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Research Article

Highly Sensitive Electrochemical Sensor for the Determination of 8-Hydroxy-2′-deoxyguanosine Incorporating SWCNTs-Nafion Composite Film

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8-Hydroxy-2′-deoxyguanosine (8-OHdG) is a typical biomarker of oxidative DNA damage and has attracted much attention in recent years since the level of 8-OHdG in body fluids is typically associated with various diseases. In this work, a simple and highly sensitive electrochemical sensor for the determination of 8-OHdG was fabricated incorporating single wall carbon nanotubes-(SWCNTs-) Nafion composite film coated on glassy carbon electrode. Nafion was chosen as an optimal adhesive agent from a series of adhesive agents and acted as a binder, enrichment, and exclusion film. Due to the strong cation-exchange ability of Nafion and the outstanding electronic properties of SWCNTs, the prepared SWCNTs-Nafion film can strongly enhance the electrochemical response to oxidation of 8-OHdG and efficiently alleviate the interferences from uric acid and ascorbic acid. The oxidation peak currents are linear with the concentration of 8-OHdG in the range of 0.03 to 1.25 μM with a detection limit of 8.0 nM (S/N = 3). This work demonstrates that SWCNTs-Nafion film can improve the sensitivity, selectivity, reproducibility, and stability, making it an ideal candidate for electrochemical detection of 8-OHdG.

1. Introduction

8-Hydroxy-2′-deoxyguanosine (8-OHdG), an oxidized form of the nucleoside 2′-deoxyguanosine (2′-dG), is well known as an important biomarker of oxidative DNA damage [1–3]. It is generated in the reaction between the eighth position of the guanine molecule of DNA and reactive oxygen species such as hydroxyl radicals, superoxide radicals, and hydrogen peroxide [2]. The level of 8-OHdG in body fluids is typically associated with the cancers [2, 4], diabetes [5, 6], aging [7], and neurological disorders [8, 9]. Nowadays, it also acts as a significant biomarker of genotoxicity [10, 11]. The development of analytical methods for the determination of 8-OHdG with simplicity, high sensitivity, and selectivity is of great importance in clinic tests.

The analytical methods for quantifying 8-OHdG have been developed, including high-performance liquid chromatography-electrochemical detection [12], high-performance liquid chromatography-electrochemical detection combined with solid-phase extraction [13, 14], gas/liquid chromatography-mass spectrometry [15, 16] or liquid chromatography-mass spectrometry [17–19], enzyme-linked immunosorbent assay [20, 21], and capillary electrophoresis amperometric detection after solid-phase extraction [22, 23]. These methods provide high sensitivity and high throughput. However, most of these methods have obvious drawbacks; for example, they either require sophisticated equipment and trained personnel or involve tedious pretreatment procedures such as solid-phase extraction. Electrochemical methods for quantifying 8-OHdG, based on the electrochemical oxidation

activity of 8-OHdG, have displayed many advantages, such as high sensitivity, their fast implementation, and the simplicity of the instruments. In direct electrochemical methods, most of them are conducted at bare electrodes. Langmaier et al. [24] investigated the electrochemical oxidation mechanism of 8-OHdG at glassy carbon electrode (GCE) and Au, Pt, and SnO_2 electrode using cyclic voltammetry and indicated that the rate of the charge transfer reaction decreased with the increasing solution pH and depended on the nature of the electrode material following the sequence GC > Pt, Au $\gg$ SnO_2. Rebelo et al. [25] reported a pH-dependent oxidation mechanism over a wide pH range of 1–12 and the best sensitivity observed at pH 6 for the differential pulse voltammetry (DPV) determination of 8-OHdG in the presence of uric acid with GCE. Brett et al. [26] reported electrochemical oxidation of 8-oxoguanine on GCE for the detection of DNA damage with a detection limit of $0.8\,\mu$M. In a nutshell, the sensitivity and selectivity of direct electrochemical methods for quantifying 8-OHdG are limited.

Some efforts have been made to improve the sensitivity and selectivity of electrochemical sensors for quantifying 8-OHdG, mainly by modification of GCE using nanomaterials and polymers. In 2007, Li et al. [27] reported an electrochemical sensor for quantifying 8-OHdG on a poly(3-methylthiophene) modified GCE with a detection limit of $0.10\,\mu$M. Other work [28] they did in 2013 was on the electrochemical reduction synthesis of graphene/Nafion nanocomposite film and their results showed a high level of electrochemical performance on the oxidation of 8-OHdG. A wide linear range of 0.07–$33.04\,\mu$M and a low detection limit of 1.12 nM for 8-OHdG were obtained using linear sweep voltammetry. In 2008, Gutiérrez et al. [29] reported HPLC-amperometric detection of 8-OHdG using electrostatic and covalent adsorption of poly(amidoamine) (PAMAM) dendrimers on a thiol-modified gold electrode with a detection limit of 1.2 nM in synthetic samples and matrix interference elimination. In 2011, Gutiérrez et al. [30] also reported differential pulse anodic stripping voltammetry for quantifying 8-OHdG on multiple wall carbon nanotubes (MWCNTs)/polyethylenimine (PEI) modified electrodes with a detection limit of $0.10\,\mu$M and high selectivity. Electrochemical sensors using nanomaterials and polymers are an efficient way for electrochemical quantification of 8-OHdG.

Carbon nanotubes (CNTs) have a wide application in electrochemical sensors [31, 32] and biosensors [33, 34] since they possess the characteristic of unique properties [31, 35, 36], such as high electrical conductivity, outstanding catalytic activities, high adsorptive property, and facilitating electron transfer. CNTs have two distinct types of structures, including MWCNTs and single wall carbon nanotubes (SWCNTs). MWCNTs are composed of concentric and closed graphene tubules, each with a rolled-up graphene sheet, formed in a range of diameters, typically between 2 and 25 nm. SWCNTs are made of a single graphite sheet rolled seamlessly, with a diameter between 1 and 2 nm, arranged in a regular pattern of bundles that consist of tens to hundreds of nanotubes in parallel and in contact with one another [37]. Moreover, CNTs-based electrochemical sensors have shown many distinct advantages in the analysis of electroactive substances such as

cytochrome c [38], dopamine, epinephrine, and ascorbic acid [39] (on SWCNTs/GCE), and NADH [40], myoglobin [41], and warfarin [42] (on MWCNTs/GCE).

Nafion, a perfluorosulfonated and negatively charged polymer, is a cation-exchange polymer. Nafion films have been widely used as an electrode modifier in applications of electrochemical sensors and biosensors because of their chemical and thermal stability, high cation conductivity [43], and high permeability to cations coupled with their near impermeability to anions [44]. Meanwhile, Nafion can also be used as a binder to help other modifiers effectively adhere on substrate electrode [45]. Wang et al. [46] demonstrated CNTs in the presence of Nafion can be homogeneously dispersed into ethanol. To the best of our knowledge, an electrochemical sensor for the determination of 8-OHdG based on SWCNTs-Nafion modified electrode has not been reported.

The aim of this work was to develop a sensitive electrochemical sensor for the determination of 8-OHdG, based on the combination of the extraordinary properties of SWCNTs and the adhesive ability coupled with selective permeation of Nafion. A SWCNTs-Nafion film modified electrode was prepared by drop-coating SWCNTs-Nafion dispersion on the surface of GCE. Here, SWCNTs contributed to enhancing the electrochemical response while Nafion played a crucial role in the renewability and stability of the modified electrode, as well as in alleviating the interferences. In this paper, selection of an adhesive agent, characterization of the SWCNTs-Nafion nanocomposite film, optimal test conditions, and electrochemical performance and determination of 8-OHdG by developed method are presented. The proposed electrochemical method showed many advantages such as high sensitivity, reproducibility, good selectivity, and simplicity.

2. Materials and Methods

2.1. Reagents and Materials. 8-Hydroxy-2′-deoxyguanosine (8-OHdG), deoxyguanosine (dG), Nafion (5 wt% solution in water and lower aliphatic alcohols), polyethylenimine (PEI, average MW 750000), and streptavidin (SA) were purchased from Sigma-Aldrich (USA). N,N-dimethylformamide (DMF), sodium dodecyl sulfate (SDS) were obtained from Shanghai Reagent Corporation (Shanghai, China). Uricase (2 U/mL) was obtained from Sigma-Aldrich (USA). High purity single wall carbon nanotubes (SWCNTs, outer diameter < 2 nm, length = 5~30 μm, and purity: >95%) and short multiwalled carbon nanotubes (MWCNTs, outer diameter: 8~15 nm, length = 0.5~2 μm, and purity: >95%) were obtained from Institute of Chengdu Organic Chemicals Co., Ltd. (Chengdu, China). The other reagents were of analytical grade and used without any further purification. Aqueous solutions were all prepared with Millipore Milli-Q water ($\rho = 18.2\,\Omega$M cm).

0.1 M phosphate buffer saline (PBS, pH 7.40, 0.1 M NaH_2PO_4 + 0.1 M Na_2HPO_4 + 0.1 M KCl) was used as a supporting electrolyte in all measurements.

2.2. Apparatus. All the electrochemical measurements including cyclic voltammetry (CV) and differential pulse

voltammetry (DPV) were performed on a CHI 660E electrochemical workstation (Shanghai Chenhua Apparatus Co., Ltd., China). The three-electrode system was composed of a bare disk GCE with a diameter of 2 mm or an electrochemical sensor as the working electrode, a platinum wire as the counter electrode, and Ag/AgCl (saturated KCl) as the reference electrode. All potentials were in reference to this reference electrode. A digital control ultrasonic instrument (KQ5200DE, 100 W, Kun Shan Ultrasonic Instruments Co., Ltd., China) was used for dispersing CNTs well. A HZ85-2 magnetic stirrer (Beijing Zhongxing Weiye Instrument Co., Ltd., China) was used for stirring the solution during electrochemical measurements.

A Quanta 200 scanning electron microscope (SEM, FEI Company, USA) and a JEM-2100 transmission electron microscope (JEOL, Japan) were used to obtain the microimages of the SWCNTs-Nafion film.

2.3. Preparation of CNTs Dispersions

2.3.1. The Pretreatment of CNTs. SWCNTs/MWCNTs were pretreated according to [47] with some modification. Briefly, 500 mg of the pristine SWCNTs/MWCNTs was pretreated in 80 mL of mixture of concentrated H_2SO_4/HNO_3 (v/v, 3 : 1), ultrasonicated for 4 h, followed by centrifuging and rinsing with water several times until the filtrate was neutral. Finally, the washed CNTs were dried in an oven overnight at 100°C.

2.3.2. Preparation of the CNTs Dispersion. The SWCNTs-DMF/MWCNTs-DMF dispersion was prepared by dispersing 1.0 mg of the pretreated SWCNTs/MWCNTs in 1.0 mL of DMF with the aid of ultrasonication for 15–30 minutes. The SWCNTs-Nafion dispersion was prepared in the same manner described above, but using 1.0 mL of 0.5% Nafion instead. Other SWCNTs-binder (SDS, PEI, SA) dispersions were prepared by dispersing 1.0 mg of the pretreated SWCNTs in 1.0 mL of 1.0 mg/mL binder prepared using 1:1 (V/V) ethanol/water solution.

2.4. Fabrication of Sensor.
The GCE was polished manually with a 0.3 μm and 0.05 μm alumina slurry on a polishing cloth, respectively, followed by ultrasonication in ethanol and water for 3 min, respectively, and was finally rinsed with water and dried with nitrogen steam. The electrochemical sensor was fabricated, typically, by drop-coating 9 μL of SWCNTs-Nafion dispersion on the surface of the cleaned GCE, following its exposure to air to be dried. Subsequent modified GCEs were fabricated with the same protocol.

2.5. Electrochemical Measurements.
All electrochemical experiments were performed in 0.1 M pH 7.4 PBS at room temperature, 25 ± 1°C. CV measurements were conducted to obtain the electrochemical response of 8-OHdG, as well as select adhesive agents after an unstirred accumulation over 5 min.

DPV measurements for the detection for 8-OHdG were performed after the modified electrode had accumulated under magnetic stirring for 9 min. DPV parameters were
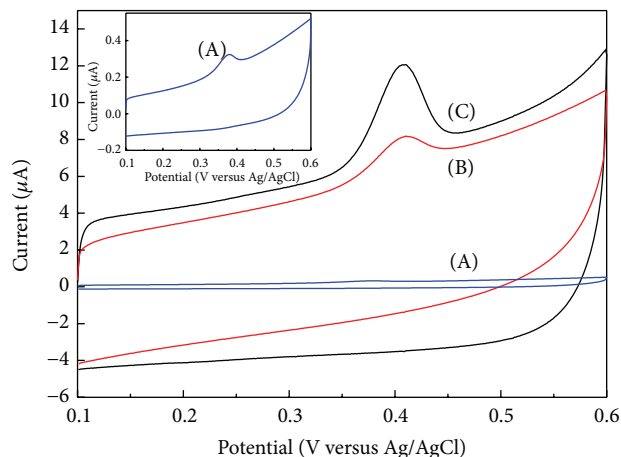

FIGURE 1: Cyclic voltammograms on different electrodes in 0.1 M PBS (pH 7.4) containing 5 μM 8-OHdG. (A) Bare GCE, (B) MWC-NTs/GCE, and (C) SWCNTs/GCE. Cyclic voltammetric measurements were performed at a scan rate of 50 mV/s after the electrode was immersed in the tested solution under the condition of 5.0 min accumulation (unstirring).

selected to attain a pulse amplitude of 50 mV, a pulse width of 0.05 s, and a pulse period of 0.5 s.

Recycling the sensors required a renewal process to remove the adsorbed analyte which was performed as follows: the used sensors were immersed in 0.1 M PBS (pH 7.4) and then electrochemically treated by successive cyclic voltammetric scanning for 1–3 min in the potential range between +0.1 and +0.6 V at a scan rate of 100 mV s^{-1} until a stable cyclic voltammogram was obtained and, finally, dried with nitrogen steam.

3. Results and Discussion

3.1. Electrochemical Behaviors of 8-OHdG on CNTs-Coated GCE. In the preliminary experiments, SWCNTs and MWC-NTs were separately dispersed in DMF and then drop-coated on the surface of GCE. Figure 1 shows the cyclic voltammograms of 8-OHdG on bare GCE (curve (A)), MWCNTs/GCE (curve (B)), and SWCNTs/GCE (curve (C)). On bare GCE, the anodic peak potential of 8-OHdG appears at about +0.38 V. This is in agreement with the reports by Li et al. [27] and Gutiérrez et al. [30]. On MWCNTs/GCE and SWCNTs/GCE, the anodic peak potentials all positively shift from +0.38 V to +0.41 V. This suggests that MWCNTs and SWCNTs should not have an observed catalytic function for electrochemical oxidation of 8-OHdG. It is notable that the oxidation peak currents of 8-OHdG on MWCNTs/GCE and SWCNTs/GCE were significantly enhanced. Compared to the bare GCE, there was about a 20-fold enhancement in the peak current obtained by subtracting capacitive current from the observed current using MWCNTs/GCE and about a 47-fold enhancement in the peak current obtained by subtracting capacitive current from the observed current using SWC-NTs/GCE. This may be attributed to an increase of adsorption amount of 8-OHdG on the surface of the electrodes, and

the high conductivity of MWCNTs or SWCNTs. This indicates that the enhanced current on SWCNTs/GCE is much larger than that on MWCNTs/GCE. Therefore, SWCNTs were chosen as the modified material in the following experiments.

3.2. Effect of the Adhesive Agents. The common methods to fabricate the electrochemical sensors rely not only on the SWCNTs homogeneous dispersion but also on their ability to adhere onto the surface of the substrate electrode. SWCNTs were often dispersed in organic solvents, such as DMF [38, 39], acetonitrile [48], and cyclohexane [49] to obtain a homogeneous suspension for electrochemical sensors. In addition, polymer composites and conjugation chemistry were employed to enhance the adhesion of nanomaterials to the surfaces of the electrodes and to reduce interferers from the complex samples. The choice of a suitable adhesive agent as binder is very important since it decides the physical stability of the SWCNTs modified electrode. If the adhesive agent has an excellent dispersant property, not only will the adhesive force between SWCNTs film and GCE interface be enhanced, but also the uniformity of SWCNTs dispersion will be improved. Typically, from a physical perspective, binding reagents can assist SWCNTs in firmly attaching onto the surface of the substrate electrode to avoid SWCNTs film exfoliation from the substrate electrode. Therefore, in our work, five reagents including Nafion, DMF, SDS, PEI, and SA were chosen as binding reagents. Additionally, since the chosen dispersants are partially solid or sticky fluid, ethanol/water (V/V = 1:1) was used as the solvent. Preparation of SWCNTs dispersion as described in Section 2.3 and the experiments for the investigation of the effect of dispersants on electrochemical properties of SWCNTs/GCE were performed using CV measurements.

At first, the adhesive ability of the binding agents for SWCNTs on the surface of GCE was checked. It was found that both SWCNTs-DMF and SWCNTs-SDS films formed by drop-coating on the surface of GCE were observed to be easily wiped off from the surface of GCE. This is attributed to the fact that both DMF and SDS have a low adhesive ability. It was found that the electrodes modified with SWCNTs-Nafion, SWCNTs-PEI, and SWCNTs-SA films were observed to be firmly attached to the surface of the GCE. Figure 2 shows the voltammograms of 8-OHdG at SWCNTs-Nafion (curve (A)), SWCNTs-PEI (curve (B)), SWCNTs-SA (curve (C)), and SWCNTs (curve (D), ethanol/water V/V = 1:1 as solvent) film modified GCE. Comparing curve (A) with (D), the oxidation peak current increases from 24.23 μA to 54.15 μA. This indicates that 8-OHdG can be accumulated in SWCNTs-Nafion film. Comparing curve (B) with (D), the anodic peak potential negatively shifts from 0.41 V to 0.32 V, indicating that PEI could overcome the overpotential of the oxidation of 8-OHdG. This is consistent with the report by Gutiérrez et al. [30]. Comparing curve (C) with (D), the oxidation peak current slightly decreases. This indicates that SA could not improve the oxidation of 8-OHdG. In order to obtain the high sensitivity and stability required, Nafion was selected as the binding reagent in subsequent experiments.
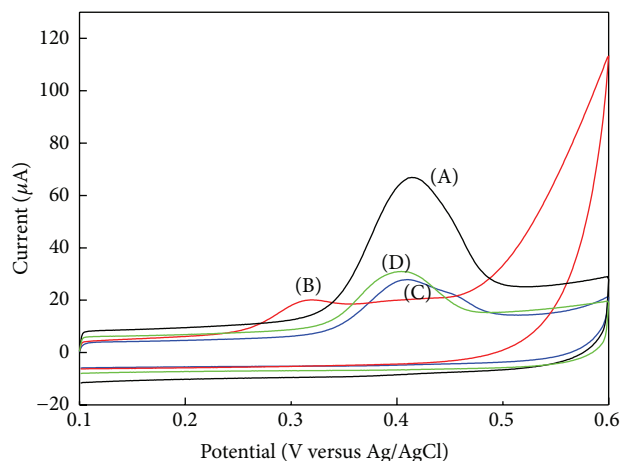

Figure 2: Cyclic voltammograms on different SWCNTs film modified electrodes in 0.1 M PBS (pH 7.4) containing 50 μM 8-OHdG with a scan rate of 50 mV/s. (A) SWCNTs-Nafion/GCE, (B) SWCNTs-PEI/GCE, (C) SWCNTs-SA/GCE, and (D) SWC-NTs/GCE. Cyclic voltammetric measurements conditions are the same as in Figure 1.
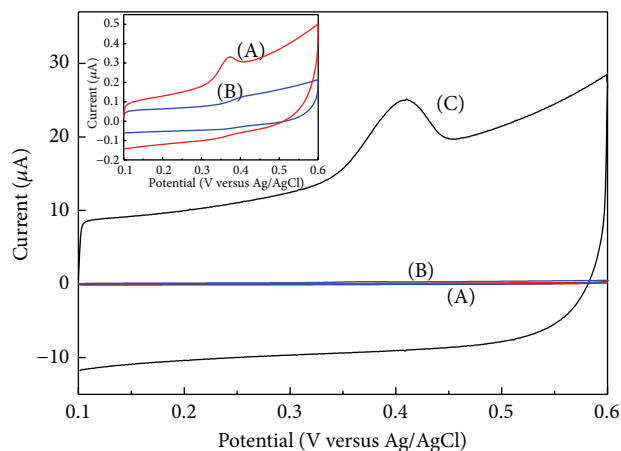

Figure 3: Cyclic voltammograms on different electrodes in 0.1 M PBS (pH 7.4) containing 5 μM 8-OHdG. (A) Bare GCE, (B) Nafion/GCE, and (C) SWCNTs-Nafion/GCE. Cyclic voltammetric measurements conditions are the same as in Figure 1.

To investigate the functions of Nafion and SWCNTs, CV measurements are performed on 8-OHdG with three different electrodes including bare GCE, Nafion/GCE, and SWCNTs-Nafion/GCE, as showed in Figure 3. The results showed that the oxidation peak current of the bare GCE (curve (A)) was higher than that of Nafion/GCE (curve (B)). This is attributed to the fact that the diffusion coefficient of 8-OHdG is lower in the Nafion polymer film than in aqueous solution. This indicates that the Nafion polymer film slightly blocks the electron transfer between the surface of GCE and the electrolyte. The oxidation peak current of SWCNTs-Nafion/GCE (9.30 μA) (curve (C)) was much higher than that of bare GCE (0.128 μA), indicating that SWCNTs-Nafion/GCE can enhance the peak current about
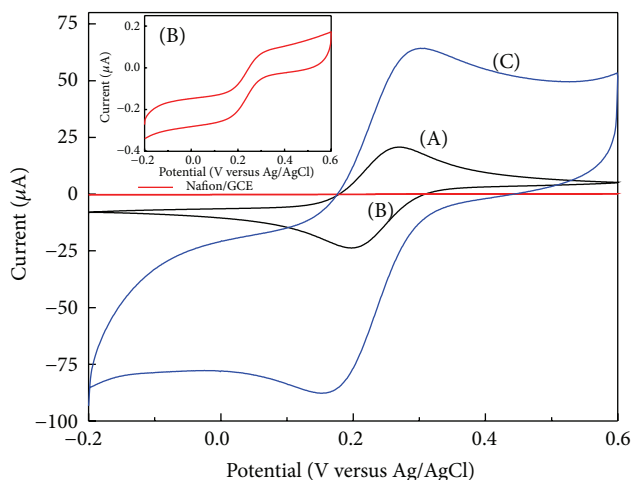
FIGURE 4: Cyclic voltammograms on different electrodes at a scan rate of 50 mV/s in 0.1 M PBS (pH 7.4) containing 5.0 mM $K_3Fe(CN)_6$–5.0 mM $K_4[Fe(CN)_6]$. (A) Bare GCE, (B) Nafion/GCE, and (C) SWCNTs-Nafion/GCE.

73-fold when compared to a bare GCE. This may be attributed to the unique microstructure characteristics inherent to the special SWCNTs and Nafion.

To obtain information on the SWCNTs-Nafion film, a potassium ferricyanide system was used as an electrochemical redox probe. The large differences in cyclic voltammograms of $[Fe(CN)_6]^{3-/4-}$ were clearly observed for three different electrodes including bare GCE, Nafion/GCE, and SWCNTs-Nafion/GCE from Figure 4. For the bare GCE (curve (A)), a well-defined cyclic voltammogram can be seen, and the anodic peak current (i_{pa}) and cathodic peak current (i_{pc}) were 25.2 μA and -25.5 μA, respectively, with a peak potential separation (ΔEp) of 0.065 V. After the GCE was modified with Nafion (curve (B)), the redox peak currents were greatly reduced. This can be ascribed to the fact that negatively charged Nafion films partly hinder the diffusion of $[Fe(CN)_6]^{3-/4-}$ through the film, which have been illustrated in some previous reports [45, 50]. i_{pa} and i_{pc} for the SWCNTs-Nafion/GCE (curve (C)) were 69.2 μA and -70.5 μA, respectively, with ΔEp of 0.15 V. The introduction of SWCNTs with Nafion films resulted in a considerable increase of the peak currents, indicating that SWCNTs provided the conducting bridges for the electron transfer of $[Fe(CN)_6]^{3-/4}$ [50]. This confirms that the combination of SWCNTs and Nafion film can increase the currents of the analytes.

To obtain the microstructure information of the SWCNTs-Nafion dispersion, scanning electron microscopy (SEM) in combination with transmission electron microscopy (TEM) was used to characterize the micromorphology of the SWCNTs-Nafion dispersion. As displayed in Figure 5(a), a uniform and homogeneous distribution of SWCNTs-Nafion film was formed. Typical TEM images in Figure 5(b) displayed a scattered distribution of well-dispersed SWCNT clusters. The results indicate that Nafion can disperse SWCNTs well to form a uniform and homogeneous distribution of SWCNTs-Nafion film on GCE.

Additionally, the effects of scan rates on the electrochemical oxidation of 8-OHdG on SWCNTs-Nafion/GCE were investigated. The result was showed in Figure 6. It can be seen that the oxidation peak currents increased with the up of scan rate (Figure 6(a)) and were proportional to the scan rate (5~500 mV/s) (Figure 6(b)), relying on the linear regression equation: i_p (μA) = 0.2391 + 0.7318 v (mV/s) (R = 0.9996). This indicates that the electrochemical oxidation process of 8-OHdG on SWCNTs-Nafion/GCE was a surface-defined controlled process.

3.3. Effect of Modification Volume of SWCNTs-Nafion Dispersion and Accumulation Time.

We found that stirring of the tested solution during accumulation time when the electrochemical sensors were immersed in the solution affected the peak current. Cyclic voltammetric measurements were performed after different accumulation conditions. Figure 7(a) shows cyclic voltammograms obtained on the sensors after an accumulation time of 5 min without stirring (curve (A)) and with a constant stirring (curve (B)). The result shows that stirring the tested solution can increase the peak current of 8-OHdG about 2.7-fold when compared to an unstirred case.

As expected, modification volume of SWCNTs-Nafion dispersion decides the amount of the SWCNTs-Nafion on the GCE and further affects the sensitivity. Thus, the effect of the modification volume of SWCNTs-Nafion on the peak current was checked using a fixed concentration of SWCNTs-Nafion (1.0 mg/mL) and stirring for 5 min. The result in Figure 7(b) shows the dependence of the peak current on the volume of SWCNTs-Nafion dispersion. From Figure 7(b), it can be seen that the peak currents linearly increase from 1 to 7 μL. This is attributed to the fact that the amount of 8-OHdG in SWCNTs-Nafion film on the electrode increases. And then, the peak current reaches a stable platform between 7 μL and 11 μL. When the volume is higher than 11 μL, the signal declines. This can be ascribed to the formation of a thicker film, which increases the resistance of 8-OHdG from the bulk solution to the surface of the electrode. Therefore, the volume of 9 μL was chosen as the optimum volume.

Effect of accumulation time on the peak current was checked under moderate stirring with a magnetic stirrer, as shown in Figure 7(c). The peak current linearly increases from 1 to 7 min. This is attributed to the fact that the amount of 8-OHdG in SWCNTs-Nafion film on the electrode increases. And then, the peak current reaches a stable plateau between 7 and 13 min. This is attributed to the fact that the amount of 8-OHdG to be concentrated in the SWCNTs-Nafion film reaches a saturation state of adsorption, as expected for a process under adsorptive control, which is consistent with the inference above. Therefore, the optimal accumulation time of 9 min was chosen for further experiments.

3.4. DPV Determination of 8-OHdG.

Differential pulse voltammetry (DPV) is a highly sensitive and selective tool for quantitative analysis when compared to the linear scan voltammetry. Therefore, the electrochemical determination of 8-OHdG was examined using DPV at the fabricated
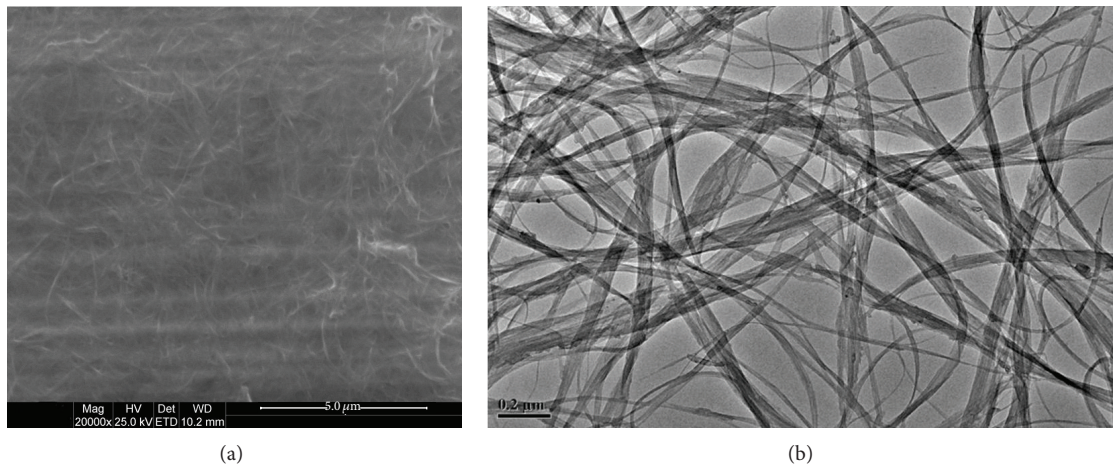
(a)

(b)

Figure 5: (a) SEM image of SWCNTs-Nafion film. Acceleration voltage, 25 kV. Magnification 20,000x (scale bar = 500 nm). (b) TEM micrograph of SWCNTs-Nafion film (scale bar = 200 nm).
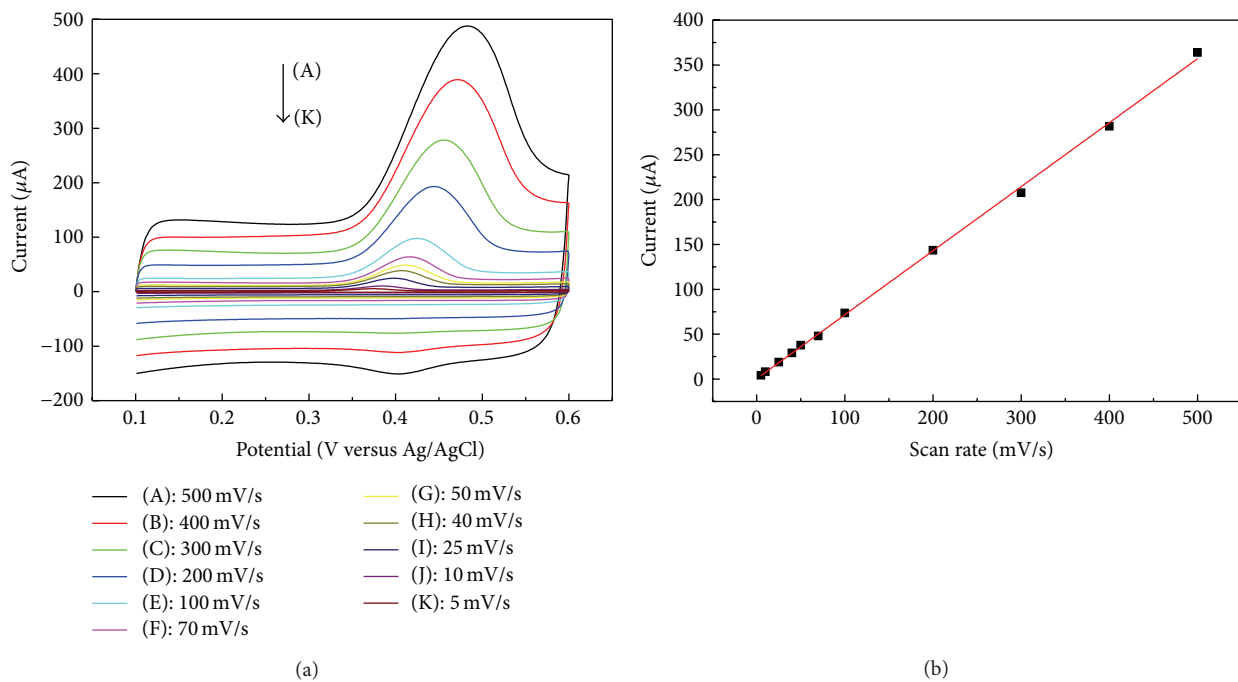

- (A): 500 mV/s
- (B): 400 mV/s
- (C): 300 mV/s
- (D): 200 mV/s
- (E): 100 mV/s
- (F): 70 mV/s
- (G): 50 mV/s
- (H): 40 mV/s
- (I): 25 mV/s
- (J): 10 mV/s
- (K): 5 mV/s

(a)

(b)

Figure 6: (a) Cyclic voltammograms in 0.1 M PBS (pH 7.4) containing 5 μM 8-OHdG at different scan rates from 5 mV/s to 500 mV/s on the SWCNTs-Nafion/GCE. (b) Dependence of the peak current on the scan rates from 5 mV/s to 500 mV/s.

sensors under the stated optimal conditions. Figure 8(a) shows the DPV response curves of 8-OHdG in the concentration range of 0 to 8.75 μM. Figure 8(b) shows the corresponding dependence of the oxidation currents on the concentration of 8-OHdG. The peak currents are proportional to the concentration of 8-OHdG over two concentration intervals: 0.03~1.25 μM (line (A)) and 1.25~8.75 μM (line (B)). The linear regression equations are expressed as follows: i_p (μA) = 0.233 + 16.731C (μM) (R = 0.9995, 0.03~1.25 μM) and i_p (μA) = 10.030 + 9.229C (μM) (R = 0.9987, 1.25~8.75 μM). The detection limit (S/N = 3) was estimated to be 8.0 nM. The slopes of the two linear ranges are 16.731 μA/μM and

9.229 μA/μM, respectively. The detection limit in this work (8.0 nM) is much lower than that reported using poly(3-methylthiophene) modified GCE (0.10 μM) [27] and MWC-NTs/PEI modified electrode (0.10 μM) [30]. The slope of the linear range at low concentrations in this work is much higher than that reported using poly(3-methylthiophene) modified GCE (0.361 μA/μM, Φ = 3 mm) [27] and using MWC-NTs/PEI modified electrodes (2.67 μA/μM, Φ = 3 mm) [30]. However, the detection limit in this work is only slightly higher than that reported using electrochemically graphene/Nafion nanocomposite film modified GCE (linear range is 0.07~3.64 μM with the detection limit of 1.12 nM)
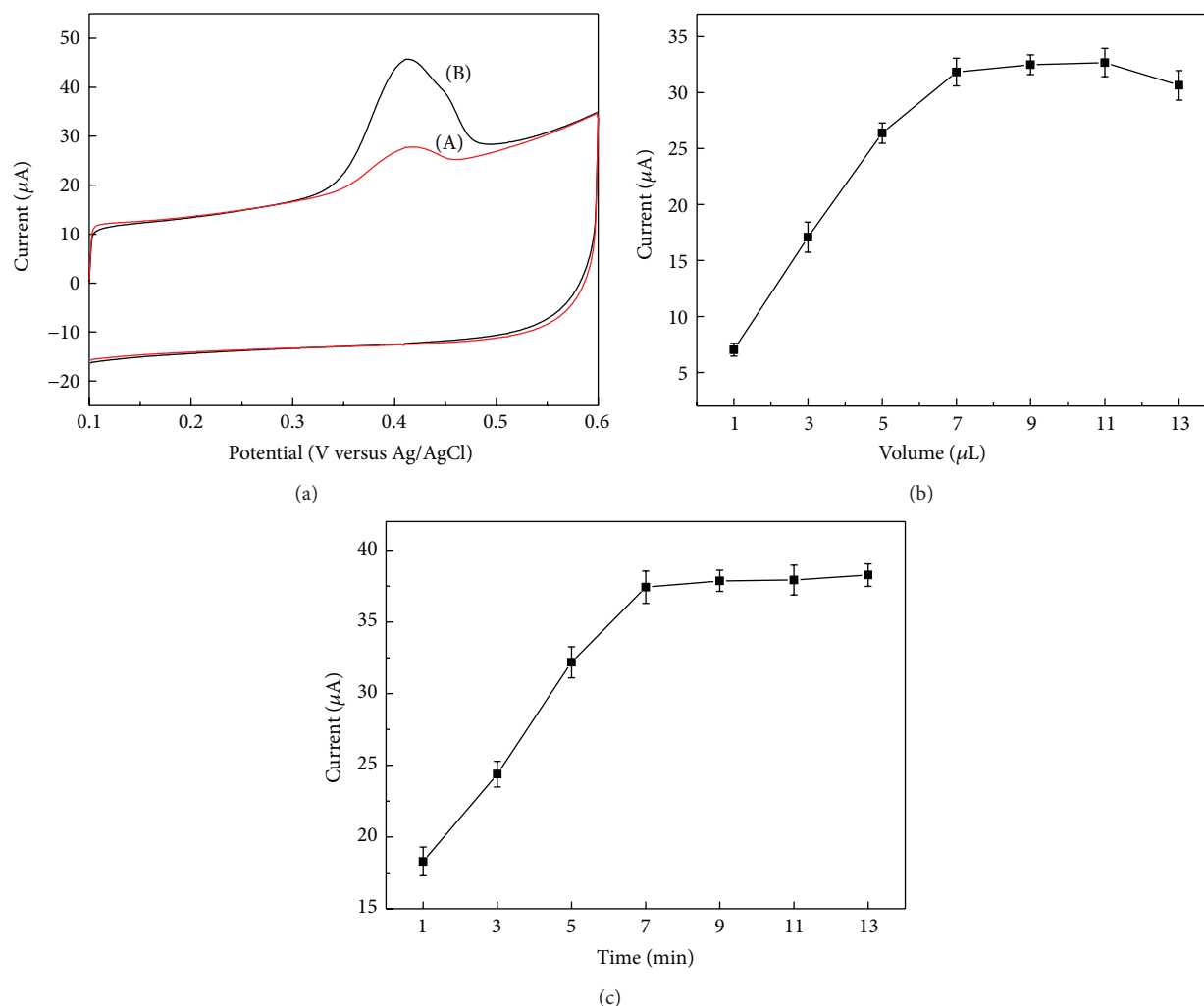
(a)

(b)

(c)

FIGURE 7: (a) Cyclic voltammograms on SWCNTs-Nafion/GCE under different accumulation conditions for 5 min. (A) Without stirring. (B) With stirring. (b) Dependence of the peak current on the volume of SWCNTs-Nafion dispersion. (c) Dependence of the peak current on the accumulation time at SWCNTs-Nafion/GCE. Cyclic voltammetric measurements were performed in pH 7.4 PBS solution containing 5 μM 8-OHdG at a scan rate of 50 mV/s.

[28], in which it was required that graphene be synthesized electrochemically from graphite oxide. A lower detection limit of the proposed method is, therefore, feasible.

The reproducibility of the sensors for quantification of 8-OHdG was evaluated by testing 7 sensors fabricated. The results showed that the relative standard deviation (RSD) was 6.1%. This indicates that the Nafion-SWCNTs/GCE fabrication process has a good level of reproducibility.

The renewability of the sensors is an important issue in the application of the sensors. Although the modification process proposed in this work is simple, the renewable ability of the sensors was also checked. After each DPV determination, the sensor was renewed as described in Section 2.5. The results showed that the RSD was 3.9% for one sensor in 7 repeat measurements. A satisfactory renewability of the modified electrodes is, therefore, evident.

3.5. Specificity Tests. Uric acid (UA) and ascorbic acid (AA) are generally considered as the main interferers in the electrochemical determination of 8-OHdG since they are electroactive coexistent compounds. Therefore, the influence of UA and AA on the DPV peak current of 8-OHdG was examined using fabricated sensors. In the case of our study, the oxidation peak potential of AA, UA, and 8-OHdG appeared at about -0.10 V, $+0.30$ V, and $+0.38$ V, respectively. The oxidation peak current of 0.5 μM 8-OHdG only decreased 1.3% in the presence of 0.25 mM AA (500-fold of 8-OHdG). This indicates that AA caused a negligible response. The oxidation peak current of 8-OHdG only decreased 5.0% in the presence of 0.05 mM UA (100-fold of 8-OHdG). This indicates that UA did not cause a significant response. When the concentration of UA was increased to 0.1 mM (200-fold) and 0.25 mM (500-fold), the oxidation peak currents of 8-OHdG were decreased by 6.7% and 10%, respectively. The high selectivity of the developed method in this work may be attributed to the fact that the negatively charged SWCNTs-Nafion film repels AA and UA anions and provides a transport channel only for 8-OHdG cations,
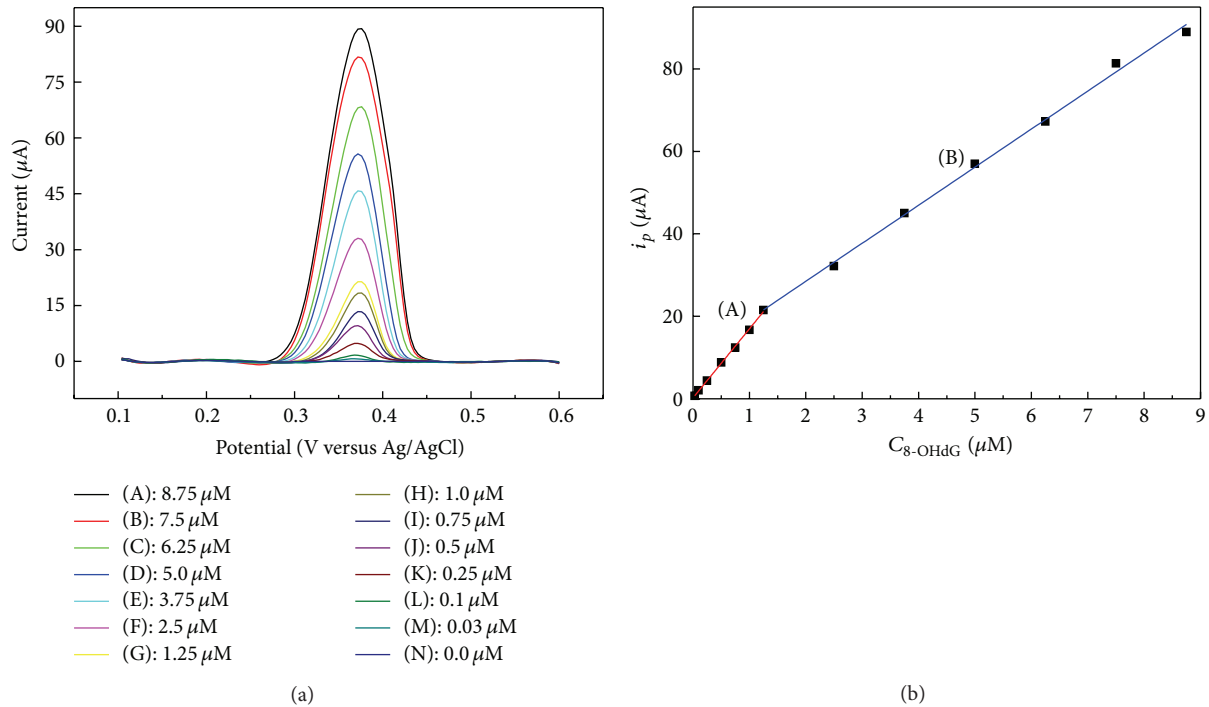
FIGURE 8: (a) Differential pulse voltammograms of different concentration of 8-OHdG with the subtraction of background current on SWCNTs-Nafion/GCE. (b) Calibration curve of the concentration of 8-OHdG.

since in pH 7.4 PBS 8-OHdG (pK_{a1} = 8.6 and pK_{a2} = 11.7) exists in cationic form, while AA (pK_a = 4.17) and UA (pK_a = 5.7) are anionic. Therefore, the prepared SWCNTs-Nafion/GCE greatly improved the selectivity towards 8-OHdG. Additionally, deoxyguanosine (dG), which is the oxidation precursor of 8-OHdG, was also examined as an interference for evaluating oxidative DNA damage. It was found that, in the case of optimal conditions as in this work, the oxidation peak potential of dG appeared at about +0.92 V while the presence of high concentration of dG (3 μM, 6-fold of 8-OHdG) caused a 10% decrease of oxidation peak of 8-OHdG. It can be seen that increased concentration of dG led to a greater decline of peak of 8-OHdG (see Table 1). This may be explained by the fact that dG clogged the mass transferring pores in Nafion film on GCE.

3.6. Analysis of Spiked Urine Samples. The application of the fabricated sensors was evaluated using a spiked recovery of urine samples. The urine samples from healthy volunteers were centrifuged at 5000 rpm for 10 min to remove precipitation. The supernatant was diluted with 0.10 M pH 7.4 PBS at the dilution ratio of 1 : 10 and 1 : 1, respectively. The results showed that the spiked recovery of 95.0% ~103.6% was obtained with 10-fold-diluted samples (n = 3) for 8-OHdG (Table 2). For the onefold-diluted samples, 0.6 mg/mL uricase can effectively eliminate the interference of UA. In the presence of 0.6 mg/mL uricase, a linear regression equation (i_p (μA) = 0.452 + 8.805C (μM)) was obtained in the range of 0.1 μM~1.5 μM with a correlation coefficient of 0.9991 for addition of 8-OHdG into onefold-diluted samples. Based on

TABLE 1: Current data of 8-OHdG obtained from DPV measurements before and after adding a certain concentration of dG.

$C_{8\text{-OHdG}} : C_{dG}$	$ip_{8\text{-OHdG}}/\mu$A (after added dG)	The decline of current
1 : 2	8.15 ± 0.06	5.2%
1 : 4	7.90 ± 0.05	8.1%
1 : 6	7.74 ± 0.10	10%
1 : 8	7.23 ± 0.11	15.9%
1 : 10	6.73 ± 0.07	21.7%

A fixed concentration of 8-OHdG ($C_{8\text{-OHdG}}$) is 0.5 μM, and the corresponding peak current ($ip_{8\text{-OHdG}}$) is 8.60 ± 0.12 μA. $C_{8\text{-OHdG}} : C_{dG}$ and the peak currents of 8-OHdG after added dG are listed above. The decline of the currents was calculated according to $ip_{8\text{-OHdG}}$ before and after added dG as listed above. The results represent the mean ± standard deviation (SD), calculated from three independent experiments (n = 3).

this equation, recovery for 8-OHdG in simulated patient urine samples [51] was tested. The results are listed in Table 2. The satisfactory recovery for 8-OHdG was obtained. This indicates that the developed method may provide a potential application for the estimation of 8-OHdG levels in urine from patients suffering from 8-OHdG-related diseases.

4. Conclusion

A novel electrochemical sensor incorporating a SWCNTs-Nafion composite film coated on GCE for the determination of 8-OHdG was developed. This electrochemical sensor was extremely sensitive, highly selective, and sufficiently accurate

Table 2: Recovery results for 8-OHdG from different dilution urine samples.

Sample dilution	Added (μM)	Found (μM)	Recovery (%)
1 : 10[a]	0.05	0.0475 ± 0.03	95.0
	0.15	0.152 ± 0.03	101.0
	0.50	0.518 ± 0.05	103.6
1 : 1[a]	0.20	0.191 ± 0.03	95.5
	0.30	0.286 ± 0.04	95.3
	0.40	0.413 ± 0.02	103.3

[a] The results represent the mean ± standard deviation (SD) from three independent experiments ($n = 3$).

towards 8-OHdG detection and quantification. Examinations on the regeneration ability and the spiked recovery of the sensors for urine samples also gave satisfactory results. This work demonstrates that SWCNTs-Nafion films can improve the sensitivity, selectivity, reproducibility, and stability of the electrochemical sensors for the determination of 8-OHdG, thereby making it an ideal candidate for electrochemical detection of 8-OHdG. The research work is going on to improve the selectivity by minimizing interferers from other electrochemical activated molecules, such as dG and UA. Further, the highly sensitive system will be used to quantitatively assess oxidative DNA damage induced by various nonmaterials' exposure.

Conflict of Interests

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

Acknowledgments

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