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Graphene and Carbon Quantum Dots-based Biosensors for Use with Biomaterials

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Abstract

Biosensors, which are analysis devices used to convert biological reactions into electric signals, are made up of a receptor component and a signal transduction part. Graphene quantum dots (GQDs) and carbon quantum dots (CQDs) are new types of carbon nanoparticles that have drawn a significant amount of attention in nanoparticle research. The unique features exhibited by GQDs and CQDs are their excellent fluorescence, biocompatibility, and low cytotoxicity. As a result of these features, carbon nanomaterials have been extensively studied in bioengineering, including biosensing and bioimaging. It is extremely important to find biomaterials that participate in biological processes. Biomaterials have been studied in the development of fluorescence-based detection methods. This review provides an overview of recent advances and new trends in the area of biosensors based on GQDs and CQDs as biosensor platforms for the detection of biomaterials using fluorescence. The sensing methods are classified based on the types of biomaterials, including nucleic acids, vitamins, amino acids, and glucose.

Index Terms: Biosensors, Carbon Quantum Dots, Fluorescence, Graphene Quantum Dots

I. INTRODUCTION

Biosensors are analysis devices that convert a biological reaction into an electric signal and make it possible to track small particles of interest in living cells in real time [1-3]. A biosensor is made up of a sensing component able to detect target materials, and a signal transduction component used to change the sensing event into signals including fluorescence, chemical luminescence, color, or electrochemical signals [4-6]. A fluorescent biosensor is a device used to convert information in a certain sample into a fluorescent signal both analytically and quantitatively [7]. A fluorescence detection-based assay is a commonly used technique because fluorescent spectroscopy is highly sensitive, easily measured, and inexpensive [8, 9]. Because fluorescence-based probes have such advantages, they are significantly in demand for sensor designs. Nanomaterials used as an effective fluorescence quencher, such as gold nanoparticles, carbon nanotubes, and grapheme, are currently being studied for biosensing platforms [10-12].

Carbon quantum dots (CQDs) are a new type of carbon nanoparticle of less than 15 nm in size, and have drawn significant attention in nanoparticle research [13-15] owing to their superior and unique properties. Such properties include fluorescence with high adjustability, an easy introduction of the synthetic and functional groups, an excellent photostability, biocompatibility, low cytotoxicity, and photobleaching stability [16-18]. In particular, CQDs have an extremely strong and adjustable fluorescence and thus can be applied to bioengineering applications such as biosensors, bioimaging, and catalysts. Another important property is a high solubility that makes it possible to develop homogeneous sensing assays, which are particularly favorable for the detection of biomaterials [19-21]. Traditionally, CQDs have been synthe-

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sized through the surface functionalization of carbon nanoparticles using organic molecules and polymers. Most synthesis methods utilize some form of carbon in the precursor structure. Common carbon sources in the production of CQDs include fruit juices, watermelon, pomegranate skin, other food items, or plant matter. In contrast, graphene quantum dots (GQDs) have zero-dimensional carbon nanostructures, with several layers of graphene sheets of less than 100 nm in diameter [22, 23]. The unique and excellent properties of GQDs, which are similar to those of CQDs, can also be used for biosensing and bioimaging applications. The wide range of excitation wavelengths of GQDs can serve as FRET acceptors or donors depending on the sensing platform requiring a certain emission wavelength [24, 25]. In electron delocalization, which occurs in a wide sp^2 network, GQDs are graphene-based nanostructures that achieve the physical absorption of biomaterials on the surface of the nanoparticles through non-covalent π–π stacking interactions and hydrophobic interactions. These points make it possible for GQDs to detect even minimal amounts of biomaterials. In addition to the many described advantages of GQDs, they do not include heavy metals with a high cytotoxicity for general semiconductor QDs. GQDs have an extremely large surface area and can use this characteristic to interact with organic particles or drugs, which is an excellent intrinsic property applied to drug-delivery, bio-sensing agents, and tissue engineering applications.

CQDs and GQDs can be differentiated depending on their shape, surrounding functional groups, and manufacturing elements. CQDs, which have spherical shapes, are amorphous carbon particles mixed with sp^2 with a size of less than 15 nm. CQDs can be synthesized using such methods as the electrochemical exfoliation of carbon fibers, a chemical oxidative treatment, and the pyrolysis of organic precursors [26]. Meanwhile GQDs have crystalline nanostructures with some layers of graphene and are synthesized from graphene-like structure substances such as carbon nanotubes (CNTs) and polycyclic aromatic hydrocarbons, or grapheme-based precursors. GQDs show a quantum confinement, and have lateral side lengths of up to 100 nm with multiple functional groups such as hydroxyl, amine, and carboxyl groups. CQDs are crystalline nanoparticles with sp^2 bonds and graphitic properties. The biggest advantage of GQDs and CQDs in comparison with semiconductor QDs is their lower environmental and biological risk owing to such excellent properties as an inertness, excellent solubility, stable photoluminescence, and low cytotoxicity [27, 28].

The purpose of this review is to summarize the recent advances and newer trends in biosensors based on GQDs and CQDs used as biosensor platforms for the detection of biomaterials. Because of the excellent fluorescent properties of carbon nanomaterials (CQD and GQD), this review focuses on fluorescence as a sensing method, and owing to their importance in biological processes, certain types of biomaterials such as nucleic acids, vitamins, amino acids, and glucose are focused upon.

II. BIOSENSORS FOR VARIOUS TYPES OF BIOMATERIALS

It is important to accurately measure the biological materials participating in biological processes, namely nucleic acid, amino acids, vitamins, glucose, and other small metabolites. Biomaterials have been intensively researched in the development of detection methods applied to direct or indirect sensing process techniques based on fluorescence [29, 30]. An enormous amount of effort is being spent in developing detection methods for deoxyribonucleic acid (DNA). Because deoxyribonucleic acid (DNA) contains genetic information, it is essential to understand its role in the proper functioning of biological systems and the treatment of diseases. There is also a significant interest in amino acid analyses owing to their relationship with various diseases. Ascorbic acid (AA) is a type of vitamin with anti-oxidation characteristics and is widely distributed in food, drugs, and other items. Accurate measurements regarding the amount of glucose have long been important owing to the need to manage diabetic events. There are many methods used in detecting biomaterials, including electrochemistry, chromatography, capillary electrophoresis, colorimetry, and fluorescence spectroscopy. Because a fluorescence method has advantages such as a fast analysis and high sensitivity, the fluorescence technique is popular for the detection of various materials.

A. Biosensors for Nucleic Acids

Deoxyribonucleic acid (DNA) is made up of molecules that deliver the majority of human genetic information [31, 32], and as a result, fluorescence probes have been highly researched for their utility in the analysis of DNA. Although organic dyes have been widely used, it is well known that organic substances have certain disadvantages such as a low solubility, low photoluminescence, and high cytotoxicity. Although semiconductor nanomaterials such as CdTe quantum dots with excellent fluorescence intensity, which show high sensitivity and selectivity, have been popularly applied to overcome the disadvantages of organic dyes, the heavy metals of semiconductor nanomaterials continue to have toxic effects. Therefore, biosensors with carbon-based CQDs or GQDs are gradually drawing attention as a biomaterial detection platform. Nanomaterials based on carbon, including CQDs or GQDs, have a wide sp^2 network and can serve as FRET acceptors or donors through the absorption in both non-covalent π–π stacking and hydrophobic interactions with biomaterials such as ssDNA [33, 34]. Guo et al. [35] pro-

posed the use of N and S co-doped CD (P-CD) biosensing DNA as a biosensing platform as a ratiometric method acting as both a nanoquencher and reference signal. As shown in Fig. 1A, P-CDs were synthesized through a pyrolysis method used to heat a compound of citric acid monohydrate and L-glutathione applied as a carbon source and doping element at 180°C. The P-CDs created are 2.7 nm in diameter and 2.0–3.0 nm in uniform height with a 0.22-nm lattice spacing and a quasi-spherical shape. P-CDs can quench fluorophore-modified DNA, allowing it to achieve fluorescence as an internal reference signal. In addition, P-CDs peform dual roles of reference signal and nanoquencher and are thus suitable for use in a ratiometric method. Fluorophore-modified DNA is quenched through π-π stacking interactions with P-CDs, and a target ssDNA with a complementary sequence is then added, thereby allowing the fluorescence to gradually recover. The concentration of the target DNA for the ratio of fluorophore-modified fluorescence of the DNA and the P-CD fluorescence ($F_{FAM}/F_{P\text{-}CDs}$ and Target-ssDNA) shows a linear relationship within the range of 0.05–1.0 nM, with a limit of detection (LOD) of 34 pM.

Yew et al. [36] sonicated calcined petroleum coke using sulfuric and nitric acids, and then heated them at 100°C for 24 h for the synthesis of GQDs used as a DNA biosensor. The synthesized GQDs seem to have a wide size distribution of 30–550 nm according to data measured through dynamic light scattering (DLS). The complementary DNA target (cDNA, 5'ATG GAG GAC GTG TGC GGC CGC CTG GT 3') is detected in two ways. First, FAM-Lprobe (5'[6FAM] ACC AGG CGG CCG CAC ACG TCC TCC AT 3') and π-π stacking interactions and hydrophobic interactions trigger the absorption of GQDs, and consequently the fluorescence signals of FAM-Lprobe are quenched. FAM-Lprobe is mixed with cDNA and thus two single-stranded DNA oligonucleotides achieve a DNA assembly (ds–cDNA–FAM-Lprobe) through a combination of strands. GQDs have a low affinity to dsDNA and are thus not absorbed into the GQDs, and maintain their fluorescence signals. A nanoquencher is used to measure a change in the intensity of fluorescence along with an increase in the concentration of the target cDNA. Thus, the concentration of the target cDNA was measured. A linear detection range was found to be within the concentration range of 0.004–4 nM, and the LOD was reported to be 0.004 nM. The strategy used by Loo et al. [37] is similar to that of Yew et al. [36]. As a fluorescent sensing platform used as a nanoquencher to detect nucleic acid, carboxylic CQDs (cCQD) rather than GQD were applied. As a cCQD carbon source, citric or malic acid was used and heated to 205°C for 15 min to achieve a synthesis. The sensing method for fluorescent nucleic acid is based on the manner in which the fluorescently labeled single-stranded DNA (ssDNA) probe (FAM-Lprobe) absorbs the cCQD and achieves fluorescence quenching. FAM-Lprobe creates double-stranded DNA (dsDNA) in combination with its complementary DNA target. Because the gravitation between cCQD and dsDNA is weak, the dsDNA moves away from the cCQD and thus FAM-Lprobe maintains its fluorescence. Hydrophobic π–π interactions created through the π–π stackings between the surfaces of the hydrophobic regions of DNA nucleobases and cCQD have a competitive relationship with the electrostatic repulsion of phosphodiester backbone of DNA negative charge and cCQD carboxylic groups, and an interaction between DNA and cCQD is therefore created. Malic acid QD has a detection range of 0.04–400 nM, whereas citric acid QD has a detection range of 0.4–400 nM. The LOD of malic acid QD is 17.4 nM, and that of citric acid QD is 45.6 nM. The relatively wide detection range of malic acid QD, or lower LOD, is expected to be due to the presence of more carboxylic groups than in citric acid QD. Qian et al. [38] heated graphite powder in a H_2SO_4 and HNO_3 solution at 80°C for 24 h to obtain the GQDs and then heated the mixture with sodium borohydride in a tetrahydrofuran solution at 70°C for 8 h to synthesize the reduced graphene quantum dots (rGQDs). The synthesized rGQDs and carbon nanotubes were used to detect the DNA. The rGQDs have a strong fluorescence (quantum yield of 0.21) and create a pair with DNA selectively. The oxidized CNT, which was obtained by oxidizing multi-walled carbon nanotubes (MWNT) in a H_2SO_4/HNO_3 solution, is an electron acceptor and serves as an efficient quenching agent. A specific fluorescence "on-off-on" process that uses the fluorescence quenching through

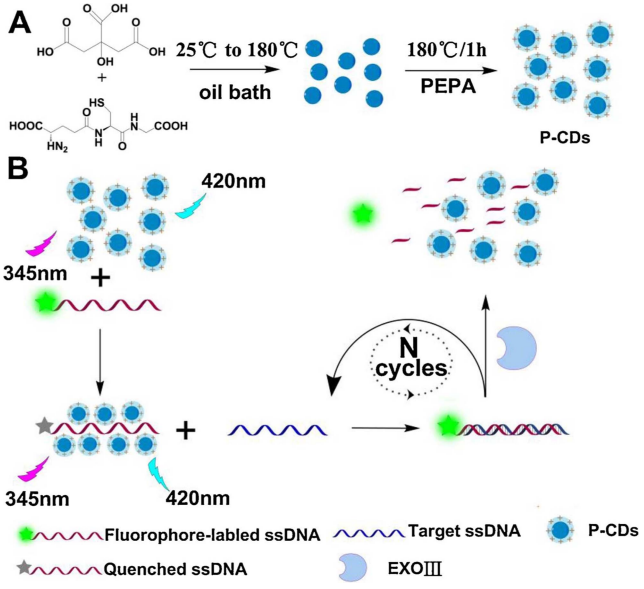

Fig. 1. (A) Synthesis of P-CDs and (B) the quenching of fluorophore-labeled ssDNA using P-CDs while retaining their stable fluorescence intensity, enabling a ratiometric analytical method for Gardnerella vaginalis DNA with the target sequence circulating under the assistance of Exo III (reproduced from [35]).

Table 1. Comparison of reported techniques for the detection of DNA and amino acids

Sensing materials	Method	Linear range (nM)	LOD (nM)	References
DNA	Fluor	0.05–1	0.034	35
DNA	Fluor	0.004–4	0.004	36
DNA	Fluor	0.04–400	17.4	37
DNA	Fluor	1.5–133.0	0.4	38
Cysteine	Fluor	1–40,000	1.01	41
Cysteine	Fluor	10,000–120,000	350	49
Cysteine	Fluor	200–45,000	50	50
Cysteine	Fluor	0.5–120	0.30	51
Cysteine	Fluor	10–600	4.5	52
Cysteine	Color	1–1000,000	1	52
Arginine	Fluor	1,000–5,000	450	56
Cysteine	Fluor	10–5,000	4.9	57
Cysteine	Fluor	0–50	2.5	58
Cysteine	Color	100–100,000	100	59
DNA	Color	10–1000,000	3.5	60
DNA	Fluor	0.05–1	0.034	61

Color, Colorimetric method; E-chem, electrochemiluminescence method; Fluor, fluorimetric method; LOD, limit of detection

the FRET phenomenon between rGQDs and oxidized CNT, and the fluorescence reproduction created through the separation of a double-stranded DNA probe, make it possible to quantitatively analyze the target DNA.

A quantitative analysis of the target DNA (tDNA) has three stages. In the first stage, DNA and rGQDs are coupled to synthesize a single-stranded DNA probe (ssDNA–rGQDs). In the second stage, ssDNA–rGQDs with a strong blue fluorescence are mixed with oxidized CNTs, and thus an electrostatic attraction and a π–π stacking interaction result in ssDNA–rGQD absorption on the surface of oxidized CNTs. As a result, fluorescent-quenched ssDNA–rGQDs/CNTs are created. In the last stage, tDNA is coupled with the ssDNA–rGQDs of ssDNA–rGQDs/CNTs and is thereby separated from CNT in a type of dsDNA–rGQDs; the fluorescence is therefore recovered through the free dsDNA–rGQDs. Regarding the relationship between the intensity of the fluorescence and the concentration of the tDNA in the detection of the DNA, a linear relationship remains within the concentration range of 1.5–133.0 nM, and the LOD is 0.4 nM. This is shown in Table 1, where various DNA analysis methods are compared.

B. Biosensors for Amino Acids

Amino acids are widely distributed in biological fluids and are involved in many biological processes including the synthesis of proteins and fats. The exact amount of amino acids in a biological fluid can fluctuate according to the presence or absence of disease. For this reason, there has been a significant amount of interest in the analysis on amino acids for the prediction, diagnosis, treatment, and understanding of diseases. Small biomolecules, such as amino acids, vitamins, carbohydrates, or other types of metabolites have been researched using direct or indirect sensing process techniques based on the turn-on or turn-off actions [39, 40].

Cysteine, a type of amino acid, includes sulfur, as do glutathione (GSH) and homocysteine (HCys). These sulfur-containing amino acids, called biothiols, play a critical role in the biochemical and physical processes of living organisms. Cysteine has an antioxidation ability, and as the main source of sulfur in the human metabolism, has been linked with Alzheimer's and Parkinson's diseases [41]. Therefore, it is important to quantify the amounts of Cys in living organisms. Although methods such as high-performance liquid chromatography (HPLC) [42, 43], mass spectrometry [44, 45], and capillary electrophoresis [46, 47] have been used for Cys quantification, simple, fast, and economic Cys sensors are gradually receiving attention. Nevertheless, because semiconductor quantum dots (QDs) are frequently used owing to their excellent fluorescence, their risk of toxicity is becoming an issue. Electrochemical sensor systems are used to detect biothiol owing to their low prices and high sensitivity. Owing to their problem of selectivity, carbon and graphene quantum dots, which have an excellent fluorescent property good for biosensing, are non-toxic, and are biocompatible, have been widely used in the detection of amino acids, and are quickly being developed. Yang et al. [48] synthesized a fluorescent sensor in which 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), known as Ellman's reagent, is coupled with N-doped carbon quantum dots (N-CQDs). N-CQDs have an optimal λ_{ex} of 409 nm and λ_{em} of 512 nm. DTNB has shown an excellent selective reactivity to the –SH functional group. N-CQDs have excellent fluorescence with a 29% quantum yield. A sensor with coupled N-CQDs and DTNB has a strongly green fluorescence. When Cys is added, the fluorescence of the –SH group and DTNB of Cys is quenched through strong gravitation. Therefore, in a real sample, the sensor shows its capability as a Cys detecting biosensor (Fig. 2). A biosensor with a coupling of DTND and N-CQD has a linear relationship with L-Cys within the range of 1 nM to 40 μM, and the LOD is 1.01 nM.

Liao et al. [49] heated citric acid (CA) and thiamine hydrochloride (VB1) in an autoclave at 160 °C for 5 h, and then made S,N-CQDs for the selective detection of Ag^+ and Cys when the fluorescence quantum yield (QY) reaches 63.82%. Here, S,N-CQDs is able to detect Cys through a phenomenon in which fluorescence quenching is created by Ag^+ and fluorescence recovery is selectively generated through Cys. The N-CQDs/Ag^+ system has a good linear correlation with Cys within the range of 10–120 μM, and the

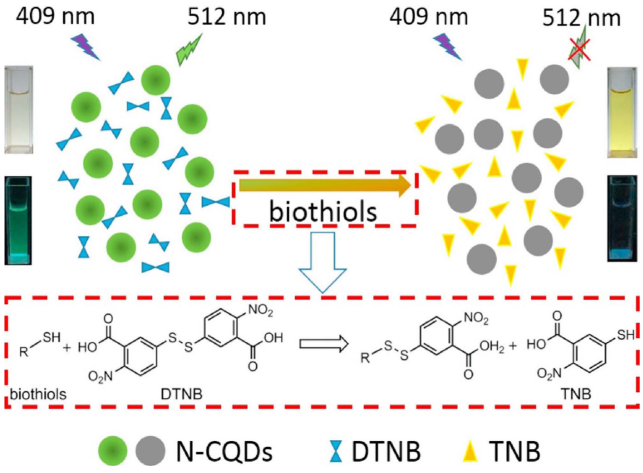

Fig. 2. Schematic illustration of the fluorescence detection of biothiols based on NCQDs (reproduced from [48]).

(LOD) is 0.35 μM. Hou et al. [50] developed CQDs through the sonication and microwaving of a mixture of triammonium citrate and Na_2HPO_4, and detected Cys through the recovery of the fluorescence intensity of a CQDs-Hg(II) system. The Hg(II) of the CQDs-Hg(II) system has a strong affinity with Cys. With the addition of Cys, its fluorescence intensity increases. These CQDs show a similar phenomenon not only in Cys, but also in GSH or His. It was therefore proven that CQDs are applicable to an analysis of Cys, GSH, and His in human serum samples. The CQDs-Hg(II) system has a linear relationship with Cys within the range of 0.2–45 μM, and the LOD is 0.05 μM. There has been significant progress in the research on biosensors used in the detection of Cys based on the excellent electric and optical properties of GQDs. Ojodomo et al. [51] reported a biosensor developed to detect biothiol in connection with GQDs and maleimide as a Michael acceptor. According to their research results, maleimide-derivatized zinc phthalocyanine has noncovalent interaction through GQD and π-π stacking, and fluorescence quenching consequently occurs. When biothiols such as Cys have a Michael reaction with the biothiol maleimide part of maleimide-derived GQD, the π coupling of maleimide disappears and no additional π-π stacking occurs. As a result, maleimide-derivatized zinc phthalocyanine is separated from GQD and the fluorescence is recovered. Therefore, the authors used this phenomenon in the detection of Cys. The LOD of Cys and GSH is 0.85 and 3.2 nM, respectively. Li et al. [52] developed a biosensor to detect the turn on-turn off Cys of fluorescence through the use of GQDs and Hg(II). Regarding the GQDs obtained after a pyrolysis of citric acid, the emission of FL was 450 nm, which demonstrated excitation at 365 nm. When Hg(II) was added, fluorescence quenching occurred. Next, when Cys was added, the fluorescence intensity increased. Therefore, Cys was detected based on this phenomenon. A linear relationship with Cys was shown within the range of 0.01–0.6 μM, and the LOD was 4.5 nM.

Arginine (Arg) is one of 20 essential amino acids and has many biological roles, such as an involvement in protein production and platelet coagulation. In particular, as a physiological precursor of NO, it plays a critical role in vascular homeostasis [53]. The arginine content in the human body is therefore extremely important, and various methods are used in the detection of arginine. Methods using GQDs or CQDs have recently been introduced [54, 55]. Liu et al. [56] used ethylene glycol as a carbon source and heated it along with a NaOH solution in an autoclave at 180°C for 2 h, and then synthesized CQDs using a hydrothermal method. In terms of the CQDs, if $HAuCl_4$ is added, an Au/CQD composite with fluorescence quenching is obtained. However, if arginine is first added to $HAuCl_4$ and CQDs are then applied, an Au/CQD composite is not created. As a result, arginine is impossible to detect. A linear relationship within the range of 1–5 μM was demonstrated according to the Arg concentration, and the limit of the detection was 450 nM. Notable results can be seen in Table 1, which compares the reported techniques used in the detection of DNA.

C. Biosensors for Vitamins

Ascorbic acid (AA), also known as vitamin C, is a type of vitamin with an anti-oxidation effect. It is a strong reducing agent that serves as a free radical scavenger. Because AA is widely distributed in food, drugs, and other materials, it is important to detect and quantify the free radical scavengers [62, 63]. Although electrochemistry, chromatography, capillary electrophoresis, and colorimetry are used for AA quantification, the fluorescence technique is popular owing to such advantages as a fast analysis and high sensitivity. Many studies on this technique have been conducted [64, 65]. Liu et al. [66] developed a turn-on based AA detection method by creating GQDs with a fluorescence emission peak of 540 nm from graphite oxide through the use of Hummer's technique. The AA detection technique is presented in Fig. 3. Catechol is oxidized into O-benzoquinone using horse radish peroxidase (HRP) and hydrogen peroxide (H_2O_2), which act as oxidation catalysts, and the oxidation product quenches the GQDs. At this time, if the AA serving as an effective antioxidant is added, H_2O_2 and free radicals are effectively removed and thus the O-benzoquinone generation can be impeded. On balance, based on the increased fluorescence intensity, it is possible to quantify the AA. In the proposed system, the AA concentration and fluorescence intensity have a linear relationship within the concentration range of 1.11–300 μM, with an LOD of 0.32 μM.

Liu et al. [67] also used the antioxidation property of AA, and applied a strong resultant fluorescence when Cu^{2+} was

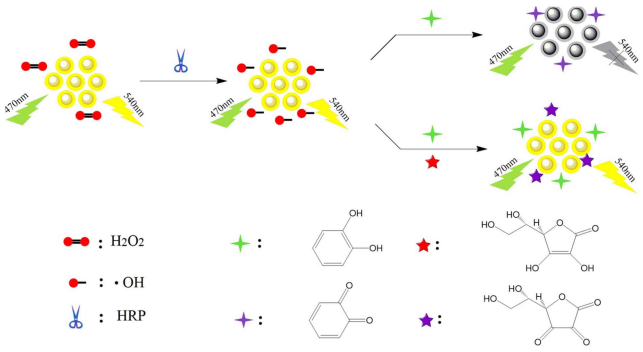

Fig. 3. Schematic illustration of the process used for AA recognition (reproduced from [66]).

added to GQDs obtained through the heating of citric acid at 200 °C. If Cu^{2+} is added to a DA-GQD complex generated through the addition of dopamine (DA) in GQDs, the dopamine is oxidized by Cu^{2+} and o-semiquinone is therefore created, which quenches the fluorescence of the GQDs. If AA is added to the quenched GQD complex, AA with a strong reduction turns on the fluorescence of the GQDs. The DA-GQD complex and fluorescence have a linear relationship within the range of 0.05–6 μM, with an LOD of 0.021 μM.

Liu et al. [68] synthesized GLY functionalized GQDs (GLY-GQDs) obtained through the heating of glycine and ethylene glycol as carbon sources at 170°C and used the synthesized matter as a probe for the detection of AA. If Ce(IV) is added to GLY-GQDs, a quenching occurs. If AA is added, the fluorescence is switched on through a reduction in oxidation between AA and Ce(IV). This effect shows excellent selectivity and high sensitivity to the interference of dopamine, glutathione, or uric acid. A GLY-GQD probe has a linear relationship with the fluorescence within the range of 0.03–3.3 μM, and the LOD is 25 nM. Zhu et al. [69] heated a powdered mixture of sodium alginate as a carbon source and tryptophan as a nitrogen source in an autoclave at 220 °C for 6 h to obtain nitrogen-doped carbon nanoparticles (N-CNPs) and used the resulting matter as a nanoprobe for AA detection in blood. If AA is added to N-CNPs, it is possible to detect the AA through the synergistic effect of the inner filter and static quenching effects. Logarithmic types with quenching efficiency (F_0/F) for AA detection and concentration have a strong linear relationship within the range of 0.2–150 μM, and the LOD is 50 nM. Notable results are shown in Table 2, which compares the reported techniques for the detection of AA.

D. Biosensors for Glucose and Other Small Molecules

Accurately measuring the amount of glucose is crucial in the detection of diabetes. Because the detection of glucose in the blood is interfered with by various types of matters in the

Table 2. Comparison of reported techniques for the detection of glucose and pyrophosphate ions

Sensing materials	Method	Linear range (μM)	LOD (μM)	References
CuO nanourchin	E-chem	100–3000	1.52	64
Ascorbic acid	Fluor	1.11–300	0.32	66
Ascorbic acid	Fluor	0.05–6.0	0.021	67
Ascorbic acid	Fluor	0.03–3.3	0.025	68
Ascorbic acid	Fluor	0.2–150	0.050	69
Glucose	Fluor	0.1–30	0.021	75
Glucose	Fluor	2.0–400	0.67	76
Pyrophosphate ion	Fluor	1–1000	0.81	77
Glucose	E-chem	100–3000	1.52	78
Glucose	Color	100–2000	100	79
Glucose	E-chem	20–4200	8.4	80
Glucose	Color	1–20	1.0	81
Dopamine	Fluor	0.25–50.0	0.09	82

Color: Colorimetric method; E-chem: electrochemical method; Fluor: flluorimetric method; LOD: limit of detection

blood, it is important to detect glucose with high sensitivity and selectivity for diagnosis and treatment. There are many methods used to assay glucose such as surface-enhanced Raman scattering, colorimetric, liquid chromatography, and mass spectrometry methods [70, 71]. However, these methods have certain problems in terms of a complex synthesis and extraction and the use of expensive devices. In comparison, methods using the fluorescence property are extremely simple, resulting in their recent development. Although CdTe nanoparticle, silver nanoparticle, carbon nanodot, and gold nanoparticle techniques are popular, they have a problem with toxicity. As a result, biocompatible materials such as GQDs or CQDs have drawn more attention [72–74]. As a glucose probe, Liu et al. [75] used GQDs synthesized from graphite oxide through Hummer's method. Fe^{2+} weakly quenches the fluorescence of GQDs, whereas a Fe^{3+} or Fe^{2+}/H_2O_2 mixture more strongly quenches the fluorescence. A GQDs/Fe^{2+} system has no change in fluorescence with the addition of uric acid, glucose, uricase, or GOx. H_2O_2 is generated through the enzymatic reaction of GOx and uricase of uric acid and glucose. The H_2O_2 generated oxidizes Fe^{2+} into Fe^{3+}, thereby considerably weakening the fluorescence of GQDs. This phenomenon was used to quantitatively detect the presence of glucose. The fluorescence of GQDs (Fig. 5) is quenched using Fe^{3+} created from the reaction of Fe^{2+} and H_2O_2 generated through the enzyme oxidizing of glucose into gluconic acid. The fluorescence intensity of the GQDs/Fe^{2+}/GOx system gradually decreases with an increase in the glucose concentration. Accordingly, the glucose concentration and fluorescence intensity have a strong linear relationship (with a corresponding regression coefficient (R^2) of

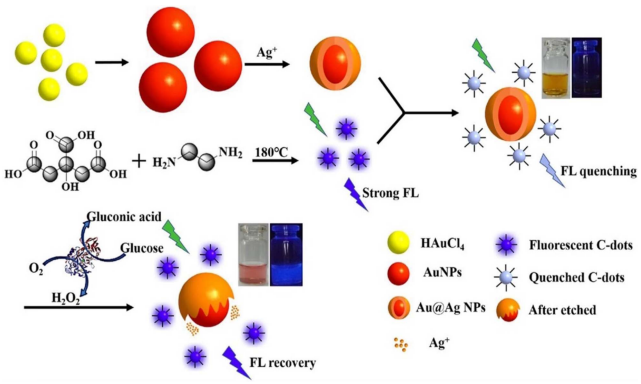

Fig. 4. Schematic of fluorometric and colorimetric assay for glucose detection based on Au@Ag NPs and C-dots (reproduced from [76]).

0.9973) within the range of 0.1–30 μM, where the LOD is 0.021 μM. Liu et al. [76] reported a fluorometric and colorimetric dual-signal sensor for glucose detection based on Au@Ag NPs and C-dots. C-dots were synthesized by heating citric acid and ethylene diamine at 180 °C for 6 h using a typical hydrothermal method. As shown in Fig. 4, Au@Ag NPs were obtained through a reaction with $AgNO_3$ and Au NP by the reduction of $HAuCl_4 \cdot 3H_2O$ by sodium citrate. When Au@Ag NPs are mixed with C-dots through a hydrothermal method, the C-dots become energy donors and the fluorescence is quenched using Au@Ag NPs, which have silver shells as acceptors. Glucose is oxidized into gluconic acid through the enzyme oxidation of glucose oxidase (GOx), and the silver shells (Ag^0) become Ag^+. In addition, oxygen generates H_2O_2, and the fluorescence of the C-dots is consequently recovered. At this time, the color of the Au@Ag NPs changes from orange-yellow to pink. In the glucose oxidation process, the dual-signal fluorescence recovery and color-change serve as a fluorometric and colorimetric dual-signal sensor for glucose sensing.

The fluorescence of C-dots gradually increases as the glucose concentration increases from 0.5 to 1000 μM. There is a linear relationship within the concentration range of 2.0–400 μM, with an LOD of 0.67 μM. In the GOx-mediated enzymatic reaction process of glucose, the absorbance at 405 nm changes from orange-yellow to pink along with an increase in glucose concentration. The fluorescence intensity (A/A_0) and glucose concentration have a relatively linear relationship within the range of 0.50–300 μM, and the LOD is 0.20 μM.

Pyrophosphate ions ($P_2O_7^{4-}$, PPi) are a critical biological metabolite involved in biochemical reactions such as ATP hydrolysis and DNQ polymerization. The quantitative analyses of PPi for disease diagnosis, such as chondrocalcinosis or calcium pyrophosphate dihydrate (CPPD) crystal deposition, are important research themes. Liu et al. [77] pyrolyzed citric acid to generate N and S co-doped graphene quantum dots (N-S/GQDs), which can assemble Fe^{3+} on the surface, and were used as an AA detection probe regarding the phenomenon of quenching the fluorescence of N-S/GQD based on the electron transfer effect of Fe^{3+}. If PPi is added to N-S/GQDs including Fe^{3+}, the fluorescence is switched on and PPi can be detected. The fluorescence and PPi concentration have a strong linear relationship within the range of 1–1000 μM, and the LOD is 0.81 μM. Notable results are shown in Table 2, which compares the reported techniques on the detection of glucose and pyrophosphate ions (Table 2).

Dopamine (3, 4-dihydroxyphenylethylamine, DA) is a neurotransmitter found in the central nervous system of various animals. If a problem with dopamine secretion control occurs, various types of disorders such as schizophrenia or Parkinson's disease. There has been a large amount of relevant research concerned with the importance of dopamine quantification and detection [83, 84]. Qu et al. [83] synthesized blue-luminescent GQDs that have a high sensitivity and selectivity to DA. Their research made use of the principle in which dopamine is oxidized well into quinine, and the oxidized quinine has an interaction with GQDs, quenching the fluorescence. The synthesized GQDs show a strong fluorescence without DA. The hydroxyl or carboxyl group in the GQD surface is able to interact non-covalently through electrostatic interactions with diol, the amine functional group, and the phenyl group of DA, through **π-π** stacking and hydrogen bonding. Under alkaline conditions, DA absorbs electrons from photoexcited GQDs and becomes oxidized into dopamine–quinine, thereby quenching the fluorescence. The fluorescence intensity ratio and DA concentration have a good linear relationship within a DA concentration range of 0.25–50.0, with an LOD of 0.09 μM.

III. CONCLUSION

In this review, biosensors used to detect various biomaterials such as DNA, cysteine, ascorbic acid, glucose, and dopamine with GQDs and CQDs as sensor platforms were summarized. GQDs and CQDs have potential as biosensor and bioimaging agent replacements because they have multiple relevant properties, such as a high surface area, excellent physical structure, and unique optical properties, which make them suitable for biological applications. Furthermore, GQDs have crystalline nanostructures with layers of graphene, and are synthesized from graphene-like structural substances such as CNTs and polycyclic aromatic hydrocarbons, or from grapheme-based precursors. In addition, CQDs, which have spherical shapes, are amorphous carbon particles mixed with sp^2, and with a size of less than 15 nm. CQDs can be synthesized using methods such as the electrochemical exfoliation of carbon fibers, chemical oxidative treatment, and the pyrolysis of organic precursors.

The unique properties of GQDs and CQDs are applicable

to sensor biomaterials. Although these carbon nanomaterials have drawn significant attention as possible biomaterial sensor candidates, it is necessary to conduct further research on CQDs and GQDs applied as FRET nanosensors in the detection of biomaterials. In fact, research on FRET nanoquenchers remains in the initial stages, and many researchers are involved in the development of ever-improving biosensors using these carbon nanomaterials (GQDs and CQDs).

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