Carbon Dots (CDs) - A versatile Biosensor

(Mini review)

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Introduction

Biosensors are devices that can engulf receptor-transducers to envision analytical values of any preferred target analyte, which highly depends on the type of bioreceptor [1–3]. Response time, sensitivity, and specificity are the biosensing parameters expecting generally in a sensor particle [4–7]. It has always been a scientific challenge for biosensors to fulfil the expectation for accurate, precise, and early diagnosis of emerging diseases [8, 9]. They also have wide applications in food security, environmental monitoring, and biosafety [2]. The risen need for biosensors in recent decades, inspired scientific research on new sensing nanomaterials which satisfy the requisites such as cost-effectiveness, high sensitivity, and high selectivity along with other biosensor parameters [10–12].

Recently it is observed that Carbon Dots (CDs) have a wide scope in the biosensing field, since they are chemically inert, biologically compatible, and less cytotoxic and also generates a defined signal-response for molecular recognition [13, 14]. But it comes with a challenge, that, for sensing they need to be incorporated with powerful components exhibiting affinity with targeting biomolecule [13]. Carbon quantum dot (CQDs)s, a new class of nano-carbon particles exhibit brilliant fluorescent properties which is efficiently, cheaply, and rapidly synthesizable in large scale using environmental-friendly methods like calcination, ultrasonication, electrochemical oxidation, microwave-assisted methods [15–17]. etc which can aptly perform as intelligent biosensor fulfilling the mentioned requisites along with high photostability, being novel sensing element, and easy synthesis [17, 18]. The important aspect of carbon quantum dots differing it from being the same carbon-nano biosensing elements like nanotubes, graphene dots or quantum dots is its ability of high fabrication simplicity [19, 20].

Carbon quantum dots composed of carboxyl, amine, and hydroxyl groups which provides an abundant surface area that contributes to the strong binding and chelating affinity for metal ion detection by complexation resulting in different mechanisms, making an account for its potent future in biosensors [17, 20-22]. In this mini review, the synthesis, mechanism of sensing application of CDs towards biosensing of few biomolecules biosensing properties are explained considering the research works reported from 2017 till 2023 in form of a mini review.

Synthesis

Many convenient precursors, such as natural sources that are renewable, economical, non-toxic and, from the other hand, organic solvents or small molecules (Ex: Ethylenediamine) that are quick, highly efficient providing good quantum yield, etc., can prepare CQDs, contrarily bigger molecules or materials can be break into pieces to synthesize them. Since the serendipitous discovery of this zero-dimensional carbon dots by Xu et al in 2004 two key techniques are used to generate CQDs are: either bottom-up or top-down methods defined by the implementation criteria [23, 24].

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i. Top-down methods

"Top down" involves the decomposition/break-down of large pieces through a rough operation of vast sections of raw carbon material such as carbon soot, carbon fibre, activated carbon and carbon black. Synthetic solutions include predominantly are laser ablation, arc release, exfoliation and treatment with oxidizing acids. Because of the extreme conditions applied to these reactions, instruments and devices that absorb high energy are typically needed with high pressure, high temperatures which leads to higher costs.

ii. Bottom-up methods

“Bottom up” involves the synthesis of CDs from carbon containing molecules through a “decomposition-polymerisation-carbonization” process. The carbon containing molecules could be small organic molecules such as citric acid, polyols and amino acids, synthetic polymers* and natural products as well as biomass. Preparation methods mainly include pyrolysis-solvothermal, hydrothermal carbonization and microwave/ultrasonication.

iii. Green Route Synthesis

Green chemistry reflects on the relationship between organisms, chemistry, and the environment. As a consequence, the primary purpose of green chemistry is to develop products and procedures that minimize the use and production of hazardous substances. The theme of green chemistry is to optimize the integration of the starting material into the finished product and to create a strategy by adding smaller fundamental building blocks (at the molecular level) to synthesize a desired product rather than breaking down a larger material to eliminate any products that are undesirable. There are also several green routes for the synthesis of carbon dots that have arisen [22]. For bioimaging and biosensing purposes, Sahu et al synthesized an extremely luminescent carbon dot from orange juice for some of the green work on carbon dots. They have a PL quantum yield, low toxicity, and high photostability of 26% [25]. The nitrogen-doped carbon dot is prepared from milk by Li Wang et al. Monodispersed intensely fluorescent carbon dots of around 3 nM in size were synthesized by hydrothermal milk heating. This is highly recommended for brain glioma cancer cell imaging [26]. Bibekananda et al from banana juice worked to synthesize the water-soluble carbon dots for a green and simple route. Green luminescent water-soluble oxygeneous carbon dots of 3nM size were developed by simply heating banana juice for 4 hours at 150 C. Quantum yield was 8.95 with 360 nM wavelength on excitation [27]. For sensing and imaging, X. Yang et al synthesized novel carbon dots from honey. Their synthesis was based on an innovative and green technique. For the first time, the quantum yield of almost 19.8% has been developed successfully [28]. A one-step green approach for the synthesis of carbon nanodots from bamboo leaves was followed by Y Liu et al for the detection of copper (II). Experimental findings reveal that the synthesized CQDs have an average size of 3.6 nM and a quantum yield of 7.1 %. This allows sensitive detection of Cu2+ with a detection limit of 115 nM and a linear range of 0.333 to 66.6μM [29]. Using rose flowers as the carbon source for the sensing of tetracycline sensing, Y. Feng et al found an innovative and simple method for carbon dot synthesis. Detection has been established by the suggested technique with a detecting limit of 3 x 10-9 mol/L limit and a linear spectrum range of 1.0×10^{-8} - 1.0×10^{-4} mol/L [30]. V N Mehta et al synthesized carbon dots from apple juice via a one-step hydrothermal approach for mycobacterium and fungal cell

imaging, another exciting work. Under UV light, the CDs displayed a bright blue emission. The findings revealed that the prepared CDs had no toxic impact on the cells, demonstrating the strong biocompatibility of the produced CDs [31]. For the green synthesis of biocompatible carbon dots, Mewada et al worked on aqueous Trapa bispinosa peel extract. Without adding any additional oxidizing agent at 90 C, they reported the synthesis of an extremely economical plant-based process for the preparation of luminescent water soluble Cdots using Indian water plant Trapa bispinosa peel extract. They find that it has a prominent green fluorescence. Cdots synthesized by this method were found to be remarkably biocompatible [32]. Zhou et al. synthesized carbon dots from the watermelon peel. They had a small particle size of about 2 nM and a clear blue luminescence [33]. D Gu et al, synthesized nitrogen doped carbon dots from lotus root for the identification of Hg (II) ions. The one pot microwave treatment of the lotus root provided a simple, green, and quick method of synthesis of carbon dots without using any other surface passive agents. They demonstrated a maximum of 18.7 nM for detection and a linear spectrum from 0.1 to 60.0 μM [34]. A green synthesis technique was introduced by W Liu et al for the Fe3+ identification and cell imaging by utilizing rose-heart radish as a carbon source for carbon dot synthesis. The prepared CDs demonstrate outstanding benefits, including a high quantum yield of 13.6 percent, low toxicity, excellent biocompatibility and chemical stability agreement. The N-CDs for Fe^{3+} also produce a good fluorescence response [35]. Like this, for the sustainable growth of human kind, so many works focused on green routes for carbon dots like making up from waste tea are coming up every day [36].

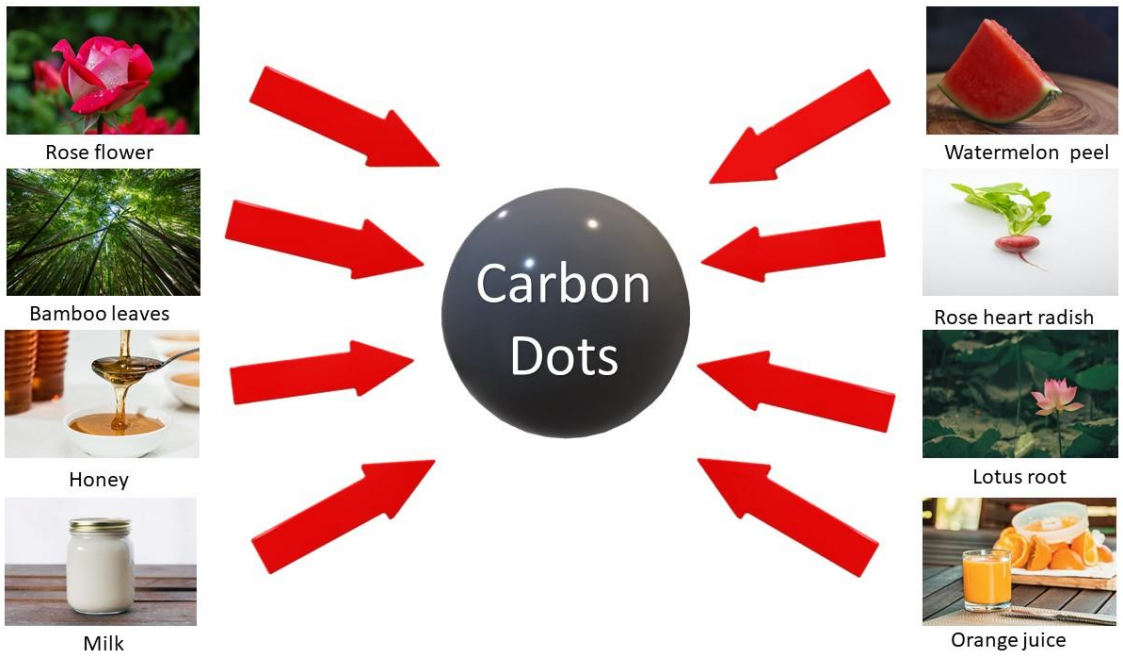

Fig.1 Various sources of green routes for carbon dot synthesis. All images used are royalty-free images obtained from pexels.com

Mechanism

Liu et al explains that due to their intrinsic fluorescent properties, high sensitivity, rapid response, low cost, and convenient preparation methods CQDs have been widely used as fluorescent probes to identify different analytes in the atmosphere or biological systems. They also say that CQDs are very reactive and responsive to the ambient environment, such as

temperature, ionic strength and solvent, due to the large abundant surface of many functional groups, resulting in change of their optical properties, such as fluorescence enhancement/activation (turn-on) and quenching (turn-off) [37]. The fluorescence origin of the CQDs is a controversial issue which depends on carbon source, experimental conditions, and functional groups [38].

Mechanisms used for Sensing Biomolecules

CDs which function as the recognition system uses various mechanisms so as to function as the sensor probe. Theoretically, the mechanisms mainly include Static quenching, Dynamic quenching, photo-induced electron transfer (PET), fluorescence resonance energy transfer (FRET), and the inner filter effect (IFE).

Static Quenching

The interaction of CDs and quencher results in the formation of a non-fluorescent ground-state complex, known as static quenching. When the complex absorbs light, it returns to its ground state quickly without emitting a photon. For static quenching (a) $\tau 0/\tau = 1$; (b) The formation of the ground-state complex will cause a shift in the CDs' absorption spectra; (c) The stability of the ground-state complex might deteriorate as the temperature rises, so reduces the effect of static quenching [39].

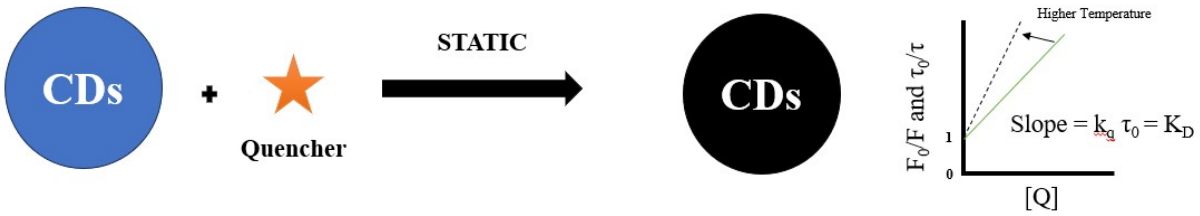

Fig 2. Schematic illustration on formation of non-fluorescent CDs due to static quenching

Dynamic Quenching

The excited state of CDs returns to the ground state due to a collision between the quencher and CDs with the mechanism of energy transfer or the mechanism of charge transfer, which is known as dynamic quenching. (Fig 3)

When compared to static quenching, there are a few differences. (a) In the lack and presence of quencher, the lifetime of CDs would differ. (b) The excited states of the CDs were solely impacted by dynamic quenching, therefore no changes in the absorption spectra of the CDs were detected. (c) The effect of dynamic quenching can be amplified as temperature rises.

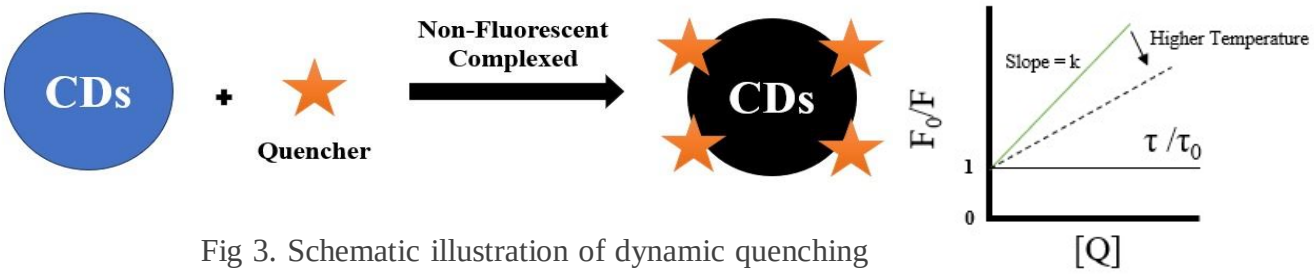

Fig 3. Schematic illustration of dynamic quenching of CDs

Photo-induced Electron Transfer

The electron transfer happened between the CDs (electron donor or electron receptor) and the quencher (electron receptor or electron donor), resulting in the formation of the cation and anion radicals, respectively. Between the electron donor and the electron receptor, a complex was created that may return to the ground state without emitting a photon. There ae two types of process in PET (Fig 4 and Fig 5), Reductive PET and Oxidative PET. CDs, as electron receptors, received electrons from the electron source in reductive PET. Oxidative PET was the absolute opposite of reductive PET. The energy gap between the lowest unoccupied molecular orbitals (LUMO) of quencher and the highest occupied molecular orbitals (HOMO) CDs was the driving factor for reductive electron transfer. The energy difference between the LUMO of the CDs and the LUMO of the quencher was the driving factor for oxidative electron transfer [39].

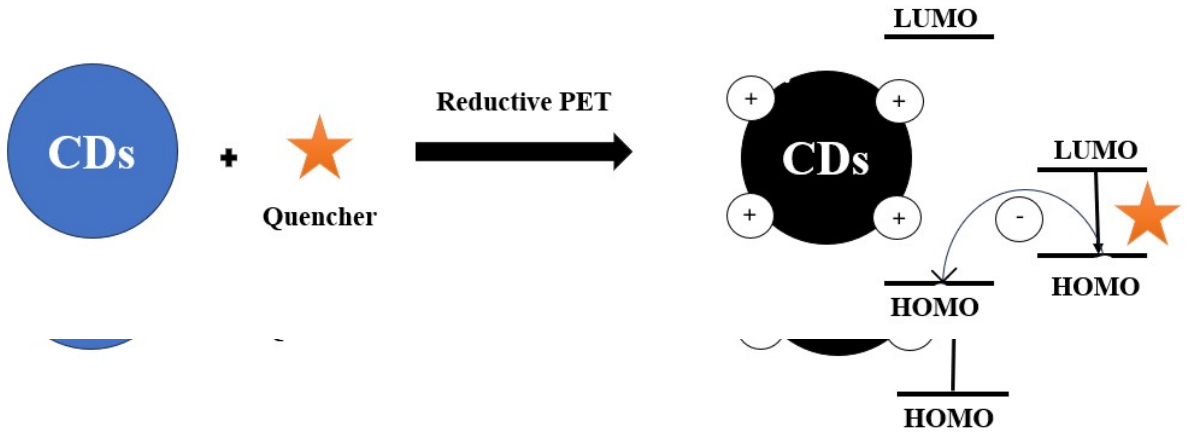

Fig 4. Schematic illustration of reductive PET (CDs accepts electron from the electron sources)

Fig 5. Schematic illustration of oxidative PET (CDs donate electrons to the electron source)

FRET

With classical physics we can explain FRET, as an electrodynamic phenomenon. When the emission spectra of CDs coincide with the absorption spectrum of the quencher, FRET occurs between CDs in the excited state and quencher in the ground state (Fig 6). Due to long-range dipole–dipole interactions between CDs and quencher, FRET occurs without the appearance of a photon. The distance between the CDs and the quencher was between 10 Å and 100 Å. Hence, (a) CDs' fluorescence spectra and the quencher's absorbance spectra intersected, (b) CDs' fluorescence lifespan would be reduced and (c) The CDs quencher distance would be in the range of 10 Å –100 Å, indicating that the CDs-quenching mechanism was FRET [39].

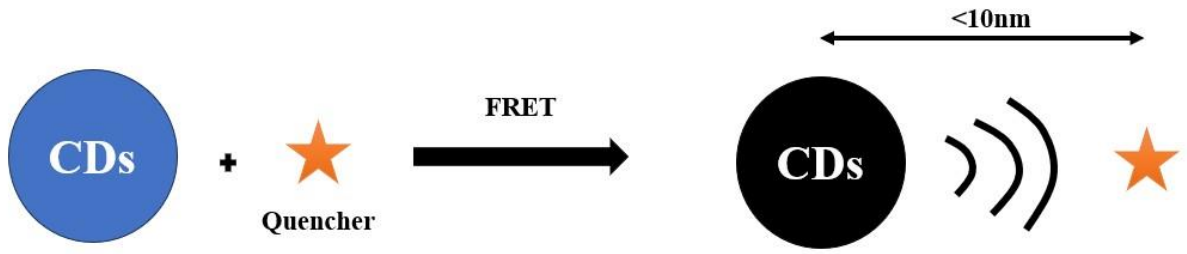

Fig 6. Schematic illustration on emission spectra of CDs coinciding with the absorption spectrum of the quencher (FRET)

IFE

The absorption spectrum of the quencher in the detection system collided with the excitation or emission spectra of CDs, resulting in IFE (Fig 7). IFE is frequently referred to as apparent quenching, although it is caused by an attenuation of the excitation beam or absorption of emitted radiation caused by an excess concentration of CDs or the quencher in solution, rather than by a quenching process. Although this effect causes a drop in intensity (but not decay time), it should not be referred to as "quenching." Instead, a second absorber merely filters out a particle's emission. This can also happen if the distance between the emitter and the re-absorber is more than 10 nm. Because IFE does not belong to either the static or dynamic quenching processes, the absorption peaks of the CDs do not shift, indicating that no new material is forming. As a result, CD fluorescence lifespan will remain unchanged.

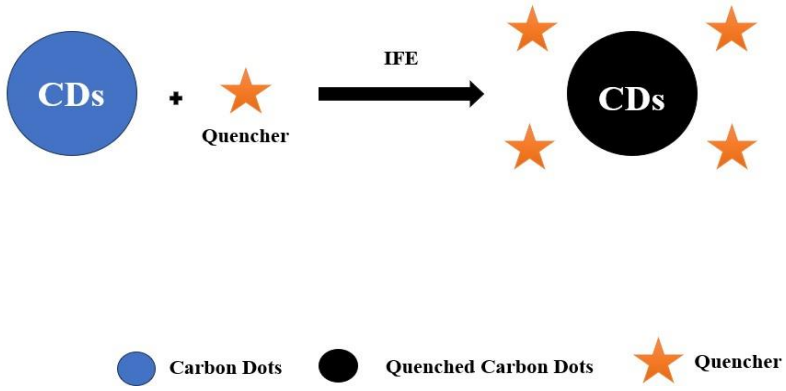

Fig 7. Schematic illustration of IFE of CDs

Significant characteristics of Carbon dots as a biomolecule sensor

CDs have a high two-photon excitation cross-section, which makes them superior candidates in bio-oriented application. What makes CDs function as a potential candidate in the field of biosensor? The pictorial representation given below explains how Cdots function as a biomolecule sensor.

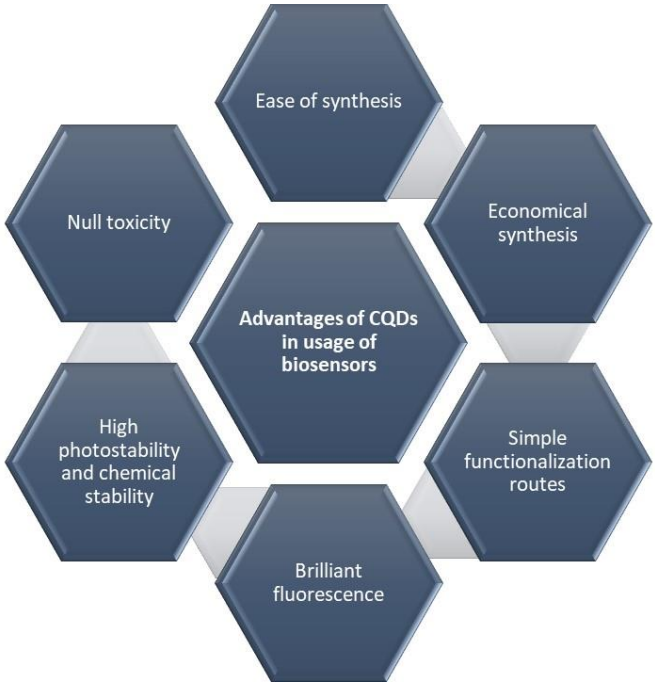

Fig 8. Pictorial representation of advantages of CDs in the field of biosensors

CDs a versatile biomolecule Sensor

i. Detection of Ascorbic acid

Anjali Devi et al reports Ascorbic acid (AA) as an essential micronutrient, antioxidant, and enzyme cofactor [40]. As a neuromodulator in the human brain, accurate selective testing of AA in biological fluids is highly desirable in different fields including cell biology, medical diagnostics of oxidative stress disorders and therapeutic screening, [41]. So, they formulated a turn on fluorescence assay for ascorbic acid using Nitrogen doped Carbon dots (NCDs) and Fe^{3+} ion modulation. Citric acid and Urea used as carbon and nitrogen sources and microwave assisted method. They found out that fluorescence of NCDs is quenched (turn off) in presence of Fe^{3+} and recovered (turn on) in the presence of AA (Fig 9). Fe^{3+} ions being an abundant transition metal ion in human body, NCDs have the potential to be used as fluorescent turn on sensor for AA [42, 43]. Turn off sensors are always preferred due to their high selectivity and reasonable detection nature [40, 44]. NCD/Fe^{3+} detects 0 to 3755.8 µm concentration of AA with a detection limit of 96 µm.

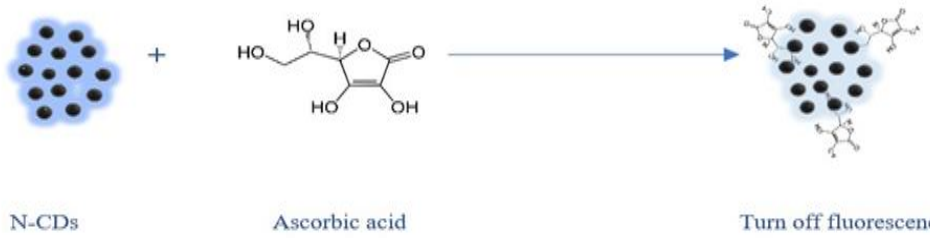

Fig 9. Pictorial representation of Ascorbic acid sensing using N-CDs

Wei et al, reported a fluorescent/colorimetric probe for real-time detection of Hypochlorite and AA in cell and body fluid where they reported the CDs with good recovery by AA. They used UV-Vis to detect AA in a colorimetric manner with a linear range of 1-30 μM [45]. Carbon quantum dots (CQDs) were synthesized by microwave irradiation [46] and were electropolymerized on glassy carbon electrode (GCE) to establish an electrochemical sensor for the selective detection of ascorbic acid (AA). Electrochemical behaviours of the prepared sensor were investigated by cyclic voltammetry (CV), differential pulse voltammetry (DPV), and electrochemical impedance spectroscopy (EIS). Two wide linear responses are reported in ranges of 0.01-3 mM and 4-12 mM with a low detection limit of 10 μM to AA. High sensitivities (44.13 $\mu A^{-1}\ \mu M^{-1}\ cm^{-2}$, 9.66 $\mu A^{-1}\ \mu M^{-1}\ cm^{-2}$, respectively) corresponding to the linear ranges are also achieved. In addition, the electrochemical sensor exhibited good selectivity and robust anti-interference ability toward AA in the presence of dopamine (DA) and uric acid (UA). An "on-off-on" fluorescent sensor of sulfur and nitrogen co-doped carbon dots (S, N-CDs) was reported for the identification of Cr (VI) and ascorbic acid (AA) [47] which showed a good selectivity and anti-interfere ability to more than 30 interfering substances. The fluorescence recognition was realized in liquid and solid media under optimal conditions based on the internal filtration effect (IFE). In liquid medium, the linear dynamic range of Cr (VI) was 0.03–50 μM and the limit of detection (LOD) was 21.14 nM. The linear detection range and the LOD of AA were 1–1000 μM and 0.28 μM, respectively. For solid-phase detection S, N-CDs were embedded into polyvinyl alcohol (PVA) to synthesize a visual fluorescent film sensor, which was irradiated by 365 nm ultraviolet light, for easily and accurately detecting Cr (VI) and AA on-site. The ranges of linearity were 0.1–50 μM and 10–500 μM, respectively, and the LODs were 92.48 nM and 6.99 μM, respectively. Fluorescent nitrogen doped carbon dots (N-CDs) were synthesized by microwave digestion method using glucosamine and ethylenediamine as raw materials for carbon and amine sources[48].The synthesized N-CDs were used to explore its sensing ability against 4-nitrophenol (4-NP), Cr(VI), and Ascorbic acid. The sensing strategies of 4-NP, Cr (VI) and Cr (VI)/ascorbic acid had showed the promising detection limits such as 0.05, 0.08 and 0.15 μM respectively. The investigation related to the fluorescence emission quenching of N-CDs against 4-NP and Cr(VI) were attributed to the inner filter effect (IFE), however in case of AA sensing strategy, it was due to the weakening on IFE, results in restoring of fluorescence emission from 0.25 to 175 μM concentration range of AA against N-CDs/Cr(VI) fluorescent probe.

ii. Detection of Arginine

Arginine plays a vital role in cell division, trauma recovery. Administration of arginine improves the immune system, digestive functions and works against carcinogenesis. Zhang et al [49], developed a fluorescence sensor based on Magnesium ion doped Carbon dots (Mg-CDs) for rapid detection of Arginine with Adenosine triphosphate (ATP) as a switch (Fig 10), which also enhances the fluorescence due to electrostatic interaction exhibiting covalent stability between arginine and ATP. Citric acid and Urea were used as source for carbon and nitrogen to synthesise CDs by hydrothermal method with Magnesium acetate as doping agent. On detection of samples, they found out that the recovery rate of samples was within 97.0% to 100.4%, reproducibility was 0.18% to 0.40%, linear range of 0.3 to 140 µmol/L and the detection limit was 0.15 µmol/L. They concluded that the use of Mg-CDs as a fluorescence probe had good precision, stability, and no matrix interference, making it as a powerful tool in clinical trials for the quantitative detection of Arginine. Wang et al [50], with an easy fabrication method synthesised dual emission fluorescence carbon quantum dots by using o-phenylenediamine and 2-hydroxy-3-methoxybenzaldehyde as a precursor, which can detect arginine via ratiometric fluorescence method in 100% water solution. Detecting the samples, they found out that Arginine recovery ranged from 95.8%-108.9%, specified that Arginine in water samples can accurately be measured with greater recovery, fast response, excellent photostability, good stability in presence of higher concentrations of NaCl and strong anti-inference ability, suggesting this probe detecting Arginine in water samples which have a linear detection range of 27 to 107 µm [50].

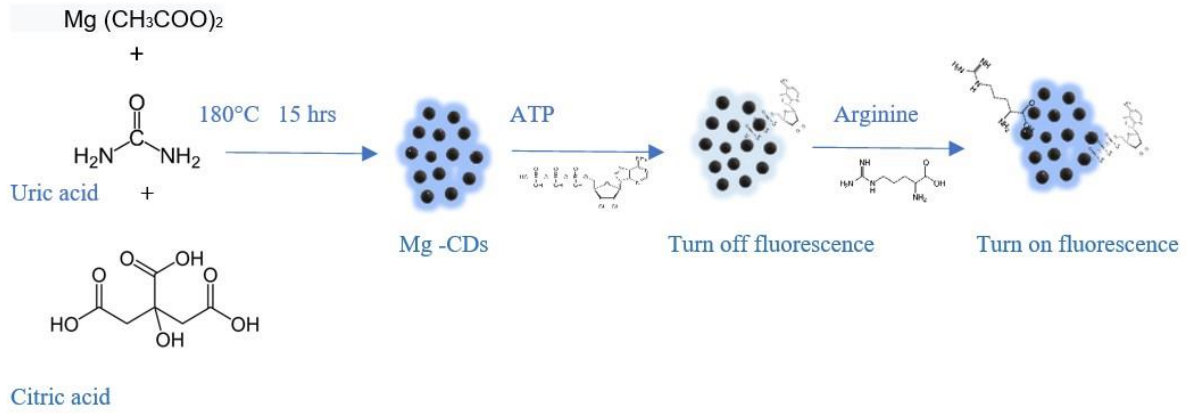

Fig 10. Pictorial representation of Arginine sensing using Mg-CDs

A ratiometric fluorescent hybrid nanoprobe CDs-1 for arginine (Arg),[49] exhibiting high sensitivity (the limit of detection, LOD, being 6.5 × 10−8 mol/L) and excellent selectivity and anti-interference ability, was fabricated through fluorescence resonance energy transfer (FRET) and the electrostatic attraction between positively-charged hemicyanine molecules and negatively-charged carbon dots (CDs). Arg can be quantitatively detected in the concentration range from 6.0 × 10−5 mol/L to 2.7 × 10−4 mol/L. Nitrogen-doped carbon dots (*N*-CDs) were developed [51] using a simple one-pot hydrothermal carbonization method in sensing cinnamaldehyde (CAL) and L-Arginine/L-Lysine (L-Arg/L-Lys). The as-prepared CDs as a highly efficient fluorescent probe possessed significant sensitivity and selectivity toward CAL and L-Arg/L-Lys over other analytes with a low detection limit of 58 nM and 16 nM/18 nM, respectively. The fluorescence of *N*-CDs could be quenched by CAL through an electron transfer process. The strong electrostatic interaction between L-Arg/L-Lys and *N*-CDs induced the efficient fluorescence recovery. CQDs with excellent fluorescence properties were

synthesized by one-step microwave assisted method [52]. AuNPs/ CQDs composites were characterized and their quenching mechanism was analysed. The amount of AuNPs/ CQDs, the pH value and the reaction time were optimal. Under the optimum conditions, the fluorescence system was used to detect the content of arginine, showing a good linear relationship (R2=0.993) between fluorescence intensity and concentration of arginine in the range of 0. 1-10. 0 μmol/ L, and the detection limit was 5. 8 nmol/ L. Finally, the content of arginine in grape juice was determined by this method with recoveries of 105. 4%-110. 8%, which indicated that the proposed FRET system had the potential for practical detection of arginine in fruit juice.

iii. Detection of Melamine

Melamine contamination in milk products can cause reproductive and urinary system damage, urinary calculi, acute renal failure, bladder cancer, and infant death. As a consequence, both US and China have set a melamine content limit for infant formula powder of one part per million (ppm). [53,54] Dai et al [55], constructed a fluorescence resonance energy transfer (FRET) system between amino-functionalized carbon dots (C-dots) and gold nanoparticles (AuNPs). C-dots were used as energy donors, while AuNPs were used as energy acceptors. The authors optimised key factors such as incubation time, AuNPs concentration, and media pH, all of which have an effect on the FRET system's performance. Melamine was detected based on the fluorescence strength of C-dots with a linear relationship between 50 nM and 500 nM under optimised experimental conditions, with a detection limit of 36 nM. In 2019, Hu et al [56] used a smartphone for visual detection of melamine in milk based on Au@Carbon quantum dots nanocomposites. The fluorescence standard array and smartphone were used to visually detect the average concentration of melamine adulterated in milk samples based on fluorescence light. For detection of melamine in the range of 1 μM to 10 μM, a calibration curve and fluorescence standard array were created. The quantification and detection limits were 12 nM and 36 nM, respectively. The fluorescence standard array in milk can be used to detect melamine rapidly, reliably, and visually, often outside of the lab and without the use of specialised instruments. It is ideal for detecting melamine concentration in milk and determining milk safety.

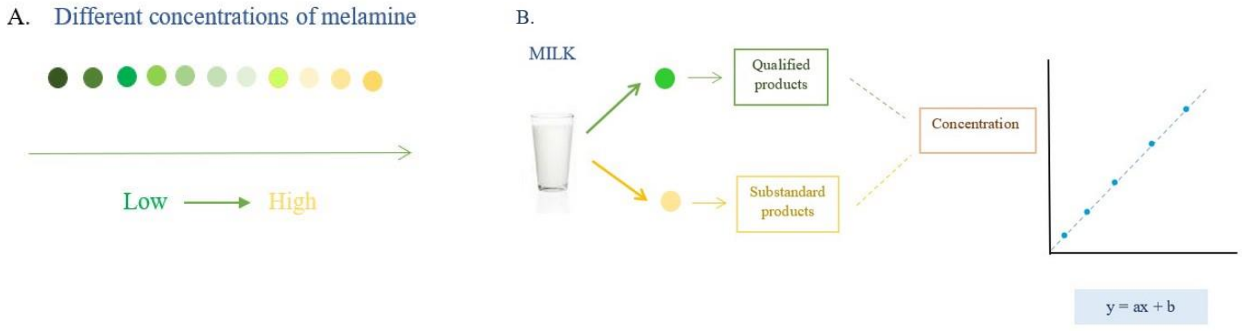

Fig 11. A. Au@CQD based fluorescence method for detecting melamine B. Detection of milk adulterated by melamine

iv. Detection of Cholesterol

Cholesterol is a fatty component found in food that is formed by the liver. Steroid hormones, vitamin D, and bile are all produced as a result of it. But maintaining a particular concentration of cholesterol in our body is a key balance for a healthy lifestyle. A simple, highly sensitive, selective, rapid, and cost-effective cholesterol biosensor was developed by Trang Thi Bui and Soo-Young Park [57] using a fluorescence method by CD-Haemoglobin complex. The basic mechanism of cholesterol sensing is that when CD interacts with cholesterol, its fluorescence is enhanced, while disturbed – interactions (π-π) between CD and Hb, quenches CD fluorescence. The CD/Hb combination allowed for selective cholesterol detection throughout a linear range of 0 to 800 µM, with a detection limit of 56 µM in blood plasma. (Carbon dot–haemoglobin complex-based biosensor for cholesterol detection).

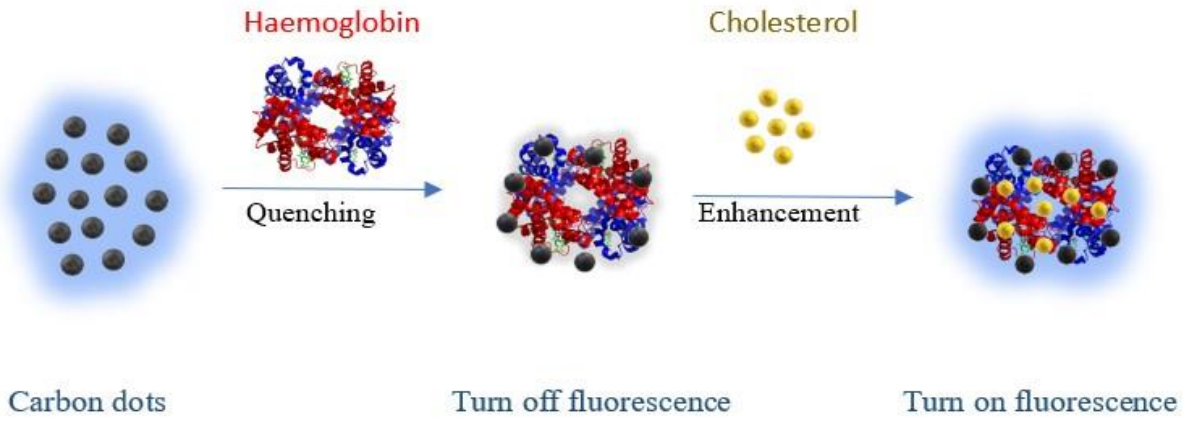

Fig 12. Pictorial representation of Cholesterol biosensor detection by the formation of CD-Haemoglobin complex

A highly rapid and non-enzymatic method for cholesterol measuring based on carbon nitride quantum dots (CNQDs) as fluorescent nanoprobes were synthesized [58] through chemical oxidation. the fluorescence of CNQDs could be quenched more than 90% within 30 seconds by cholesterol through the formation of hydrogen bonds between $–NH_2$, –NH on the surface of CNQDs and cholesterol containing –OH. According to this phenomenon, a cholesterol detection method was constructed with a wide linear region over the range of 0–500 µmol L^{-1} and a detection limit as low as 10.93 µmol L^{-1}, and it possessed the obvious advantages of being a very rapid process and avoiding the use of enzymes. A new kind of well selective and highly sensitive ratiometric fluorescent probe for cholesterol and uric acid determination in human blood serum was innovatively developed [59] on the basis of the inner filter effect (IFE) process of nitrogen, cobalt co-doped carbon dots (N,Co-CDs) with 2,3-diaminophenazine (DAP). Fluorescent magnetic N,Co-CDs possessing blue emission and magnetic property were prepared through a facile one-pot hydrothermal strategy by using citric acid, diethylenetriamine, and cobalt (II) chloride hexahydrate as precursors. IFE process between N,Co-CDs and DAP, N,Co-CDs were applied to establish ratiometric fluorescent probes for the indirect detection of cholesterol and uric acid that participated in enzyme-catalyzed H_2O_2-generation reactions. The established IFE-based fluorescent probes exhibited relatively low detection limits of 3.6 nM for cholesterol and 3.4 nM for uric acid.

v. Detection of Uric acid

Uric acid (UA) is a vital biological substance and the primary end product of purine metabolism in the human body (Highly specific and sensitive non-enzymatic determination of uric acid in serum and urine by extended gate field effect transistor sensors). The level of UA in a healthy person's blood sample should be in the range of 0.15–0.42 mM. Gout, high blood pressure, kidney illness, leukaemia, pneumonia, cardiovascular illnesses, high cholesterol, and multiple sclerosis are all disorders that can be caused by UA.Wang et al, synthesized S, N co-doped Carbon dots which has brilliant fluorescence that quenched to hydroxyl radicals generated on Fenton reaction between H_2O_2 and Fe^{2+} which is facilitated by enzymatic reaction occurring in Uric acid, with that way they developed S, N co-doped Carbon dots as Uric acid biosensor. This built nanosensor has several notable advantages, including good selectivity, rapid response, and a wide response range, which enable it to be used to determine UA in real samples with a linear range of range of 0.08–10 µM and 10–50 µM and detection limit upto 0.07 µM [60]..

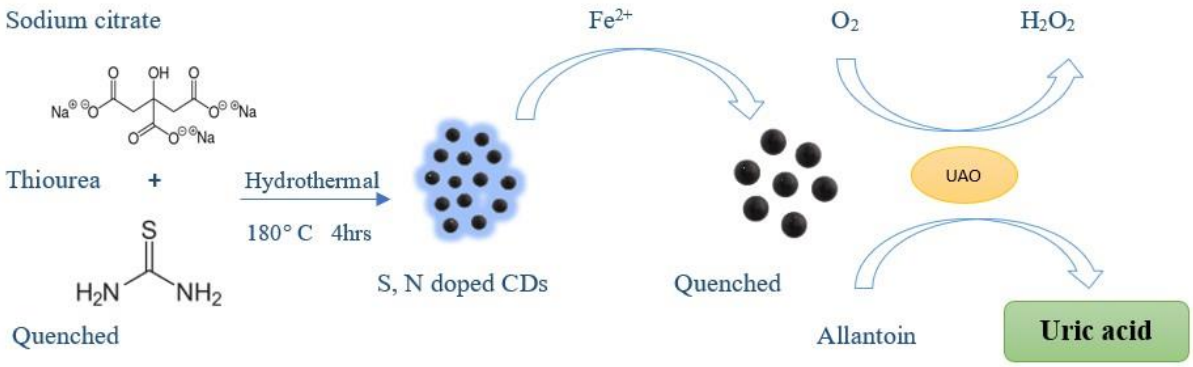

Fig 13. Pictorial representation of detection of Uric acid using S, N co-doped CDs

Mathew et al, in a novel method found a way to reduce Cr (VI) to Cr (III)/ Cr (0) using Uric acid as a reducing agent. Fundamentally, N-CDs they synthesised were used to detect Cr as a turn-off sensor due to Inner filter effect, which has been eliminated by FRET mechanism induced when UA is added into the sample, make it work as a Turn-off-on sensor. They can detect UA with a limit upto 2.5 nM concentrations [61]. Green fluorescent Nitrogen doped Carbon Dots (N-CDs) was synthesized by solvent free pyrolysis technique . Using the synthesized N-CDs, for first time we report the synthesis of Blue fluorescent Nitrogen doped silver and copper carbon dot nano composite using a Simple, Solvent free Green method. The N-CDs function as reducing agent to reduce Ag+ and Cu2+ ions to Ag0 and Cu0 which leads to the formation of composite. The synthesized N-CDs and nano composites were applied as Uric Acid(UA) sensor. With addition of Uric acid there was a quench in fluorescence which is immediately visible by our naked eye The quench in fluorescence is due to the synergistic effect between the fluorescence Inner Filter Effect (IFE) and the static quenching effect, with a Lower detection limit (LDL) of 4µM thus functioning as a highly rapid UA biosensor[62]

vi. Detection of Dopamine

Dopamine (DA) is a catecholamine and a neurotransmitter that plays a key part in the functions of renal, cardiovascular, and central nervous systems. Deficiency in DA is primarily responsible for neurological disorders, including dementia, Parkinson's disease, schizophrenia, epilepsy, and attention deficit hyperactivity disorder. Louleb et al [63] proposed a method for obtaining N-CDs in order to identify DA in human fluids at nanomolar concentrations with rapid and highly sensitive. The function of the biosensor was studied with DFT calculations which revealed that the bonding between the $-NH_3^+$ moiety of DA and the corresponding N-CD surface ligand consists formation of hydrogen bonds. It was found that the linear range is 0 and 652 nM and the detection limit is 4 nM.

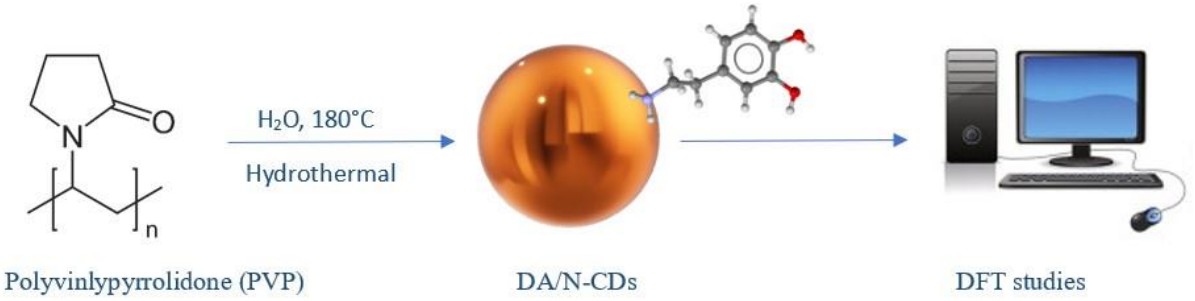

Fig 14. Schematic illustration of detection of dopamine and DFT studies using N-CDs

Carbon quantum dot (CQD)-based refractive index Surface plasmon resonance (SPR) sensor was designed [64] and the sensor performance was evaluated for various concentrations of DA. Increasing DA levels yielded blue-shifted SPR dips. The experimental findings revealed an excellent sensitivity response of 0.138°/pM in a linear range from 0.001 to 100 pM and a high binding affinity of 6.234 TM^{-1}. The observed reduction in surface roughness using AFM demonstrated that DA was bound to the sensor layer. This, in turn, explained the blue shift in SPR reflectance curves. A facile fabrication of an electrochemical sensor from carbon quantum dots CQDs and copper oxide (CuO) nanocomposite for dopamine detection is reported [65]where a nanocomposite (CQDs/CuO) was applied for modification of glassy carbon electrode (GCE). The electroanalysis of DA at CQDs/CuO nanocomposite modified GCE showed that DA detection can best be achieved at about 0.3 V. The detection limit of this sensor (GCE/CQDs/CuO) determined via square wave voltammetry (SWV) was 25.40 µM over a wide linear range of 1–180 µM. A novel dual-emission ratiometric fluorescence sensing system based on a hybrid of carbon dots (CDs) and 7-amino-4-methylcoumarin (AMC) to quickly monitor the DA concentration is been reported by Jia An et.al [66].Linked via amide bonds, the CDs and AMC offered dual-emissions with peaks located at 455 and 505 nm, respectively, under a single excitation wavelength of 300 nm. Attributed to the fluorescence of the CDs and AMC in the nanohybrid system can be quenched by DA, the concentration of DA could be quantitatively detected by monitoring the ratiometric ratio change in fluorescent intensity. More importantly, the CDs-AMC-based dual-emission ratiometric fluorescence sensing system demonstrated a remarkable linear relationship in the range of 0–33.6 µM to detection of DA, and a low detection limit of 5.67 nm. A boronic acid-functionalized fluorescent sensor was developed by adapting the conveniently accessible biomass such as coffee waste for the detection of neurotransmitters like DA. In this context,

we synthesized carbon dots (CDs) using coffee waste via a simple hydrothermal treatment (C-CDs). The fluorescent sensor was designed using phenylboronic acid namely 3-aminophenylboronic acid (APBA)-modification to the C-CDs through 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide/N-hydroxy-succinimide (EDC/NHS) coupling chemistry (B-CDs). Both C-CDs and B-CDs have shown photoluminescence (PL) emission maxima around 452 and 469 nm under the excitation maxima of 335 and 371 nm, respectively. Further, their optical properties were studied through PL response, which showed the distinct excitation-dependent and independent emission behavior, when shifting the excitation wavelengths from 300–500 nm to 300–390 nm, respectively. The C-CDs and B-CDs have displayed light and strong-blue colored emissions under ultraviolet (UV)-illumination, respectively. The B-CDs have shown fluorescence quenching against DA concentrations ranging from 0 to 30 µM with a lower detection limit of 4.25 nM. The applicability of the proposed sensor was investigated in real samples like the human serum, which exhibited good recovery values of 95.9–101.35 % [67].

vii. Detection of Tryptophan

Tryptophan (Trp) is an essential amino acid for appropriate new-born growth and adult nitrogen balance. In the human body, Trp can be metabolised to important neurotransmitters like serotonin, melatonin, and nicotinamide. Trp can induce confusion, nausea, and a loss of appetite, as well as produce a toxic waste substance in the brain that causes psychotic symptoms, when digested improperly. Wenshuai Li et al [68] proposed a novel method to detect Trp with rapid and highly effective way. They synthesised Pyridine functionalized carbon dots by typical one pot hydrothermal method, the mechanism works with Py-CDs' surface pyridine ring served as an active site, forming a non-fluorescence composite with Trp. It just consumes a quarter of a minute and performs highly sensitive and selective towards Trp. This proposed method gives us a linear range of 0.02–20 µM and limit of detection at 5.7 nM.

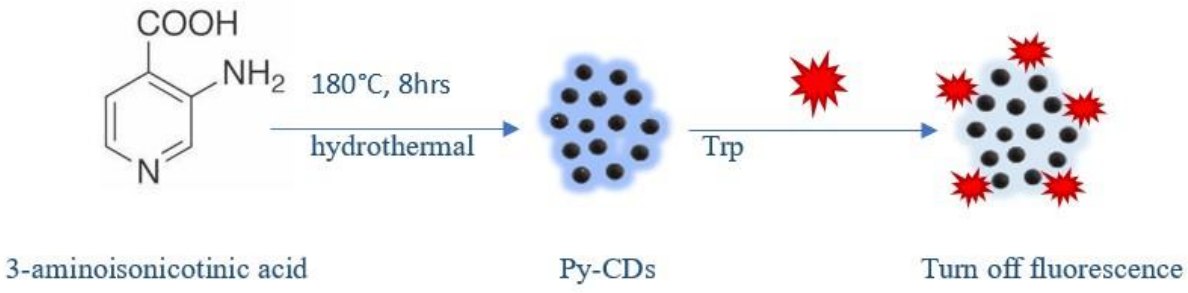

Fig 15. Pictorial representation of biosensing of Tryptophan using Py-CDs

Fluorescent nitrogen and fluorine doped carbon dots (CDs) were prepared by a hydrothermal method [69]. A using levofloxacin (LVFX) and cucurbit [6] uril (Q [6]) as the nitrogen and carbon sources. The synthesized *N*,*N*′-DLH containing Q [6]-CDs emitted intense blue fluorescence with high photostability and exhibited stability at high ionic strength. the obtained Q [6]-CDs, an efficient sensing method for L-tryptophan (L-Trp) and capecitabine (CAP) has been developed based on macrocyclic host–guest chemistry. Under applicable conditions, the detection limits for L-Trp and CAP were calculated to be 5.13×10^{-8} M and 1.48×10^{-8} M. A

novel nanocomposite was fabricated using overoxidized polypyrrole film doped with nano-carbon dots (nano-CDs) on the pencil graphite electrode (PGE) surface for sensitive evaluation of Trp in human serum [70]. Using square wave voltammetry (SWV), the overoxidized polypyrrole/carbon dots/pencil graphite electrode (Ov-Ox PPy/CDs/PGE) achieved excellent electrochemical catalytic activity for evaluating Trp. The modifed electrode, known as Ov-Ox PPy/CDs/PGE, demonstrated superior electrochemical catalytic activity compared to bare PGE, CDs/PGE, PPy/PGE, and PPy/CDs/PGE for evaluation of Trp. The method's excellent sensitivity was confirmed by the low limits of detection (LOD=0.003 µmol L−1) and limit of quantitation (LOQ=0.009 µmol L−1). The biosensor that was developed can measure tryptophan (Trp) levels in the serum of both healthy individuals and female breast cancer patients with high accuracy and sensitivity.

viii. Detection of Cysteine

Cysteine is an essential amino acid that plays an important role in protein synthesis, detoxification, and metabolism. Novel magnesium and nitrogen co-doped carbon quantum dots (Mg-N-CQDs) were developed [71] as a fluorescent switch for sensitive and selective sensing of Hg (II) and cysteine (Cys). The fluorescence of the Mg-N-CQDs aqueous solution containing Hg (II) could be recovered gradually in the presence of Cys, due to the stronger binding affinity of Hg (II) toward Cys than toward Mg-N-CQDs. Liao et al. [73] developed a low-cost method for synthesising multifunctional S, N-CQDs with a high fluorescence quantum yield of 63.82 percent, which can be used as a signal-on sensor for cysteine in aqueous medium. They have a linear range of 10-120 µm as well as a detection limit of 0.35 µm. Furthermore, the extent of cysteine research with carbon dots have been emerged enough to be getting derived from Cys itself [72]. Apart from Ag+, various inorganic metal ions such as Cu2+ and Hg2+, as well as organic compounds such as fluazinam and lucigenin, have been used in such mechanism. [71-78].

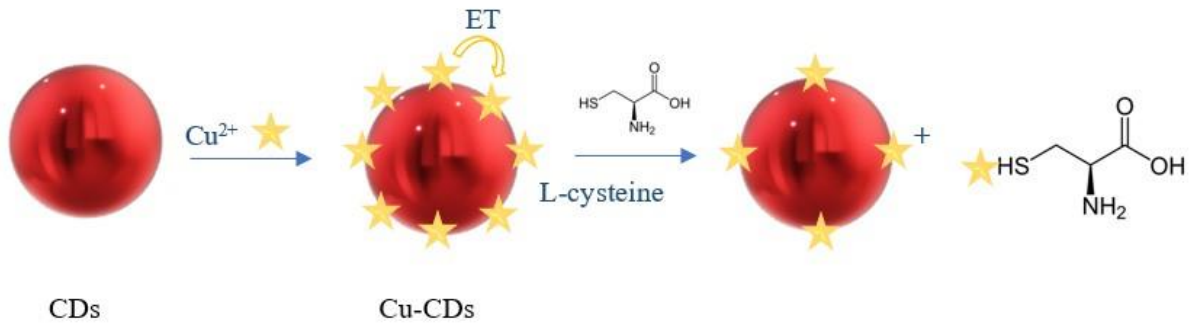

Fig 16. Schematic illustration of Cu^{2+} and L-cysteine detection using CDs

ix. Detection of Bilirubin

Toxic levels of Bilirubin (BR) cause neurotoxicity in neonates, resulting in neurodevelopmental problems such as cognitive impairment, athetosis, and, in rare cases, intellectual impairments, and even death or lasting neurologic sequelae (kernicterus). The only approach to avoid this dangerous condition is to diagnose and treat hyperbilirubinemia as soon as possible. Anjana et al, synthesized S, N-CDs which emits a brilliant blue fluorescence emission. The fluorescence is quenched by addition of Fe (III) and recovered in presence of Bilirubin. In the 0.2 nM to 2 nM linear range, the quenched fluorescent probe shows remarkable selectivity and sensitivity for bilirubin, with a detection limit of 0.12 nM [79].

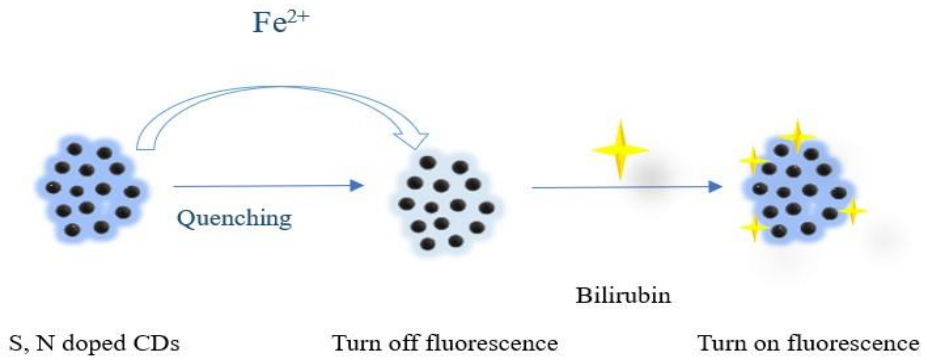

Fig 17. Schematic representation of detection of bilirubin using S, N doped CDs

Sasikumar et al [80] reported the useof CDs for the highly sensitive and selective detection of bilirubin in human urine. The CDs showed the fluorescent emission, which peaked at the wavelength of 511 nm under the excitation wavelength of 435 nm. The CDs' emission intensity reduced with increasing the bilirubin concentration, which was ascribed to the strong inner filter effect (IFE). The excellent spectral match between the bilirubin absorbance and the CDs excitation allowed the fluorescence sensor to be markedly specific only to the presence of bilirubin, permitting the identification of bilirubin even in the presence of other potentially interfering elements. The fluorescence sensor displayed a good linear response to the bilirubin concentration in the wide range of 3.5–45.5 μM with a limit of detection (LOD) of 34 nM. Carbon dots have been reported [81] from resorcinol and sucrose (rsCDs) hydrothermally, which show green emission at 525 nm with a fluorescence quantum yield (PLQY) of 17.2%. The intense emission of rsCDs is quenched upon the addition of Cu^{2+}. In the presence of bilirubin (BR), the emission intensity is enhanced due to the competitive binding of Cu^{2+} with bilirubin and hence releasing rsCDs to the sensing medium. It is the first-time report on turn-on fluorescence sensing towards BR with a detection limit of 85 nM. Even in the presence of other comparable biomolecules, the sensor is selective and ultrasensitive to bilirubin. A cellulose paper-based sensor strip has also been designed for the naked-eye detection of BR in blood serum. yellow emissive carbon dots (Y-CDs, λ_{ex} 430 nm, λ_{em} 550 nm) synthesized utilizing a one-pot solvothermal approach with *o*-phenylenediamine (oPDA) as a precursor is reported [82]. The fluorescence of Y-CDs was quenched with the addition of bilirubin due to the inner filter effect mechanism. The fluorescence intensity of Y-CDs decreases as bilirubin concentration increases and can be completely quenched with approximately 90 μM bilirubin. Over other coexisting interferents (26 interferents), the Y-CD probe exhibited great selectivity for bilirubin. More crucially, a smartphone can capture the

visible color intensity change of the Y-CD probe under a 365 nm UV lamp and later with the aid of computer software, RGB (red/green/blue) analysis was performed for the quantification of colors. This provides computer vision-based detection and sensitive bilirubin assay with a linear range of 4.0–225 μM and a limit of detection of 1.37 μM. Furthermore, the proposed fluorescent probe was applied in real samples (newborn serum, serum and urine of adults with hyperbilirubinemia) with satisfactory recoveries (96–102%).

x. Detection of Aspartate transaminase

The liver enzyme aspartate transaminase is mostly present in hepatocellular tissues. The apparent increase in mortality owing to liver diseases such as liver cirrhosis highlighted the urgent need for quick and precise disease detection. One of the most important indicators for the diagnosis and study of liver disorders is liver enzymes. Thus, Krishna et al [83] developed blue fluorescent N-CDs to detect the enzyme Aspartate transaminase by monitoring its biomarker Oxaloacetate either, directly or indirectly. The abnormally high quantity of AST in the blood causes a rise in oxaloacetate levels. For the direct detection of AST, fluorescent carbon dots are employed as a probe. With an increase in AST concentration, the fluorescence intensity of NCDs was quenched. The probe was able to detect oxaloacetate concentrations up to 100 μM using the indirect approach.

xi. Detection of Glucose

Chemiluminescence (CL) assays have recieved a lot of attention as a flexible analytical technique because of its rapidity, high sensitivity, and wide variety of applications. A natural enzyme, such as horseradish peroxidase, is used in a conventional CL immunoassay approach. Natural enzymes, on the other hand, are frequently restricted due to significant flaws. CDs, have a unique electron transfer, a large specific surface area, broad light-absorbing capacities, function as artificial enzymes when functionalized with metal nanoparticles and MOFs. Duan et al [84], speculated a Copper doped Carbon dot as a catalyst for CL detection of sensitive and selective determination of Glucose. Sensitive detection of glucose through the H_2O_2 mediated oxidation reaction was done in serum samples and allows them to detect analyte because of its peroxidase like behaviour of Cu-CDs even under wide pH ranges and temperatures. Thus, Cu-CDs were utilised as new CL sensing catalyst for very sensitive glucose detection with a detection limit of 0.32 μM.

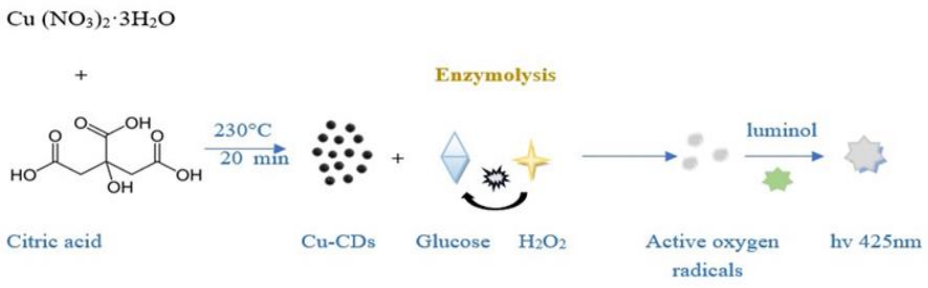

Fig 18. Pictorial representation of chemiluminescence detection of glucose using Cu-CDs

A fluorescent and colorimetric sensing of hydrogen peroxide (H_2O_2) and glucose sensor [84,85] based on the metal oxide – carbon-dot hybrid structure was reported by Hung Hur et. al. The sensing system is related to the catalytic oxidation reaction of glucose-by-glucose oxidase (GOx) to H_2O_2 In this study, a metal oxide hybrid with nitrogen-doped carbon dots (MFNCDs) showed intrinsic peroxidase-like activity, was synthesized and used as a catalyst instead of GOx to oxidize 3,3′,5,5′-tetramethylbenzidine (TMB) to blue-emitting oxidized TMB (oxTMB) in the presence of hydrogen peroxide (H_2O_2). The fluorescence of MFNCDs/TMB at 405 nm was quenched in the presence of H_2O_2 through the inner filter effect (IFE) and electron transfer within MFNCDs, oxTMB, and glucose system. the detection limit for H_2O_2 and glucose based on the fluorescent method were as low as 97 nM and 0.85 mM. Non-enzymatic amperometric sensor for the determination of glucose was designed based on carbon nanodots (C-dots) and copper oxide (CuO) nanocomposites (CuO-C-dots) [86]. The CuO-C-dots nanocomposites were modified on the surface of a screen-printed carbon electrode (SPCE) to increase the sensitivity and selectivity of the glucose sensor. The SPCE modified with CuO-C-dots possess desirable electrocatalytic properties for glucose oxidation in alkaline solutions. Moreover, the proposed sensing platform exhibited a linear range of 0.5 to 2 and 2 to 5 mM for glucose detection with high sensitivity (110 and 63.3 μA $mM^{-1}cm^{-2}$), and good selectivity and stability; and could potentially serve as an effective alternative method of glucose detection. A facile one-pot hydrothermal route was employed to synthesize a series of fluorescent carbon dots (CDs) by using 20 natural amino acids, respectively, as the starting materials [87]. It was found that the CDs synthesized using phenylalanine could possess the intrinsic peroxidase-like activity that could effectively catalyze a traditional peroxidase substrate like 3, 3', 5, 5'- tetramethylbenzidine (TMB) in the presence of H_2O_2 to produce a blue solution; thereby, a catalytic sensing system for H_2O_2 has been developed. On the basis of this catalytic reaction, together with the fact that glucose oxidase (GOx) can catalyze the hydrolysis of glucose to generate H_2O_2, a sensitive catalytic sensing system for glucose could be further established. Limit of detections (LODs) of H_2O_2 and glucose were estimated to be 6.5 and 0.84 μM, respectively.

Detection of Vitamin B_{12}

Vitamins are chemical molecules that are required for proper human function. Vitamin B12 (VB12) is a cobalt tetra azamacrocyclic complex that aids in the production of red blood cells and the upkeep of nerve cells. Anemia, metabolic problems, and psychosis are among symptoms of VB12 insufficiency, which is permanent. Excessive V B12 absorption might potentially have unintended consequences. As a result, the identification of VB12 has gotten a lot of interest in recent decades. Jilong Wang et al [88] introduced a novel FRET-based optical sensor of CDs to detect VB12. Thermally reduced Carbon dots (t-CDs) was synthesised from Citric acid for CDs then they reduced thermally using TGA to obtain t-CDs. T- CDs is able to detect VB12 in aqueous solutions containing concentrations ranging from 1 to 12 g ml^{-1}, with a limit of detection (LOD) as low as 0.1 g ml^{-1}. Meng et al [89] developed orange emission fluorescent multifunctional carbon dots (O-CDs) for label-free vitamin B12 detection using safranine T and ethanol as precursors. The O-CDs with excitation-independent properties were made in a one-step hydrothermal method. VB12 was used as a quencher to quench the

fluorescence of O-CDs due to internal filtering effect. The detection limit was determined as 0.62 µM.

xii. Detection of Chlorpromazine

An antipsychotic drug called chlorpromazine is generally used to treat psychotic conditions such as schizophrenia, bipolar disorder, and acute psychosis. It belongs to a special class of neuroleptic drugs termed first-generation antipsychotics. It belongs to the family of phenothiazines and works as a dopamine receptor inhibitor in the brain. Carbon dots synthesized from kiwi peel by Zhiwei Lu et al. [90] modified Au/N-GOQDs/NiS_2/BC/MIP/GCE composites by electrochemical polymerization. Since chlorpromazine is an electrochemically active drug, it uses a single electron mechanism that is based on the electrochemical oxidation of nitrogen atoms. The sensing system that was carried out during the experiment proved to have a good selectivity for chlorpromazine. Chlorpromazine's electrochemical oxidation is discovered by Au/N-GOGD's /NIS2/BC/ MIP/ GCE electrode. It was decided to calculate the electrochemical behaviour using the electron transfer process that is occurring in CPZ. So, the electrochemical oxidation process of CPZ is determined by the CDs modified nanocomposite's good catalytic behaviour ability. For comparison, DPV was performed under optimized parameters for simultaneous determination of DA (2–40.0 µM) and CPZ (0.2–2.0 µM) by Au/N-GOQDs/NiS2/BC/NIP/GCE.

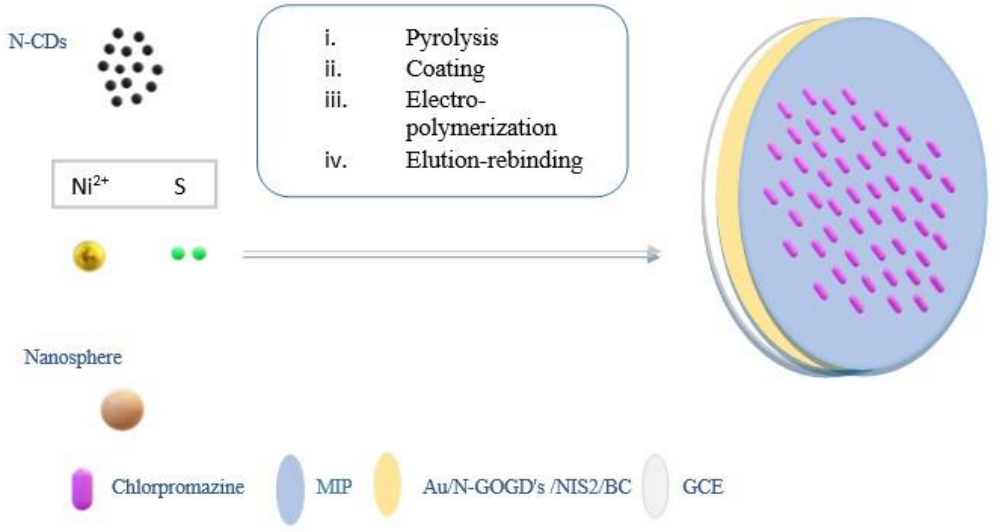

Fig 19. Pictorial representation of electrochemical detection of chlorpromazine

xiii. Detection of metronidazole

Metronidazole belongs to the group of nitroimidazoles, which are often prescribed antibiotics. It is employed to treat parasite infections such as giardiasis, trichomoniasis, and amebiasis, as well as gastrointestinal infections. It is also used as a preventative after surgery

to treat Crohn's disease. Studies have shown that it is also utilised to treat periodontal problems and prevent preterm deliveries. Haiyan Qi et al. [91] synthesized novel N-doped carbon dots from urea and citric acid. According to the investigations, pH and response time play a crucial role in selecting a more accurate quantitative analysis of N-CDs for metronidazole detection. The findings showed that under strong acidic conditions, N-CD fluorescence intensity falls within 5 s and remains constant and unchanged within 100 s. This demonstrated how quickly metronidazole have been detected in the analysis process.

Metronidazole enhances the fluorescence intensity of N-CDs, indicating the formation of a complex between the metronidazole and N-CDs. The paper's evidence showed that IFE is responsible for the quenching mechanism.

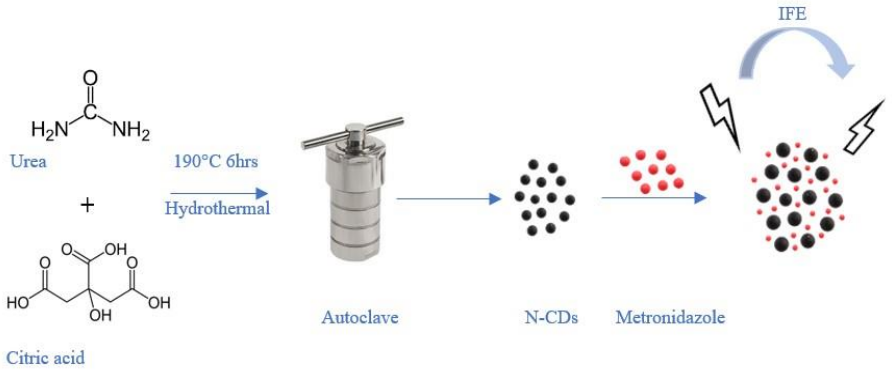

Fig 20. Schematic illustration of synthesis of N-CDs for the detection of metronidazole

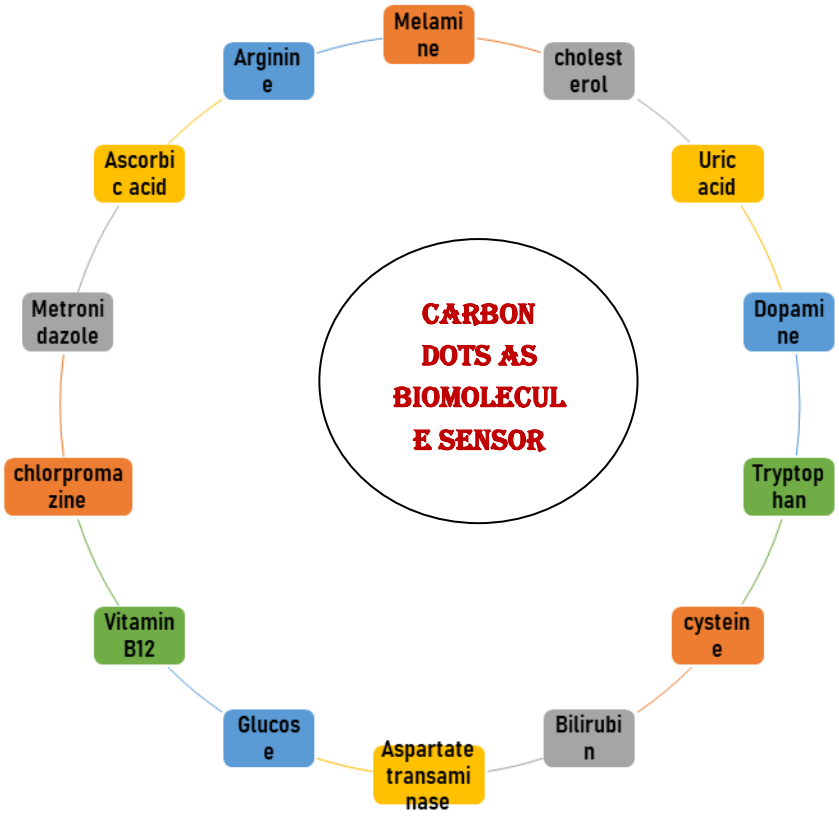

Fig 21. Systematic smart art of Cdots as a sensor for the various Biomolecules

Table 1 A comparative table showing the types of Carbon dots, synthesis, mechanism used in sensing the biomolecule and their detection limit.

Biomolecule	Type of Carbon Quantum Dots	Precursor	Method	Mechanism used for sensing Biomolecule	Detection Limit	Reference
Ascorbic acid	NCDs	Urea, Citric acid	Microwave assisted	TBA -	96 µm -	[44]
	RD-CDs	2,5-Diaminobenzenesulfonic acid, ethanol	hydrothermal	oxidation and reduction of surface functional groups of RD-CDs by ClO− and AA	83 nM	[45]
Arginine	Mg-CDs	Urea, Citric acid	Hydrothermal	Electrostatic interaction	0.15 µmol/L -	[49]
	CDS	o-phenylenediamine, 2-hydroxy-3-methoxybenzaldehyde	Hydrothermal	Ratiometric fluorescence	27 to 107 µM	[50]
Cholesterol	CD/Hb	Citric acid, EDA	Hydrothermal	hydrophobic interactions	56 µM	[57]
Uric Acid	S, N-CDs	Sodium citrate, thiourea	Hydrothermal	TBA	0.07 µM	[60]
Biomolecule	**Type of Carbon Quantum Dots**	**Precursor**	**Method**	**Mechanism**	**Detection Limit**	**Reference**
	NCDs	Monoethanolamine, H_2O_2	Hydrothermal	FRET	2 nM	[61]
	Cu/NCDs & Ag/NCDs	Monoethanolamine, H2O2	Hydrothermal	IFE, static quencing	4µM	[62]
Dopamine	NCDs	Polyvinylpyrrolidone	Hydrothermal	electrostatic, hydrogen bonding	4 nM	[63]
Tryptophan	Pyridine functionalized carbon dots	Pyridine	hydrothermal method	static quenching process	5.7 nM	[68]
Cysteine	magnesium and nitrogen co-doped carbon quantum dots	citric acid, Mg $(OH)_2$, ethylenediamine (EDA)	hydrothermal method	fluorescent complex	9–15 µM	[71]
	SWNT–DNA-5 conjugates	Single-Walled Carbon-Nanotube	SONICATION	p–p stacking interactions between nucleotide bases and SWNT sidewalls	9.5 nm	[72]

	S, N-CQDs – Ag+	Citric acid, thiamine hydrochloride	Hydrothermal	- Cys exhibited stronger complexation capability towards Ag+ than S, N-CQDs	0.36 µM	[73]
Bilirubin	S, N-CDs	Citric acid, L-Cysteine	Microwave	Electron transfer	0.12 nM	[79]
Aspartate transaminase	N-CDs	Tris-Acetate-EDTA, Starch	Microwave	unclear	100 µM	[83]
Glucose	Cu-CDs	Citric acid, Cupric nitrate	Pyrolysis	Charge transfer	0.32 µM	[84]
	metal oxide hybrid with nitrogen-doped carbon dots (MFNCDs)	CH_3COONa ethylene glycol (EG). $MnCl_2$&$4H_2O$, $FeCl_3$&$6H_2O$	hydrothermal	inner filter effect (IFE) and electron transfer	0.85 mM	[86]
Vit B12	thermally reduced carbon dots.	carbonization of citric acid	thermal	FRET	0.1 mg ml1	[87]
	orange emission fluorescent multifunctional carbon dots (O-CDs)	safranine T and ethanol	hydrothermal process	internal filtration effect (IFE)	0.06 µM	[89]
Biomolecule	**Type of Carbon Quantum Dots**	**Precursor**	**Method**	**Mechanism**	**Detection Limit**	**Reference**
chlorpromazine	nitrogen-doped graphene oxide quantum dots coated on NiS_2/biomass carbon	Kiwi peel	electrochemical polymerization	electron transfer process	0.25 nM	[90]
metronidazole	N-doped carbon dots	citric acid and urea	hydrothermal method	inner filter effect	0.25 µM	[91]

Conclusion

Carbon Dots are potential candidates towards Biomolecule sensing. This chapter, a mini review summarizes on the recent advances on the various types of CDs synthesised, technique used for the synthesis of CDs, mechanisms applied towards sensing of biomolecules, limit of detection and advantages of CDs as biosensor probe. Only a few biomolecule detection methodologies are explained as it is a mini review.

Author contribution: Writing— All the authors have equally contributed towards the original draft preparation and have read and agreed for the published version of the book chapter.

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