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Glucose biosensor based on activated carbon – NiFe₂O₄ nanoparticles composite modified carbon paste electrode

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ABSTRACT

Carbon-based materials continue to pique the interest of many scientists due to their desirable characteristics such as large surface area, high electrical conductivity, and stability. This study aimed to describe the use of local coconut shell-based activated carbon (AC) to produce carbon paste electrodes used in the development of glucose biosensor. Subsequently, the performance of the carbon paste electrode was enhanced by using NiFe₂O₄ nanoparticles (NiFe-nps) to improve the electron transfer and redox potential behavior. The results showed that the best carbon paste electrode contains an activated carbon-paraffin oil ratio of 2:0.75b/b, with 8% of NiFe-nps added to the activated carbon. The detection of hydrogen peroxide using an AC-NiFe₂O₄/CPE electrode showed an oxidation peak at 0.35 V and reduction peak at -0.5 V, with the optimum operational condition using 100 mM phosphate buffer and optimum pH of 7.5. The glucose oxidase enzyme (GOx) was immobilized on the AC-NiFe₂O₄/CPE electrode for glucose determination, and the modified GOx-AC- NiFe₂O₄/CPE showed a linear response to detect glucose in both the oxidation (0.12 V) and reduction (-0.4 V) peaks. This analysis was conducted using cyclic voltammetry under optimal conditions. The fabricated glucose biosensor did not reveal any significant difference in detecting glucose in blood samples when compared to the standard method used in the hospital.

1. Introduction

Diabetes mellitus has recently emerged as the most studied and lethal degenerative disease. According to WHO, approximately 43% of the 3.7 million deaths caused by diabetes mellitus occur before the age of 70 years, with the percentage of these deaths being higher in developing countries [1]. According to the *International Diabetes Federation* (IDF), the global prevalence of diabetes mellitus was 424.9 million people in 2017 and is expected to reach 628.6 million in 2045 [2]. Furthermore, diabetes mellitus was one of the top four comorbid diseases among Covid-19 patients in Indonesia, in 2020. The percentages of COVID-19 patients who were infected with the disease and those who died from it were 34.5% and 11.6%, respectively [3].

Early detection of blood glucose is one of the most essential measure for reducing diabetes mellitus, and the detection is best achieved using biosensors [4]. The biosensor is an analytical method that combines the biologically active compound with a transducer to convert biological interactions into readable signals [5]. Glucose biosensors mostly utilize

the enzyme of glucose oxidase as biological sensing and coupling with electrochemical detection. Biosensors are still worth developing because they offer several advantages such as being easy to prepare in a small portable system, being relatively inexpensive, having high sensitivity and selectivity and allowing *real-time* measurements [6].

Biosensors are typically developed to increase their sensitivity, selectivity, stability and effectiveness, as well as reduce their production costs. The performance improvement strategies could be done in the biological sensing elements (enzymes, antibodies, cells), supporting materials for sensing immobilization or developing new detectors. Alternatively, several new materials, such as carbon nanoparticles [7], gold nanoparticles [8] and nickel nanoparticles [9] have been claimed to improve the performance of biosensors that use electrochemical detection.

Carbon-based modified materials have recently received attention due to their numerous benefits such as large specific surface area, good electrical conductivity, and stability. Furthermore, some of the carbon materials that have been explored included nanotubes [7], graphene

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[10], mesoporous [11], carbon black [12] and activated carbon [13]. Preliminary study shows that the activated carbon gotten from local coconut shells has a high porosity, surface area, and high electronic conductivity, making it promise to be applied in various technological innovation.

This study examined the design of a glucose biosensor using activated carbon as a base material, which is derived from coconut shells. The aim was to use the activated carbon to produce a carbon paste incorporated with NiFe₂O₄ nanoparticles. There have also been a few reports of the use of activated carbon from local coconut shells, specifically for biosensor applications.

2. Experimental

2.1. Materials

Activated carbon was prepared from local coconut shell, glucose oxidase from *Aspergillus niger* (type II, >= 15,000 U/g solid, Sigma) NiCl₂·6H₂O (Merck, Germany), FeCl₃·6H₂O (Merck, Germany), glutaraldehyde 25% (Sigma), albumin from bovine serum (BSA) (Sigma), glucose anhydrous (≥98.0%) (Sigma), hydrogen peroxide 30% (Merck, Germany), sodium hydroxide (Merck, Germany), disodium hydrogen phosphate (Merck, Germany) and sodium dihydrogen phosphate (Merck, Germany).

2.2. Apparatus and measurements

The morphology of carbon paste electrodes was examined using Scanning Electron Microscopy (SEM) (JSM-6510 LA, JEOL, Japan), operating at 15 kV. A three-electrode system was used for electrochemical analysis, along with an Ag/AgCl (3 M KCl) reference electrode (Metrohm, Switzerland) consist of 3 M KCl, a carbon paste electrode as a working electrode, and a stainless-steel rod as a counter electrode. Furthermore, a potentiostat was used to conduct the electrochemical measurements (Rodeostat, IORodeo Smart Lab Technology, US).

2.3. Coconut shell activated carbon preparation

The carbonization process was used to create activated carbon (AC), which involved burning coconut shells at 300 °C for an hour in an oxygen-depleted environment to remove the organic elements found in the shells. Consequently, this loss of organic molecules led to the formation of carbon pores and the physical activation of the carbon from charred coconut shells. The severance of carbon chains from organic molecules was enabled by intense heat and water vapor, which was used to remove impurities and impure hydrocarbons from the activated carbon during the physical activation process. The resulting carbon was heated to a temperature of 800–900 °C after the water vapor streaming. Usually, carbon monoxide, carbon dioxide, and hydrogen are produced when water vapor reacts with carbon. Lastly, the activated carbon was pulverized using a mill shaker for 100 min to obtain micrometer-sized particles.

2.4. NiFe₂O₄ nanoparticles (NiFe-nps) preparation

The coprecipitation method [14] was used to synthesize NiFe-nps with NiCl₂·6H₂O and FeCl₃·6H₂O as ion provider Ni²⁺ and Fe³⁺. The mole fraction ratio used was 1:2, by dissolving 1.188 g of NiCl₂·6H₂O in 20 mL distilled water and 2,701 g of FeCl₃·6H₂O in 20 mL of distilled water in a separate glass beaker. The two solutions were then homogeneously mixed, and NaOH precipitation agent was then dropped into the mixture of Ni and Fe while stirring (1000 rpm) at 85 °C for 60 min. The resulting nanoparticles were then precipitated continued by washing distilled water for approximately 7 times of 50 mL. The retrieved precipitated nanoparticles were dried at 90 °C and the brown nanoparticles powder was then used for further procedures.

2.5. Carbon paste electrode manufacture

The carbon paste electrodes (CPE) were made by mixing AC and paraffin oil 5:4 w/w ratio [15]. Subsequently, the mixture was homogenized with a mortar and pestle for 30 min, and the resulting composite was placed in a 5 mm inner diameter polylactic acid (PLA) tube. The PLA tube was then added with a 5 mm graphite rod as a connector, and the lower side of the electrode was polished with HVS paper until a flat and shiny surface was observed, which indicated that the electrode of carbon paste electrode from activated carbon (AC/CPE) was ready for use. The 5 mm diameter of carbon paste electrode gives the active surface area of the electrode of 19.63 cm².

2.6. Electrode testing on hydrogen peroxide

This test was conducted to determine the sensitivity of the carbon paste electrode to detect hydrogen peroxide without any modification. The electrochemical method used was cyclic voltammetry to easily observe the oxidation and reduction peaks of hydrogen peroxide. The hydrogen peroxide solution was prepared in 50 mM phosphate buffer with pH of 7.0 and concentrations of 2,4,6,8 and 10 mM.

2.7. Carbon paste electrode composite optimization

The composition of the carbon paste electrode was optimized by adding NiFe-nps to improve the electrical conductivity. This optimization was carried out in the same way as the manufacture of electrode paste, with the addition of nanoparticles at various concentrations of 2, 4, 8, and 10% w/w. The AC was mixed with NiFe-nps at a certain ratio and homogenized using mortar and pestle for about 30 min. The homogenous mixture was then added paraffin oil with the best ratio previously optimized and molded in the electrode cover to get the carbon paste electrode contains activated carbon and NiFe₂O₄ nanoparticles (AC-NiFe₂O₄/CPE). The modified electrodes along with various nanoparticle compositions were then tested with hydrogen peroxide and compared to carbon paste without NiFe-nps.

2.8. Modified electrode detection test on hydrogen peroxide

This test was conducted to determine the sensitivity of the modified electrode tested to hydrogen peroxide. Consequently, the Cyclic Voltammetry (CV) method was employed, and the test solution was hydrogen peroxide in 50 mM phosphate buffer pH 7. The hydrogen peroxide concentration used was 0–10 mM.

2.9. Optimization of the cyclic voltammetry method

Cyclic voltammetry optimization was conducted to determine the optimal condition of the electrochemical cell with a scan rate. Determination of the optimal condition of the electrolyte solution was carried out with the concentration of 5 mM H₂O₂ solution in phosphate buffer pH of 7. The scan rate used was 0.05 to 0.2 V/s to see the optimum oxidation–reduction potential current. Then measurements were made using the CV method with the potential used between 1 to –1 Volt, every 3 repetitions.

2.10. Buffer pH and concentration optimization

This test was conducted to determine the optimal conditions for electrochemical cells with varying buffer pH and concentration. The modified electrode was used to measure the hydrogen peroxide using CV with various buffer pH (6.0 – 8.0) and concentration (25 – 200 mM).

2.12. Testing of modified electrodes with GOx enzyme at various glucose concentrations

This test was conducted to determine the sensitivity of the modified electrode containing the glucose oxidase (GOx) enzyme after an electrochemical test on a glucose standard solution. The GOx was immobilization on the AC-NiFe₂O₄/CPE was performed according to the previous study [16]. In brief, 25 μL glucose oxidase enzyme (5 U/μl) was mixed with 7.5 μL (5 mg/250 μL) of bovine serum albumin (BSA) in phosphate buffer and 10 μL of 2.5% glutaraldehyde. The mixture was then dropped onto the surface of the activated carbon electrode and allowed to dry at room temperature. The excess of glucose oxidase enzyme was rinsed with phosphate buffer and the resulting the immobilized glucose oxidase on the carbon paste electrode of activated carbon and NiFe₂O₄ nanoparticles (GOx- AC-NiFe₂O₄/CPE) was kept at the refrigerator at 4 °C for later use. Glucose solution with concentrations ranging from 1 to 10 mM was tested. The linearity, limit of detection and limit of quantification were further calculated from the responses of the glucose standard solution.

2.13. Glucose determination in blood samples

Blood plasma as real samples were collected from the Wijayakusuma hospital, Purwokerto, Indonesia. Before blood analysis, a standard curve of glucose solution was prepared. The blood plasma samples were then dissolved five times in 50 mM phosphate buffer pH 7.0 to reduce the possibility of matrix effect. The plasma samples were then analyzed using the optimal GOx-AC-NiFe₂O₄/CPE condition, and the oxidation peak of 0.12 V was used to determine the glucose concentration. The results of glucose determination of plasma samples using the modified electrode were statistically compared to the results of the hospital's standard spectrophotometric method using Wilcoxon Signed-Rank test.

3. Results and discussion

3.1. NiFe₂O₄ nanoparticles preparation

The co-precipitation method was used in this study to synthesize NiFe-nps, with FeCl₂, FeCl₃ as precursors and NaOH as precipitation agent [17]. The NiFe₂O₄ nanoparticles should be formed in the alkaline condition [18], therefore, NaOH was added dropwise until the pH reached 11. The resulting NiFe₂O₄ nanoparticles were brown powder.

3.2. Carbon paste electrode preparation

The carbon paste electrode (AC/CPE) was created by mixing AC (Fig. 1a) with paraffin oil. The AC was molded into a paste using paraffin oil as an adhesive. The greater amount of paraffin oil used, the softer the carbon paste and the lower the electrical conductivity. However, the lower of paraffin oil ratio, the greater the electrical conductivity produced, but the more difficult it would be obtaining the paste. Therefore, the formation of carbon paste formation requires accurate proportion to get the best carbon paste. The ratio of AC and paraffin oil used were 2:1.5, 2:1, and 2: 0.75. The best condition was a ratio of 2:0.75 (b/b), whereas the lower ratio was too dry and difficult to make the paste. The carbon paste electrode was prepared using an insulator with a diameter of 10 mm, with a hole of 5 mm for the electrode, and the thickness of the carbon paste of 2 mm. The connector used is graphite with a diameter of 5 mm (Fig. 1b). The carbon active used in this research was local coconut shell carbon active with special treatment of customized milling process. The carbon active showed a structure showed a phase transformation from cubic to the rhombohedral crystal structure. The activated carbon was also showed large specific surface area and improve microwave absorption [19].

3.3. Modification of AC-NiFe₂O₄/CPE

The glucose biosensor based on the use of glucose oxidase enzyme with electrochemical detection principle according to the reaction below [7]. Therefore, the study for developing glucose biosensor modification could be performed by easily direct detection of the hydrogen peroxide in the buffer solution. The hydrogen peroxide could be electrochemically detected using the oxidation or reduction [20] peaks using cyclic voltammetry method.



The electrochemical detection used three electrode system of Ag/AgCl (3 M KCl) reference electrode, a counter electrode and fabricated carbon paste as working electrode. The carbon paste used activated carbon as main building material and NiFe-nps as conductivity enhancer. The nanoparticles used in this study were added to the carbon paste to increase its conductivity. The nanoparticles added were NiFe-nps at concentration of 2,4,6,8 and 10% w/w. The results showed that NiFe-nps of 2 to 8% had a significant increase in conductivity

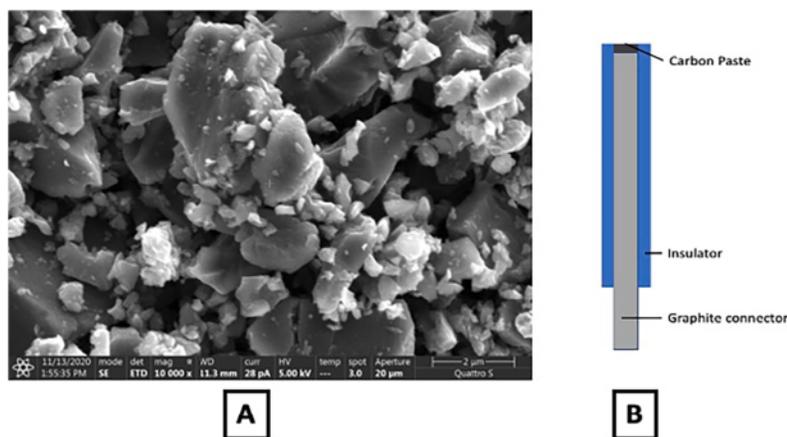


Fig. 1. The morphology of activated carbon from coconut shell (AC) was observed using a scanning electron microscope (a). The design of carbon paste electrode for glucose biosensor using an insulator from polylactic acid (PLA) printed using a 3D printer and a graphite rod as a connector (b).

significantly, while higher concentration did not (Fig. 2).

The morphology of the carbon paste and carbon paste electrodes containing NiFe-nps was observed using an electron microscope. There was not much difference between carbon paste and carbon paste with NiFe-nps. This could be due to the small proportion of addition of nanoparticles, only about 10% and because both, activated carbon and NiFe-nps, were conductive materials with varying sizes (Fig. 3).

The modified AC/CPE electrode with and without NiFe-nps were determine the electrochemical properties using hydrogen peroxide. The AC-NiFe₂O₄/CPE electrode showed a higher oxidation peak with a higher background current compared to the activated carbon paste electrode without NiFe-nps (Fig. 4). Therefore, the nickel ferrite nanoparticles were improved the electron transfer rate of the modified electrode.

3.4. Modified electrode for hydrogen peroxide determination

The carbon paste electrodes were tested for performance in various comparisons using hydrogen peroxide at a concentration of 1 mM in a 5 mM phosphate buffer solvent with a pH of 7.0. The applied potential mention in the electrochemical method used was versus Ag/AgCl (3 M KCl) reference electrode.

The test was carried out using a cyclic voltammetry method with a potential range of -1 to 2 V, scan rate of 0.1 V/s and three-times scanning. The carbon paste electrode showed an increasing oxidation peak with increasing of hydrogen peroxide concentration (Fig. 5). The oxidation peak was observed at about 0.35 V and the reduction peak decreased by about -0.5 V.

3.5. Buffer optimization

The buffer pH and concentration were optimized to achieve the best conditions for the determination of hydrogen peroxide. The pH of the solution affects the behavior of electroactive compounds on the oxidation and reduction reactions in electrochemical systems. In this study, a variation of pH 6 to 8. The 6 to 8 range has been selected for further application of the modified electrode using glucose oxidase enzyme. Buffer pH of highly acidic or alkaline could destroy the enzyme structure, thus resulting in a low response of glucose oxidase. The results showed that pH 7.5 had the highest change in oxidation peak change compared to other pH values, while measuring the oxidation of hydrogen peroxide at a concentration of 5 mM (Fig. 6a). The concentrations of the phosphate buffer have been reported to affect the

electrochemical determination of hydrogen peroxide. The mechanism could be occur through the phosphate-mediated binding site or the phosphate free precursor site [21]. In this study, 25 to 200 mM was used. The results further showed that an increase in buffer concentration from 25 to 100 mM indicating an increase in the difference in oxidation peak currents of hydrogen peroxide. However, the higher buffer concentrations did not result in an increase in the oxidation peak (Fig. 6b). For further study, the 100 mM of buffer concentration was used, since the responses was higher than 25 and 50 mM. The selection of low buffer concentration of 100 mM instead of 150 mM and 200 mM was also due the following reason (1) to eliminate the possible interference of buffer capacity in electroanalysis and (2) to reduce the use of relatively expensive buffer as electrolyte [22].

3.6. Glucose measurement

Glucose oxidase (GOx) has been immobilized on the AC-NiFe₂O₄/CPE electrode using glutaraldehyde as a crosslinker and bovine serum albumin as a stabilizing agent. The use of albumin and glutaraldehyde has been previously reported to offer excellent maintenance the glucose oxidase immobilization in the glucose biosensor [7]. The glucose standard solution was measured using cyclic voltammetry under previously obtained optimal conditions.

Fig. 7A shows the cyclic voltammogram of the modified electrode used to detect standard glucose solution ranging from 2 to 10 mM. Both oxidation and reduction peaks increase with the addition of glucose concentration. Furthermore, the oxidation peak at 0.12 V had the highest sensitivity with a slope of 32.01 x (Fig. 7B) compared to reduction peaks at -0.35 V and -0.4 V (Fig. 7C-D). However, reduction peaks are preferable in glucose biosensors development to avoid the common interference that appear at the oxidation potential, such as 4-acetaminophen at 0.6 V [23], ascorbic acid at 0.4 V and uric acid at 0.5 V against Ag/AgCl (3 M KCl) reference electrode [10].

The reduction peaks were then analyzed at -0.35 V and 0.4 V to get the best equation needed to determine glucose. The reduction potential of -0.35 V was chosen for potential a lower reduction potential close to zero volts to avoid the possible electroactive interferences. The presence of NiFe₂O₄ nanoparticles in the carbon paste electrode improves the electrocatalytic performance of the modified working electrode. The nanoparticles and activated carbon of the carbon paste electrode provided a large number of molecules for electron transfer of hydrogen peroxide detection with a redox potential close to zero, which is similar to the previously reports on metallized carbon [24] to avoid the

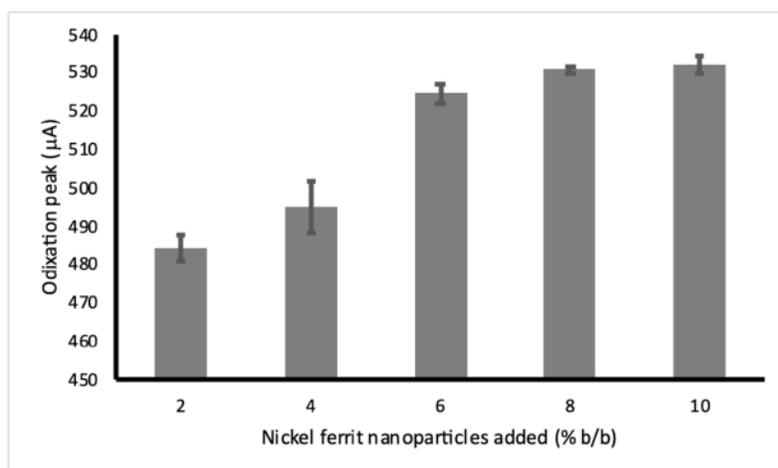


Fig. 2. Effect of the NiFe₂O₄ nanoparticles addition on the AC-NiFe₂O₄/CPE performance.

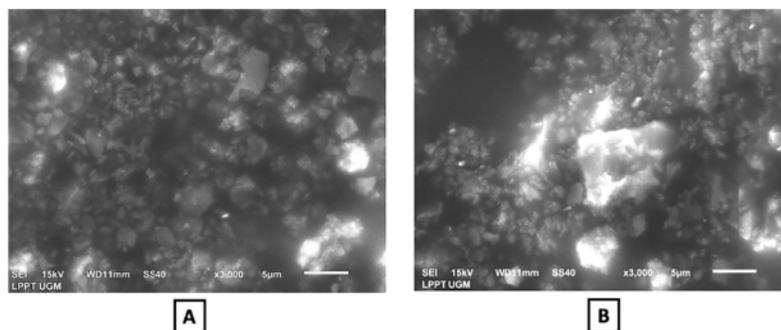


Fig. 3. Scanning electron microscope image of carbon paste electrode (A) and Carbon paste with NiFe-nps modified electrode (B).

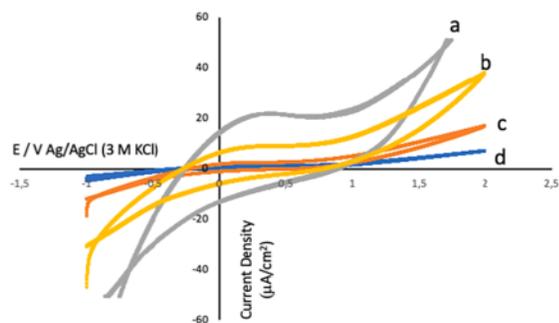


Fig. 4. AC/CPE modified electrode with NiFe-nps for hydrogen peroxide determination (a) and without the addition of NiFe-nps (b). The baseline without hydrogen peroxide was shown in c and d voltammogram respectively.

unwanted electrochemical reactions of common interfering substances. Additionally, the reduction potential at -0.4 V was also analyzed because the CV voltammogram showed that the larger peak increased with an increase in the reduction potential. Thereafter, the reduction peaks changes at -0.4 V with increasing glucose concentration showed better sensitivity and coefficient of determinant with the regression equation of $y = -21.11x - 259.46$ and coefficient of determination of $R^2 = 0.9905$. The calculated limit of detection and limit of quantification were 1.1 mM and 3.7 mM respectively. Table 1 compares the fabricated glucose biosensor to previously reported carbon paste electrode / activated carbon-based amperometry glucose biosensor. Most of modified electrode with activated carbon or carbon paste electrodes had relatively high applied potentials of about 0.4 – 0.55 V, while this study had a

low applied potential of 0.12 V or negative applied potential of -0.35 to -0.4 V. The low applied potential in the amperometric glucose biosensor has a great advantage of avoiding the common electroactive interferences such as uric acid and ascorbic acid.

3.6. Glucose measurement in blood samples

The fabricated glucose biosensor using GOx-AC-NiFe₂O₄/CPE electrode was validated for glucose determination in blood samples. Subsequently, six blood plasma samples were collected from local hospital laboratory. The results showed the comparison of the glucose concentration of blood plasma samples obtained using fabricated glucose biosensor with the standard (spectrophotometric) method using a reagent based on glucose oxidase and peroxidase [30,31] performed in the hospital laboratory (Table 2). The Wilcoxon Signed-Rank test also revealed that there was no significant difference between the fabricated glucose biosensor and the standard method ($P > 0.05$). The blood glucose measurement was another important analytical performance which showed the reliability of the fabricated glucose biosensor. The composition of the activated carbon and nanoparticles used could be applied in the electrode fabrication in both solid electrode and screen-printed electrode in the future application of glucose biosensor.

4. Conclusion

The carbon paste electrode for the electrochemical glucose biosensor was made of composite AC and NiFe-nps. The optimal condition obtained were the AC – paraffin oil ratio of $2:0.75$ and the addition of NiFe-nps of 8% w/w. The buffer phosphate used was optimum at a pH of 7.5 and a concentration of 100 mM. The modified electrode also detected a success to detect standard glucose with a linear response at 2 mM to 10 mM. Furthermore, the fabricated glucose biosensor also produced

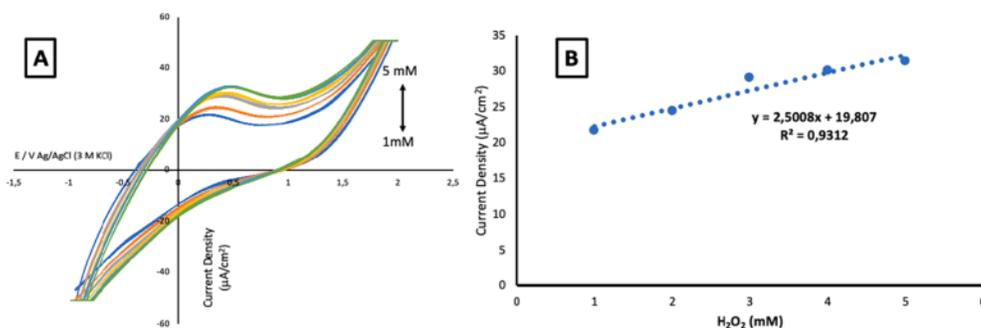


Fig. 5. Cyclic voltammogram of carbon paste electrodes in various concentrations of hydrogen peroxide (1–5 mM) in phosphate buffer (A). The linearity of increasing oxidation peak with the hydrogen peroxide concentration at 0.35 V vs Ag/AgCl (3 M KCl) (B).

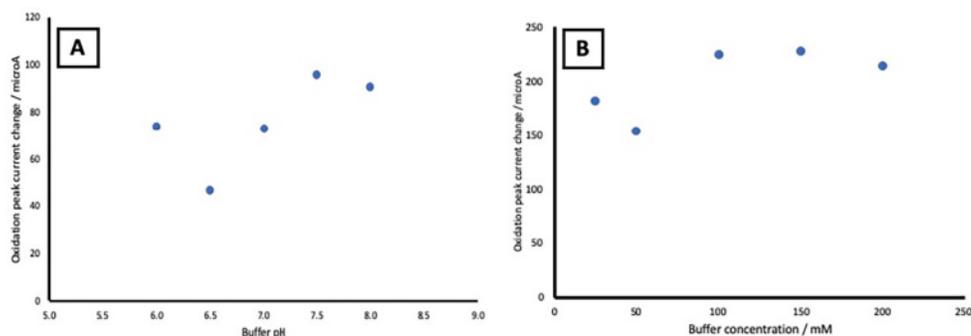


Fig. 6. Effect of buffer pH (a) and buffer concentration (b) in the oxidation peak change of 5 mM hydrogen peroxide.

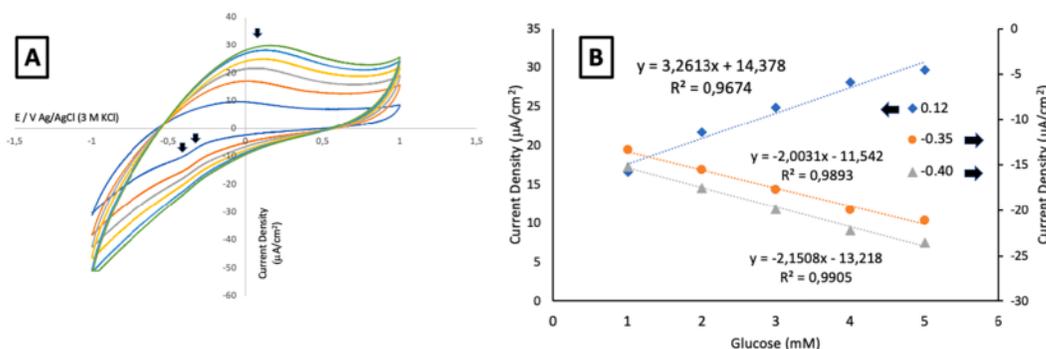


Fig. 7. Glucose determination using GOx-AC-NiFe₂O₄/CPE electrode showed increasing oxidation and reduction peaks by cyclic voltammetry (A). The recorded potential of the oxidation and reduction peaks marked with black arrow. The increasing peaks with the glucose concentration showed at 0.12 V for oxidation (primary y axis), -0.35 V and -0.4 V vs Ag/AgCl (3 M KCl) for reduction potential (secondary y axis) (B).

Table 1

Comparison of activated carbon / carbon paste electrode for amperometry glucose biosensor.

Electrode structure	Linear range	Applied potential	Reference
GOx-PtNPs-PAA-aSPCEs	20 μ M–2.3 mM	0.2 V	[25]
GOx/MCPE	0.5 μ M–10 μ M	0.4 V	[26]
AuNi@AC	0.41 μ M–1.7 mM	0.55 V	[27]
Ni-Pd@AC/GCE NCs	0.01 mM–1 mM	0.5 V	[28]
NiO-HAC/GCE	10 μ M– mM	0.55 V	[29]
FMPS-Gly	0.5 mM – 10 mM	0.5 V	[16]
GOx-AC-NiFe ₂ O ₄ /CPE	2–10 mM	0.12 V, -0.35 V and -0.4 V	This work

GOx, glucose oxidase; PtNPs, platinum nanoparticles; PAA, poly azure a; MCPE, modified carbon paste electrode; AuNi, Au-Ni alloy; AC, activated carbon; Ni, nickel; Pd, palladium; GCE, glassy carbon electrode; NCs, nanocomposites; HAC, heteroatom-enriched activated carbon; FMPS, 4-formyl-3-methoxyphenoxy-methyl)polystyrene; gly, glycine; Gr, graphite.

similar responses in the detection of glucose in blood sample when compared to the standard method used in the hospital. The highlight finding in this research was the use of local activated carbon with special treatment for glucose biosensor application with showed a good analytical performance with a low-cost material.

CRedit authorship contribution statement

Amin Fatoni: Conceptualization, Methodology, Investigation,

Table 2

Blood glucose concentration obtained by fabricated biosensor and standard spectrophotometric method performed in the hospital laboratory.

Sample	Fabricated biosensor (mg/dL) 3 replications	Standard spectrophotometric method (mg/dL)
1	137.5 \pm 2.5	139
2	114.4 \pm 0.7	114
3	97.5 \pm 1.6	97
4	129.4 \pm 2.5	128
5	287.1 \pm 2.6	288
6	131.4 \pm 1.6	131

Writing – review & editing, Funding acquisition, Writing – original draft, Data curation, Supervision, Resources. **Wahyu Widanarto**: Validation, Writing – review & editing, Visualization, Data curation. **Mekar Dwi Anggraeni**: Validation, Writing – review & editing, Writing – original draft, Data curation, Project administration. **Dian Windy Dwiasi**: Validation, Data curation, Formal analysis, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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