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Synthesis of gold nanoparticles@reduced porous graphene-modified ITO electrode for spectroelectrochemical detection of SARS-CoV-2 spike protein

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**HIGHLIGHTS**

- Au NPs/porous graphene modified ITO electrode was used as a COVID-19 biosensor.
- The spectroelectrochemical biosensor was used to monitor the COVID-19 S protein.
- The developed sensor showed a lower detection limit of 39.5 fmol L⁻¹.
- The spectroelectrochemical sensor is based on SERS, CV and SWV techniques.

**GRAPHICAL ABSTRACT**

**ABSTRACT**

Here, we reported the synthesis of reduced porous graphene oxide (rPGO) decorated with gold nanoparticles (Au NPs) to modify the ITO electrode. Then we used this highly uniform Au NPs@rPGO modified ITO electrode as a surface-enhanced Raman spectroscopy-active surface and a working electrode. The uses of the Au nanoparticles and porous graphene enhance the Raman signals and the electrochemical conductivity. COVID-19 protein-based biosensor was developed based on immobilization of anti-COVID-19 antibodies onto the modified electrode and its uses as a probe for capturing the COVID-19 protein. The developed biosensor showed the capability of monitoring the COVID-19 protein within a concentration range from 100 nmol/L to 1 pmol/L with a limit of detection (LOD) of 75 fmol/L. Furthermore, COVID-19 protein was detected based on electrochemical techniques within a concentration range from 100 nmol/L to 500 fmol/L that showed a LOD of 39.5 fmol/L. Finally, three concentrations of COVID-19 protein spiked in human serum were investigated. Thus, the present sensor showed high efficiency towards the detection of COVID-19.

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1. Introduction

Several coronavirus strains were identified, including SARS-CoV, HCoV-229E, HCoV-OC43, HCoVHKU1, and MERS-CoV [1]. In addition, a new coronavirus (COVID-19) has reported at the end of 2019 [2-6]. The COVID-19 has fast spread worldwide in a short time compared with other coronaviruses [5,6]. However, the early diagnosis is difficult because there are no initial characteristic symptoms of COVID-19 in the early stage of infection; besides, many cases did not show the common signs [7]. Thus, there is an
urgent need to find antiviral drugs besides developing an accurate, simple, and sensitive sensing method.

The real-time reverse transcription-polymerase chain reaction (rRT-PCR) is the golden technique for detecting COVID-19. However, its costly, needs specialist laboratories, skilled persons, and consumed a long time, which has limited their use [8,9]. Thus, it is of great urgency to develop rapid, reproducible, cost-effective, easy-to-use, accurate, sensitive, and selective assays for the early diagnosis of COVID-19 in different specimens.

Therefore, it is urgently needed to develop cost-effective, easy-to-use, fast, accurate, sensitive, selective, and real-time detection assays for the early diagnosis of COVID-19 infection. Biosensors have several advantages, such as the rapid response and the high sensitivity and selectivity towards many biological species. Raman spectroscopy is one of the promising labelless, specific, accurate, sensitive, and nondestructive assays. Ramans specificity is related to the fact that Raman showed fingerprints biochemical composition of the analyzed samples. Thus, Raman spectroscopy is one of the most promising techniques for real-time detection of different biological samples without sample preparation. However, the weak Raman signals are the main disadvantages of Raman spectroscopy as a comprehensive analytical technique. Surface-enhanced Raman scattering (SERS) is one of the widely used methods to overcome this inherent limitation and enhance the signals strength based on the uses of nanostructured metallic surfaces (gold and silver) [10,11]. Hence, SERS has widely used for biosensing applications [12-19].

Furthermore, electrochemical biosensors detect the most easy-to-use, accurate, quick, and sensitive biomarkers [14,20,21]. Several nanostructures modified electrodes have been reported to enhance the sensitivity and selectivity of the electrochemical biosensors [22-28]. MWNTs modified electrode was also used as an electrochemical sensor for detecting the ROS/H2O2 in the COVID-19 samples. Hence, it could use for the early-stage screening, which showed a good agreement between the electrochemical results and the clinical diagnostics [29].

Besides the exclusive properties of the graphene-based materials [30-32]. Graphene is an extraordinary 2D material that can enhance the electrochemical conductivity of the traditional electrodes and enhance the Raman effect based on graphene-enhanced Raman scattering (GERS) [30,31]. Moreover, metals nanostructures have wildly reported for improving the electrochemical conductivity and the Raman scattering. Thus, the graphene/metal NPs hybrids could improve the graphene/metal nanocomposites electrical conductivity compared with the pure graphene or metal NPs [32,33]. Thus, these nanocomposites have shown promising applications in several fields, including catalysis, energy conversion, and chemosensors [32,33].

Here, we have reported on the uses of the Au NPs@reduced porous graphene oxide (rPGO) modified ITO substrate as a SERS-active surface and act as a scaffold for immobilization of the anti-COVID-19 antibodies. Besides, we have used these Au NPs decorated rPGO to improve the Raman signals and the electrochemical conductivity. The anti-COVID-19 antibodies were used as probes for monitoring the COVID-19 based on Raman spectroscopy, cyclic voltammetry (CV), and square wave voltammetry (SWV) techniques. This spectroelectrochemical biosensor showed a capability to detect the COVID-19 protein within a concentration range from 100 nmol/L to 500 fmol/L with a limit of detection (LOD) of 39.5 fmol L-1 based on the SWV technique. Finally, this spectroelectrochemical sensor was used to detect different concentrations of COVID-19 protein in human serum samples that showed a good recovery percentage.

2. Experimental details

2.1. Materials and reagents

Chloroauric acid (H3AuCl4·4H2O), ascorbic acid, and phosphate buffer saline (PBS) (1x, pH = 7.4) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Graphene oxide (GO) nanosheets were obtained from Graphene Supermarket (Ronkonkoma, New York 11779, USA) as a suspension in water. COVID-19 antibody (S1N-M122, monoclonal antibody, IgG1) and COVID-19 S1 protein (S1N-CS2H2, MWt = 76.9 kDa) were purchased from ACROBiosystems (Newark, Delaware, USA). All other chemicals were analytical-grade reagents.

2.2. Preparation of porous graphene oxide (PGO)

PGO was prepared based on the etching method by using an H2O2 solution. Typically, 50 mL of 1 mg/mL GO sheets suspension was mixed with 5 mL of H2O2 (30 %) aqueous solution. The mixture was dispersed by sonication for 30 min and then heated at 100 °C for 4 h. Next, the PGO was obtained by centrifuging, and the residual of H2O2 was removed by washing the PGO with DIW. Finally, the PGO was re-dispersed in DIW by ultrasonication for 20 s.

2.3. Preparation of reduced porous graphene oxide (rPGO)

rPGO was prepared by using ascorbic acid as a reducing agent. Typically, 0.5 mL of 1 M ascorbic acid was mixed with 10 mL 1 mg/mL PGO and then heated for 2 h at 100 °C. The rPGO was purified by using DIW.

2.4. Preparation of Au nanoparticles/reduced porous graphene and its modified ITO electrode

Au NPs@rPGO was prepared under the same condition as the rPGO but in the presence of chloroauric acid. Typically, 1 mL of PGO (1 mg/mL) was mixed with 50 mL of HAuCl4 (1 mmol L-1) aqueous solution and 0.5 mL of 1 M ascorbic acid and then heated at 100 °C for 1 h. The rPGO was obtained by centrifuging and dried at room temperature. Furthermore, Au NPs@rPGO modified ITO substrates were also prepared according to the same condition but by insert ITO (0.5 cm × 2 cm) inside the reaction’s vessel and keeping the conducting surface upward.

2.5. Fabrication of the COVID-19 spectroelectrochemical sensor

Au NPs@rPGO modified ITO substrate was cleaned by rinsed with ethanol and dried under an N2 stream. Next, a 50 μL of the anti-COVID-19 antibody (10 μg/mL) in a 10 mM PBS buffer was immobilized onto the ITO substrate and kept overnight at 4 °C. We then rinsed the substrates three times using 1x PBS. Subsequently, 50 μL of COVID-19 protein solutions with different concentrations were interacted with the anti-COVID-19 antibody/Au NPs@rPGO modified ITO substrate for a further 1 h at 4 °C. Finally, the substrate was washed with 10 mM PBS and DIW and dried under N2 gas.

2.6. Instruments

The SERS spectra were collected on Raman spectroscopy with a SENTERRA inverted confocal Raman microscope (Bruker Optics Inc., Germany) comprises a CCD camera detection system and OPUS software for data acquisition. The spectra were recorded using NIR laser emitting light at a wavelength of 785 nm and a power of 50 mW at the sample. Ten scans of 5 s from 500 cm-1 to 3400 cm-1.
to 2000 cm\(^{-1}\) were recorded, and the average data were represented.

Furthermore, the AUTOLAB electrochemical workstation instrument (Metrohm, Herisau, Switzerland) was used to record the electrochemical data. A three-electrode-based homemade electrochemical cell consisting of Ag/AgCl as the reference electrode, anti-COVID antibodies/Au NPs/rPGO modified working electrode, and Pt wire auxiliary electrode was reported. All the electrochemical measurements were performed in 10 mM PBS (pH = 7.4) electrolyte within the potential window from \(-0.1\) V to +0.7 V at a scan rate of 50 mV/s.

The surface morphology of reduced porous graphene and Au NPs decorated reduced porous graphene-modified ITO substrates were analyzed by a scanning electron microscope (SEM) (ISI DS-130C, Akashi Co., Tokyo, Japan).

2.7. Sensing of COVID-19 in spiked samples

To prepare a representative of the real model, we have admixed different concentrations of the COVID-19 protein with 50 \(\mu\)g human serum. About 50 \(\mu\)L of the mixture was directly immobilized onto antiCOVID-19 antibody/Au NPs decorated reduced porous graphene/ITO for about 6 h at room temperature. Finally, the substrate was directly used to investigate the COVID-19 protein based on SERS, CV, and SWV techniques.

3. Results and discussion

3.1. Fabrication of COVID-19 biosensor based on SERS technique

Here, we have developed a simple, easy, and nondestructive COVID-19 spectroelectrochemical biosensor based on the SERS and electrochemical techniques, as shown in Scheme 1. The sensing process utilizes the Au NPs@rPGO modified electrode as a SERS-active surface and a working electrode. Firstly, we synthesized porous graphene sheets based on the treatment of GO sheets with \(\text{H}_2\text{O}_2\). Fig. 1a showed the SEM image of PGO, which showed the formation of highly uniform porous GO sheets over a large area. Then, simultaneously PGO was reduced to form rPGO, and Au NPs were formed by using ascorbic acid as a reducing agent. Fig. 1b showed the SEM image of Au NPs@rPGO that illustrated the formation of spherical Au NPs with a diameter of about 100 nm.

Furthermore, the formation of rPGO was confirmed using Raman spectroscopy (Fig. 1c), which showed the characteristics of G and D Raman bands of the graphene. Both Raman signals and electrochemical conductivity will be enhanced based on both Au NPs (noble metal NPs) and graphene material (2D material). The development of the COVID-19 sensor, including the immobilization of anti-COVID-19 antibody onto the Au NPs@rPGO modified ITO, followed by the capturing of the COVID-19 protein with the anti-COVID-19 antibody and monitoring this interaction based on the SERS and electrochemical techniques.

3.2. SERS detection of SARS-CoV-2 protein

Anti-COVID-19 antibody was firstly bound with the Au NPs@rPGO modified ITO substrate, and the immobilization was investigated using SERS spectroscopy. The SERS spectrum of the anti-COVID-19 was illustrated in Fig. 2a within a range from 500 cm\(^{-1}\) to 2000 cm\(^{-1}\). The spectrum indicated the immobilization of the anti-COVID-19 based on the appearance of the SERS bands at 543 cm\(^{-1}\) (SS bond of protein), 936 cm\(^{-1}\) (\(\alpha\)-helix, str. C–C, str. C–N), 1190 cm\(^{-1}\) (tryptophan, phenylalanine, str. C–N

Scheme 1. Schematic diagram of COVID-19 biosensor that including, (i) synthesis of porous graphene oxide, (ii) reduction of porous graphene oxide and deposition of Au NPs onto ITO electrode, (iii) immobilization of antiCOVID-19 antibody, and (iv) capture of COVID-19 protein.
Fig. 1. (a) SEM image of porous graphene oxide sheets, (b) SEM image of Au NPs@reduced porous graphene oxide sheets, and (b) Raman spectrum of Au NPs@reduced porous graphene oxide sheets.

Fig. 2. (a) SERS spectrum of anti-COVID-19 antibody/Au NPs@rPGO modified ITO, (b) SERS spectra of different concentrations of anti-COVID-19 antibody/Au NPs@rPGO modified ITO, (c) SERS spectrum of 100 pmol/L COVID-19 protein/anti-COVID-19 antibody/Au NPs@rPGO modified ITO, (d) SERS spectra of different concentrations of COVID-19 protein within a range from 100 nM to 1 pM, and (e) the relationship between the SERS intensities and the concentrations of the anti-COVID-19 antibody at Raman shift of 927 cm⁻¹.
and bending N–H of Amide III), 1318 cm⁻¹ (α-helix, Amide III), and 1448 cm⁻¹ (Amide II/N–H bending, C–N stretch, bending CH₂ of proteins) [34-39].

Different amounts of the anti-COVID-19 (from 10 nmol L⁻¹ to 100 nmol L⁻¹) were immobilized onto the Au NPs@rPGO modified ITO substrate to study the effect of the anti-COVID-19 antibody. Then, their corresponding SERS spectra were represented in Fig. 2b to detect the optimum amount of the anti-COVID-19 antibody. The results showed that the SERS’ intensities were increased with increasing the concentration of the anti-COVID-19 antibody until it reachedsaturation at a concentration of 50 nmol L⁻¹. Hence, we have used this amount for all the further measurements.

After immobilizing the anti-COVID-19 antibody onto the Au NPs decorated rPGO/ITO substrate, a 50 µL of the COVID-19 protein interacted with the anti-COVID-19 antibody for 6 h 4 °C, then washed the substrate with DIW. The capturing of the COVID-19 protein using anti-COVID-19 antibody was monitoring based on the SERS spectrum. The capturing of the COVID-19 protein with the anti-COVID-19 antibody/Au NPs@rPGO modified ITO substrate was confirmed based on the SERS technique (Fig. 2c), which showed a set of SERS bands. The assignment of these bands was tabulated in Table 1.

To study the efficiency of the developed sensor, the SERS spectra of different concentrations of COVID-19 protein after interaction with anti-COVID-19 antibody immobilized on Au NPs@rPGO modified ITO substrate as shown in Fig. 2d. The results indicated the increase of the SERS signals’ intensities with increasing the concentration of the COVID-19 protein. The relationship between the COVID-19 protein concentrations and the SERS signals’ intensities at Raman shifts 927 cm⁻¹ within a concentration range of 100 nM to 1 pM. The results showed a linear plot, as shown in Fig. 2e. The limit of detection (LOD) was calculated based on LOD = 3.3*SD/slope, which was 75 fmol L⁻¹.

3.3. Electrochemical detection of SARS-Cov-2 protein

Fig. 3a showed the cyclic voltammogram of the bare Au NPs@rPGO modified ITO electrode, which showed no redox peaks. Fig. 3b showed the cyclic voltammograms of different concentrations of COVID-19 protein after captured with the anti-COVID-19 antibody/Au NPs@rPGO modified ITO electrode, which illustrated the appearance of two redox peaks, cathodic and anodic peaks at about 0.42 V and 0.52 V, respectively. Furthermore, the results showed that the current peak was increased with increasing the concentration of the COVID-19 protein. The relationship between the COVID-19 protein concentrations and the current peak at 0.52 V (Fig. 3c) showed a linear plot within a concentration range from 1 pM to 100 nM.

Fig. 4a showed the anodic SWV voltammogram of the anti-COVID-19 antibody/Au NPs@rPGO modified ITO electrode. The results indicated the appearance of a broad and week anodic peak at about 0.2 V. Furthermore, the SWV voltammogram of 100 pM of COVID-19 protein after interacting with the anti-COVID-19 antibody/Au microcuboid electrode displayed an anodic peak at about 0.42 V (Fig. 4b).

The SWV voltammograms corresponding to the interaction of different concentrations of COVID-19 protein within a range from 500 fM to 100 nM with an anti-COVID-19 antibody/Au NPs@rPGO modified ITO electrode were studied to investigate the efficiency of the presented sensor (Fig. 4c). It was observed that the anodic current peak was increased with increasing the concentration of the COVID-19 protein. Furthermore, the relationship between the anodic current peak and the corresponding COVID-19 protein concentrations exhibited a linear plot with a slope of 6.23 and R² of 0.993 (Fig. 4d). Therefore, the LOD of the presented sensor was found to be 39.5 fM. Table 2 showed the LOD for several COVID-19 sensors, which indicated although some of the previously reported sensors showed a lower LOD compared with our sensor; however, the present sensor has a good LOD besides its easy-to-use and fast response advantages [40-50].

3.4. Performance of the developed sensor for monitoring spiked COVID-19 protein

To investigate the efficiency of the developed sensor for monitoring COVID-19 protein in a real sample, we have mixed different concentrations of COVID-19 protein with 50 µg of human serum and detected these mixtures. The mixtures of the COVID-19 protein and the human serum allowed to capture with the anti-COVID-19 antibody immobilized on Au NPs@rPGO modified ITO electrode. Fig. 4e showed the SERS spectra of different concentrations of COVID-19 protein after interaction with anti-COVID-19 antibody immobilized on Au NPs@rPGO modified ITO electrode in the presence of human serum. The SERS spectra of the various mixtures of COVID-19 protein and human serum have exhibited a set of SERS signals, especially SERS bands at Raman shifts of 372 cm⁻¹, 518–533 cm⁻¹, 651 cm⁻¹, 724–838 cm⁻¹, 936 cm⁻¹, 946 cm⁻¹, 1038 cm⁻¹, 1086 cm⁻¹, 1288 cm⁻¹, 1314 cm⁻¹, 1413 cm⁻¹, and 1596 cm⁻¹. In addition, these data showed the shifting of some peaks besides the disappearance of the SERS peak at 290 cm⁻¹ comparing the SERS spectrum of COVID-19 protein in PBS.

In the present work, the selectivity of the developed sensor is based on two key points (1) the uses of the COVID-19 antibody and (2) the fact that Raman showed fingerprints biochemical composition of the analyzed samples [16]. It is easy to observe the difference between the Raman spectra for COVID-19 in PBS and mixed with the human serum (Figs. 2c and 4e), which realerted to the presence of other proteins in the serum. However, the characteristics’ peaks for the COVID-19 protein were also observed in the presence of the serum. Although we could eliminate the serum’s effect by subtracting its spectrum, we have used the raw data to confirm the capability of the Raman spectroscopy to detect COVID-19 in the presence of a complexed matrix. Besides, Fig. 4e confirmed that the Raman peak intensities were increased with increasing the concentration of the spiked COVID-19 protein. The concentration of COVID-19 protein spiked in human serum was measured based on the intensity of the Raman peak at 927 cm⁻¹ and calculate the concentration of the COVID-19 protein based on the calibration curve (Fig. 4d). The recovery percentages were investigated and represented in Table 3. The results confirmed that the presented sensor has an excellent recovery percentage of COVID-19 protein in real samples with high sensitivity and selectivity.

### Table 1

**assignments of the Raman bands for COVID-19 protein after capture with the anti-COVID-19 antibody/Au NPs@rPGO modified ITO substrate.**

| Raman Shift (cm⁻¹) | Assignment                                                     |
|--------------------|----------------------------------------------------------------|
| 518                | S-S                                                            |
| 651                | tryptophan, sidechain/indole ring modes                        |
| 772                | tryptophan, sidechain/indole ring modes                        |
| 927                | α-helix, Backbone skeletal stretch/C–C, C–N stretches          |
| 1030               | phenylalanine, sidechain/phenyl ring modes                      |
| 1144 & 1186        | tyrosine & phenylalanine (sidechain/indole ring mode)          |
| 1323               | α-helix, Amide III (C–N stretch) and N–H deformation           |
| 1422               | Symmetric COO– stretching                                      |
| 1456               | Amide II (N–H bending) and C–N stretch                         |
| 1544 & 1586        | Tryptophan and Amide II (indole ring mode)                     |
| 1680               | β-sheet and Amide I (C=O stretch)                              |
4. Conclusion

Here, we have successfully fabricated Au NPs decorated rPGO modified ITO based on a simple method. The modification process is based on firstly the fabrication of PGO followed by in-situ reduction of Au$^{3+}$ and PGO. The use of hybrid Au NPs and reduced porous graphene results in enhancing both the Raman effect and the electrochemical conductivity of the developed sensor. This sensor...
Table 2
Comparison between the developed sensor and the previously reported COVID-19 sensors.

| Sensor                          | LOD  | Reference |
|--------------------------------|------|-----------|
| Plasmonic metasensors          | 4.2 fmol L⁻¹ | 41        |
| Oligonucleotide Capped Plasmonic Nanoparticles | 0.18 ng µL⁻¹ | 42        |
| DNA nanoscaffold hybrid chain reaction | 0.96 pMol L⁻¹ | 43        |
| quantum dot-based              | 10 ng mL⁻¹ | 44        |
| SARS-CoV-2 immunodiagnostics kit | 250 pg mL⁻¹ | 45        |
| Electrochemical Impedance Spectroscopy (EIS) | 2.8 fmol L⁻¹ | 46        |
| (Nanoprinted Reduced-Graphene-Oxide) Field-Effect Transistor-Based Biosensor | 1 fg M⁻¹ | 47        |
| Dual-functional plasmonic photothermal | 0.22 pMol L⁻¹ | 48        |
| Optical biosensor (Au and Ag NPs) | 4.2 fmol L⁻¹ | 49        |
| Square wave voltammetry        | 39.5 fmol L⁻¹ | This work |

Table 3
Determination of COVID-19 protein in human serum samples.

| Samples | Added (pmol/L) | Found (pmol/L) | RSD (%) | Recovery (%) |
|---------|---------------|----------------|---------|--------------|
| 1       | 50            | 49.64          | 2.1     | 99           |
| 2       | 100           | 103.03         | 1.7     | 103          |
| 3       | 250           | 256.95         | 1.9     | 103          |

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