An improved non-enzymatic electrochemical sensor amplified with CuO nanostructures for sensitive determination of uric acid

Abstract: This study displays the facile and fluent electrochemical determination of uric acid (UA) through exceptional copper oxide nanostructures (CuO), as an effective sensing probe. The copper oxide nanostructures were fabricated via an aqueous chemical growth method using sodium hydroxide as a reducing agent, which massively hold hydroxide source. Copper oxide nanostructures showed astonishing electrocatalytic behavior in the detection of UA. Different characterization techniques such as XRD, FESEM, and EDS were exploited to determine crystalline nature, morphologies, and elemental composition of synthesized nanostructures. The cyclic voltammetry (CV) was subjected to investigate the electrochemical performance of UA using copper oxide nanostructures modified glassy carbon electrode CuO/GCE. The CV parameters were optimized at a scan rate of 50 mV/s with −0.7 to 0.9 potential range, and the UA response was investigated at 0.4 mV. PBS buffer of pH 7.4 was exploited as a supporting electrolyte. The linear dynamic range for UA was 0.001–351 mM with a very low limit of detection observed as 0.6 µM. The proposed sensor was successfully applied in urine samples for the detection of UA with improved sensitivity and selectivity.

Keywords: copper oxide nanostructures, electrochemical sensor, modified sensor, uric acid sensor

1 Introduction

The exceptional chemical and physical properties of nanomaterials make them a prominent aspirant to design an appropriate and improved sensing device, mainly electrochemical and biosensors [1–7]. Various kinds of nanomaterials, e.g., metal and metal oxide nanomaterials, viz, NiO, SnO, ZnO, Co3O4, MgO, semiconductor nanoparticles, as well as carbon- and silicon-based nanosized materials have been efficiently employed in constructing the wide varieties of electrochemical and biosensors [8–14]. Among these metal oxide nanoparticles, CuO nanostructures exhibited exception properties that enable them to be utilized in different applications such as chemical sensing devices, magnetic storage media, catalysis, sensors, semiconductors, etc. [15]. Copper oxide is a transition metal oxide and a potential aspirant with a narrow band gap of 1.2–1.5 eV, which makes it a brilliant candidate in electrochemical and photochemical applications [16]. CuO hold outstanding applications and advantages such as wide antibacterial and antifungal activities, inhibits the development...
of microorganism, does not cause skin irritation, and safe for humans when used externally at lower levels [17]. Besides the antimicrobial and biocide properties, CuO nanostructures hold excellent electrochemical properties [18]. CuO is a prominent material in the fabrication of different electrodes for electrochemical sensing. It is widely used in the modification of different electrodes such as glassy carbon electrode and carbon paste electrode, which greatly enhances the sensing capability of electrode utilized for detection of different analytes [19]. The nanostructures provide an important function to the sensing devices, which mainly include catalytic properties of nanomaterials in electrochemical sensing, enhanced electron transfer between analyte and electrode surface, immobilization and labeling of biomolecules, and the capability of acting as reactant [20–22]. Electrochemical sensors are widely employed for the detection of environmental contaminants and organic pollutants, which badly cause lethal diseases [23–26]. The uric acid (UA) is one of the organic compounds named 2,6,8-trihydroxy purine, which is the end-product of purine metabolism or generally known as protein waste [27]. The concentration of UA in the human body varies at different concentrations, and the abnormal level of UA is a major reason for several diseases, for instance, hyperglycemia, Lesch-Nyan syndrome, and gout symptoms [28]. The UA content in normal humans is 149–416 μM in males and 89–357 μM in females. The maximum concentration of UA causes acidic changes to the body fluids, which severely affects the functioning of human cells and subsequently creates the risk of hematuria, renal failure, and leukemia. Henceforth, the determination of UA is very crucial in the diagnosis of various diseases [29–32]. Generally, the methods such as spectroscopic [33], electroanalytical [34], capillary electrophoresis (CE) [35], chemiluminescence [36], and chromatographic techniques [37] are developed for the detection of UA. Nonetheless, these traditional tools consume too much time, require pretreatment of samples, and are very costly. Among these determination tools, the electroanalytical methods are more reliable, cost-effective, simple, sensitive, and more convenient for sensing UA at a very low level of concentration. The determination of UA is also studied through electroanalytical methods [38–44]. UA is one of the electroactive entities that can be irreversibly oxidized into allantoin in an aqueous solution; therefore, number of researchers have focused to quantify UA in different parts of living beings through electrochemical methods via fabricating varieties of electrochemical sensors which are proved to be a promising alternative to traditional methods [45]. In the diagnosis and treatment of different diseases, employing biosensors to detect UA is very convenient because of their fast response, low cost, great sensitivity, selectivity, and direct detection. Biosensors have shown an immense contribution to the sensing devices and flourished the concept of chemically modified electrodes [46]. The modification of electrodes via different chemicals has greatly enhanced their activity and larger surface-to-volume ratio which significantly increases the electron transfer mechanism toward the analyte and electrode surface. The electro-catalytic performance of electrochemical sensors can be enhanced by modifying nanocomposites on the electrode surface [47].

Various polymeric and nanomaterials have also been fabricated for the modification of electrodes to detect UA along with different essential compounds as well as contaminants, which are either beneficial or can severely affect living beings. The materials for the modification of electrodes include aminobenzene sulfonic acid-modified, glassy-carbon electrodes [48], TiO2-modified carbon-paste electrodes [49], poly(3,4-ethylenedioxythiophene)-modified electrodes [50], dimethylfuran (DMF)-modified screen-printed carbon electrodes [51], MnS2 nanosheet/carbon nanofiber-modified electrodes [52], l-cysteine self-assembled gold electrodes [53], Pt nanocomposite-based beta-lactoglobulin functionalized multiwall carbon nanotubes modified electrodes [54], penicillamine self-assembled gold electrodes [55], AuNPs-modified glassy carbon electrodes [56], multiwall carbon nanotubes/AuNPs composites modified electrodes [57], and ruthenium oxide nanoparticles modified electrodes [58].

This work describes the synthesis of copper oxide (CuO) nanostructures via an aqueous chemical growth method using sodium hydroxide as (OH) source. The as-prepared copper oxide nanostructures are then employed for the determination of uric acid (UA) in the presence of various interfering agents. CuO nanostructure-based electrochemical sensors showed good linear response over a wide range of UA. The proposed sensor offers a simple and practically feasible method, free from sample pretreatment, complicated experimental setup, prolonged analysis time, and signifies valuable advancement in the field. Scheme 1 shows the oxidation of uric acid at a modified electrode.

2 Experimental work

2.1 Reagents and solutions

Copper acetate and sodium hydroxide (E Merck, Germany), urea, lactic acid, glucose, uric acid, ethanol, NaCl, and KCl were purchased from Sigma-Aldrich. All the chemicals were
highly pure and used as received. All the glassware used in the experiment were thoroughly washed and then rinsed four times with deionized water. The glassware was dried at 100°C in an oven. 0.1 M PBS buffer solution of pH 7.4 was prepared in deionized water and was used as a supporting electrolyte. 0.1 M uric acid stock solution was prepared in deionized water, and further dilution was followed by the standard addition method for overall electrochemical measurements. The characterization tools such as field emission scanning electron microscopy (FESEM – JSM 7800F) and X-ray diffraction (XRD-7000-Shimadzu scientific instruments) were used to investigate the morphology and crystalline nature of prepared nanostructures, and the electrochemical workstation model (Auto-Lab CHI-760-USA with three-electrode systems) was used for the determination of UA.

2.2 Synthesis procedure for CuO nanostructures

Copper oxide nanostructures were synthesized through the aqueous chemical growth method reported in [59]. Copper acetate \([\text{Cu(CH}_3\text{COO)}_2]\) precursor salt was used with 0.1 M solution in 100 mL milli-Q water. Sodium hydroxide was exploited to provide (OH) to copper acetate that turned copper precursor into CuO nanostructures. A 0.1 M solution of NaOH was separately prepared in Milli-Q water of 100 mL capacity and properly mixed with 0.1 M copper acetate then left on stirring until the solution become completely homogenized. After that, the homogenized solution was covered with aluminum foil and kept in a furnace heated up at 90°C for 4 h. Afterward, the precipitates of copper hydroxide were taken out and washed with deionized water to remove the rest of the impurities. The hydroxide precipitates were then filtered and dried at room temperature. Finally obtained copper hydroxide \(\text{Cu(OH)}_2\) precipitates were annealed at 500°C for 4 h to convert copper hydroxide into the pure CuO nanostructures.

Ethical approval: The conducted research is not related to either human or animal use.

3 Results and discussion

3.1 Characterization of CuO nanostructures

To determine the crystalline nature and the purity of prepared nanostructures of CuO, the powder XRD technique was utilized. Figure 1 displays the XRD diffraction patterns of synthesized CuO nanostructures. The XRD pattern shows the high intensity of the peaks with other supported peaks as well. The diffracted peaks at 2-degree
theta of 35.5 and 38.8, which displays the high crystalline nature of CuO nanostructures, and 32.5, 48.8, 53.6, 58.4, 61.6, 66.2, 68.1, and 72.5 diffraction peaks indicated the monoclinic phase of CuO nanostructures.

All the diffraction peaks are indexed according to the JCPDS No 45-0937. No additional peak was observed in the XRD pattern for commonly accruing impurities, e.g., Cu₂O or Cu(OH)₂ that confirmed the crystallinity of CuO nanostructures with the monoclinic phase. The overall XRD patterns witnessed the high crystallinity and purity of prepared nanostructures. The size of the prepared nanostructures was also calculated by using the Debye Sherer equation, and the average size of CuO nanostructures was found to be 18.4 nm. The morphology of prepared nanostructures was inspected by FESEM. Sodium hydroxide is a well-known compound that massively holds OH source, which gives beautiful and uniform morphology to CuO nanostructures. A highly uniform nanoflakes morphology of fabricated nanostructures can be seen through FESEM images. The low- and high-resolution FESEM images of CuO are manifested in Figure 2. The elemental composition of synthesized CuO nanostructures was determined through energy dispersive spectroscopy (EDS) analysis. The EDS spectra of CuO nanostructures manifested the elemental composition of copper and oxygen with a maximum percentage. The overall EDS spectra are in good agreement with XRD and FESEM images.

3.2 Modification of glassy carbon electrode (GCE)

The procedure for the deposition of metal oxide nanostructures on a glassy carbon electrode was followed via a reported study [60]. First, the glassy carbon electrode was polished with 0.5 µm pore size aluminum powder, washed with deionized water several times, and then sonicated for 20 min in ethanol to make the surface of the glassy electrode clear for modification. For the deposition process, 10 mg of CuO nanostructures was dissolved in 2.5 mL of deionized water, and simultaneously, 500 µL of 5% Nafion was added in it and sonicated for 20 min. Then, 5 µL of CuO nanostructures were deposited on a glassy carbon electrode following the drop-casting method. After modification, the glassy carbon electrode (GCE) was dried at room temperature for 15 min. Afterward, the modified electrode was ready for electrochemical analysis. After modification, the electrode was labeled as copper oxide-modified glassy carbon electrode (CuO/GCE), throughout the text.

3.3 Electrochemical measurements

The electrochemical workstation model (Auto-Lab CHI-760-USA with three-electrode systems; glassy carbon,
platinum wire, and Ag/AgCl used as working, counter, and reference electrode) was utilized for all the voltammetry measurements. Three-electrode-based conventional assembly was used for the detection of UA with 5–10 mL capacity of an electrochemical cell. A 0.1 M stock solution of UA was prepared in deionized water, and similarly, 0.1 M solution of PBS buffer of pH 7.4 was also prepared and used as a supporting electrolyte. UA was diluted to various concentrations by dilution method for electrochemical measurements. 0.1 mM solutions of different interfering agents were prepared in deionized water. The interfering substances such as urea, lactic acid, ethanol, glucose, sodium chloride, and potassium chloride were used for the interference study. To monitor the selectivity of the CuO nanostructures sensor for UA, an equal volume of all interferent substances and UA was taken for voltammetry measurements. The buffer study was carried out using three different buffers: borate buffer at pH 8.0, NaOH at pH 12, and phosphate buffer at pH 7.4. CuO/GCE exploited as a working electrode having a diameter of 2 mm, and the electrochemical cell was completed when Ag/AgCl reference electrode and platinum (Pt) wire counter electrode combined with the working electrode. Before and after each measurement, the modified electrode was manually cleaned by a mechanical polishing procedure using aluminum powder on the polishing cloth. The analytical application of a proposed sensor was carried out in urine samples using the recovery method. Three different urine samples were collected from healthy volunteers in the early morning.

3.4 Voltammetric measurements of uric acid

Figure 3 displays the cyclic voltammogram response of a bare electrode and CuO/GCE in 0.1 M PBS at pH 7.4 and 0.1 mM UA. Whenever bare glassy carbon electrode was employed for the determination of UA, an irregular peak shape as well as current response was observed, but a highly intense peak at +0.4 V is recorded over a measured potential range from −0.7 to 0.9 V when CuO/GCE electrode was employed, which indicates excellent electrocatalytic properties of CuO toward oxidation of UA. The capability of CuO nanostructures is based on the synthesis procedure for CuO which decides the size of particles during preparation. We have exploited the aqueous chemical growth method for the preparation of CuO nanostructures, which not only controlled the size of particles but gave them an excellent electrocatalytic capability for the determination of uric acid when compared with bare electrode could be seen through mentioned figures. As it has been reported in the literature that the conductivity of copper oxide nanoparticles could be enhanced by increasing the temperature above 300°C, in our present study, the synthesis of the temperature of CuO was 500°C; at this temperature, the conductivity of particles could be significantly increased, which increases the electron transfer kinetics between the analyte and nanostructures. Another way to increase the electron transfer rate is to synthesize the smaller-sized nanoparticles with open morphology that can provide enhanced surface as an electrocatalyst and could improve the peak current response in the electrochemical process for the fluent determination of the analyte.

3.5 Effect of supporting electrolyte

The supporting electrolytes perform the function of charge transfer that’s why we have selected three different electrolytes to investigate the influence of electrolytes on CV’s peak current response. The supporting electrolytes included 0.1 PBS pH (7.4), 0.1 M NaOH pH (12), and 0.1 borate pH (8.1). The buffer study was carried out from neutral pH to highly basic medium at around pH (12), and as it is manifested in Figure 4, the highest peak current response recorded was 1 mM UA in 0.1 PBS pH (7.4); therefore, the phosphate buffer was selected as a supporting electrolyte for further measurements.

3.6 Effect of varying scan rate on peak current response

The kinetics of CuO/GCE was monitored to determine the diffusion-controlled process; several scans were taken
and the CV's response was supervised. Figure 5a shows the cyclic voltammogram of 1 mM UA solution at various scan rates. The oxidation process of UA at the modified electrode was examined in increasing order, which reflects well-resolved anodic peak current response of UA by CuO nanostructures. The response of the proposed sensor at varied scans is directly proportional to the peak current when investigated in 1 mM UA solution; hence, the behavior of the proposed sensor was diffusion-controlled. Figure 5b indicates the square root of scan rates \((\text{mV/s})^{1/2}\) vs anodic peak current with \(R^2 = 0.994\).

### 3.7 Calibration study of UA

Figure 6a indicates the calibration curve for the uric acid detection, and it displays a linear response of peak current vs UA concentration ranging from 0.001 to 351 mM. The \(R^2\) value of linear response is found to be 0.998, which describes the good analytical behavior of CuO/GCE in the said linear range. The CV response at various concentrations and its linear peak current response are shown in Figure 6b. The LOD and LOQ of the proposed method for the detection of UA were calculated to be 3.3 and 10 times the standard deviation of blank divided by the slope of calibration curve \([61]\) and was found to be 0.6 and 1.98 \(\mu\)M.

### 3.8 Effect of interference, reproducibility, and stability

To examine the specificity of the proposed sensor, different interferants such as urea, lactic acid, ethanol, glucose, \(K^+\), and \(Na^+\) with 1 mM concentration were tested in presence of 1 mM of uric acid as shown in Figure 7a. From the cyclic voltammogram \(I_{pa}\) of UA, there is no noticeable impact of common interfering agents in the detection of UA was seen. A little change in the \(I_{pa}\) response of UA was observed with a maximum relative standard deviation of 4.8% when foreign interferant urea was added. Due to the possible reason that both UA and urea contain \((-CO-NH)\) group that might be the cause of interference with the \(I_{pa}\) response of UA with a maximum relative...
standard deviation (RSD) of 4.8%. While other inorganic ions and organic compounds did not make a significant change in the Ipa response of UA. For making the determination process of UA systematic, the (RSD) with \( n = 4 \) for each interferant was tested against UA. However, the maximum RSD was calculated to be \(<\pm 5\%\) which manifested the good selective nature of modified electrode toward electrochemical oxidation of UA. The Ipa response indicates that the proposed sensor is very selective toward the detection of UA; therefore, the proposed sensor can be selectively used for the detection of UA in real samples. To investigate the stability of the proposed sensor for the detection of UA and the reproducibility measurements, 25 repetitive runs were recorded in 3 mM concentration of UA shown in Figure 7b. A relative standard deviation of 1.2% in the peak current difference was recorded in this case, which confirms the excellent reproducibility and stability of CuO/GCE for the determination of UA.

### 3.9 Analytical application

To check the accuracy of UA in real samples, a recovery test was performed to investigate the feasibility of the UA sensor. The proposed sensor was applied to monitor the
concentration of UA in three different urine samples. The urine samples were collected from volunteers in the morning to check the maximum concentration of UA. The freshly collected urine samples were taken to the laboratory and were filtered using a 0.3-µm pore-sized filter paper. The urine samples were diluted to 0.1 phosphate buffer making the ratio of 1:10 volume/volume, and then, the standard method was exploited to monitor the accuracy of UA in urine samples by spiking them with a standard concentration of UA whose concentration was previously recorded. To know the effect of the matrix and estimating the concentration of UA from the calibration curves, the recovery experiments were performed.

The reproducibility of real samples, as well as spiked standard concentration of UA, was also determined by performing each measurement \( n = 3 \), and a well-resolved peak current response was recorded for three different urine samples. Recovery values of all urine samples are listed in Table 1.

The recovery percentage of UA varies from 95 to 104% with linear segments, which not only shows great sensitivity but also acceptable percent recovery values. It is clear from the results that the proposed sensor detected UA in urine samples with great suitability and sensitivity. Table 2 lists the comparison of the electrochemical performance of various sensors for the detection of UA. In addition, most of the reported sensors are either complicated in use or more expensive which are not suitable for under-developing countries. While some of them are less expensive but showed poor sensitivity toward the detection of UA. Our proposed sensor is being highly stable, cheap, and extremely sensitive toward the determination of the proposed analyte which makes it differentiated from other reported sensors.

### Table 1: Results of real sample analysis

| Sample | Spiked (mM) | Detected (mM) | RSD (%) | Recovery (%) \( n = 3 \) |
|--------|-------------|---------------|---------|--------------------------|
| Urine 1 | 0           | 0.068         | 0.52    | —                        |
|        | 0.5         | 0.503         | 0.21    | 100.6                    |
|        | 1           | 0.955         | 2.58    | 95.56                    |
|        | 1.5         | 1.54          | 1.67    | 102.6                    |
| Urine 2 | 0           | 0.135         | 1.76    | —                        |
|        | 0.5         | 0.523         | 1.80    | 104                      |
|        | 1           | 0.989         | 2.01    | 98.9                     |
|        | 1.5         | 1.45          | 1.22    | 96.45                    |
| Urine 3 | 0           | 0.335         | 1.81    | —                        |
|        | 0.5         | 0.502         | 2.19    | 100.4                    |
|        | 1           | 0.991         | 1.93    | 99.1                     |
|        | 1.5         | 1.52          | 2.39    | 101.2                    |

### Table 2: Comparison study of reported sensors for uric acid detection

| Sensing materials and electrodes | Method | Electrolyte | pH | Scan rate | Linear range | LOD | Ref. |
|---------------------------------|--------|-------------|----|-----------|--------------|-----|------|
| Poly(3,4-ethylenedioxythiophene) modified glassy carbon electrode | CV     | Phosphate   | 7.4 | 50 | 1–20 | 1 | [50] |
| Penicillamine self-assembled gold electrode | CV & DPV | KCl | — | 100 | — | 1 | [55] |
| L-Cysteine self-assembled gold electrode | CV & DPV | Phosphate | 7.0 | 100 | 10–80 | 2 | [53] |
| TiO₂ Modified carbon paste electrode | DPV | Phosphate | 8.0 | 10 | 200–1,500 | 12 | [49] |
| Poly(p-aminobenzene sulfonic acid) modified glassy carbon electrode | CV & DPV | Phosphate | 7.0 | 100 | 1 × 10⁻³ to 1 × 10⁻⁴ | 1.125 | [48] |
| Ruthenium oxide nanoparticles glassy carbon electrode | DPV | Phosphate | 7.0 | — | 3–7,586 | 0.67 | [58] |
| Azure A-interlinked multi-wall carbon nanotubes/gold nanoparticles composite modified electrode | CV & DPV | Phosphate | 7.0 | — | 0.5–50 | 0.028 | [57] |
| Gold nanoparticles modified glassy carbon electrode | CV & DPV | Phosphate | 7.0 | 50 | 2.8–57.5 | [56] |
| β-lactoglobulin functionalized multiwall carbon nanotube/platinum nanocomposite glassy carbon electrode | CV | KCl | 7.0 | 100 | 0.02–0.5 | 0.8 | [54] |
| MoS₂ nanosheet arrays/carbon nanofibers | CV & DPV | KCl | 7.0 | 100 | 1–60 | 1 | [52] |
| CuO nano-rice modified electrode | CV & DPV | Phosphate | 7.0 | — | 1–60 | 1.2 | [62] |
| ZnO/graphene/ITO | CV & DPV | Phosphate | 7.4 | 50 | 50–80 × 10⁻⁶ | 5 | [63] |
| Nickel hexa-cyanoferrate/CPE | CV & DPV | Phosphate | 9 | 100 | 2–12 × 10⁻⁶ | 1.8 | [64] |
| Copper oxide nanostructures/modifed glassy carbon electrode | CV | Phosphate | 7.4 | 50 | 0.001–351 × 10⁻³ | 0.6 | Present work |
4 Conclusion

In summary, highly discerning copper oxide nanostructures were synthesized through an efficient and reliable aqueous chemical growth method. The FESEM, XRD, and EDS results confirm the suitable morphology, monoclinic phase structure with the average size of 18.4 nm, and maximum percent elemental composition of copper and oxygen. The prepared nanostructures were exploited for electrochemical determination of uric acid via cyclic voltammetry. The maximum anodic peak current response for UA was investigated at 0.4 V vs Ag/AgCl, and the linear dynamic range was 0.001–351 mM with a very low limit of detection observed as 0.6 µM. The proposed sensor was then subjected to urine samples that suggested the way as a diagnostic tool for uric acid determination with improved selectivity and sensitivity.

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