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Review

Applications of Electrochemical and Optical Biosensing Techniques Based on Nanomaterials for Detection of SARS-COV-2 Specific Antibodies: An Update Review

Saade Abdalkareem Jasim,[1] Trias Mahmudiono,[2,*] Maria Jade Catalan Opulencia,[3] Dmitry Olegovich Bokov,[4,5] Dinh Tran Ngoc Huy,[6] Djakhangir F. Shamsiev,[7] Zahraa Haleem Al-qaim,[8] Nguyen Dinh Trung,[9] Yasser Fakri Mustafa,[10] and Walid Kamal Abdelbasset[11,12]

[1]*Al-maarif University College, Medical Laboratory Techniques Department, Al-anbar-Ramadi, Iraq*
[2]*Department of Nutrition, Faculty of Public Health, Universitas Airlangga, Indonesia*
[3]*College of Business Administration, Ajman University, Ajman, United Arab Emirates*
[4]*Institute of Pharmacy, Sechenov First Moscow State Medical University, 8 Trubetskaya St., bldg. 2, Moscow, 119991, Russian Federation*
[5]*Laboratory of Food Chemistry, Federal Research Center of Nutrition, Biotechnology and Food Safety, 2/14 Ustyinsky pr., Moscow, 109240, Russian Federation*
[6]*Banking university HCMC Ho Chi Minh city Vietnam- International University of Japan, Niigata, Japan*
[7]*Professor, Doctor of Medical Sciences, Head of the Department of ENT Diseases, Tashkent State Dental Institute, Makhtumkuli Street 103, Tashkent, 100147, Uzbekistan*
[8]*Department of Anesthesia techniques, Al-Mustaqbal University College, Iraq*
[9]*National Economics University (NEU), Hanoi Vietnam*
[10]*Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul-41001, Iraq*
[11]*Department of Health and Rehabilitation Sciences, College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University, Al Kharj, Saudi Arabia*
[12]*Department of Physical Therapy, Kasr Al-Aini Hospital, Cairo University, Giza, Egypt*

*Corresponding Author, Tel.: 096254874562
E-Mails: trias-m@fkm.unair.ac.id; T.Mahmudiono1400@gmail.com

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Abstract- Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) caused the burden of coronavirus infectious disease 2019 (COVID-19) and spread all of the world. Evaluation of antibodies is the most typical diagnostic method is utilized to detect SARS-COV-2. Quick and high-specific diagnosis of specific antibodies can be the best way to evaluate the vaccine efficiency and decrease the number of the disease. In this study, before discussing the types of biosensors designed for the specific detection of SARS CoV-2 virus in these few years, we have summarized the serological methods in antibody detection and pointed out some of its advantages and disadvantages. In recent decade, biosensors have appeared to complement ELISA and PCR for pathogen detection. In two years ago, Electrochemical, colorimetric and fluorescence biosensors based on various nanomaterials are developed for SARS-COV-2 specific Abs detection with high specificity and sensitivity. This article specifically deals with the detection of specific antibodies of Covid-19 by biosensor methods and it is an update of similar articles. Considering that one of our goals was to investigate new biosensor methods for diagnosis, we tried to select studies related to Covid-19 specific Abs mostly between 2019 and 2021.

Keywords- Covid-19; SARS-COV-2; Electrochemical; Optical; Biosensor

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1. INTRODUCTION

Coronaviruses as the huge viruses known group cause disorders in various animals within the range of the common cold to more severe diseases. Recently, 7 various coronaviruses have been known alpha and beta infecting and causing illnesses in people. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) led to the burden of coronavirus infectious disease 2019 (COVID-19) spreading to 220 countries, territories or areas with more than 63 million cases confirmed experimentally and over 1.4 million deaths [1]. Number of results of the clinical symptoms and manifestation of the disease has been approved. Although, there is little data about the pathogenic mechanism of the covid-19. Important symptoms of COVID-19 are fatigue, dry cough, fever, and pneumonia-like features [2]. However, the best way to suppress spread of the disorder is general vaccination, but given the prevalence of new species, sensitive

diagnostic methods are still the best way to control the disease. Quick and high-specific diagnosis could be the way to decrease the number of the disease and broke the widespread chain of this deadly covid-19 infection. For detection of Covid-19 antigens and antibodies, some commercialized rapid antigen (Ag) detection (RAD) tests have been examined and most have showed a lack of sensitivity. RAD immunoassays have exhibited as a valuable alternate to RT-PCR to diagnose SARS-CoV-2 infection in patients showing with compatible COVID-19 clinically [3]. Today, detection of viral RNA based on PCR is almost the only method to approve the detection of this disease. The best function of this method depends on important factors including the various stage of infection in patients, the skill of sample collection, sample types, and the consistency and quality of the PCR assays being used [4,5]. These reasons resulted in noteworthy delay of early detection and following management and propose important challenge to preparing timely life support treatment and prohibiting quarantine [6]. Antibodies detection compared with PCR technique have features such as excellent throughput faster turn-around time and less workload. The important point is that according to the review of the researches revealed in Scopus in the field of detection of SARS-Cov-2 specific Abs through biosensor methods, it can be mentioned that more than 90% of the studies are related to the last 3 years. Serological evaluation is among the most typical diagnostic methods utilized for the detection of various virus infections. Biosensors are of enhancing interest for the detection of antibodies or antigens in many applications containing of animal and plant health, human, or food and water safety [7]. In this review, we have examined new studies about different types of biosensors for the detection of antibodies against Covid-19 various antigens between 2019 and 2021.

2. SEROLOGICAL METHODS OF SARS-COV-2 SPECIFIC ABS DETECTION AND CHALLENGES

Coronaviruses (CoVs) are single-stranded positive-sense RNA viruses such as alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV. Each of these genres is highly spread among animals and humans [8]. There are 6 types of CoVs creating human infectious, which can be categorized into two groups of slightly disease and highly disease CoVs. In the highly pathogenic CoVs group, both Middle East respiratory syndrome coronavirus (MERS-CoV, 2012, Saudi Arabia) and severe acute respiratory syndrome coronavirus (SARS-CoV, 2002, southern China), are known and can influence people while infecting mostly the lower airways and generating serious fatal pneumonia, [9]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is member of beta-CoV genus sharing 51.8% and 79.0% nucleotide identity with MERS-CoV and SARS-CoV, respectively [10]. The receptor-binding domain (RBD) RBD and spike (S) antigens of Covid-19 facilitates binding of virus to human cells via its counter receptor angiotensin-converting enzyme 2 (ACE-2) as well as neutralization antibodies (Abs) were demonstrated to target the RBD [11]. S1 that has role for receptor binding and S2 that is

responsible for membrane fusion are two regions of spike proteins and the extra-viral S1 region contains within its second domain the RBD [12]. Other antigens that employed in the most serological test for evaluation of covid-19 Abs are the nucleocapsid proteins (N) [10]. Serological tests evaluate blood anti-SARS-COV-2 IgM/IgG concentrations and show results about present exposure to SARS-CoV-2 (IgG and IgM positive) and past infection (IgG positive and IgM negative) [13]. Detection of specific Abs against Covid-19 in patient samples is important way for diagnosis of SARS-CoV-2. It is approved that IgM exhibits the first line of defense during viral infections before creating the high affinity adaptive, immunoglobulin G (IgG) responses which are responsible for immunological and long-term immunity memory [14]. Serology or antibody tests are urgently required. Research laboratories companies competitively create tests for detecting COVID-19 Abs with suitable sensitivity and specificity. Most studies have proved that the different antibodies to SARS-CoV-2 RBD, spike and N antigens are discovered in the blood. The most highly utilized serological techniques are the lateral flow test strip (LFTS) or lateral flow immunoassay (LFIA) and the enzyme-linked immunosorbent assay (ELISA) [15]. The ELISA test is rapid, taking between 10 to 30 min to complete, but tends to demonstrate lower specificity and sensitivity than flow [16]. However, flow technique needs expensive equipment for its automation and analysis. These reasons have caused main challenges in the implementation of diagnostic testing strategies. Biosensor devices in comparison with mentioned tests have appropriate specificity, sensitivity and also are cheaper methods.

3. BIOSENSORS AND SARS-COV-2

A biosensor is a method that evaluates chemical or biological reactions by producing signals proportional to the concentration of target markers in the reaction. Biosensors can be categorized into various groups depending on the method of signal transduction: electrochemical, optical, thermometric, magnetic or piezoelectric [17]. Common features of all of them are high sensitivity, specificity, cost-effectiveness and small size. Moreover, in recent year, have been proved biosensors can provide instruments that can be cost-saving, simple to use, have excellent precision and adaptive in the current COVID-19 pandemic. In recent decade, biosensors have appeared to complement ELISA and PCR for pathogen detection. Biosensors are based on the direct integration of a sensitive transducer element and a selective biorecognition element and prepare complementary platforms to ELISA and PCR for analyte diagnosis [18]. Biosensors provide suitable situation for both pathogen operation and host response information within a shorter time. This could facilitate the prevention process and fast detection for these viruses as covid-19 [19]. Samson et al. [20] have prepared new biosensors containing electrochemical biosensor, surface plasmon resonance (SPR), and optical biosensor (OB), are utilized for the diagnosis of RNA viruses as “clustered frequently interspaced short palindromic repeats-associated protein 9 (CRISPR-Cas9)” in terms of a aptamer, paper strip,

antigen-Au/Ag nanomaterials, and nucleic acid- based. Soo-sou and his colleges [21] have fabricated a novel fluorescence resonance energy transfer (FRET)-based human angiotensin-converting enzyme 2 (hACE2) biosensor via immobilizing the RBD module derived from SARS-CoV-2, which can sensitively monitor ACE2 activity with excellent spatiotemporal resolutions. So biosensors can help to evaluation of drugs by suppressing hACE2-RBD interaction and finally this study approved that using biosensor method for therapeutic approach of SARS-COV-2. Moreover, Abs can be detector elements in the structure of biosensors. For example, Mojsoska et al. [22] have designed a electrochemical biosensor for quick detection of SARS-CoV-2 S antigen, using screen printed electrode (SPE) functionalized with monoclonal anti-spike (S) Abs. Also, Using Gold nanoparticles capped with thiol-modified antisense oligonucleotides (ASOs) [AuNPs-ASOs] in the colorimetric biosensor can be a reliable and simple method for the naked-eye detection of viral infectious diseases, needing no complex method; a colorimetric biosensing method was examined for the diagnosis of SARS-CoV-2 [23]. Abs begin exhibiting in the first week after the symptoms of disease development. IgM, IgG, and IgA can be detected with IgA producing somewhat earlier than IgM and IgG. Most patients seroconvert by two weeks after symptoms. IgG has effect for several months following infection unlike IgM and IgA [24,25]. In addition, serological assays will help to evaluate of immunity after vaccination. Numbers of serological methods that have mentioned are suffering from low specificities and sensitivities. So, biosensors can be crucial device in evaluation of Abs in covid-19 patients and finally suppressing the pandemic and understanding and facilitating of the role of Abs in COVID-19 immunity. Recent advances in recent two years for evaluation of Abs that released against SARS-COV-2 by various biosensors have reviewed in this paper.

4. MONITORING OF COVID-19 SPECIFIC ABS WITH BIOSENSORS

4.1. Electrochemical types

Electrochemical sensors operate by reaction of with the target molecule of interest for generation of an electrical signal proportionate to the target factor concentration. A usual electrochemical biosensor including a reference electrode and a sensing electrode (working electrode) separated by an electrolyte [26]. The basic operation of electrochemical biosensor is that the biological reaction between analyte and bioreceptor can consume or create electrons or an ion that changes the electric potential, current, or other electrical features of the solution [27]. Transducer and Receptors are the two essential factors in electrochemical biosensors. The transducer changes the binding activity into a detectable signal sensitively and the receptor specifically distinguishes the analyte [28]. In electrochemical biosensors, the electrodes are employed as a transducer. The enormous development in the field of nanotechnology that has

taken place over the recent years or so has been utilized in sensors and biosensors due to take advantage of some of the highly desirable properties of nanoparticles (Table1).

Table 1. different electrochemical bioanalytical systems and detection of Covid-19 specific Abs

Biosensor method	**Sensing platform**	**Types of Abs**	**LOD**	**References**
Electrochemical	Au electrode/Spike protein	IgG	0.7 ng/ml	[30]
Electrochemical/SWV	SP RBD/GO	IgG, IgM	0.96 & 0.14 ng/ml	[32]
Electrochemical/SWV/CV	Au/GCE/ GluAl	-	0.01 ag/ml	[36]
Electrochemical impedance	Au electrode/Spike protein	-	-	[40]
Electrochemical/EIS	ZnoNW/carbon layer	IgG	10 ng/ml	[46]
SPEEDS	streptavidin biotinylated RBD protein	IgG, IgM	10.1 ng/ml	[38]
Amperial™ electrochemical	Au electrode/Spike protein/ streptavidin biotinylated	IgG	18.75 ng/ml	[48]
Electrochemical ELISA	SCPE/spike protein/HRP	IgG, IgM	-	[51]
Electrochemical/SWV	Spike protein/GCE	-	10 pg/ml	[37]
Electrochemical/CV/EIS	Au nanostar/ graphene/GCE	IgG	0.18×10−19 %V/V	[79]

Graphene oxide (GO), Square-wave voltammetry (SWV), spike protein containing receptor-binding domain (SP RBD), glutaraldehyde (GluAl), Glassy Carbon Electrode (GCE), Cyclic Voltammetry (CV), ZnO nanowires (NWs), Serological testing Platform for rapid ElectrochEmical Detection of SARS-CoV-2 antibodies (SPEEDS), screen carbon printed electrodes (SCPE), Horseradish Peroxidase (HRP)

Saliva is an oral fluid that is earned non-invasively and easily. Previous studies demonstrate that the Abs profile in saliva is approximately similar to that of plasma [29]. Exhibiting of anti-SARS-CoV-2 IgG in saliva samples by electrochemical device that modified gold electrode with S proteins are approved with 98% specificity of and 89% sensitivity [30]. Paper-based biosensors, combining electrochemical detection and a paper substrate, appear to be very convenient for various healthcare scenarios. Cellulose paper is eco-friendly, highly-available, flexible, biocompatible, inexpensive, hydrophilic light- and weight [31]. A label-free paper-based electrochemical sensor is a suitable way to measurement of IgG and IgM without using of multiple Abs that are necessary in lateral flow-based assays (LFAs) [32]. Yakoh et al. [32] have constructed a label-free paper-based electrochemical device that electrode was modified with graphene oxide (GO) solution and carboxylic groups (–COOH) of GO are activated by NHS and EDC. The spike protein receptor-binding domains (SP RBD) were coated on modified electrode and serum samples including of Abs were added. Finally, the Square-wave voltammetry (SWV) technique have detected the Abs concentrations with 1ng/ml limit of

detection (LOD) [32]. Gold nanoparticles (AuNPs), which display appropriate surface plasmon absorption features, have been used in different analytical techniques, containing of biosensing, surface-enhanced Raman spectroscopy and biological optical imaging [33]. Self-assembly procedure is the spontaneous organization of materials into specific metal surfaces. Self-assembled monolayer (SAM) of various materials have usually employed for improvement of microarrays, biosensors, molecular switches and biochips [34]. Monolayer protected clusters (MPCs) have created a large amount of interest as binding platforms for multifunctional nanomaterials which have roles in biological molecules detection [35]. In a study, by using from cyclic voltammetry, the Au-clusters were fabricated on the glassy carbon electrode (GCE) electrode surface and then the cysteamine and glutaraldehyde (GluAl) were immobilized on Au/GCE electrode [36]. In this immunosensor, the SARS-COV-2 Ags via amine group have binded to glutaraldehyde and detected SARS-CoV-2 spike Abs varied from 0.1 to 1000 ag/mL (Figure 1).

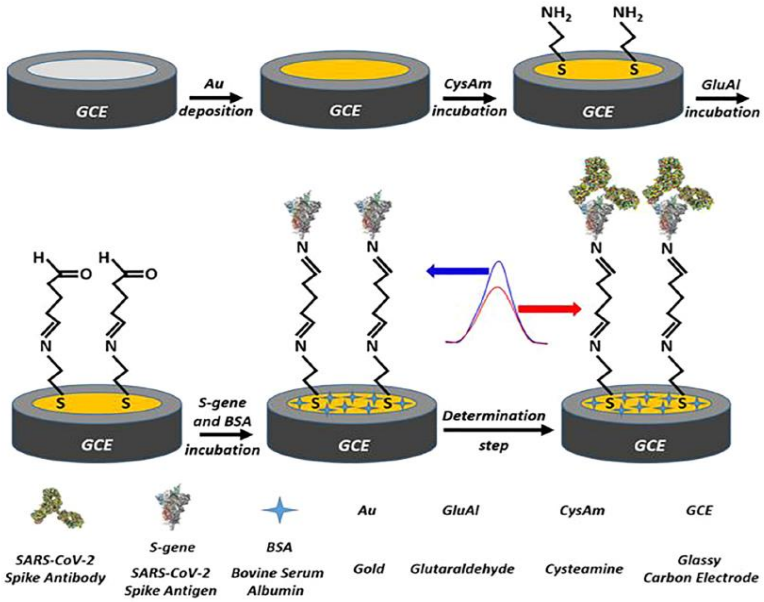

Figure 1. The Au-clusters were fabricated on the glassy carbon electrode (GCE) electrode surface and then the cysteamine and glutaraldehyde (GluAl) were immobilized on Au/GCE electrode. The SRS-COV-2 spike antigen could be recognized; reprint with permission from reference [36]; copyrights, Elsevier 2022

Moreover in a another study that have been done by Liv et al [37] the gold clusters immobilized on the glassy carbon electrode surface in the same way as in previous study that have mentioned [36]. Onto this electrode was deposited cysteamine (Cys) for 60 min to generate Au/GCE/cysteamine, after which the thiol sites of CysOH were chemisorbed and hydroxyl terminals were coated facing the outside of the electrode. Then, spike antigen was dropped on the surface of Au/GCE/cysteamine to fabricate an interaction between groups of –C = O spike Ag and –H CysOH groups [37]. This method responses to the SARS-CoV-2 spike

Abs from 0.1 fg/mL to 10 pg/mL. These two studies described were performed by two same groups and in both studies Au cluster and cysteamine were used to prepare the biosensor. The main difference between two these researches is how the spike Ag binds to modified surface which causes differences in sensitivity. These studies that have been mentioned are suggest, number of electrochemical immunosensors based various materials can be ultra-sensitivity, relative simplicity, and a wide analytical range devices for Specific SARS-COV-2 Abs. Peng and his colleges [38] have constructed a Serological testing Platform for fast ElectrochEmical Detection of SARS-CoV-2 antibodies (SPEEDS) includes an electrochemical immunosensor and three screen electrode such as CE: counter electrode, RE: reference electrode, and WE: working electrode [38]. The WE electrode was activated by streptavidin and modified with biotinylated RBD protein as the capture probe. This device could measure the IgG and IgM in patient serum samples collected at various levels between 10.1 ng/mL − 60 μg/mL (Figure 2).

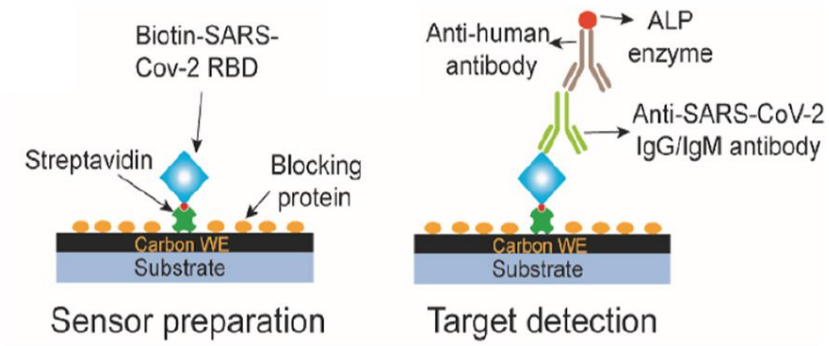

Figure 2. The WE electrode was activated via streptavidin and improved with biotinylated RBD protein as the capture probe. This device could measure the IgG and IgM in patient serum samples collected at various levels between 10.1 ng/mL-60 μg/mL; reprint with permission from reference [38]; copyrights, Elsevier 2022

Among the electrochemical biosensing methods, electrochemical impedance-based sensing (EIS) technique is highly used because of some specific features such as enable appropriate precision for detection of pathogens or antibodies and label-free [39]. Also, evaluating the impedance across various frequencies is benefit for complete biosensing functions. ACEA Biosciences, a part of Agilent Technologies, is the developer real time cellular analysis systems and manufacturer of highly innovative flow cytometers [40]. ACEA Biosciences design for non-invasive EIS detecting the cell morphology changes, proliferation and attachment quality. Rashed et al. [40] have fabricated an ACEA biosensor based on RBD of SARS-CoV-2 spike protein and have been able for discovering the anti-SARS-CoV-2 Abs by EIS technique with 0.1 μg/ml, 1.0 μg/ml and 10 μg/ml concentrations. This approach is one of the excellent electrochemical methods for rapid diagnosis of Covid-19 Abs. microfluidic paper-based

analytical devices (μPADs) are relatively new group of analytical devices and utilize cellulose as substrate to use as paper-based analytical devices (PADs) for the biosensing, biomedical and pharmaceutical analysis, point-of-care diagnosis, environmental monitoring, clinical detection, and forensic medicine [41,42]. The popularity of PADs is based on some important properties, containing of power-free because of cellulose fiber networks and very low-cost [43]. Four main detection methods have been approved for the detection of target molecules in paper-based microfluidics: chemiluminescence (CL), electrochemiluminescence (ECL), electrochemical (EC), and colorimetric [44]. So, EIS biosensing on μPADs can be a useful device for electrochemical detection. ZnO nanowires (NWs) have recently attracted much attention owing to their different potential applications and remarkable physical features [45]. Zinc oxide nanowires (ZnO NWs) can directly immobilized on paper electrodes via hydrothermal growth [46]. Li et al. [46] have constructed a electrochemical biosensor in four steps: (1) cutting paper pieces into the shape of working electrode, (2) printing a layer of carbon to the paper pieces, (3) immobilizing ZnO NWs on the modified surface, (4) and finally coating the p24 antigen as a detection probe of SARS-Cov-2 Abs. this new device could evaluate covid-19 specific IgG with 10ng/ml LOD. The Electric Field Induced Release and Measurement (EFIRM™) or Amperial™ technology, is a new device capable of performing quantitation of analytes in different samples [47]. The device works by immobilization of capture moieties on an electrode structure's surface for targeting molecules and then quantification of the target factors via electrochemically signaling oxidation-reduction between tetramethylbenzidine substrate and peroxidase enzyme and a hydrogen peroxide [48]. In a study a specific Amperial™ electrochemical tool was developed through immobilizing SARS-Cov-2 spike antigen on gold electrode and adding saliva samples that have specific Abs at different concentrations [48]. Then, Biotinylated anti-human IgG Abs was incubated on the electrode to bind with a specific Ab and finally streptavidin-HRP was added. The Amperial™ reader could measure the electrochemical signaling at -200 mV (Figure 3) [48].

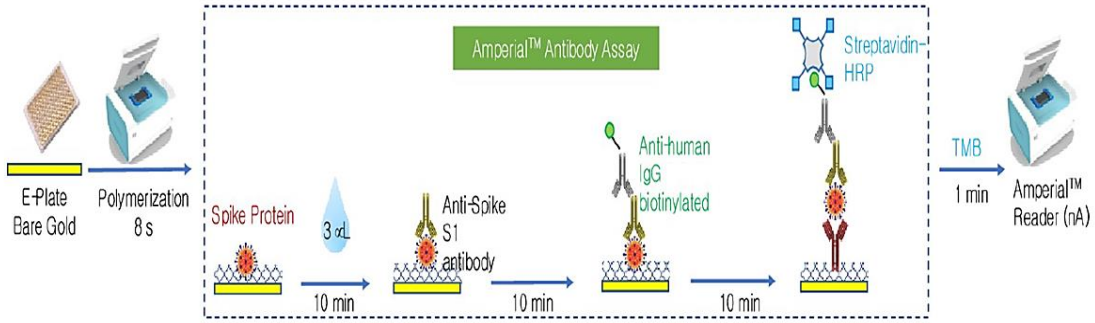

Figure 3. For fabrication of Amperial™, the Biotinylated anti-human IgG Abs was incubated on the electrode to bind with a specific Ab and finally streptavidin-HRP was added; reprint with permission from reference [48]; copyrights, Elsevier 2022

This study has suggested this electrochemical method is a cost-effective, non-invasive, acceptably specific, home collection based, and highly sensitive test. Electrochemical ELISA combining a sandwich ELISA method with electrochemical biosensor, is a powerful method that can prepare high specificity because of using a sandwich assay and excellent sensitivity because of utilize of improved detection electrochemical measurement and tags [49]. Commonly electrochemical ELISA has effective role in the binding of electrochemical signal recognition and biomolecules on the sensor electrode surface [50]. For developing electrochemical ELISA biosensor, the SARS-CoV-2 Spike proteins were conjugated with Horseradish Peroxidase (HRP) and immobilized on carbon screen printed electrodes [51]. This modified device can create accurate and fast quantitative examination of total IgG and IgM concentration in blood samples.

4.2. Optical Biosensors

Optical biosensors have described as sensor technique which makes use of optical methods for the transduction of a biochemical interaction into appropriate detectable signals [52]. The bimolecular interaction on the sensor surface regulates the light characteristics of the transducer and the biosensing signals can be measured through the change in different optical methods containing of refractive index luminescence, absorption, or, fluorescence, among others [53]. This type of biosensors exhibits highly specific, rapid, high-frequency monitoring, and real-time, without any high costs or needing more time for measurement. Moreover, optical biosensors have suitable operations in the fields of food safety, diagnosis, environmental monitoring, drug development and biomedical research [54,55]. In recent years, surface plasmons, colorimetry and Fluorescence techniques are used to detect influenza virus, Ebola, HIV, and norovirus [56].

4.2.1 Surface Plasmon Surface (SPR)

Optical biosensors based on surface plasmon resonance (SPR) are expansively used to prove the kinetics of number of macromolecular interactions and high- and low-affinity small analytes interactions [57]. Biomolecular interaction analysis consists of proteins-proteins, protein–lipid, DNA–DNA, DNA–protein, and antigens-Abs can be studied by SPR. A surface plasmon is excited at the interface between a dielectric medium (superstrate) and a metal film, alterations in the refractive index of which are to be detected. Finally, alterations in the refractive index of the superstrate generate changes in the propagation constant of the surface Plasmon [58]. SPR can be a best device based on Abs, and it can be utilized for fast and simple detection of Abs against SARS-Cov-2 antigens. Localized SPR (LSPR) is a strong method for biological and chemical molecules sensing. Also, the LSPR has role in the electromagnetic-field improvement that causes surface-increased spectroscopic processes and surface-enhanced

Raman scattering (SERS) [59]. Association of the wavelength shift of the LSPR peak of gold nanospike in the SPR biosensor upon binding correlations with the Covid-19 spike Ags and with electrodeposition method, the opto-LSPR sensing device with gold nanospikes was constructed by Funari et al. [60]. This biosensor could detect spike protein specific Abs in real human plasma with high specificity and sensitivity, and lable-free, which can be develop as an excellent technique for point-of-care Ab detection with 0.08ng/ml LOD. angiotensin converting enzyme2 (ACE2) receptor expressed in various types of cells such as kidneys, epithelial cells and can binds spike protein RBD of SARS-CoV-2 domain [61]. The binding of ACE2 and spike Ag domain cause virus to preserve efficient cell entry while eluding immune surveillance [62]. In a study that have been done in 2020 by SPR, the affinity of the ACE2 receptor and RBD of SARS-CoV and SARS-CoV-2 were reported 31 nM and KD~5 nM [63]. High avidity anti-RBD Abs are effective to interrupt ACE2 mediated entry. So, Abs and vaccines have role in the control emerging variants. Schashfoort et al. [61] have fabricated the SPRi system via spotting the sera to an RBD coupled surface and have measured the strength of binding of various isotypes of Abs (IgG, IgM, IgA) levels with the RBD.

The SARS-CoV-2 genome encodes four main structural proteins including membrane protein, spike protein, nucleoprotein (NP) and envelope protein [64]. The NP is highly expressed in patients and has a linkage region with C- and N-terminal binding domains. Moreover, the NP is commonly utilized in serological tests and vaccine technology [65]. The NP infects the host cell with viral RNA and has role in viral release, replication and, particle assembly [66]. In a new study the NP SARS-COV-2 Ags were immobilized on the gold SPR chip and NP specific Abs were calculated approximately 1.02 pM LOD and 185 pM binding constant (Kd) [67]. In conclusion, These researches are demonstrated one of the best strategy to measurement of the strength of binding between some specific Abs against various antigens of SARS-COV-2 is SPR and have been proven this technique can be an attractive method for quantitative detection of Abs and simultaneous monitor of analytes interaction because of its unique features such as low-costs, label-free, real-time (Table1) [68].

4.2.2. Colorimetric & fluorescent Assay

Colorimetric biosensors can be employed in the detection of the particular molecules via color changes easily by simple portable optical detectors or naked eyes for quantitative evaluation. So, it is attracted high attention for point-of-care detections of some molecules such as antigens or antibodies to suppress potential pandemic outbreak, Ags/Abs reactions and concentration of molecules in various samples [69]. IgA has efficient effect on the mucosal epithelium for homeostatic regulation and protection of the respiratory [70]. So, IgA can be a useful immunoglobulin compared with IgM in the early monitoring of COVID-19 infection and as an alternative test for efficacy of various vaccines [71]. Nanotechnology plays a crucial role in colorimetric technology. For instance, nanomaterials like Cu, Ag, Au, are expansively

utilized in visual detection owing to its optical features. Roda et al. [71] have fabricated a colorimetric immunosensor with an anti-IgA labelled with gold nanoparticles (GNP) as the probe and the recombinant nucleocapsid protein from SARS-CoV-2 for capturing Abs specific to the virus. This sensor is a rapid and easy detection method to quantify the colour at the test line, which is correlated to IgA levels. A fluorescent biosensor is a technique that semiquantitatively or quantitatively converts information about the presence of a certain analyte to a detectable optical signal [72]. In recent decade, the diagnosis of single fluorescent molecule comes true, greatly increasing novel highly sensitive biosensors. Fluorescent biosensors can prepare appropriate situation to reveal small proteins signals and quantify and monitor various molecules activity in living cells with excellent temporal and spatial resolution [73,74]. Song and his colleagues [75] have immobilized spike antigens on the optical fiber surface and samples containing different amounts of IgG against spike proteins were added to binds to the antigens on the optical fiber surface via Ag/Ab reactions. Finally, for exhibiting of Abs and Ags reactions, the anti-IgG labeled with the fluorescence intensity Abs were added. The sensitivity of this fluorescent biosensor is 12.5ng/ml LOD (Figure 4).

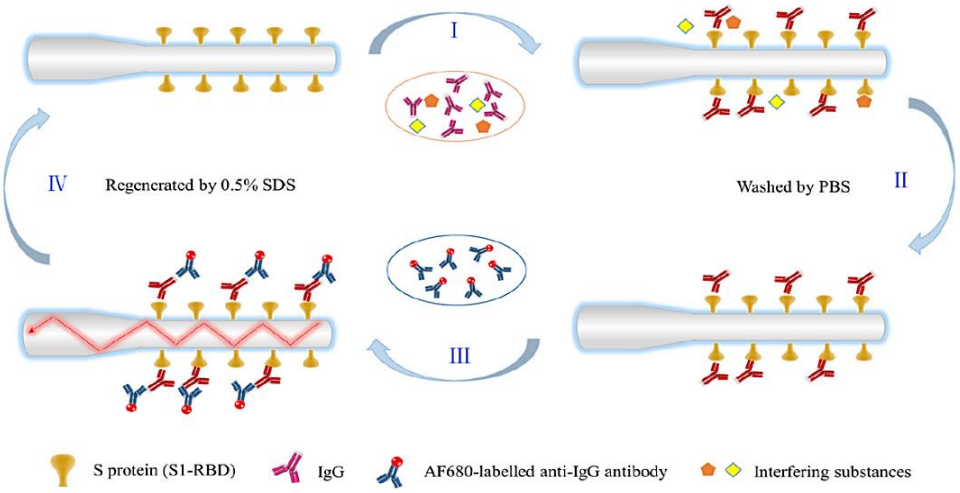

Figure 4. S pike antigens were immobilized on the optical fiber surface and samples containing different concentrations of IgG against spike proteins were added to binds to the antigens on the optical fiber surface via Ag/Ab reactions. Moreover, for exhibiting of Abs and Ags reactions, the anti-IgG labeled with the fluorescence intensity Abs were added; Reprint with permission from reference [75]; copyrights, Elsevier 2022

Colloidal gold (Au NP)-based lateral flow immunoassay (LFIA) is commonly the most mature point-of-care testing (POCT) technique but the main disadvantage of the Au NP-based LFIA has the lower sensitivity based on the colorimetric method [76]. For solving this problem, quantum dots (QDs) are highly employed as fluorescence labels in the LFIA system to increase

quantitative ability and sensitivity due to their suitable optical features, such as high light stability, detectable fluorescence intensity, and broad excitation [77,78]. A colorimetric-fluorescent dual-mode LFIA biosensor based on spike (S) proteinconjugated SiO_2@Au@QD nanobeads (NBs) as a label for binding of specific IgG and IgM against S proteins have been designed with 100% specificity [76]. In general, studies performed by colorimetric and fluorescent methods show that these approaches, along with electrochemical methods can be useful for measuring specific Abs (Table2).

Table 2. Covid-19 specific Antibodies detection with optical bioanalytical systems

Biosensor method	**Sensing platform**	**Types of Abs**	**LOD**	**References**
LSPR	Gold nanospike	IgG	0.08 ng/ml	[60]
SPR	RBD protein modified surface	IgG, IgM, IgA	-	[61]
SPRi	RBD protein modified surface	IgG	-	[80]
SPR	Nucleoprotein	IgG	1.02 pM	[67]
Fluorescent	Spike protein	IgG	12.5 ng/ml	[75]

Localized surface plasmon resonance (LSPR), Surface Plasmon Resonance imaging (SPRi)

5. CONCLUSION

The COVID-19 as a severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) rapidly spread to the entire world. Immunoassays distinguish binding of Abs to a specific antigen and can be utilized to assessment the presence and amount of specific Abs to approve if a patient has been previously infected and determine the prevalence of the disease. However, some routine immunological methods require complicated procedures, long assay time, and expensive reagents. In two years ago, Optical biosensors such as colorimetric and fluorescent and electrochemical types are appropriate and reliable devices for detecting various types pf Abs against different SARS-COV-2 Ags. Almost all of the studies cited in this review study have proven to be relatively sensitive and also cheaper than immunological and serological methods. It is essential that other biosensor devices such as quartz crystal microbalance (QCM) and fluorescence resonance energy transfer (FRET) be developed in the future to detect covid-19 specific Abs.

Abbreviations

SARS CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2
CoVs: Coronaviruses
RBD: receptor-binding domain
ACE-2: angiotensin-converting enzyme 2
LFIA: Lateral flow immunoassay
ELISA: Enzyme-linked immunosorbent assay
SPR: surface plasmon resonance
GO: graphene oxide
Cys: cysteamine

Funding

Not applicable

Conflict of Interest

The authors have no conflict of interest.

Ethics approval and consent to participate

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Availability of data and materials

Not applicable

Conflict of interest

Author Saade Abdalkareem Jasim, Author Trias Mahmudiono, Author Maria Jade Catalan Opulencia, Author Dmitry Olegovich Bokov, Author Dinh Tran Ngoc Huy, Author Djakhangir F. Shamsiev, Author Zahraa Haleem Al-qaim, Author Nguyen Dinh Trung, Author Yasser Fakri Mustafa, and Author Walid Kamal Abdelbasset declare that they have no competing interests.

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