Ultrasensitive non-enzymatic uric acid electrochemical sensor based on Silicon nanowires (SiNWs) modified screen-printed carbon electrode (SPCE)

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ABSTRACT

A non-enzymatic electrochemical sensor using a disposable Screen Printed Carbon electrode (SPCE) modified with SiNWs was developed for the determination of uric acid (UA). The surface morphology of SiNWs-modified SPGE was observed by Field Emission Scanning Electron Microscopy (FESEM) and its electrochemical behavior was investigated by cyclic voltammetry (CV) and different pulse voltammetry (DPV). The SPGE modified with SiNWs showed a good electrocatalytic activity towards uric acid compared with the unmodified SPCE. Under optimal condition, the developed electrochemical enzyme exhibited a wide linear range for determination of UA ranging from 100 µM to 0.1 nM with detection limits of 3.5 nM (S/N=3). In addition, the SiNWs-modified SPGE also had good selectivity and stability.

1. Introduction

Monitoring uric acid (UA) levels in various body fluids, such as saliva, serum, plasma, and wound fluid, has become an important biomarker, providing valuable information about the progression and prognosis of certain diseases. For instance, elevated UA levels are associated with the progression of gout [1], cardiovascular disorders [2], metabolic syndrome [3], wound infections [4], and neurodegenerative disorders [5]. Conversely, Parkinson's disease and impaired kidney function are associated with low UA levels [6]. This suggests that abnormal UA levels hold promising potential for early diagnosis and could become a valuable predictive tool in disease diagnostics. The current technique for UA determination in blood or urine using a different approaches such as Raman spectroscopy (SERS) and high-performance liquid chromatography (HPLC) [7], Capillary Electrophoresis [8], Mass Spectrometry [8], Nuclear Magnetic Resonance (NMR) [9], Spectroscopy Spectrophotometric[9]. Although all these methods are reliable and have been proven to accurately determine the level of UA in samples, they are limited by several drawbacks such as the use of sophisticated instruments that require skilled personnel to operate, complicated and tedious procedures, and expensive procedures that restrict their use in less developed countries.

Furthermore, in the era of digital health, diagnostic devices are increasingly moving towards the concept of a developing Point of Care (POC) setting. As a result, there is a demand for uric acid diagnostic devices that are based on the POC setting concept, which are more portable, user-friendly, and reliable compared to the current diagnostic devices. The electrochemical-based biosensor approach seems to fulfill the demand for a low-cost analytical technique in point-of-care (POC) settings. This approach can be miniaturized into portable devices, making it easy to use, fast, and suitable for on-site detection due to its portability. In addition to its simple set-up, this approach relies on the change in redox reactions, resulting in different electrochemical signals with and without the presence of the analyte, which can be detected by a potentiostat. Numerous research studies on uric acid-based electrochemical biosensors have been reported [10-14]. However, despite the high selectivity and specificity of enzymatic uric acid biosensors, which utilize the uricase enzyme for the oxidation of uric acid, there are significant drawbacks that need to be reconsidered before their application. Among them, one of the challenges is the immobilization of uricase on the surface of the electrode without peeling off while maintaining its enzyme activity [9]. The immobilization process should ensure that the enzyme remains attached to the electrode surface and maintains its catalytic activity. Furthermore, the protein nature of the immobilized enzyme can be susceptible to interference from environmental conditions such as temperature, pH, and humidity, which can affect its activity and stability [15]. The conditions under which the modified electrode is stored and used can impact the reproducibility of the results. Therefore, it is crucial to carefully control these factors during the fabrication and storage of the immobilized uricase biosensor. The half-life of the immobilized enzyme-functionalized electrode may not be as long as desired, leading to a decrease in enzyme activity over time. This necessitates proper storage conditions to maintain the stability and activity of the immobilized enzyme [16]. However, the specific storage requirements can add complexity and cost to the production process of the biosensor.

Therefore, a non-enzymatic uric acid biosensor is a more desirable, low-cost, and stable method since it does not depend on the use of enzymes and is not influenced by environmental factors and interfering substances such as ascorbic acid. Thanks to the redox properties of uric acid, it can be oxidized when subjected to a potential charge in non-enzymatic approaches without the use of a redox label. However, it requires a high operating potential, which can affect the selectivity and sensitivity. Recent studies have shown that the use of nanomaterials can enhance the performance of uric acid biosensors through various mechanisms, such as providing a high surface area of the electrode, mimicking the activity of catalytic enzymes, and enhancing the electron transfer between the solution and the electrode. One such nanomaterial is silicon nanowires (SiNWs), which have been explored as a sensing material to improve the performance of electrochemical biosensors for various detections, such as glucose [17], mebendazole drug [18], dengue virus nucleic acid [19], dopamine [20], ascorbic acid [20], serum albumin[21], ethanol [22], glutamate [23], pesticide [24], glutamine [25], E. Coli Microbial cell [26]. This is attributed to the unique properties of SiNWs, including their small size (≈1–100 nm), which provides a high surface area-to-volume ratio, resulting in high sensitivity by facilitating electron transfer and yielding a fast response [27]. Additionally, SiNWs are highly biocompatible with biological and chemical species making it is highly suitable for the development of non-enzymatic of uric acid biosensor. To our knowledge, there is a limited report on the utilization of SiNWs as a sensing material for uric acid determination, and the ability of SiNWs to catalyze the oxidation of uric acid is still unknown. This work could be of great interest for further investigation in this study. Hence, this work, we employ SiNWs as sensing material to be functionalized with our screen printed electrode (SPCE) for the determination of uric acid.

2. Methodology

2.1 Materials, chemicals and instrumentation

Polydisperse silicon nanowires (SiNWs) (Diameter x length; 40 nm x 1-20 nm), uric acid, sodium hydroxide (NaOH), Sodium Chloride (NaCl), potassium chloride (KCl), potassium hydroxide (KOH), urea,(3-aminopropyl) triethoxysilane (APTES) were purchased from Sigma-Aldrich (St. Louis, MO, USA) (www.sigmaaldrich.com). Potassium hexacyanoferrate III ($K_3Fe(CN)_6$, L-Cysteine ($C_3H_7NO_2S$), glucose ($C_6H_{12}O_6$), citric Acid ($C_6H_80_7$), oxalic Acid, ($C_2H_2O_4$), acetone (C_3H_6O), ethanol (C_2H_6O) and hydrochloric acid (HCl) were purchased R & M Chemicals (Malaysia) (www.evergainful.com). All chemical and reagent were of analytical reagent and used without further purification. All solution was prepared using double distilled water. All electrochemical measurement was carried out using μAUTOLAB (III) electrochemical potentiostat (Eco Chemie, Utrecht, The Netherlands) that is operated by general purpose electrochemical system (GPES) software version 4.9. The screen-printed carbon electrode (SPCE) which consists of carbon as working and counter electrode, respectively and silver reference electrode were purchased from DropSens (Spain) (www.dropsense.com). Surface morphology of modified electrode were observed using Field emission scanning electron microscopy (FESEM) (JSM-7600F, JEOL, (Japan)). The pH solution was adjusted using a pH Mettler Toledo Model Seven Easy™ S20 (Shanghai, China).

2.1 Preparation of SiNWs-modified SPCE

The carbon working electrode was polished carefully using 3-μm alumina powder, cleaned subsequently with deionized water, and dried with nitrogen gas (N_2). SPCE was pre-treated by dropping KOH (1%) on the working electrode surface for 10 min and washed subsequently with deionized water to form a monolayer of hydroxy group. Polydisperse SiNWs (1 mg) was dispersed uniformly in 1 mL of 2% APTES under sonication for 2 hours. The SiNWs suspension of 5 μl was dropped cast on working SPGE surface and incubated for 3 hours at room temperature, rinsed with ethanol and baked at 100 °C for 30 min. The SiNWs-modified SPCE was ready be use for the next experiment.

2.3 Electrochemical measurement

Cyclic voltammetry (CV) technique was performed in 0.1 M PBS (pH 8) containing 5 mM $[Fe(CN)_6]^{3-/4-}$ solution at the potential range of −0.5 to 0.8 V with a scan rate of 0.1 V/s to characterize the electrochemical response at different electrode. CV and different pulse voltammetry (DPV) technique were employed for electrochemical detection of UA at different concentrations in 0.1 M PBS (pH 8) from -0.15 to 0.8 V at a scan rate of 0.1 V/s. All the experiments were carried out in the triplicate at the room temperature (25±1 ˚C). The overall process of the fabrication of electrochemical UA sensor in this study was summarized as below Fig. 1.

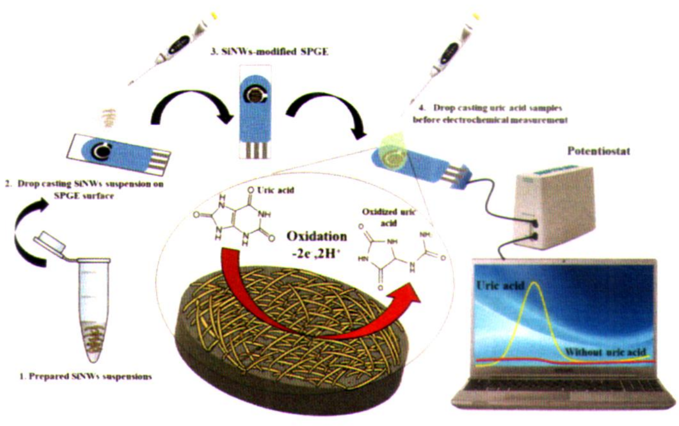

Fig. 1 The schematic process of the fabrication of electrochemical UA sensor

3. Result and Discussion

3.1 Surface morphology of SiNWs-modified SPGE

FESEM image show that our prepared SiNWs suspension are homegenously dispersed and distributed on the SPGE surface (Fig.2). It is clearly shows that that SiNWs are closely packed together to form randomly porous assembled SiNWs on the surface of electrode. This porous rod like appearance provided a larger surface area for a better electron transfer between uric acid and modified electrode surface.

Fig. 2. FESEM image of surface morphology of SiNWs-modified SPCE

3.1 Electrochemical behavior of SiNWs-modified SPCE

In this characterization work, potassium ferricyanide ($[Fe(CN)_6]^{3-}$) was employed to evaluate the electrochemical performance of our new SiNWs-modified SPCE by monitoring its redox properties. Fig. 3 a) shows that the cyclic voltammetry (CV) curves for SiNWs-modified SPCE and bare SPCE in 0.1 M KCl solution containing 5 mM $[Fe(CN)_6]^{3-}$. It was shown that both of electrodes provided a pair of well-defined redox peak due to oxidation and reduction of $[Fe(CN)_6]^{3-}$. An obvious increased in the redox peak current for $[Fe(CN)_6]^{3-}$ was observed after modification with SiNWs. This is can be attributed to the excellent conductive properties and high surface volume to ratio of SiNWs that can accelerates electron transfer at the modified electrode. The electrochemical active surface area (A) for bare SPCE and SPCE-modified SiNWs were calculated based on Randles-Sevcik equation Eq. (1). [28]. FESEM image show that our prepared SiNWs suspension are homegenously dispersed and distributed on the SPGE surface (Fig.2). It is clearly shows that that SiNWs are closely packed together to form randomly porous assembled SiNWs on the surface of electrode. This porous rod like appearance provided a larger surface area for a better electron transfer between uric acid and modified electrode surface.

$$I_p = (2.69 \times 10^5)\, n^{3/2} A D^{1/2}\ C v^{1/2} \quad (1)$$

Where Ip = redox peak current; n is the number of electrons involve in redox reaction (n=1); A is active surface area; D is diffusion coefficient of 0.1 M KCl containing 5 mM [Fe $(CN)^6]^{3-}$(D= 6.7 x 10^{-6} cm^2 s^{-1}), C is the concentration of probe (mol cm^{-3}) and V is the scan rate (V s^{-1}). The electroactive surface area of bare SPCE and SiNWs-modified SPCE were calculated as 0.056 cm^2 and 0.458 cm^3 respectively. This indicate that the surface area of modified electrode was enhance about 8.2 times compared to the bare electrode. The result reveal that the presence of SiNWs can enlarge the surface area of electrode, thus improve the electrochemical sensing performance.

The unique characteristic of UA molecules, which can be oxidized and reduced [29], allows for the direct detection of uric acid without labels in an electrochemical system, simplifying the electrochemical detection process. Thus, in Fig. 3b demonstrated that the comparison performance for the electrocatalytic oxidation of uric acid between bare SPCE and SiNWs-modified SPCE in 0.1 M PBS containing 100 μM UA at the scan rate of 100 mV/s. For bare SPCE, a weak peak oxidation current (ipa = 0.125 μA) in CV response was observed at the potential of 0.322 V. In contrast, the oxidation peak current response of UA at SiNWs-modified SPCE are greatly improved with ipa of 0.407 μA about 2.5-3 folds higher than that of bare SPCE indicated that SiNWs significantly catalyzed the oxidation of UA process. Furthermore, the peak potential separation of SiNWs-modified SPCE was obvious reduced to 0.1432 V compare to the bare SPCE with 0.458 V. This reduction of peak separation revealed that SiNWs can enhance the electron transfer rate between UA and electrode. Although the redox properties of uric acid are not as excellent as like $[Fe(CN)_6]^{3-}$, interestingly, the SPCE modified with SiNWs shows a clear double peak current response for oxidation and reduction, whereas the bare SPCE without modification does not display a clear peak current response. This further demonstrates that the use of SiNWs has the potential to enhance the redox behavior of the bare electrode.

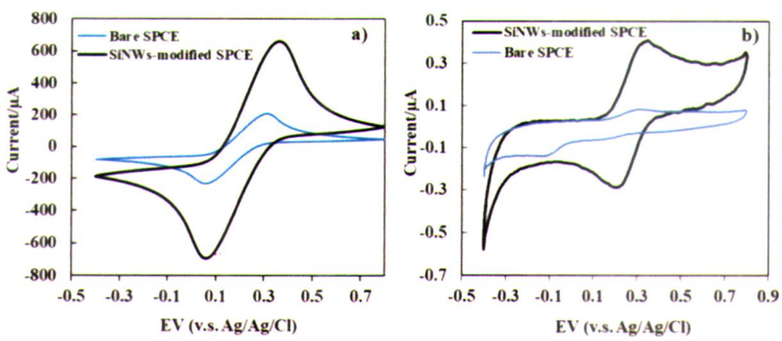

Fig. 3. CV characterization at SiNWs-modified electrode and bare SPCE in 0.1 M KCl solution containing 5 mM $[Fe(CN)_6]^{3-}$ at scan rate of 100 mV/s; b) CV of 100 μM uric acid at SiNWs-modified electrode and bare SPCE.

3.1 The effect of SiNWs concentration and pH supporting electrolyte on the electro-oxidation of uric acid based electrochemical approach.

The success of utilizing SiNWs as a sensing material in the electro oxidation of uric acid as shown in Fig. 3 a where this developed biosensor based SiNWs can discriminate the electrochemical signal with and without uric acid. In this optimization work, we investigated the effect concentration of immobilized SiNWs on the surface of SPCE and pH solution in the oxidation of uric acid using DPV technique. The first graph in Fig. 4a shows the effect of varying concentrations (0-5 mg/ml) of SiNWs suspension on the peak current. The role of SiNWs enhancement in the oxidation of uric acid clearly noticed when there is an huge improvement in the uric acid oxidation once introducing immobilized SiNWs suspension at concentration from 0.5 to 2 mg/ml. This suggests that SiNWs may enhance the surface area and active sites for electron transfer between uric acid and the electrode. The properties of SiNWs provide a high surface area on the bare SPCE, which leads to an improvement in electron transfer. This finding aligns with the understanding that SiNWs can offer an increased surface area for electrochemical reactions. However, above a concentration of 2 mg/mL SINWs-casted drop, the peak current appeared to stabilize or even decrease slightly. This could be attributed to saturation effects or potential hindrance in electron transfer at very high SiNWs concentrations due to formation of SiNWs agglomeration. Although there is limited study on the effect of SiNWs concentration on the electrochemical sensor's performance in previous work, similarities with other suspension nanomaterials such as graphene oxide (GO) have been observed. Similar observations by our previous work [30] of found that at high concentrations of GO beyond the optimum point, the current signal decreased due to an increase in the thickness of the GO layer. This trend can be explained by the decrease in electrochemical performance as SiNWs concentration increases.

Fig. 4b shows the influence of the pH range of the supporting electrolyte (0.1 M PBS) from 4 to 10 on the electro-oxidation of uric acid on SiNWs-modified SPCE. It is evident that as the pH increases from 4 to 7, there is a corresponding increase in the electrochemical current signal. The lower current signal at acidic conditions can be attributed to several factors. Firstly, under low acidic conditions, there could be detrimental effects on the covalent bonding between immobilized SiNWs and SPCE, leading to leaching out and a decrease in surface area and conductivity. Secondly, acidic conditions can result in H^+ ions which may repel the positively charged form of uric acid, thereby reducing adsorption and consequently decreasing the electrochemical signal. At a pH of around 7, the highest current signal reached 0.268 ± 0.004 µA, and the current signal for UA began to decrease as the pH increased beyond 7. Just like acidity, excessive basicity can also influence the surface morphology of a modified electrode and impact the ionization of uric acid, potentially leading to decreased adsorption. Therefore, 2 mg/mL SINWs-casted drop and pH 7 were chosen as the optimum condition for electro-oxidation of uric acid and used in the following studies.

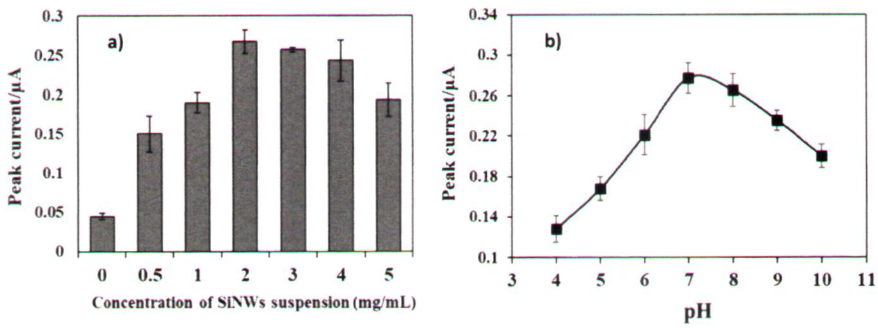

Fig. 4 The effect of a) SiNWs concentration and b) pH supporting electrolyte on electrochemical determination of UA

3.2 Analytical performance of developed electrochemical UA sensor

Using our previous optimum conditions, the developed SiNWs-sensor is evaluated of its analytical performance in terms of sensitivity, interference and reproducibility. In this sensitivity studies, the developed SiNWs-sensor were tested its performance at different concentrations of UA ranging from 100 µM to 0.1 nM UA in PBS (pH 7.0). As depict in Fig. 5a, as increasing concentration of UA leading to an increase of DPV peak current demonstrated the developed SiNWs -biosensor stable and good response over the entire concentration range. It occurrence was due to the high molecule of UA present in system, more it can be oxidized leading to high current. The interesting about this system, this developed biosensor purely depends on the oxidation of uric acid in blank supporting electrolyte without addition of redox molecules such as Ferricyanide solution as enhancement of current signal which proven the role of SiNWs as an enhancement of signal. The calibration curve as shown Insert Fig. 5a shows that DPV peak current of SiNWs-Biosensor was linear to UA concentration according to linear regression equation of Y=0.0243X +0.3516 where Y was the peak current (Ip, µA) and X was UA concentration (µM) with high R^2 of 0.98. It was shown that the limit of detection (LOD) was found to be 3.5nM determined using the following formula using formula of LOD = 3S/M where S is standard deviation while M is gradient of calibration curve. It was shown that detection limit for this current work been compared with other previous work as shown in Table 1. Thus, developed SiNWs-biosensor shows high sensitivity detection when compared with other previous work and demonstrated the potential as alternative approach for UA determination.

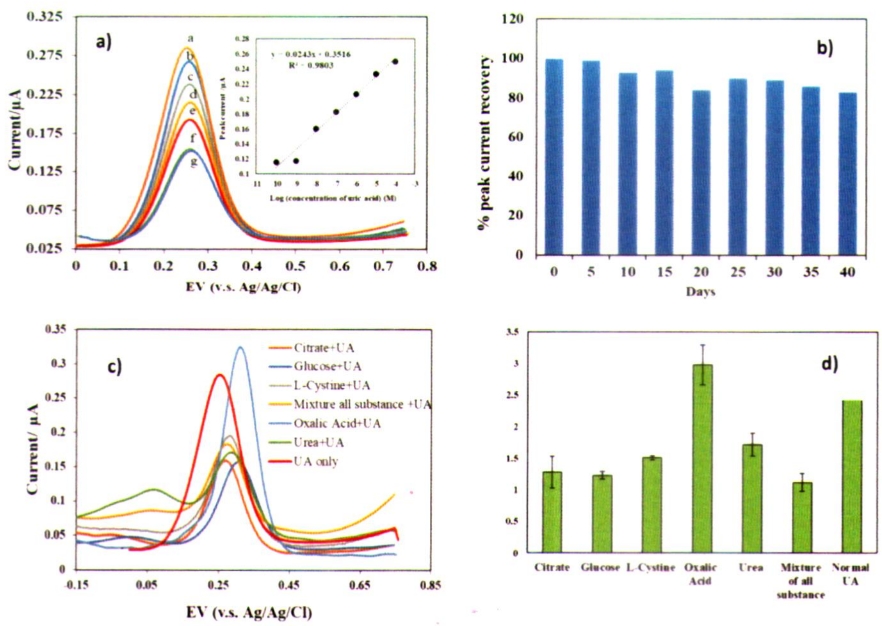

Fig. 3 The Analytical performance of developed electrochemical UA sensor

The selectivity of developed biosensor towards to uric acid in the presence of 0.2 mM of each common interferences in real samples such as Citrate, Glucose, L-Cystine, Oxalic acid and Urea were investigated and represent by the bar of graphs (Fig. 5 c,d). The addition of interferences such as Citrate, Glucose, L-Cystine, urea and a mixture of all was shown to result in a 50% reduction in DPV peak current from UA alone. On the other hand, the addition of oxalic acid interference enhanced the DPV current of UA. Despite this abnormal finding in DPV current with added interferences, UA's presence remained detectable at common potential around 0.25-0.28 without any other DPV peak currents appearing apart from the peak of UA. The stability storage of SiNWs-modified SPCE was investigated up to 40 days at room temperature in open air conditions (Fig 4 b). During this period, the triplicate SiNWs-modified SPCE electrodes were tested for measuring 0.1μM uric acid at intervals of every 5 days over a span of 40 days. The findings demonstrated a stable activity of DPV peak current of UA, with less than 10% loss of DPV current observed after 40 days. This finding shows that the storage conditions for these SiNWs-modified SPCE electrodes are simple and do not require special attention to maintain electrode performance. Unlike other electrodes, which need specific conditions and careful handling, particularly when using enzymes in uric acid detection, as shown by previous studies [31, 32].

Table 2

Comparative results of different non-enzymatic electrochemical sensor-based nanomaterial for the determination of UA

Nanomaterials-modified electrode	*Linear range*	*Limit of detection*	*References*
Molecularly imprinted polymer /reduced graphene oxide (MIP/RGO) composite-modified glassy carbon electrode (GSE)	0.01 μM-1.0 μM	0.0032 μM	[33]
PEDOT/Au nanospheres- modified GCE	1.5 μM-150 μM	0.08 μM	[34]
Graphene foam /carbon nanotubes/gold nanoparticles (GF/CNTs/AuNPs)-modified GSE	0.50 μM-60 μM	33.03 nM	[35]
Chrysanthemum-like titanium nitride (CL-TiN)-modified GSE	10 μM-300 μM	0.28 μM	[36]
Multiwalled carbon nanotubes/gold nanoparticles (MWCNTs/AuNPs)-modified GSE	0.1 μM-300 μM	40 nM	[37]
Quantum dots (CQDs)-modified GSE	0.21 μM-13.4 μM	1.3 μM	[38]
Fe3O4@SiO2/GO nanocomposite	0.5 μM-250 μM	70 nM	[39]
CTS/ZnWO4/CILE	0.2 μM-800 μM	0.0637 μM	[40]
Fe_3O_4/SnO_2/Gr-modified GSE	0.015 μM-2.4 μM	0.05 μM	[41]
rGO/ReO3	1–10.5 μM	0.06 μM	[42]
SiNWs-modified SPCE	100 μM to 0.1 nM	3.5 nM	This work

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4. Conclusion

In this study, we successfully utilized SiNWs as a sensing material in an electrochemical system for simple and low-cost determination of UA at a wide range of concentrations, from 100 µM to 0.1 nM, with a LOD of 3.5 nM. The results clearly show that SNWs can enhance the sensitivity and improve the electrochemical current signal. However, there is a need for improvement in order to enhance the selectivity of UA when it is present alongside interference in samples. One potential future direction for this study is to introduce UA biorecognition elements such as aptamers or molecularly imprinted polymers to address the selectivity issue. Additionally, this work could be expanded further by including clinical samples such as serum.

Conflict of interest
No conflict of interest

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