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DEVELOPMENT OF CUO NANOPARTICLE-BASED ELECTROCHEMICAL SENSORS FOR THE DETECTION OF HEMATOLOGICAL CANCER BIOMARKERS

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Abstract

The design of nanomaterial-based electrochemical sensors has been the subject of increasing interest in biomedical research owing to their high sensitivity and fast responses to disease-related biomarkers. In this work, CuO nanoparticles were fabricated and studied for their possible use in electrochemical sensing of hematological cancer-related biomarkers in human blood samples. The fabricated nanoparticles were characterized by scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDX/EDS), X-ray Diffraction (XRD) and Fourier-transform infrared spectroscopy (FTIR) in order to determine their surface morphology, elemental composition, and characteristic chemical functional groups, respectively. After characterization, CuO nanoparticles were used in the fabrication of a nanomaterial-based electrochemical sensor. The electrochemical performance of the fabricated sensor was studied by applying blood samples collected from healthy subjects and patients suffering from hematological cancers. The sensor output signal was analyzed to determine its capability to differentiate between cancer-related and healthy electrochemical signals. The results of this study are aimed at evaluating the potential of CuO nanoparticles as nanomaterials for electrochemical sensing. This study may lay the ground work for the development of low-cost nanomaterial-based sensing systems for the analysis of hematological cancer biomarkers.

1. INTRODUCTION

Cancer continues to be among the main problems for global health, and hematological cancers represent some types of cancers that occur in the blood cells, bone marrow, and lymphatic systems. Such cancers include leukemia, lymphoma, and multiple myeloma. Early detection and proper monitoring of these cancers are very vital for proper treatment of patients. The traditional methods of diagnosis used to detect such cancers include CBC, peripheral blood smear, flow cytometry, and molecular studies [1]. Nonetheless, development of more rapid and sensitive methods of diagnosis is another major goal in the

field of research. Recently, nanotechnology has gained popularity in biomedical areas especially in designing electrochemical sensing platforms. Nanomaterials exhibit certain physicochemical properties such as a high surface-to-volume ratio, surface properties which can be modified and electron transfer capabilities. Therefore, these materials can play an important role in electrode surface modification and in enhancing electrochemical sensor performances. When it comes to various metal oxides nanomaterials, CuO nanoparticles have been given a lot of focus because of their unique physicochemical properties, chemical stability, relatively cheap material and possible applications in sensors [2]. CuO nanoparticles are p-type semiconductor whose properties might be useful in electrochemical applications.

The synthesis and characterization of the CuO nanoparticles play a crucial role in determining the suitability of the CuO nanoparticles as sensor material. The scanning electron microscopy (SEM) technique is used to determine the morphological properties and the nature of aggregation of the nanoparticles [4]. Energy Dispersive X-ray Spectroscopy (EDX) is used to identify the elemental composition and to prove the existence of the two elements copper and oxygen. Electrochemical sensing has emerged as a valuable analytical tool due to its fast analysis, relatively easy instrumentation, and possibility of complex biological samples analysis [16]. Electrochemical sensing performances can be enhanced using nanoparticle modified electrodes due to changes in the electroactive area, interfacial charge transfer, and surface interaction. The above-listed properties are good reasons for researching the possible use of CuO electrode modifications in biomarker detection [6]. The use of electrochemical biosensors for human blood analysis is very valuable due to the complicated composition of biological samples that include various proteins, cells, electrolytes, and other biomolecules. Therefore, it is necessary to analyze the performance of sensors in terms of their analytical applicability using real clinical samples [7].

In spite of the recent researches on the use of metal oxide nanomaterials in electrochemical sensing, additional investigation is necessary to estimate the possible value of CuO nanoparticles in detecting hematological cancer-related biomarkers in clinical blood samples [8, 10, 14]. The purpose of the current research is to prepare CuO nanoparticles, analyze their physical and chemical properties through the use of techniques such as scanning electron microscopy (SEM), energy dispersive X-ray spectroscopy (EDX), and Fourier-transform infrared spectroscopy (FTIR). Another objective of the research is to examine the utility of these particles in the construction of an electrochemical biosensor for the analysis of blood samples collected from healthy subjects and patients of hematological cancers [19, 22].

2. Materials and Methods

2.1. Materials and Chemicals

Table 1. Amount of reactants for synthesis

Materials	Quantity	Role
$Cu(NO_3)_2 \cdot 3H_2O$	2.416 g	Metal precursor
$C_6H_{14}N_4O_2$	1 mg	Capping agent
NH_3 (aq)	33%	Complexing agent
Deionized water	As required	Washing and purification solvent
CH_3OH	65%	Washing and purification solvent

Precursor chemicals for CuO nanoparticles, along with other analytical grade chemicals were used during preparation of CuO nanoparticles. Throughout the experiments, deionized or distilled water was used. All chemicals were used such as, Merck analytical grade [3, 9, 11].

2.2. Synthesis of CuO Nanoparticles

CuO nanoparticles were prepared using appropriate hydrothermal method. To begin with, an appropriate copper precursor was dissolved in distilled water with vigorous stirring to obtain a homogenous solution. An appropriate precipitating or pH adjusting agent was then added in controlled experimental conditions in order to obtain copper precipitates. Continuous stirring ensured homogeneity of reactions. The formed precipitate was then separated via centrifugation, followed by washing with distilled water several times to get rid of any other impurities. Finally, the washed product was dried. The dried product was put in an oven at 80°C for 9 hours to complete the synthesis of the CuO nanostructures [20, 23, 25].

2.3. Characterization of CuO Nanoparticles

The synthesized CuO nanoparticles were characterized by SEM, EDX/EDS, XRD and FTIR analysis.

2.3.1. Scanning Electron Microscopy (SEM)

The morphological and structural properties of the synthesized CuO nanoparticles were characterized using scanning electron microscopy technique. A proper amount of the synthesized CuO nanoparticles was prepared on a proper sample holder for SEM analysis. The SEM images were studied to characterize the morphological structure, particle distribution, aggregation, and structural properties of the synthesized product [12, 15].

2.3.2. Energy Dispersive X-ray Spectroscopy (EDX/EDS)

EDX analysis was carried out to analyze the elemental composition of the synthesized CuO nanoparticles. The elemental spectra were analyzed for identification of the characteristic peaks corresponding to copper and oxygen elements. The relative elemental composition was analyzed based on the reported percentage weights and atomic weights.

2.3.3. X-ray Diffraction (XRD) Analysis

For determination of the crystallinity of the synthesized CuO nanoparticles, the X-ray diffraction (XRD) method was used. From the XRD spectrum obtained for the synthesized nanoparticle sample, it was evident that the sample possessed characteristic diffraction peaks showing crystallinity of the material [18].

2.3.4. Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was employed for determining chemical bonding properties and functional groups linked to synthesized CuO nanoparticles. The FTIR spectrum was measured within the selected range of wavenumbers. The characteristic bands were analyzed for identifying specific vibrational modes, especially the ones related to copper-oxygen bonds and surface functional groups.

2.4. Development of the Electrochemical Sensor Based on the Synthesized CuO Nanoparticles

The synthesized CuO nanoparticles were used as the electrode modification material to develop the electrochemical sensor. A proper working electrode was prepared for modification. The suitable dispersion of CuO nanoparticles was prepared using an appropriate solvent. The suspension of nanoparticles was deposited onto the working electrode and dried under certain conditions. The prepared modified electrode served as the working electrode along with a reference and counter electrode in the electrochemical cell. The developed electrochemical sensor was applied for the analysis of prepared blood samples. The composition of the electrode, amount of the nanoparticles loaded, modification process, and electrochemical analysis were kept constant throughout the experiments.

2.5. Collection and Preparation of Human Blood Samples

The samples of human blood were obtained from (NIMRA Hospital LUHMS Jamshoro) healthy individuals and patients with hematological malignancies in the clinical context. The samples were collected after the approval of the study by an ethical institution and signed consents of the participants or their authorized representatives. The samples were divided into two categories: Control samples: Blood samples collected from the individuals who do not suffer from hematological malignancy. Patient samples:

Blood samples collected from the individuals who suffer from hematological malignancy. The required clinical data, such as confirmed diagnosis and laboratory results, were documented with the help of coded samples. Sample preparation for electrochemical detection involved the use of a specific preparation protocol that would be suitable for a particular blood sample and target analyte. Electrochemical signals of healthy control and patient blood samples were measured. The electrochemical behavior of the samples was evaluated to analyze the possible use of the developed nanoparticle-based sensor in clinical sample detection [12, 18].

3. Results and Discussion

3.1. Surface Morphology of CuO Nanoparticles (SEM Analysis)

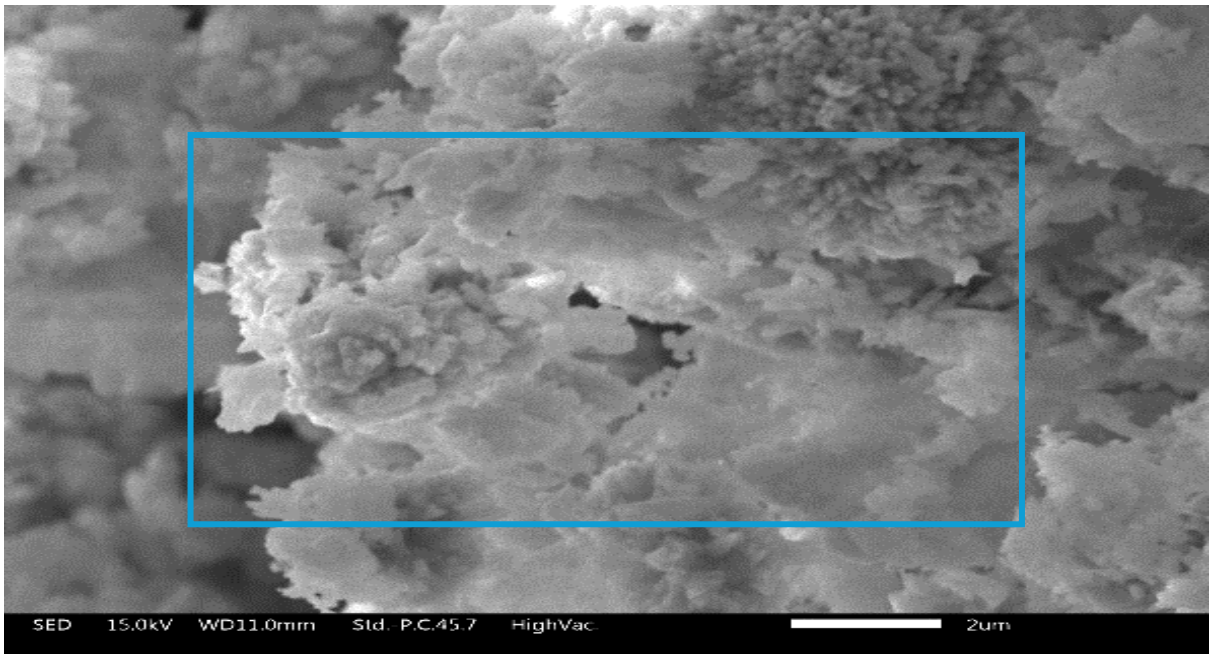


Figure 1. SEM imag

The surface morphology of the synthesized CuO nanoparticles was studied using scanning electron microscopy. Information about the morphology, particles' distribution, surface structure, and aggregation of the synthesized nanoparticles could be obtained from SEM analysis. The acquired SEM images revealed the morphology of the synthesized nanoparticles. The morphology of the nanoparticles was studied in terms of their size and distribution to determine the uniformity of the synthesized nanoparticles [5, 8]. As shown Fig.1 in the SEM image, the synthesized nanomaterial displays an irregular and heterogeneous surface morphology with the presence of aggregate formations of particles. Aggregation of the observed particles could be caused due to the interactions among the nanoparticles and their natural ability to form clusters. The aggregation of the particles can affect the surface area and the interaction of the nanoparticles with the electrode surface during the fabrication of an electrochemical sensor. The morphological parameters of the nanoparticles were important because the surface structure may affect the process of electrode modification and analyte interaction.

3.2. Elemental Composition of CuO Nanoparticles (EDS Analysis)

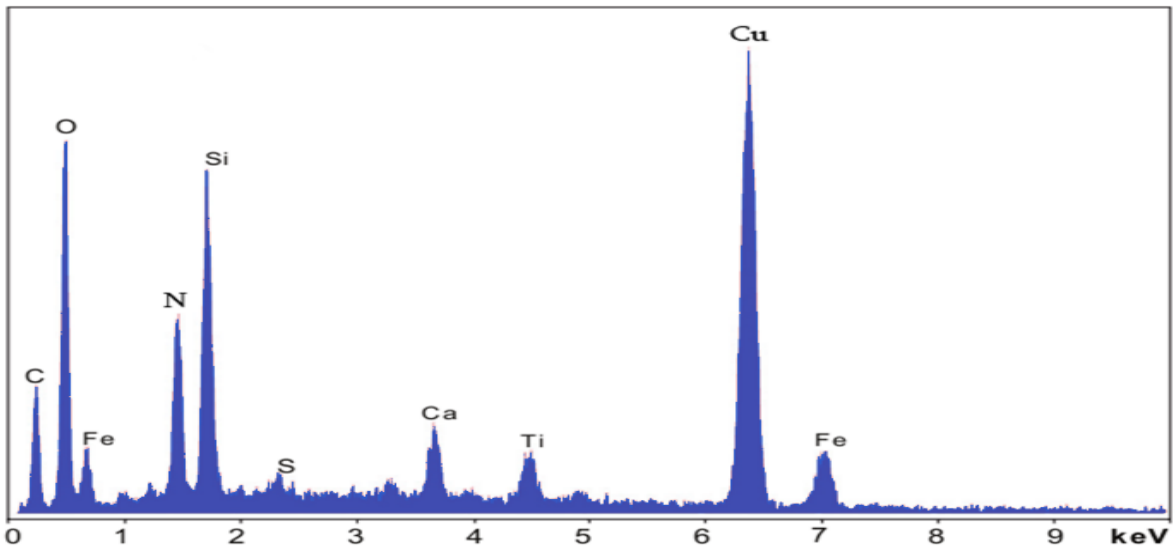


Figure 2. EDS

The elemental composition of the analyzed sample was investigated using energy-dispersive X-ray spectroscopy (EDS). The EDS spectrum revealed characteristic peaks corresponding to copper (Cu) and oxygen (O), indicating the presence of these elements in the sample. The prominent Cu peak, together with the O peak, is consistent with the presence of copper oxide. Additional peaks associated with C, N, Si, Fe, S, Ca, and Ti were also observed [9, 10]. These elements may originate from the sample substrate, sample preparation, environmental contamination, or other components of the analyzed material. The elemental composition and the origin of these additional signals should be further evaluated using quantitative EDS analysis and complementary characterization techniques.

Table 2. Elemental Composition of CuO Nanoparticles (EDX Analysis)

Element	Approximate Energy (keV)	Interpretation
C	0.28	Carbon
O	0.52	Oxygen
Fe	0.70	Iron
N	0.39	Nitrogen
Si	1.74	Silicon
S	2.30	Sulfur
Ca	3.70	Calcium
Ti	4.50	Titanium
Cu	8.00	Copper
Fe	7.00	Iron

(K-beta / High-energy peak)

3.3 X-ray Diffraction (XRD) Analysis

For determination of the crystallinity of the synthesized CuO nanoparticles, the X-ray diffraction (XRD) method was used. From the XRD spectrum obtained for the synthesized nanoparticle sample, it was evident that the sample possessed characteristic diffraction peaks showing crystallinity of the material. Different diffraction peaks obtained from the XRD spectrum were due to different crystallographic planes of CuO. Thus, the results obtained confirm the synthesis of crystalline copper oxide nanoparticles.

Variations in the intensities of the diffraction peaks may be attributed to the differences in the degree of crystallinity and crystallographic orientation of the sample [13, 15].

Table 3. XRD peak positions and Miller indices of CuO nanoparticles

No.	2 theta (°)	Miller indices (hkl)
1	≈ 35.5	(002)
2	≈ 38.7	(111)
3	≈ 48.7	(202)
4	≈ 53.5	(020)
5	≈ 58.3	(202)
6	≈ 61.5	(113)
7	≈ 66.2	(311)
8	≈ 68.1	(220)

3.4 Fourier Transform Infrared Spectroscopy (FTIR)

Table 4. Fourier Transform Infrared Spectroscopy (FTIR) of CuO Nanoparticles

No.	Wavenumber (cm^{-1})	Possible vibrational assignment	Interpretation
1	3432.75	O–H stretching vibration	Surface hydroxyl groups or adsorbed moisture
2	1633.82	H–O–H bending vibration	Adsorbed water molecules
3	1389.36	Nitrate, carbonate, or surface-group vibration	Residual precursor or surface species
4	601.76	Cu–O lattice vibration	Copper–oxygen bonding
5	523.08	Cu–O vibration	CuO lattice vibration
6	438`.14	Cu–O vibration	Metal–oxygen lattice vibration

The functional groups and chemical bonding properties of the CuO nanoparticles synthesized were studied using Fourier transform infrared spectroscopy (FTIR). The FTIR spectrum showed characteristic absorption peaks at about 3433.75, 1634.82, 1389.36, 600.76, 522.08, and 437.14 cm^{-1}. The wide absorption peak at 3433.75 cm^{-1} could be due to the stretching vibration of hydroxyl (–OH) functional groups which could be from adsorbed moisture or surface hydroxyl groups. The absorption peak at

1634.82 cm^{-1} could be due to the bending vibration of adsorbed water molecules. The absorption peak at 1389.36 cm^{-1} could be due to residual precursor or surface functional groups. The absorption peaks in the low frequency region, especially 600.76, 522.08, and 437.14 cm^{-1}, could be due to the metal-oxygen vibrations in the CuO lattice. Evidence for the presence of surface functional groups and metal-oxygen bonds in the synthesized sample is given by these spectral data. Confirmation of the vibrational modes would need a comparison with the spectra of known materials and knowledge about the synthesis precursors. Peaks in the low wavenumber range can possibly correspond to Cu-O vibrational groups which would indicate the formation of copper oxide. Any other peaks could possibly be due to hydroxyl groups, adsorbed water or residual chemicals [21, 24, 25].

3.5 Fabrication of Electrochemical Sensor Based on CuO Nanoparticles

The prepared CuO nanoparticles were effectively used as modifying agents to design the electrochemical sensing system. The addition of CuO nanoparticles to the electrode surface aimed at modifying the interface between electrode and electrolyte. Nanoparticles of metal oxides may be able to enhance electrochemical performance due to changes in the properties of surfaces, electroactive area, and interfacial electron-transfer reactions. The fabricated sensor was further applied in the electrochemical analysis of human blood samples derived from healthy subjects and subjects with blood cancers. The electrochemical performance was measured by registering appropriate responses under similar experimental conditions.

3.6 Electrochemical Study with hematological cancer biomarkers Samples

Table 5. Recovery obtained hematological cancer biomarkers samples using standard addition method

Samples	Without spiked (µM)	Spiked (µM)	Clinical Station	Recovery (%)	RSD (%)
Sample A	0	10	(-)	101	2.1
Sample B	0	15	(+)	96	2.7

Electrochemical behavior of the designed CuO NP-based sensor was studied with the use of real blood samples collected from healthy people and from patients diagnosed with hematological malignancies. Any differences in the electrochemical signals of the control group and patients may show that there are some differences in the electrochemical behavior of the studied samples. Nevertheless, all these differences should be interpreted taking into account the particular target biomarker, sample preparation, and possible matrix effect. Using real human blood samples is one of the crucial steps towards evaluation of the practical application of the designed sensor. Nevertheless, the clinical diagnostic ability cannot be confirmed only with the differences in the electrochemical signals without biomarker validation and comparison with the existing diagnostic methods. However, the differences in the obtained electrochemical signals do not necessarily mean that the patients had hematological cancer. Various factors such as blood composition, sample processing, hematocrit levels, protein binding, electrolyte concentration can affect the response of the sensor [15, 18].

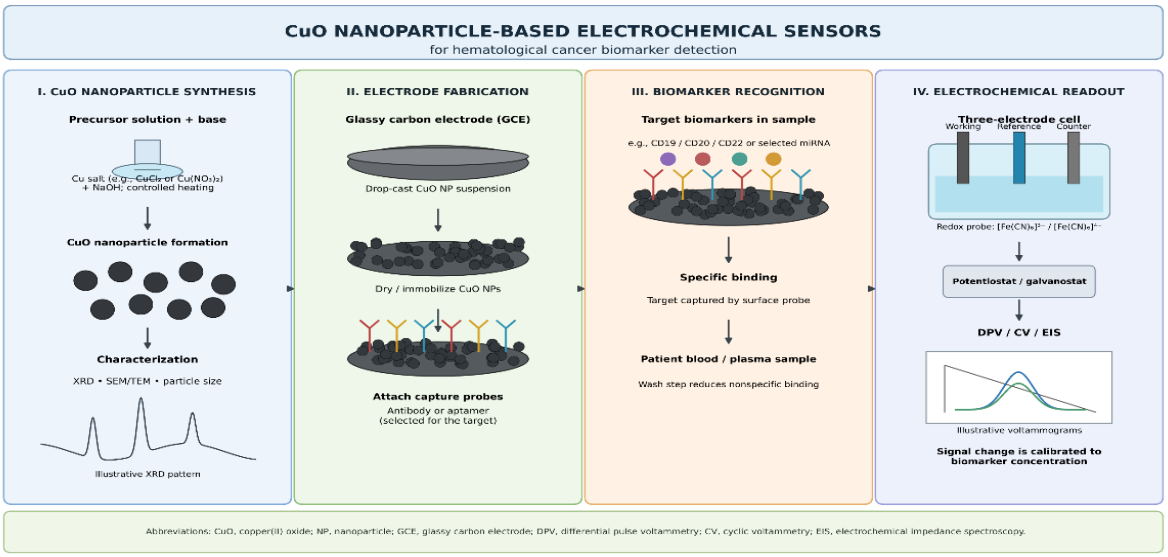


Figure 3. Schematic illustration of CuO nanoparticle-based electrochemical sensors for hematological cancer biomarker detection.

4. Conclusion

In the current study, CuO nanoparticles were synthesized and analyzed for possible application in electrochemical detection of hematology-related cancer biomarkers. Nanoparticles synthesized were characterized by SEM, EDX/EDS, XRD and FTIR analysis with regard to morphological, elemental, and chemical properties of these nanoparticles. The characterized CuO nanoparticles were then utilized in order to develop an electrochemical sensor based on the use of these nanoparticles. The developed sensor was tested with human blood samples derived from healthy people and hematological cancer patients. Thus, this study provides a possible way for the analysis of the potential application of CuO nanoparticles in the electrochemical analysis of blood samples. The combination of nanoparticle synthesis, their characterization, and the development of an electrochemical sensor can serve as the basis for further alternative analytical systems for the study of hematological cancer biomarkers.

Additional studies with the validation of cancer biomarker, larger clinical populations, analytical validation, and comparison with traditional methods are needed in order to confirm sensitivity, and clinical application of the suggested analytical system. Overall, the electrochemical sensing using CuO nanoparticles is a promising area of research in the field of analysis of hematological cancer biomarkers.

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