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Research Article

RAPID POINT-OF-CARE DIAGNOSTIC APPROACH TO COVID-19: ELECTROCHEMICAL IMMUNOSENSOR

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Abstract

The rapid spread of corona virus all over the world taught that there is an always requirement for the development of health care services. In that, development in disease diagnosis is so important for any disease to identify the same. For COVID-19, there are RT-PCR test and Rapid antigen Test which is either costly, time consuming or less effective. So, there was a real need for something which can actually help to overcome these loop holes. The electrochemical immune-sensors technology has given a hike by detecting the disease biomarkers by antigen-antibody stable complex formation, which is then converted to electric signal via transducer mechanism. The electrochemical assays are being developed to detect spiked glycoprotein, nucleo-capsid protein, N or S genes, S-RBD protein, Subunit 1-IgG, C-reactive protein, ORF1abRNA, SARS-CoV-2 monoclonal antibodies from the clinical samples of COVID patients. Use of different nano-materials such as Titanium Oxide (TiO_2) nanotubes, Graphene Oxide nano-composite has been identified to increase the performance and reducing the limit of detection. Thus the utilization of electrochemical immuno-sensor technology is new hope of ray in the ongoing crisis of the world.

Keywords: Electrochemical immunosensor, nano-materials, Diagnostic, COVID-19.

INTRODUCTION

The World Health Organisation has already declared COVID-19 disease as a worldwide state of health emergency. The rapid and uncontrollable spread of the virus with numerous mutants continues to cause catastrophic waves which results in high rate of mortality and morbidity in human beings. Due to constant change of mutation sequence of SARS-CoV-2 virus it is necessary to diagnose in early stage with proper accuracy and sensitivity. The conventional methods of diagnosis of COVID-19, RT-PCR or Rapid Antigen Testing are either costly, time consuming or having less specificity (Yadav *et al.,* 2021). They have more probability in giving false positive or false negative results. In view of these limitations, electrochemical immunosensor can give rapid, point of care, highly specific detection of virus within a very short period. Electrochemical immunosensors are type of biotransducer which can detect disease biomarkers by antigen-antibody stable complex formation, which is then converted to electric signal via transducer mechanism based on biochemical reaction between biomarker analytes and electrode surface. The principle applied here is the direct immobilization of antibodies which is followed by addition of desired analytes for electrochemical measurements (Il-Hoon Cho *et al.,* 2018). It produces electrical signals proportional to the concentration of analytes. Different types of electrical signal can be generated and they can be measured by amperometric, potentiometric, conductometric or impedometric immunosensor (Cecilia Cristea *et al.,* 2015). In case of the diagnosis of COVID-19 Impedometric electrochemical immunosensor is to be used in most of the cases where impedence change is analysed using Electrochemical Impedence Spectroscopy (EIS). This technique has wide acceptance because it is able to detect accurate and sensitive signals.

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The response produced by EIS is stable, reliable and reproducible. Some other electrochemical methods like Differential Pulse Voltammetry (DPV), Square Wave Voltammetry, Field effect Transistor (FET), Chronoamperometric immunosensing can also be implemented in result analysis of SARS-CoV-2. The electrochemical assays are being developed to detect spiked glycoprotein, nucleocapsid protein, N or S genes, S-RBD protein, Subunit 1-IgG, C-reactive protein, ORF1abRNA, SARS-CoV-2 monoclonal antibodies from the clinical samples of COVID patients. Most of these biomarkers are collected from Saliva, nasopharyngeal or oropharyngeal swab (Puspesh Ranjan *et al.,* 2021). To increase the performance of immunosensor and for receiving ultra-low Limit of Detection (LOD), different nanomaterials can be utilized as Immunosensing electrode materials, such as Titanium Oxide (TiO_2) nanotubes, Graphene Oxide nanocomposite, Gold clusters, Copper Oxide nanocubes, Silica nanoparticles etc.

Advantages of Electrochemical Immunosensors over conventional techniques of COVID-19 diagnosis

- Highly selective.
- Rapid and early detection.
- Less time-consuming.
- Fast Responsive.
- Higher specificity and Sensitivity
- Lower Limit of Detection(LOD)
- Cost effective.
- On-site monitoring.
- Point-of-care Diagnosis.
- Can be portable.

Recently reported Electrochemical Immunosensors for diagnosis of SARS-CoV-2

1) Silica Core and Redox dye incorporated silica nanoparticles based Immunosensor

This electrochemical immunosensor involves multiplex RCA(Rolling Circle Amplification) detection of N and S genes of SARS-CoV-2 from Nasopharyngeal or throat swab samples of COVID Patients. Characterization of Silicon nanoparticles are to be done and then functionalize them with Methylene Blue and Acridine Orange. This immunosensing involves sandwich hybridization of redox active label probe with RCA amplicons, which are detected by DPV(Differential Pulse Voltammetry).This assay is found to have a great LOD of 1.0 copy/mL of Viral N and S genes in less than 2 hours (Thanyarat Chaibun *et al.,* 2021).

2) Using Gold clusters, and glutaraldehyde cysteamine modified electrode

This is a novel immunoassay platform having gold clusters coated with cysteamine and glutaraldehyde where Voltammetric method is used to detect the SARS-CoV-2 spike antibody from saliva or oropharyngeal swab samples. Cyclic Voltammetry, X-Ray spectroscopy, Scanning Electron Microscopy areused for the immunosensing measurements. This method's Limit of Detection(LOD) relative to SARS-CoV-2 spike antibody is reported to be as high as 0.01ag/mL within 35 minutes (Lokman Liv, 2021).

3) Electrodeposited gold nanostructure graphene immunosensor

This is a point-of-care diagnostic system using Laser scribed graphene based electrochemical immunosensing for COVID-19 disease. The electrode would be modified with SARS-CoV-2 spike protein antibody and further characterization by X-Ray photoelectron spectroscopy, Scanning Electron Microscopy and other electrochemical techniques. The system is merged with a customised smartphone application which can be easily operated and user-friendly. The detection limit of this immunosensor is 2.9ng/mL of S-Protein found from serum samples within 1 hour (Tutku Beduk *et al.,* 2021).

4) Graphene layer Screen Printed Electrode Immunosensing

This sensor is made of a screen printed graphene layer which is functionalized with 1-pyrene butyric acid N-hydroxysuccinimide ester linker which would be bound to anti-spike monoclonal antibody. This can be used for specific detection of SARS-CoV-2 Spike subunit 1 protein obtained from Swab samples. ELISA is to be done for validation of antigen-antibody reaction and cyclic voltammetry & electrochemical impedence spectroscopy is used for Characterization and functionalization of Graphene sensors. The limit of detection is 20µg/mL of subunit 1 recombinant spike protein in about 45 minutes (Biljana Mojsoska *et al.,* 2021).

5) Using Pencil Graphite Electrodes

This is a high-frequency, cost effective diagnostic procedure of COVID-19 which can detect SARS-CoV-2 within 6.5 minutes. It uses transducer made of graphite leads modified with human Angiotensin Converting Enzyme 2(ACE2). Electrochemical characterization and functionalization is done by using cyclic voltammetry and electrochemical impedence spectroscopy. It displays high specificity and accuracy when tested using saliva, nasopharyngeal or oropharyngeal swab samples. The Limit of Detection for SARS-CoV-2 spike protein is 229 fg/mL. No cross reactivity can be observed with other viral samples and displays a shelf life of 5 days if stored at 4°C (Lucas F. de Lima *et al.,* 2021).

6) Ultrasensitive sandwich type electrochemical Immunosensor

In this Immunosensor super sandwich-type assay is used for the detection of ORF1ab RNA of SARS-CoV-2 from biological samples like Saliva, nasopharyngeal or oropharyngeal swab, sputum, plasma, urine, faeces, serum etc. Here p-sulfocalix-8-arene(SCX8) functionalized Graphene Oxide composite is made. Then a nanocomposite is formed by mixing gold nanoparticles and toluidine blue. The result is analysed by Sandwich Differential Pulse voltammetry and can be obtained via integrated smartphone within a very short time. Only two copies of the virus are necessary to perform this assay. The LOD of this immunosensor is found to be 200copies/mL (Zhao *et al.,* 2021).

7) Immunosensor with Copper Oxide nanocube coating

This is an electrochemical nanobiodevice for Coronavirus spike protein detection by using Immunoglobulin G anti-SARS-CoV-2 spike antibody on the electrode surface. Here, a screen printed carbon electrode is used modified with Copper Oxide nanocubes. Cyclic Voltammetry and electrochemical impedence spectroscopy is used to analyse the results. It is able to detect the virus in less than 20 min. The limit of detection is 0.25fg/mL to 1µg/mL (Zeinab Rahmati *et al.,* 2021).

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