unpaired valency electrons. There are various reports suggesting radicals scavenging activities of carbon nanomaterials [Liu *et al*., 2019, Zhang *et al*., 2019]. According to various reports, CNDs have a good surface-to-volume ratio because their size is less than 10 nm, and they have a variety of functional groups on their surface. CNDs demonstrate photo-induced electron and energy transfer properties as an acceptor or donor at the same time [Lin *et al.,* 2012; Sachdev *et al.*, 2015].

According to the World Health Organization, in recent times resistance to microbial agents is alarming and poses a greater threat to community health. Multidrug-resistance strains (MDR) are those microbial strains which has exhibited resistance to at least one antimicrobial drug in 3 or more antimicrobial categories. The ESKAPE group which includes *Enterococcus*, *Staphylococcus*, *Klebsiella*, *Actinobacter*, *Pseudomonas*, and *Enterobacter* has posed more threat recently. This has made research fraternity to search for novel and effective anti-microbial agents. With respect to this, CNDs can rupture the membrane or produce oxidizing species and free radicals that cause bacterial cells to die due to their high surface-to-volume ratio and small size [Hajipour *et al*., 2012].

Table 1.3. Some natural product-derived carbon nanodots for multifunctional applications.

Natural products	**Fluorescence of NPdCD**	**QY (%)**	**Size (nm)**	**Outcomes and Applications**	**Ref.**
Coriandrum sativum (Coriander)	Green	6.48	5-6	Exposure to different concentrations did not induce any grave cytotoxic effects in both Lung normal (L-132) and cancer cell lines (A549) which demonstrated the biocompatibility of CNDs for bioimaging purposes	Sachdev *et al*., 2015
Musa acuminata (Banana)	Multicolored (blue, green, and red)	48	~2.5	Exhibited viability of HeLa and MCF-7 cells of about 95% at a concentration of 0.5 mg/mL after 24 h incubation, and	Vandarkuzhali *et al*., 2017

				viability over 85% even at a concentration of 1 mg/mL.	
Panax ginseng (ginseng)	Multicolored (blue, green, and red)	15.4	4.6±0.6	The IC_{50} values of HepG2, MCF-7, and A375 were 1.05, 0.529 and 0.223 mg/mL, respectively. As compared to other anti-cancer drugs such as doxorubicin, methotrexate, and cisplatin, these CNDs exhibited efficient inhibition of cancer cells with lower toxicity to normal cells (293T)	Yao *et al.*, 2018
Juglans (Walnut oil)	Red	15.4	12.3 ± 2.7	Extremely potent cytotoxic agent against MCF-7 and PC-3 cell lines. Induction of apoptosis was accompanied by an increase in the activation of caspase-3	Arkan *et al.*, 2018
Curcuma longa (Curcumin)	Multicolored (red, yellow, and green)	8.60	4–5	IC_{50} values of 580, 408, and 413 µg/mL toward NIH 3T3 (as a normal cell model), A549, and HCT-15 cell lines, respectively. The difference in the IC_{50} values depicts	Pal *et al.*, 2018

				rapid cellular uptake in the case of cancer cells correlating its high metabolism and was absent in the case of normal cells	
Bambusoideae (bamboo)	Green and blue	9.6	2-4	Free Dox resulted in lower IC_{50} values (52.3 mg mL^{-1}) than Dox/CBBA-CDs (68.2 mg mL^{-1}). This suggested that CBBA-CDs successfully achieved delivery of Dox to the target HeLa tumor cells	Fahmi *et al.*, 2018
Algal bloom (Algae)	Blue	13	8.5 ± 5.6	Cell viability is about 60% even at the very high dose of 1 mg/mL and after long incubation times (48 h)	Ramana *et al.*, 2016
Prunus mume (Plum)	Blue	16	9	The cell survival rates exceeded 96% at all experimental concentrations, indicating non-toxicity and cytocompatibility with the MDA-MB-231 cells	Atchudan *et al.*, 2016
Vitis Vinifera (grape juice)	Bright blue	13.5	2.7± 0.5	Photoluminescence in the HeLa cell nucleus is very weak, suggesting that only a	Huang *et al.*, 2014

				few or no CNDs enter the inner nuclei, in which no genetic disruption would occur.	
Citrus limon (lemon)	Red	28	4.6	Over 95% of the HeLa cells were viable after incubation with 1000 mg/mL for 48 h, which suggests less cytotoxicity	Ding *et al*., 2017
Litchi chinensis (Lychee)	Blue	10.6	1.12	The strong fluorescence on the HepG2 cells incubated with CNDs suggested that CNDs had penetrated the cells and could label both the cell membrane and the cytoplasm of the cells.	Xue *et al*., 2015
Magnifera indica (Mango)	Green, blue and Yellow	0.48-3.92	5-15	From the overall *in vivo* bio-distribution, the differences in their distribution seem to be due to their comparative size differences, where the tiny particles were more rapidly cleared from the body than larger ones.	Jeong *et al*., 2014
Allium cepa	Blue, green,	28	7-25	Cell viability of more	Bandi *et*

(onion)	and red			than 95% up to a concentration of 0.4 mg/mL, and it can label both cell membrane and cytoplasm	*al.*, 2016
Arachis hypogaea (peanut shell)	Blue, green, and red	9.91	0.4-2.4	The HepG2 cell viabilities more than 90% over a wide concentration range of 0–1.2 mg/mL, which suggests excellent biocompatibility	Xue *et al.*, 2016
Solanum tuberosum (potato).	Blue	6.14	0.2-2.2	Exhibited good ability to enter the cytosol *via* multiple interactions with cytoplasmic proteins, suggesting its ability as nanocarriers for drug delivery. The cell viability of HeLa cells decreases from 100% to 95% when the concentration is increased from 50 to 200 µg/Ml	Mehta *et al.*, 2014
Ipomoea batatas (sweet potatoes)	Blue, green, and red	8.64	2.5-5.5	The maximum cell viability of HeLa cells was 156% when the concentration was up to 50 µg/mL, whereas the cell viability of HepG2 cells was as	Shen *et al.*, 2017

				high as 171% at the concentration of 25 µg/Ml	
Malus domestica (Apple)	bright blue	4.27	2-5	Bioimaging of *M. tuberculosis, M. oryzae cells, and P. aeruginosa*	Mehta *et al.,* 2015
Acacia Senegal (Gum Arabic)	Turbid green	0.56	4-6	Antimicrobial activity of *B. subtilis,* *S. aureus, E. coli,* and *P. aeruginosa*	Thakur *et al.,* 2014
Camellia sinensis (Tea leaf)	Multicolored (Blue and green)	26.9	2-5	Bioimaging of *S. marcescens,* *K. pneumonia,* *S. pyrogens, E. coli, and* *S. Aureus*	Shivaji *et al.,*. 2018
Spinacia oleracea (Spinach)	Blue	63.8	1.64	For cell imaging in plant-related diseases	Bajpai *et al.*, 2019
Allium sativum (Garlic)	Blue	5	5	Antioxidant activity	Yang *et al.*, 2015
Allium cepa (Onion)	Green	NM	2-4	For accelerated skin wound healing	Bankoti *et al.*, 2017
Carica papaya (Papaya)	Blue	18.39-18.98	2-6	Fluorescent sensing of *E. coli*	Wang *et al.*, 2017
Glycine max (Soybean)	Blue	3	13	bioimaging of NIH3T3 cells	Li *et al.*, 2013
Saccharum officinarum	Blue, green, and red	5.76	2.71	Bioimaging of *E. coli* and *Saccharomyces*	Mehta *et al.*, 2014

(Sugarcane)				*cerevisiae*	
Prunus avium (Cherry)	Blue	13	2-3	Detection of Fe^{3+} in water	Edison *et al.*, 2016
Chionanthus retusus (Chinese fringetree)	Blue	9	5 ± 2	Nano-probe for direct detection of Fe^{3+}	Atchudan *et al.*, 2017
Ocimum sanctum (Holy Basil)	Green	9.3	4-6	Detection of Pb^{2+} ions	Kumar *et al.*, 2017
Platanus orientalis (Oriental Plane Leaves)	Bright blue	16.4	3.7	Sensitive and selective detection of Fe^{3+}	Zhu *et al.*, 2013
Nelumbo nucifera (Lotus)	Bright blue	15.3	3-4	Sensing of Fe^{3+}	
Pinus (pine)	Bright blue	11.8	3-4	For detection of Fe^{3+}	
Mentha (mint)	Bright cyan	7.64	4	"On–Off–On"sensing of Fe^{3+}	Raveendran *et al.*, 2019
Musa acuminata (Banana)	Blue	12.43	4.5-8.5	Exhibit sensitive and selective detection of Fe^{3+}	Vikneswaran *et al.*, 2014

QY= Quantum yield of CNDs.

1.6 Conclusions

In this chapter, we have introduced various dimensions of carbon nanodots. We have discussed the synthesis, structure, properties, and application aspects of CNDs. These potential prospects of CNDs investigated in detail in this experimental work. We observed that unique opto-physical, physicochemical properties, and green hydrothermal method provides an excellent opportunity for their applications in multi-domains.

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