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REVIEW

Application of Graphene and Graphene Oxide for modification of electrochemical sensors and biosensors: A review

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Abstract

This paper gives a comprehensive review about the most recent progress in graphene and graphene oxide based electrochemical sensors and biosensors. Graphene, emerging as a true 2-dimensional material, has received increasing attention due to its unique physicochemical properties (high surface area, excellent conductivity, high mechanical strength, and ease of functionalization and mass production). The application of graphene and graphene oxide in the modification processes leads to improved sensitivity, electrocatalytic behavior, and reduced fouling. The development of graphene and graphene oxide based sensors in biosensing and detection of chemicals have been resulted in great achievements towards more sensitive health care instruments and preventing the environmental problems. To facilitate further research and development, the technical challenges are discussed, and several future research directions are also suggested in this paper.

Keywords: *Biosensors; Electrochemistry; Graphene Oxide; Graphene; Modified Electrodes; Sensors.*

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INTRODUCTION

Graphene, as one of advanced carbon nanomaterials, is a 2-dimensional single sheet of carbon atoms arranged in a hexagonal network. Graphene is the basic building block for graphitic materials of all other dimensionalities (0D fullerenes, 1D nanotubes, and 3D graphite) [1, 2]; Functionalized graphene produced through reduction of graphene oxide displays a wrinkled structure due to the presence of lattice defects and this is different than the rippled structure observed in pristine graphene shows in (Fig. 1a) [3], (Fig. 1b) relates to a low magnification TEM image of graphene nanosheets [4]. The folded regions of the sheets (Fig. 1c) were found to have average widths of 2 nm by high-resolution SEM. [3-5].

It was discovered in 2004 through a process of scotch tape peeling. Graphene has attracted strong scientific and technological interest in recent years. It has shown great promise in many applications, such as electronics [6, 7], energy storage and conversion (supercapacitors [8], batteries [9, 10], fuel cells [11-15], solar cells [16, 17], and bioscience/biotechnologies [18-23] because of its unique physicochemical properties: high surface area (theoretically 2630 m^2/g for single layer graphene), excellent thermal conductivity and electric conductivity and strong mechanical strength. Many methods have been developed to produce graphene [24, 25]. In 2004, Geim and coworkers [26] first reported graphene sheets prepared by mechanical exfoliation (repeated peeling) of highly oriented pyrolytic graphite. This method, which is called scotch tape method, is still widely used in many laboratories to obtain pristine perfect structured graphene layer(s) for basic scientific research and for making proof of concept devices. However, it is not suitable for mass production. The other method for producing defect free/defect less graphene is the mild

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exfoliation of graphite [27, 28], but the yield so far is very low [28]. Graphene has also been prepared by thermal decomposition of SiC wafer under ultrahigh vacuum (UHV) conditions or by Chemical vapor deposition (CVD) growth on metal substrates (ruthenium, Ni and Cu) or by substrate free CVD. This is a potential mass production method with the aim of producing graphene for electronics applications [29-33]. Another mass production method is chemical or thermal reduction of graphite oxide (GO). It is also considered to be the most economical way to produce graphene. Most of graphene used in electrochemistry are produced with the last method of GO reduction. Graphene from GO reduction, which is also called functionalized graphene sheets or chemically reduced graphene oxide, usually has abundant structural defects and functional groups which are advantageous for electrochemical applications. In addition, graphene can also be prepared at a larger scale by liquid phase exfoliation to form a graphene oxide (GO) intermediate, followed by reduction to restore the graphene structure (rGO). However, it has been found that the combination of sheet defects, poor dispersion, restacking and multilayer thickness can prevent the full realization of graphenes' electronic and high surface area properties [34-40]. In addition, the advanced properties of rGO make it an interesting candidate for many applications. In this review, we investigate the latest progress in modification of electrodes by graphene and graphene oxid as one of the modifiers and its improvement in detection of different analytes.

GRAPHENE OR GRAPHENE OXIDE MODIFIED ELECTRODES FOR HEAVY METALS

In a small quantity, certain heavy metals, such as manganese, copper and so on, are nutritionally essential for a healthy life. Toxic heavy metal ions are well known to be severely harmful to human health. Therefore, the development of fast and sensitive methods for their detection has drawn a great attention in recent years. It had been reported that an electrochemical sensor for detection of Tl^{+}, Pb^{2+} and Hg^{2+} was described by Bagheri and coworkers. They fabricated a composite using graphene, 1-noctylpyridinum hexa fluorophosphate (OPFP), and [2, 4-$C_{l2}C_6H_3C$ (O) $CHPPh_3$] (L) for modification electrode. The physicochemical and electrochemical characterizations of fabricated sensor were investigated in details. The advantages of the proposed composite electrode are its ability in

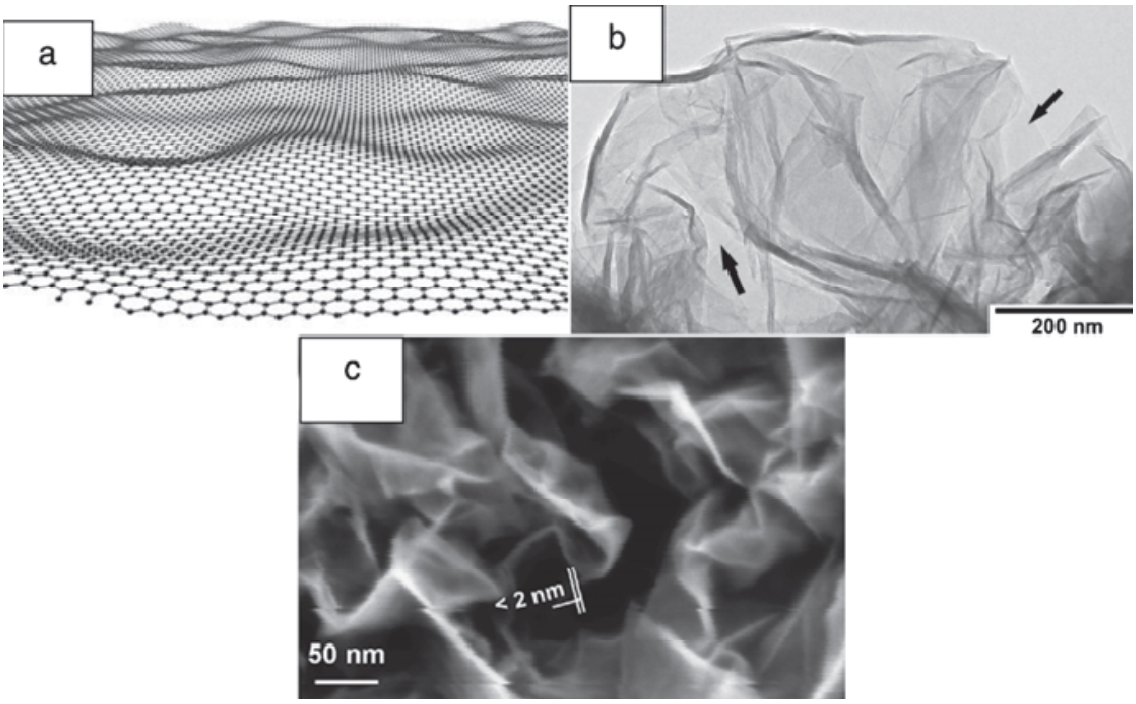

Fig. 1. (a) Structural model of pristine graphene [3], (b) TEM image of graphene [4], and (c) SEM image of graphene. Graphene in (b) and (c) are produced from chemical reduction of graphene oxide [3-5].

simultaneous electrochemical detection of Tl^{+}, Pb^{2+} and Hg^{2+} and no need for separating of the three species from complex mixtures prior to electrochemical measurements. Finally, the proposed electrochemical sensor was applied to detect trace analyte ions in various water and soil samples with satisfactory results [41].

Glassy carbon electrode (GCE) modified with L-cysteine and gold nanoparticles, reduced graphene oxide (AuNPs-RGO) composite was fabricated as an electrochemical sensor for the determination of Cu^{2+} (Fig. 2). The AuNPs-RGO composite was formed on GCE surface by electrodeposition. The L-cysteine was decorated on AuNPs by self-assembly. Experimental conditions, including electrodeposition cycle, self-assembly time, electrolyte pH and preconcentration time were studied and optimized. Stripping signals obtained from L-cysteine/ AuNPs-RGO/GCE exhibited good linear relationship with Cu^{2+} concentrations in the range from 2 to 60 mgL^{-1}, with a detection limit of 0.037 mgL^{-1}. Finally, the prepared electrode was applied for the determination of Cu^{2+} in soil samples, and the results were in agreement with those obtained by inductively coupled plasma mass spectrometry [42].

Another study focused on the determination of thallium content in grain product samples collected from a commercial brand commonly available in Poland. The samples were analyzed with the use of differential pulse anodic stripping voltammetry (DPASV) with graphene oxide based on GCE. The proposed method was successfully applied for the determination of thallium ions in samples of actual grain products. The obtained results confirmed that thallium was present in the studied cereal samples (average content at 0.0268 ± 0.0798mg/kg). Thallium has a half-life of 60 days; therefore, the consumption of foods with thallium content of approximately 0.08 mg/kg has the potential for harmful bioaccumulation in the body. Thallium contamination in cereal products should be a critical parameter for health environmental regulations [43].

The development of graphene/polyaniline/ polystyrene (G/PANI/PS) nanoporous fiber modified SPCE using electrospinning fabrication for simultaneous determination of lead (Pb^{2+}) and cadmium (Cd^{2+}) was achieved. Due to the increase of specific surface area of the electrospun G/ PANI/PS nanoporous fibers, the electrochemical sensitivity of modified SPCE was enhanced by a factor of three compared to an unmodified SPCE. In terms of application, square-wave anodic stripping voltammetry (SWASV) was employed for the simultaneous determination of Pb^{2+} and Cd^{2+} in the presence of bismuth (Bi^{3+}) on G/PANI/PS nanoporous fiber-modified SPCE. Finally, this new electrode system was successfully applied for the simultaneous determination of Pb^{2+} and Cd^{2+} in real river water samples, and the results correlated well with conventional inductively coupled plasma optical emission spectroscopy (ICP-OES) [44].

Tseliou and coworker reported the used of low dimensional Bi_2Te_3- GO hybrid films as electrode's

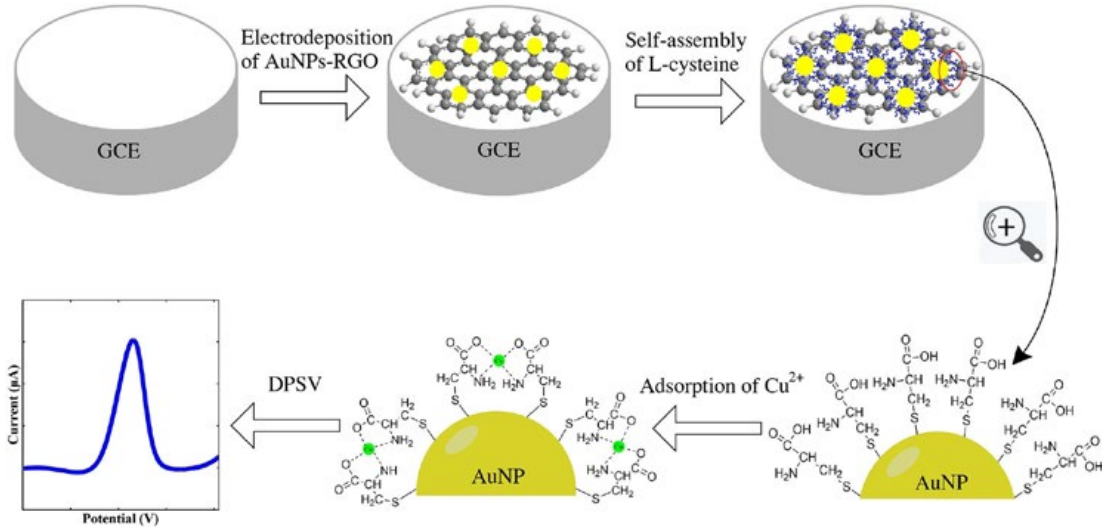

Fig. 2. Illustration of fabrication of the sensor and the measurement of Cu^{2+}.

modifiers for the ultra-sensitive determination of Pb (II) and Cd (II) ions in the sub microgram-per-liter level by using anodic stripping voltammetry. Bulk Bi_2Te_3 was exfoliated by applying an easy-to-perform, sonication-assisted liquid exfoliation method in a triple blend of 1+3+4 v/v 1-cyclohexyl-2-pyrrolidone, acetone and water. Compared with the bulk Bi_2Te_3/GO hybrid film modified GCE, exfoliated Bi_2Te_3/GO hybrid film-modified GCE exhibited remarkably enhanced detection capabilities and limits of detection (S/N=3) as low as 0.1 μgL^{-1} Pb and 0.2 μgL^{-1} Cd. This work provides new data on the facile preparation of stable dispersions of Bi_2Te_3 and Bi_2Te_3/GO composites, which could be easily cast into films offering highly sensitive sensors [45].

A sensitive electrochemical platform for the simultaneous determination of Cd^{2+}, Pb^{2+}, Cu^{2+}, and Hg^{2+} had been constructed based on N-doped graphene (NG) modified electrode using differential pulse stripping voltammetry by Xing et al. NG was synthesized by a facile, efficient and green electrochemical method. The NG modified electrode showed excellent catalytic activity for selective detection of Cd^{2+}, Pb^{2+}, Cu^{2+}, and Hg^{2+} due to its particular structure and unique electronic properties. Under optimal conditions, the limits of detection were estimated to be 0.05 µM for Cd^{2+} and Hg^{2+}, 0.005 µM for Pb^{2+} and Cu^{2+}, respectively. Finally, the method was applied to the simultaneous detection of trace metal ions in the tap water samples [46].

L-cysteine/graphene-carbon monosulfide/GCE (L-26 cys/GR-CS/GCE) was prepared by Zhou and coworker. The electrochemical behaviors of Cd^{2+} and Pb^{2+} on the proposed electrode were studied by differential pulse anodic stripping voltammetry (DPASV). Experimental parameters, such as the deposition potential and time, the pH value of buffer solution, were optimized. Under the optimized conditions, the linear equations of the DPASV response current with Cd^{2+} and Pb^{2+} concentration were I (µA) = 0.745C (µg/L) +4.539 (R=0.9986), I (µA) = 0.437C (µg/L) + 2.842 (R=0.9983), respectively, and the detection limits were 0.45 µg/L and 0.12 µg/L, respectively [47].

Simultaneous determination of Cd^{2+} and Pb^{2+} was achieved by using graphene oxide/κ-carrageenan/L-cysteine (GO/κ-Car/L-cys) nanocomposite modified GCE by SWASV. Under optimum conditions, outstanding linearity was obtained for both Cd^{2+} and Pb^{2+} in the range from 5-50 nM with the detection limits as 0.58 nM and 1.08 nM respectively. The sensitivity calculated from the slope of calibration curve was 1.39 µA/nM and 1.32 µA/nM for Cd^{2+} and Pb^{2+} respectively. The modified electrode has been applied to the detection of Cd^{2+} and Pb^{2+} present in water and milk samples, and the accessed results were satisfactory with that of AAS [48].

GRAPHENE OR GRAPHENE OXIDE MODIFIED ELECTRODES FOR BIO-SENSING APPLICATIONS

Graphene or graphene oxide is a two dimensional lattice of carbon in a honeycomb pattern which has attracted attention to a great extent as an efficient modifier in electrochemical chemistry due to its unique properties and ease of production on a large scale. In general, graphene is a nonpolar and hydrophobic modifier with a large delocalized π-electron system which can make strong π-π stacking interactions with the benzene rings. In this regard, graphene has been applied as a modifier for electrochemical determination of various analytes in biological and aqueous samples. Beitollahi and coworkers introduced a method to determine methyldopa without the interference of phenylephrine and guaifenesin. For this purpose, a carbon paste electrode (CPE) was modified with graphene and ethyl 2-(4-ferrocenyl [1, 2, 3] triazol-1-yl) acetate. This modified electrode demonstrated two linear ranges of 0.4-30.0 µM and 30.0-500.0 µM with a detection limit of 0.08 µM. No change was observed in the sensitivity of the modified electrode towards methyldopa in the presence of phenylephrine and guaifenesin, which enables the simultaneous or independent measurement of the three moieties. The efficiency of the proposed modified electrode was evaluated through the determination of these substances in real samples [49].

An electrochemical sensor was developed by Chen and coworkers for detection of dopamine (DA) based on the use of a GCE modified with NP-PtY alloy and graphene. The sensor, best operated at 0.16 V vs. SCE, has a linear range covering the 0.9 to 82 µM concentration range, a 0.36 µM detection limit (at S/N = 3), and good selectivity over tyramine, tryptamine, phenethylamine, uric acid, and ascorbic acid. It gave satisfactory results in the determination of DA in spiked samples of urine [50].

Rauf and coworkers developed for the first time a carboxylic group riched GO based disposable

electrochemical immunosensor for cancer biomarker detection using methylene blue (MB). The developed immunosensor for detection of biomarker mucin1 (MUC1) is in human serum samples. In this method, they explored highly conductive surface of carboxylic group (-COOH-) rich GO on screen-printed carbon electrodes (SPCE). This modified GO-COOH-SPCE was employed for the detection of MUC1 protein based on the reaction with methylene blue (MB) redox probe using differential pulse voltammetry (DPV) technique (Fig. 3). Analytical performance of the developed immunosensor assures the applicability in clinical diagnostic applications [51].

In the other work, GCE surface was modified by drop-coating GO and nile blue (NB) to form GO/NB/GCE. By using one-step coreduction treatment under cyclic voltammetry (CV) scanning, gold nanoparticles (AuNPs) were electrodeposited onto GO/NB/GCE surface, simultaneously generating reduced GO (rGO). AuNPs from the prepared rGO/NB/AuNPs/GCE was combined with 5´-SH-terminated aptamer of DA via Au-S coupling to fabricate aptamer-rGO/NB/AuNPs/GCE system. DA specifically combined with its aptamer modified on rGO/NB/AuNPs/GCE surface (Fig. 4). This aptasensor efficiently determined DA in real biological samples, together with high detection recoveries of 97.0-104.0% [52].

An electrochemical sensor was presented for the simultaneous determination of hydroquinone (HQ) and catechol (CT) in the water based on copper centered metal organic framework-graphene composites (Cu-MOF-GN) [Cu-MOF = Cu_3 (BTC) $_2$ (BTC=1, 3, 5- benzene tricarboxylic acid)] modified GCE (Cu-MOF-GN/GCE). The modification procedure was carried out through casting metal organic framework graphene oxide composites (Cu-MOF-GO) on the bare GCE and followed by the transformation of Cu-MOF-GO to Cu-MOF-GN by an electrochemical reduction. The electrochemical behavior of HQ and CT at Cu-MOF-GN/GCE was investigated by CV and DPV. Under the optimized conditions, the modified electrode had excellent electrocatalytic activity and high selectivity toward HQ and CT. The electrochemical sensor exhibited a linear response in the same range of 1.0×10^{-6} to 1.0×10^{-3} M with the detection limits of 5.9×10^{-7} M for HQ and 3.3×10^{-7} M for CT (S/N = 3) [53].

In the other researched, a biosensor was produced from a carbonized hybrid gold (Au)/graphene (G) nanowire fabricated upon a disposable SPCE in order to amplify signals. The processes of carbonization and electrospinning were merged in order to determine DA in a selective and sensitive manner when it was present in uric acid or ascorbic acid [54].

In the study by Arvand and coworkers, they aim to design an electrochemical DNA biosensor based

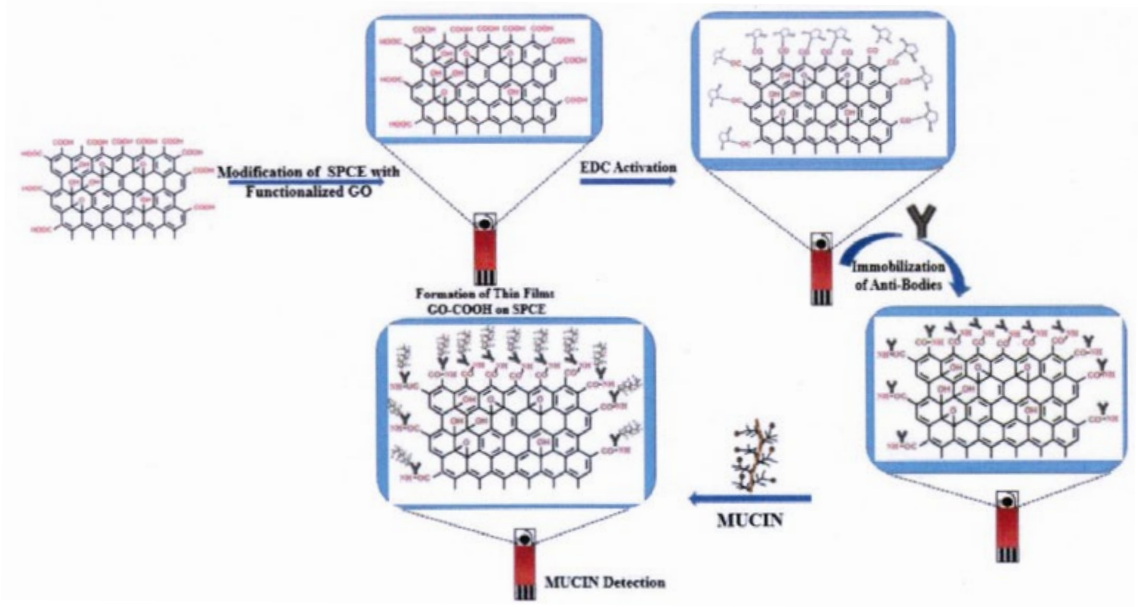

Fig. 3. Schematic illustration of the immobilization of MUC1 antibody 165 on GO-COOH 166 modified SPCE for electrochemical detection.

on a CPE modified with ds-DNA/poly(L-cysteine)/Fe_3O_4 nanoparticles graphene oxide (ds-DNA/p(L-Cys)/Fe_3O_4 NPs-GO/CPE) for sensitive detection of adenine and guanine (Fig. 5). The electrocatalytic oxidation of A and G on the electrode was explored by DPV and CV. This sensor showed separated and well defined peaks for A and G, by which one could determine these biological bases individually or simultaneously. The ds-DNA/p(L-Cys)/Fe_3O_4 NPs-GO/CPE exhibited an increase in peak currents and the electron transfer kinetics and decrease in the overpotential for the oxidation reaction of A and G [55].

An electrochemical MIP sensor for salbutamol detection based on a graphene nanocomposite modified SPE was successfully demonstrated. Insertion of the Composite films of graphene and polystyrene sulfonate doped poly (3, 4-ethylenedioxythiophene) graphene/ PEDOT-PSS layer prior to the MIP was aimed at enhancing the sensitivity of the sensor. Selection of a functional monomer was carried out using 1H-NMR titration and a computational calculation was used to further investigate the template monomer

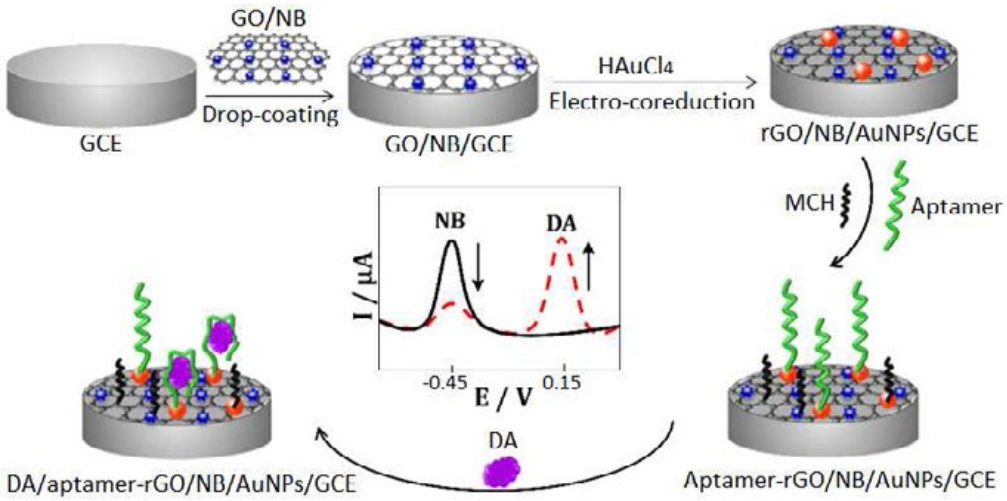

Fig. 4. Schematic illustration of the fabrication procedures of rGO/NB/AuNPs/GCE-based REAS of DA.

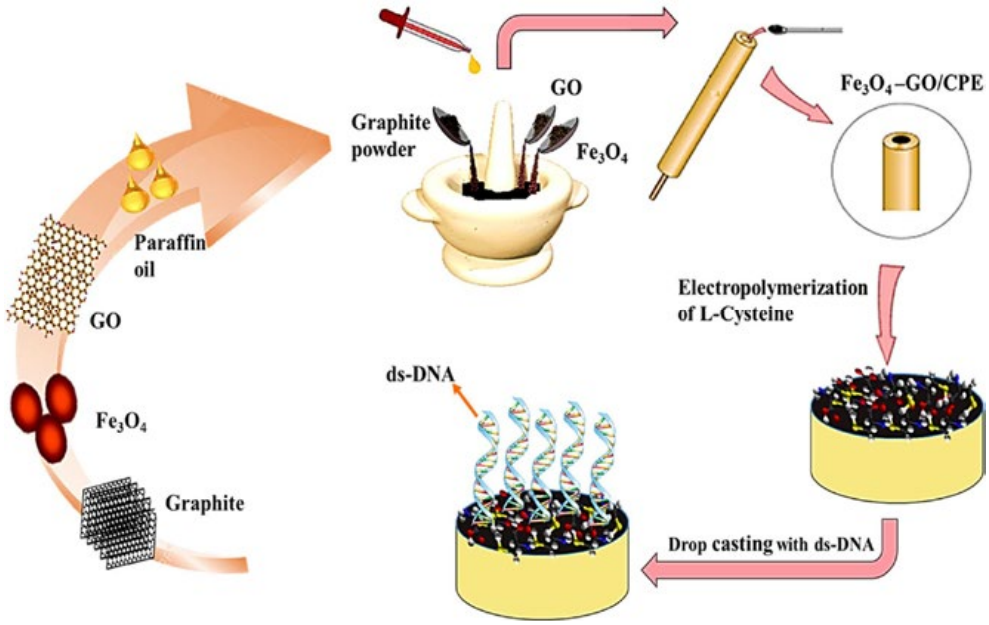

Fig. 5. Schematic representation for the fabrication process of the ds-DNA/p (L-Cys)/Fe_3O_4 NPs-GO/CPE.

interactions. The MIP layer was constructed on top of the highly conductive nanocomposite by co electropolymerization of 3-aminophenylboronic acid and o-phenylene diamine in the presence of salbutamol. Using DPV under optimal conditions, a linear response in the range of 1 nM to 1.2 mM, with an exceptional detection limit of 100 pM was obtained [56].

The graphene quantum dots (GQDs) were prepared by tuning the carbonization degree of citric acid and graphite screen-printed electrode modified with graphene quantum dots (GQDs/ SPE) was constructed by Dourandish and Beitollahi for voltammetric determination of isoproterenol. In comparison with unmodified electrode, the presence of the GQD/ SPE resulted in a remarkable increase in the peak currents. The electrochemical response characteristics of the modified electrode toward isoproterenol were studied by means of CV and DPV. The (GQDs/SPE) displays a linear range from 1.0 to 900.0 µM and a detection limit of 0.6 µM (S/N=3) to isoproterenol [57].

In the other research a three dimensional graphene (3DGR) was synthesized by electrodeposition directly on carbon ionic liquid electrode (CILE) with N-butylpyridinium hexafluorophosphate. Nanosized Pt catalyst was further electrodeposited onto 3DGR/CILE with its properties investigated through electron microscopy and electrochemistry. Electrocatalytic performances of the modified electrode (Pt/3DGR/CILE) to methanol oxidation were investigated. Experimental results demonstrated that an enhanced efficiency of Pt/3DGR nanohybrid on the electrode surface for methanol oxidation with the enhancement of the ratio of forward to backward peak current (I_f/I_b), which was due to the large surface area of nanohybrid with 3D porous structure of GR and higher dispersion of Pt nanoparticles onto the electrode surface [58].

Fe_3O_4@SiO_2/GO nanocomposite was synthesized and used for surface modification of GCE. This modified electrode was used for electrochemical determination of methyldopa (MD) in the presence of uric acid (UA). Operational parameters such as amount of solution pH and scan rate which affected the analytical performance of the modified electrode were optimized. The calibration curve for MD was linear in the range of 0.1-400.0 µM with the detection limit (S/N=3) of 86.0 nM. The modified electrode was successfully applied for the determination of MD and UA in some real samples [59].

The interaction between amsacrine and double stranded deoxyribonucleic acid (ds-DNA) was studied by a graphene paste electrode (GPE) and incubation solution using DPV. A simple and sensitive biosensor was made using the mentioned interaction for determining amsacrine. DPV shows a linear dynamic range from 7.0×10^{-7} to 1.0×10^{-4} M for amsacrine. The use of this screening method for analyzing real sample was studied with applying the proposed method to determine amsacrine in urine and blood serum. Generally, the findings indicated a DNA sensor with the ability to analyze the amsacrine in real samples effectively [60].

Castro and coworker investigated the electrochemical behavior of reduced rGO of different sizes deposited on GCE. Graphene oxide sheets were produced by the exfoliation of graphite oxide in an aqueous solution by ultrasonication. Scanning electron microscopy and transmission mode scanning electron microscopy results indicated a decrease in the size of the graphene oxide sheets with an increase in the exfoliation time or sonication power. The results of spectroscopic characterization corroborated with this behavior. X-ray diffraction analysis indicated a broadening of the peaks with crystallite size reduction while Raman spectroscopy results suggested an increase in the structural defects in the sp^2 framework of graphene oxide. Complementary X-ray photoemission spectroscopy analysis indicated a decrease in the sp^2/sp^3 ratio with respect to the amount of sp^2 framework in graphene oxide sheets upon decreasing the sheet size. Electrochemical analysis showed that the response of the GO modified GCE increased significantly with a decrease in the graphene oxide sheet size [61].

Li and coworkers utilized an electroanalytical method for the detection of bergenin in phosphate buffer solution (pH 5.0) with a graphene and chitosan nanocomposite modified GCE. Characterization of CS-GR/GCE was carried out by electrochemical impedance spectroscopy. Electrocatalytic oxidation of bergenin on CS-GR/ GCE was greatly enhanced with the improvement of the anodic peak current, which allowed the development of a voltammetric sensor for bergenin determination. Under the optimized conditions with DPV, the anodic peak responses enhanced linearly with bergenin concentration from 2.0×10^{-8} mol/L to 8.0×10^{-6} mol/L with the detection limit of 3.6 nmol/L (3σ). The analytical application of this

sensor was successfully proved by the Tabellae bergenin composite sample detection [62].

In the other studied Ganjali and coworkers introduced a modification for the surface of SPE by graphene quantum dot (GQD) in order to be used in the determination and detection of theophylline. An uncomplicated technique was employed to stabilize GQD on SPE. Function evaluation of the GQD modified SPE (GQD/SPE) by CV revealed enhanced electroactivity in the oxidation of theophylline in buffer solution of phosphate. A wide linear concentration range of 1.0-700.0 µM and detection limit of 0.2 µM (S/N = 3) obtained under optimized conditions. This sensor was successful in the assessment of theophylline in real samples [63].

In the other research, a 3D porous graphene carbon nanotube (G-CNT) network was successfully constructed on the surface of GCE by electrochemical codeposition from concentrated graphene dispersion. The large accessible surface area provided by the interpenetrated graphene backbone in one hand and the enhanced electrical conductivity of the 3D network by incorporating CNTs on the other hand, dramatically improved the electrochemical performance of GCE in determination of methotrexate (MTX) as an important electroactive drug compound. Under the optimum conditions, the electrode modification led to a significant increase in the anodic peak current (~25 times) along with a considerable shift in the peak potential (~111 mV) [64].

In the other work a bare composite graphite polyurethane electrode (EGPU) and two other modified with graphene (EGPU-GR) and functionalized multi-walled carbon nanotubes (EGPU-CNTs) were prepared and compared regarding their voltammetric response to escitalopran (EST). The modifiers were characterized by Raman spectroscopy and the resulting electrode materials by contact angle measurement with a hydrophilicity character in the ascending order for the composites: GPU > GPU-GR > GPU-CNTs and scanning electron microscopy (SEM). The electroactive areas of the EGPU, EGPU-GR, and EGPU-CNTs were 0.065, 0.080, and 0.092 cm^2, respectively, calculated from the chronocoulometry using K_3 [$Fe(CN)_6$] as a probe and the Cottrell equation. The cyclic voltammograms obtained for EST indicated irreversible electrochemical behavior, with an anodic peak at ca. +0.80 V (*vs.* SCE) [65].

Benzoylferrocene was used to construct a modified graphene paste electrode. Also, hydrophilic ionic liquid (n-hexyl-3-methylimidazolium hexafluoro phosphate) was used as a binder to prepare the modified electrode. The electro oxidation of sulfite at the surface of the modified electrode was studied using electrochemical approaches. This modified electrode offers a considerable improvement in voltammetric sensitivity toward sulfite, compared to the bare electrode. Square wave voltammetry (SWV) exhibited a linear dynamic range from 5.0×10^{-8} to 2.5×10^{-4} M and detection limit of 20.0 nM for sulfite [66].

A ferrocene derivative compound, 2-chlorobenzoyl ferrocene, was synthesized and used to construct a modified graphene oxide sheet paste electrode. The electro oxidation of hydrochlorothiazide at the surface of the modified electrode was studied. Under optimized conditions, the SWV peak current of hydrochlorothiazide increased linearly with hydrochlorothiazide concentration in the range of 5.0×10^{-8} to 2.0×10^{-4} M and a detection limit of 20.0 nM was obtained for hydrochlorothiazide. The prepared modified electrode exhibited a very good resolution between the voltammetric peaks of hydrochlorothiazide and folic acid which maked it suitable for the detection of hydrochlorothiazide in the presence of folic acid in real samples [67].

Beitollahi and coworker developed an electrochemical CPE modified with graphene and ethyl 2-(4-ferrocenyl-[1, 2, 3] triazol-1- l) acetate (EFTA) (EFTAG-CPE) for concurrent determination of isoproterenol, acetaminophen, tryptophan and theophylline. The electrode was found to offer outstanding electrocatalytic activities in the oxidations of the different analytes in phosphate buffer solution (pH=7.0) providing well resolved oxidation peaks with significant differences, i.e. 0.190 V between isoproterenol and acetaminophen, 0.510 V between isoproterenol and tryptophan, and 0.750 V between isoproterenol and theophylline [68].

In the other research, GO was explored and electrochemically characterized using a range of electrochemical redox probes, namely potassium ferrocyanide (II), N,N,N´,N´-tetramethyl-p-phenylenediamine (TMPD), dopamine hydrochloride and epinephrine. Furthermore, the electroanalytical efficacy of GO was explored towards the sensing of dopamine hydrochloride and epinephrine via

cyclic voltammetry. The electrochemical response of GO was benchmarked against pristine graphene and edge plane-/basal plane pyrolytic graphite (EPPG and BPPG respectively) alternatives, where the GO shows an enhanced electrochemical/ electroanalytical response. When using GO as an electrode material, the electrochemical response of the analytes studied herein deviate from that expected and exhibit altered electrochemical responses [69].

Chaiyo and coworker introduced analytical device for the non-enzymatic detection of glucose by modifying a SPE with cobalt phthalocyanine, graphene and an ionic liquid (CoPc/ G/IL/ SPCE). The disposable devices showed excellent conductivity and fast electron transfer kinetics. The results demonstrated that the modified electrode had excellent electrocatalytic activity towards the oxidation of glucose with NaOH as supporting electrolyte (0.1 M). The oxidation potential of glucose was negatively shifted to 0.64 V vs. the screen-printed carbon pseudo-reference electrode (Fig. 6) [70].

The nanocomposites of titanium dioxide nanoparticles decorated poly (diallyl dimethyl ammonium chloride) functionalized graphene (TiO_2-PDDA-Gr) were synthesized. By combining the merits of the PDDA-Gr and TiO_2 NPs, an electrochemical sensor was erected to detect esculetin based on the TiO_2-PDDA-Gr nanocomposites. Under the optimized conditions, a lower detection limit of 4×10^{-9} $molL^{-1}$ (S/N=3) and a wide linear detection range from 1×10^{-8} to 3.5×10^{-6} $molL^{-1}$ were achieved by DPV [71].

An electrochemical sensor for sensitive determination of ampyra (Am) based on graphene nanoribbons modified by iron-platinum bimetallic nanoparticles and uric acid (SPCE/FePtGNR/UA) dropped on the SPCE surface and magnetically captured onto an SPCE working electrode surface was reported by Hashemi and coworkers. Am determination by conventional electrochemical methods was not possible, because of it was high redox overpotential. Therefore, the DPV signals of UA were used as a redox probe for indirect electrochemical determination of Am. The limit of detection (LOD) and linear concentration range were obtained as 0.028 and 0.08-9.0 $\mu molL^{-1}$ ($3S_b$/ m=3), respectively [72].

In research by Kahlouche and coworkers, they demonstrated the benefit of electrophoretic deposition (EPD) of reduced graphene oxide/ poly ethylenimine (rGO/PEI) for the selective modification of a gold (Au) microelectrode in a microsystem comprising a Pt counter and a Ag/ AgCl reference electrode. The functionalized microsystem was successfully applied for the sensing of dopamine with a detection limit of 50 nM. Additionally, the microsystem exhibited good performance for the detection of dopamine levels in meat samples [73].

An electrochemical immunosensor for the simultaneous determination of ghrelin (GHRL) and peptide YY (PYY) using dual SPE modified with rGO was presented. Diazonium salt of 4-aminobenzoic acid (4-ABA) was electrochemically grafted on the modified electrodes allowing covalent immobilization of antibodies. After competitive immunoassays using alkaline phosphatase labelled antigens, the affinity reactions were monitored by DPV upon addition of 1-naphthyl phosphate. Calibration plots showed linear current vs. log [hormone] ranges from 10^{-3} to 100 ng/mL GHRL, and 10^{-4} to10 ng/mL PYY. The usefulness of dual

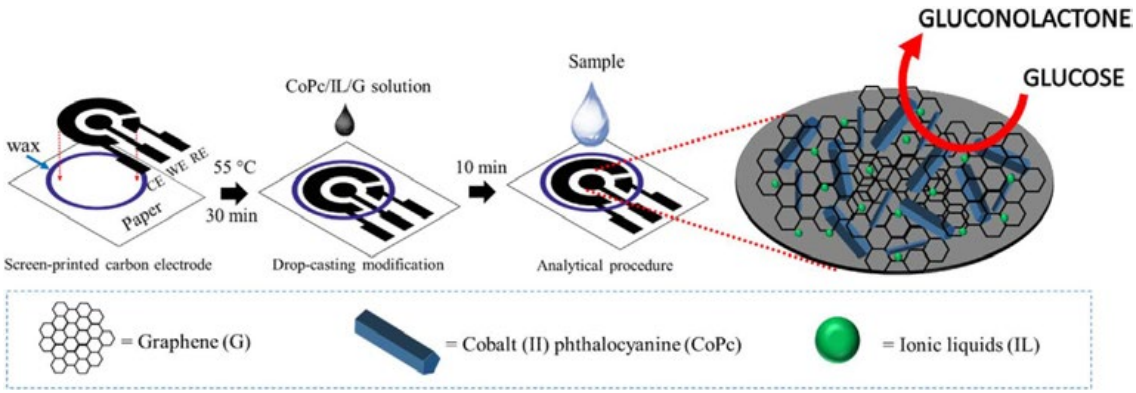

Fig. 6. Schematic representation of the fabrication, modification and analytical procedure for the glucose sensor based on the coupling of the CoPc/IL/G SPCE.

immunosensor was demonstrated by analysis of spiked human serum and saliva [74].

As an oral nonsteroidal antiestrogen drug, tamoxifen (TMX) has been widely utilized for the prevention and treatment of breast cancer. In the researched by Mahmoudi moghaddam and coworkers, using DPV, an electrochemical investigation of the interaction between TMX and salmon-sperm double-stranded DNA (ds-DNA) was conducted with a graphene paste electrode (GPE). A linear dynamic range between 8.0×10^{-7} and 8.5×10^{-5} M was exhibited by DPV for TMX. Finally this modified electrode was used for determination of TMX in TMX tablet, serum and urine samples [75].

A CPE that was chemically modified with 3-(4'-amino-3'-hydroxy-biphenyl- 4-yl)-acrylic acid (3, 4´-AA) was used as a selective electrochemical sensor for the detection of hydroxylamine. Under optimized concentration the electrocatalytic oxidation current peak for hydroxylamine increased linearly with concentration in the range of 0.025- 10.0 µM. The detection limits for hydroxylamine was 0.012 µM. Finally, the modified electrode was applied to detection hydroxylamine in water samples [76].

A CPE was modified with graphene and ethyl 2-(4-ferrocenyl-[1, 2, 3] triazol-1-yl) acetate (EFTA) and used for electrocatalytic oxidation of levodopa. Under optimum conditions and at pH 7.0, the oxidation of levodopa occurs at a potential about 280 mV (vs. Ag/AgCl) using SWV which was less positive than that of an unmodified CPE. The modified electrode could well resolve the voltammetric peaks of levodopa, acetaminophen and tyrosine. The peak current was linear in the 0.2 µM to 0.4 mM levodopa concentration range [77].

A nanosensing electrode was constructed with gold nanoparticles (AuNPs) and GR as modifiers and traditional stainless steel acupuncture needle (AN) as substrate electrode (GR/AuNPs/AN), which was applied to determination of rutin. The electrode modification process was achieved through stepwise electrodeposition of AuNPs and GR on AN surface. The morphology and characteristics of GR/AuNPs/AN were investigated by scanning electron microscopy and electrochemical techniques. This GR/AuNPs/AN was used to direct detection of rutin in tablet and human urine samples [78].

A graphene-tin oxide (G-SnO_2) nanocomposite was prepared via a facile hydrothermal route using graphene oxide and Sn precursor solution without addition of any surfactant. A homogeneous deposition of SnO_2 nanoparticles with an average particle size of 10 nm on the graphene was observed in the FESEM and HRTEM images. The G-SnO_2 nanocomposite was used to fabricate a modified electrode for the electrochemical detection of dopamine (DA) in the presence of ascorbic acid (AA). DPV showed a limit of detection (LOD) of 1 µM (S/N = 3) in the presence of AA [79].

The transducer of solid-state electrodes based on an epoxy-graphite composite was modified by two different methods, such as direct mixed and layer deposition of graphene (commercial and synthesized by electrochemical exfoliation of graphite). Voltammetric measurements, in presence of $[Fe(CN)_6]^{3-}$ as electroactive standard, determined a quasi-reversible electrochemical behavior under linear diffusion control. Electronic transference for modified and unmodified electrodes was compared. Solid-state electrode modified by inclusion of synthesized graphene showed a better electronic transference at electrode surface, due to the lower potential difference between anodic and cathodic peaks (ΔE = 125 mV) with respect to unmodified electrode (ΔE = 160 mV) [80].

Pruneanu and coworkers reported the preparation of gold electrodes modified with graphene-Au Ag (Au/Gr-Au Ag) or graphene-Au (Au/Gr-Au) composite materials as electrochemical sensors for dopamine detection. The response of the Au/Gr-Au Ag electrode to dopamine was linear within a 3×10^{-7}- 3×10^{-4} M concentration range, and the limit of detection was found to be 2.05×10^{-7} M (S/N = 3). In contrast, the Au/Gr-Au electrode exhibited a narrower linear range (10^{-5}-10^{-4} M) and a higher limit of detection (3.03×10^{-5} M) [81].

In the other research three-dimensional graphene (3D-GR) was directly formed on the surface of carbon ionic liquid electrode (CILE) by electrodeposition. By using 3D-GR/CILE as the substrate electrode, a new electrochemical biosensor was prepared by immobilization of hemoglobin (Hb) on the electrode surface with a chitosan film. Electrochemical investigation indicated that a pair of well-defined redox peaks appeared on cyclic voltammogram, indicating the realization of direct electron transfer of Hb with the underlying electrode. The result can be ascribed to the porous structure of 3D-GR with high conductivity and big surface area. Based on the electrochemical data, the electron transfer

coefficient (α) and the apparent heterogeneous electron transfer rate constant (k_s) were calculated to be 0.426 and 1.864 s^{-1}, respectively [82].

A ferrocene derivative compound, 1-(4-bromobenzyl)-4-ferrocenyl-1H-[1, 2, 3]-triazole (1, 4-BBFT) was synthesized and used to construct a modified graphene paste electrode by Tajik and coworkers. Also, hydrophilic ionic liquid (n-hexyl-3-methylimidazolium hexafluoro phosphate) was used as a binder to prepare the modified electrode. The electro-oxidation of isoproterenol at the surface of the modified electrode was studied. Under the optimized conditions, the square wave voltammetric peak current of isoproterenol increased linearly with isoproterenol concentration in the ranges of 6.0×10^{-8} to 7.0×10^{-4} $molL^{-1}$and detection limit of 12.0 $nmolL^{-1}$was obtained for isoproterenol. The diffusion coefficient and kinetic parameters (such aselectron transfer coefficient and the heterogeneous rate constant) for isoproterenol oxidation were also determined [83].

An electrochemical method was applied to prepare electrochemically reduced graphene oxide (ERGO). Compared with the bare GCE, ERGO modified GCE (ERGO/GCE) exhibits much high electrocatalytic activities toward the oxidation of dopamine (DA), ascorbic acid (AA) and uric acid (UA) with increasing of peak currents and decreasing of oxidation over potentials. DPV results show that DA, AA and UA could be detected selectively and sensitively at ERGO/GCE with peak-to-peak separation of 240 mV and 130 mV for AA-DA and DA-UA, respectively [84].

Zangh and coworkers explored and investigated the structure effect on rGO sheets modified enzyme electrode with glucose oxidase (GOD) by structure characterizations and electrochemical measurements. The rGO sheets with different defect density, layers, and oxygen concentration were chosen to modify enzyme electrode, and all modified enzyme electrode obtained excellent electrocatalytic activities and performances towards glucose. The abundant defects in rGO induce easy absorption of GOD. At low oxygen concentration, rGO sheets help to induce the direct electron transfer (DET) on electrode, and at higher oxygen concentration, reduction of H_2O_2 occurred instead of DET on the surface of electrode. When rGO modified enzyme electrode under the working model of H_2O_2 reduction, enlarge the oxygen functional group could lead the more absorption of GOD, resulting in the improvement of affinity and sensitivity to the biosensors [85].

Zeng and coworkers reported a label-free electrochemical immunosensor for sensitive and selective detection of tumor marker cytokeratin 19 fragment antigen 21-1 (CYFRA21-1). In their work, three-dimensional graphene @ gold nanoparticles (3D-G@Au) nanocomposite was modified on the GCE surface to enhance the conductivity of immunosensor. The anti-CYFRA21-1 captured and fixed on the modified GCE through the cross-linking of chitosan, glutaraldehyde and anti-CYFRA21-1. The DPV peak current change due to the specific interaction between anti-CYFRA21-1 and CYFRA21-1 on the modified electrode surface was utilized to detect CYFRA21-1. Under optimized conditions, the proposed electrochemical immunosensor was employed to detect CYFRA21-1 and exhibited a wide linear range of 0.25~800 $ng.mL^{-1}$ and low detection limit of 100 $pg.mL^{-1}$ (S/N=3). In addition, the recovery rates of serum samples were in the range from 95.2% to 108.7%. Therefore, it is expected that the proposed immunosensor based on a 3D-G@Au has great potential in clinical medical diagnosis of CYFRA21-1 [86].

An electrochemical sensor was developed for attomolar Hg^{2+} detection. Three single stranded DNA probes were rationally designed for detection of the target, which combined T-Hg^{2+}-T coordination chemistry and the characteristic of convenient modification of electrochemical signal indicator. Graphene and nano Au were successively electrodeposited on a GCE surface to improve the electrode conductivity and functionalize with the 10-mer thymine-rich DNA probe [87].

In the other work, an electrochemical biosensor was developed by electrodeposition of reduced graphene oxide quantum dots (RGOQDs) on GCE. The electrochemical behaviors of uric acid (UA), xanthine (X) and guanine (G) were studied on RGOQDs/GCE by DPV with a limit of detection of 0.024 μM, respectively. Then the electrochemical biosensor was used to evaluate the cytotoxicity of fluorene for MCF-7 cells based on the variation of G/X in MCF-7 cells solution. The result showed that fluorene exposed to MCF-7 cells at the concentration range of 0 to 0.05 mM could promote cell proliferation, the concentration above 0.05 mM exhibited inhibitory effect, which was verified by methyl-thiazolyl-tetrazolium (MTT) assay. The electrochemical biosensor

based on RGOQDs/GCE could be used not only for evaluation the cytotoxicity of PAHs, but also for detection the physiological process related to intracellular purine nucleotide metabolism [88].

Chen and coworkers immobilized DNA on a GCE modified with GO to develop an electrochemical sensor for determination of MTX. The adsorptive voltammetric behaviors of MTX on DNA sensor were investigated using DPV. The peak current response of guanine in DNA was used as a determination signal of MTX in acetate buffer solution pH 4.6. The method was applied to detect MTX in human blood serum and diluted urine samples with excellent recoveries of 97.4-102.5% [89].

The other study presented a graphene-gold nanoparticles screen-printed voltammetric sensor for the determination and quantification of rutin in pharmaceutics by means of SWV. In optimum conditions of SWV in acetate buffer solution of pH 5.0, the sensor allows the detection of rutin on a potential of 0.44 V vs. Ag/AgCl. The current of the anodic peak varies linearly with the rutin concentration ranging in the domain 0.1×10^{-6} to 15×10^{-6} M, with a detection limit of 1.1×10^{-8} M. The nanomaterials-based sensor was effectively used for the quantification of rutin in the pharmaceutical products [90].

Wang and coworker developed electrochemical sensor base on the nanohybrid of palladium-reduced graphene oxide modified with gold nanoparticles (Au/Pd/rGO) was established, which was prepared by electrodeposing Au nanoparticles on Pd/rGO modified on a GCE. Experiment results showed that the prepared Au/Pd/rGO nanohybrid exhibited excellent electrocatalytic activity toward the redox of acetaminophen (PA) and 4-aminophenol (4-AP) simultaneously [91].

An electrochemical quercetin (QR) sensor was described that was based on the use of magnetic reduced graphene oxide (MrGO) incorporated into a molecularly imprinted polymer (MIP) on the surface of a SPE. The procedures for MrGO-MIP preparation are described in (Fig. 7a). The MrGO consists of reduced graphene oxide (rGO), magnetite (Fe_3O_4) and silver nanoparticles (Ag). The analyte (QR) was electrostatically adsorbed on the surface of the MrGO. Finally, the MIP was deposited via in-situ polymerization. The electrode's schematic diagram with possible reduction mechanism for QR is shown in (Fig. 7b). Under optimal conditions, the modified electrode has a linear response in the 20 nM to 250 µM QR concentration range [92].

GO modified disposable pencil graphite electrodes (PGEs) were developed for miRNA detection by measuring the guanine oxidation signal. GO modified PGEs were used as solid phase to immobilize amino linked DNA probe and then the complementary target RNA sequence (miRNA-34a) was recognized. The optimization studied and detection of hybridization between miRNA-34a target and it was complementary DNA probe was performed by DPV. The selectivity of our assay was tested in the presence of non-complementary miRNA sequence [93].

GRAPHENE OR GRAPHENE OXIDE MODIFIED ELECTRODES FOR FOOD ANALYSIS

Bisphenol A (BPA) is a chemical used as precursor in the production of polycarbonate

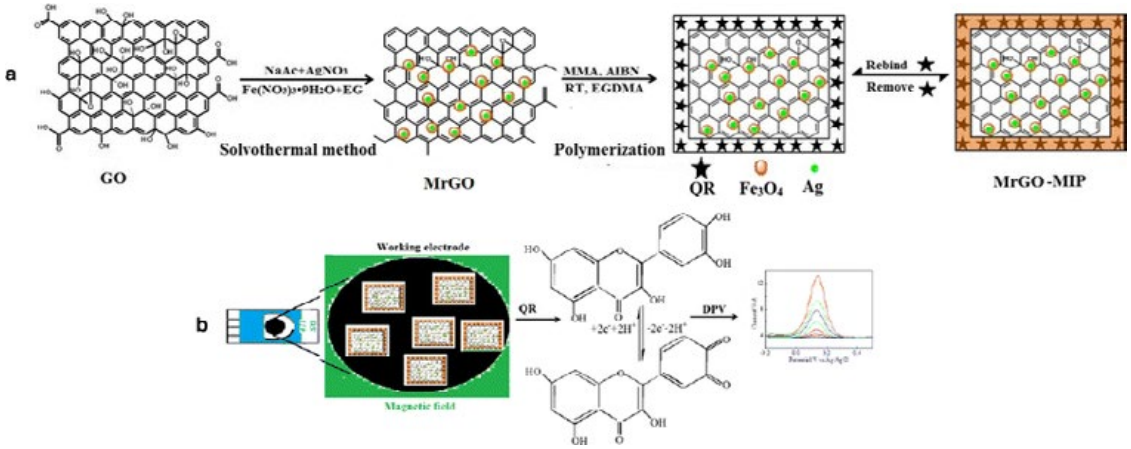

Fig. 7. Schematic illustration of the syntheses of MrGO-MIP composite (a) and the diagram of the electrode with possible reduction mechanism of QR (b) [92].

plastics and epoxy resins. Polycarbonate plastic has various applications in packaging industry including food and beverages packaging, water and infant bottles. Epoxy resins are found in inner coating of canned foods as lacquers. Concerns about the presence of BPA through the leaching into foods from drink bottles and canned foods have increased because of carcinogenic potential of this chemical. Therefore, different analytical methods have been developed for the improvement detection of BPA in real samples. A label-free electrochemical aptasensor for bisphenol A (BPA) determination was developed based on gold nanoparticles dotted graphene (GNPs/GR) nanocomposite film modified GCE. The electrochemical probe of ferricyanide was used to investigate the interactions between aptamer and BPA. The resulting GNPs/GR layer exhibited good current response for BPA detection. The aptasensor was applied successfully to determine BPA in milk products [94].

Nitrogen-doped graphene (NG)-polyvinylpyrrolidone (PVP)/ gold nanoparticles (AuNPs) modified SPE was prepared for the SWV determination of hydrazine. For electrode modification, NG-PVP nanocomposites were fabricated on SPE surface via electrospraying and then AuNPs were electrochemically deposited on top of NG-PVP nanocomposite layer. Due to the synergistic effect of NG-PVP and AuNPs, the modified SPE showed a 10-time increase in anodic peak current compared with an unmodified SPE, indicating the high sensitivity of the system. NG-PVP/AuNPs modified SPE was successfully developed and applied for the detection of hydrazine in high sugar fruit and vegetable samples [95].

CONCLUSION

The effectiveness of graphene and graphene oxide on the electrochemistry of modified electrodes in various applications have been demonstrated. The application of graphene and graphene oxide in the modification processes leads to improved sensitivity, electrocatalytic behavior, and reduced fouling. The development of graphene and graphene oxide based sensors in biosensing and detection of chemicals have been resulted in great achievements towards more sensitive health care instruments and preventing the environmental problems. This area or research is still open and growing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

ABBREVIATION

GO	Graphite Oxide
rGO	Reduced Graphene Oxide
GCE	Glassy Carbon Electrode
CPE	Carbon Paste Electrode
DA	Dopamine
SPCE	Screen-Printed Carbon Electrodes
DPV	Differential Pulse Voltammetry
CV	Cyclic Voltammetry
GR	Graphene
MIPs	Molecularly Imprinted Polymers
SWV	Square Wave Voltammetry
DPASV	Differential Pulse Anodic Stripping Voltammetry
CS	Carbon Monosulfide

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