International Journal of Scientific Research and Engineering Development-– Volume 4 Issue 5, Sep- Oct 2021

Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

State of The Art Biosensors: - Pre-Eminence Over Conventional Methods of COVID-19 Diagnosis

Nilesh Chougale[1],GandhaliVichare[1], Shivani Khataokar[1], Shivani Mantri[2], ChinmayiPise[3], Harshada Desai[3],Nikita Chavan[3], AaryaBenke[3]

Department of Biotechnology, Kolhapur Institute of Technology (Autonomous), Affiliated to Shivaji University, Kolhapur, India.

----------**********----------

Abstract:

Biosensors have been proved to be significant in the detection of the Covid-19 virus. Covid-19 caused great havoc worldwide. We did not only face economic loss, but also a lot of our beloved ones. We can control the spread of this virus by taking precautions, detecting it as early as possible, and curing it. The sanitizers, masks, personal protective equipment kits, frequently washing hands, and getting vaccinated can avoid the infection. The dreadful disease can be cured by certain medication. We can avoid future complications by detecting the viral infection early. Some conventional methods like Polymerase chain reaction, gene sequencing, ELISA, etc. are used for Covid-19 detection, but they are time-consuming and less sensitive. However, biosensors can be the best alternatives for conventional techniques. Biosensors are integrated analytical devices with biological detecting material used for the detection of the presence or concentration of a biological analyte. This review focuses on the significance of biosensors and their types in the Covid-19 detection, over conventional methods.

Keywords — Covid-19, Pandemic, Rapid detection, Biosensors, Molecular detection, Healthcare

----------**********----------

I. INTRODUCTION

Coronavirus disease (Covid-19) is a global pandemic, which is detrimental to the human race. this deleterious virus broke out in December 2019 in Wuhan, China, and affected almost 178 million people and killed almost 3.9 million people in the whole world (as of May 7, 2021). various countries like the united states, India, Brazil, etc. were severely affected by the virus and faced a copious amount of loss of life as well as economic loss. the signs and symptoms of covid-19 vary from mild ones like fever, cough, dyspnoea, diarrhea, lack of taste and smell to severe syndromes like pneumonia, loss of speech or movement, acute respiratory distress, etc [1]. asymptomatic cases are hard to identify. as Covid-19 is highly transmissible and mutable, an accurate and rapid technique for diagnosis and treatment of the virus should be devised [2].

The symptoms of the disease are non-specific for the patients except the ones having diabetes, heart disease, hypertension, etc., thus we should get rid of it as soon as possible[3]. the conventional methods of Covid-19 detection were

 ©IJSRED:All Rights are Reserved

polymerase chain reaction, gene sequencing, ELISA, but these techniques are time-consuming, need skilled labor, need expensive equipment, are less accurate, etc [4]. The widespread of this deleterious disease urges a fast, accurate, and economic technique for diagnostics and treatment.

Biosensors can be one of the best alternatives for the above conventional methods. Biosensors are integrated analytical devices with biological detecting material used for the detection of the presence or concentration of a biological analyte. It consists of a Bioreceptor, signal transducer, and a signal detector. The types of biosensors are enzyme-based, immunosensors, tissue-based, thermal and piezoelectric biosensors, and DNA biosensors. They have applications in various fields like Food industries, fermentation processes, Biosensing technology, medical science, Imaging, Biodefense, metabolic engineering, and plant biology [5].

Biosensors can be used to develop a portable device for an accurate, sensitive, rapid, and economic device for diagnosis and treatment of COVID-19 [6]. Biosensors usually use nanomaterials for diagnostics, as the viruses are of the same size in nanoscale. Nano-biosensors using aptamers are also used for an accurate diagnosis. They can also be used for the detection of viruses in people having no symptoms due to their high sensitivity [7]. The Plasmonic fiber-optic absorbance biosensors (P-FAB) are a diagnostic device used for the detection of N-protein and helps in COVID-19 confirmation [8].The current review summarizes the applications of Biosensors in the diagnosis and treatment of the COVID-19 as well as their advantages over other conventional approaches.

II. TRADITIONAL METHODS OF COVID-19 DETECTION

The early analysis of SARS-CoV-2 is important to save us from the intense outbreak of the disease and special detection techniques are being hired to come upon the detrimental situation [9]. As the signs and symptoms expressed in COVID-19 aren't always very precise, molecular testing is more accurate to locate the infection. Two sorts of diagnostic assessments were accepted by the FDA for the detection of COVID 19. The first class of check consists of the detection of the virus itself viz, its genome or antigens, at the same time the second class of check consists of serological or immunological assays (CDC, 2019). Viral assessments verify the presence of the virus at the time of detection accordingly identifies the individuals with lively infection [10]. The methods were as follows:

A. Serological Assays

Unlike molecular methods, serological methods (additionally referred to as antibody tests) may be carried out to discover past and current SARS-CoV-2 contamination and reveal the development of the disease durations and immune response [11]. The serological evaluation is characterized by the presence of antibodies (e.g., IgG, IgM, and IgA) in a COVID-19 patient's blood, serum, or plasma examination. Antibodies are produced as a protection mechanism by the immune system against SARS-CoV-2 [11 ,12]. The immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies in sputum and saliva may be checked. First, IgM is produced after some days of contamination and lasts for about weeks which are accompanied by the formation of IgG that lasts longer. Thus, detecting IgM in a patient's sample shows early-degree contamination whilst detecting IgG shows a current or earlier contamination [11 , 12]. Although these gadgets provide a user-friendly and speedy platform, they frequently show limited sensitivity and require at the least antibodies for detection [13].

B.Enzyme-Linked Immunosorbent Assay (ELISA)

ELISA is a plate-based technique that has been used for detecting and quantifying soluble materials which include proteins and antibodies in health facilities and research laboratories. It consists of direct and indirect formats. The indirect ELISA, the most famous and more sensitive than the direct ELISA, an antigen (e.g., a recombinant protein (N

 ©IJSRED: All Rights are Reserved

protein) of SARS-CoV-2 virus) is lined onto the internal surface of 96-well or 38-well polystyrene plates. A diluted patient's plasma which might have anti-SARS-CoV-2 IgG/IgM is introduced into the wells. The plate is incubated for one hour to permit the antibodies to engage with coated antigens. After washing the plate to dispose of unspecific interactions, a conjugated antibody with reported enzyme-like horseradish peroxidase (HRP) is added for the formation of sandwich complexes. These complexes are detected and quantified through the addition of a substrate (e.g.3,3′,5,5′-tetramethylbenzidine) that is used by the reporter enzyme and produces a change in reaction color. The color is detected and measured through a plate reader (Fig. 4). ELISA is pretty fast (2–5 h) and reasonably priced in comparison to RT-PCR, and it shows similarity to FLA regarding accuracy [11].

C. Lateral Flow Assays

LFA is a paper-like membrane strip overlaid with two lines [11]. In LFA, the specimen is deposited onto a sample pad of a cassette-like tool and moved through a strip via capillary action. Usually, it takes 10-30 min for the test which puts it under rapid diagnostic methods. It gives the simplest qualitative evaluation and has the benefit of easy handling and cost-effectiveness and permits direct evaluation of ongoing contamination as anti-CoV antibodies are used rather than immobilized viral antigens [14]. The first line, the test line, incorporates anti-human IgG/IgM antibodies, whilst the second line, the control line, incorporates anti-rabbit IgG antibodies. Serum samples containing the IgM and IgG when added to the specimen site bind with viral antigen lined at the conjugated pad [10]. If each test and control line gives out red color, the result is considered positive and negative whilst only the control line seems red. If both lines appear colorless or only the test line seems red, the result is invalid. The disadvantage of LFA is a qualitative approach, which tells the presence or absence of antibodies towards the virus without telling the amount in which they had been present in a patient's sample, and it is much less precise in comparison with RT-PCR [11].

D. Loop-Mediated Isothermal Amplification (LAMP)

LAMP, a new experimental study, the authorized and rapid investigative technique to perceive SARS-CoV-2 with Loop-Mediated Isothermal Amplification (LAMP) assay was developed [12 ,15]. The LAMP reaction is a single-tube method adjusted based on isothermal amplification of the SARS-CoV-2 nucleic acids and is mentioned as a sensitive and dependable tool [15 , 17]. This approach employs a DNA polymerase and a group of 4 particularly designed primers that apprehend six different regions on target genes and integrates a reverse transcription stage to locate RNA [12 ,16 ,17]. The LAMP approach can amplify a few copies of DNA to a large quantity in much less than an hour at a constant temperature of 65°C, concurrently decreasing the exhaustion of the thermocycler in addition to the specified energy[16].To report the process in real-time, the method makes use of intercalating dyes to calculate the turbidity of fluorescence [12, 17]. LAMP has excessive specificity, sensitivity, versatility, is easy to execute, and doesn't require special reagents or complicated equipment unlike PCR and its responsiveness makes it an extremely good applicant for virus detection [12, 16

E. CRISPR-BASED Assays

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a collection of nucleic acid sequences contained in bacteria. A series of bacterial enzymes referred to as CRISPR-associated enzymes, can apprehend and cut these sequences diagnosed by Cas9, Cas12, and Cas13 [10, 12]. The RNA virus is extracted from a specimen accrued from the affected person and targeted areas of N2, E, RP genes are amplified at 62°C for 20 min by particular primers with the use of isothermal recombinase polymerase amplification[10], [11].The amplified DNA is once again transcribed into RNA by T7 transcriptase. The Cas13–RNA complex attaches to the target sequence, which ends up in the activation of nuclease activity of Cas13 leading to cleavage of the desired sequence. This response takes place at

 ©IJSRED: All Rights are Reserved

37°C for 10 min and the result is visualized by a fluorescent reader or a lateral flow strip. Both genes N2 and E need to be positive to consider the specimen is positive [10]. These experiments are low-value and could be finished in as low as one hour. However, it needs troubleshooting and a particular design of all enzymes, primers, and reporters which are used in this method [11, 12].

F. RT-PCR

Ordinarily, the reverse transcription-polymerase chain reaction (RT-PCR)-based test for viral RNA detection is looked upon as the gold-standard method for diagnosing COVID-19[18]. In this method, cDNA is generated from the extracted RNA of COVID-19 virus with specific primers for the following N1 and N2 genes and RNAse P (RP; internal control) as recommended by U.S. CDC and other health agencies. If both genes (N1 and N2) were positive, it is considered a positive sample. Besides the internal control (RP), there are three controls Positive Control (Nov PC), No Template Control (NTC), and Human Specimen Control (HSC) (that must be run to make sure the result is legitimate [11]. The RT-qPCR is a version of the qPCR technique, which is unequivocally developed for RNA detection. Hence, it is being used for SARS-CoV-2 detection as it directly tests for the presence of virus RNA. Initially, it converts the virus RNA into a small complementary DNA sequence (cDNA) for special recognition of paired sequencing on viral RNA. Then, cDNA is amplified through PCR using gene-specific primers and fluorescent-labeled hydrolysis probes. The DNA produced in the first step is utilized in the second step, where it is multiplied through repeated thermal cycling and ultimately the virus is detected using a quantitative qPCR machine [14]. Till now RT-PCR is the most widely used method for detection, it is time-consuming (requires 2–5 days from collecting a sample till getting the result) and must be done in a laboratory [10]

G. CT SCAN

A computerized tomography (CT) scan incorporates a series of X-ray images captured from various sites around the body and uses computer management to produce cross-sectional images of the different organs like soft tissues, bones, and blood vessels [15]. Chest computed tomography (CT) examination can be an indispensable assistant diagnostic procedure for individuals and also one of the diagnosis techniques having high sensitivity due to which many researchers recommend its use as one of the necessary diagnostic methods for COVID-19 [7]. The typical CT imaging generally shows the response of the body to the virus. The CT demonstrates 5 stages including the ultra-early stage, early stage, rapid progression stage, consolidation stage, and dissipation stage [16]. Therefore, CT scans are a great diagnostic tool for screening COVID-19 patients, especially in the high prevalence or pandemic areas. CT scans also have some defects, such as indistinguishability from other viral pneumonia with 60–70% of specificity and slowing of abnormal CT imaging [15, 16].With all the pros of accuracy and greater sensitivity, molecular techniques were on the downside due to their requirement of complex equipment, skilled personnel, and also lengthy procedures. There was a need for fast and compact technology which would serve as a good point of care strategy, and biosensors emerged as a promising alternative to all the above methodologies.

H. Illumina NGS (New Generation Sequencing)

SystemsNext-generation sequencing (NGS) is also known as high-throughput sequencing (HTS). By this method, we will be able to diagnose inheritable diseases, cancer, and infectious diseases. NGS allows not only the discovery of novel viral strains on a massive scale. However, additionally provides very fast detection of these viruses which associate with human diseases [.[7The shotgun metagenomics based on Illumina benchtop systems is a few of the strategies which might be used for COVID-19 detection. The layout of this approach for COVID- 19detection is typically based on library

 ©IJSRED: All Rights are Reserved

formation pertained after RNA extraction with the employment of the TruSeq Stranded Total RNA Library Prep Gold kit (Illumina, USA). Later, the sequencing technique is executed on Illumina Benchtop Sequencing System, and the data evaluation may be completed with the use of the Illumina Local Run Manager (LRM) Resequencing Module for any desired reference genome [.[16But the large price of the gadget and chemical substances required on this method restricts its usage in ordinary laboratory analysis of the diseases [.[7

III. BIOSENSORS

A biosensor is a device that measures chemical and biological reactions by generating signals proportional to the concentration of an analyte in the reaction that could be used as simple, real-time, and effective devices for the detection of various infectious diseases [19]. Based on application biosensor is also known as immunosensor, optrodes, chemical canaries, resonant mirror, glucometer, biochips, etc.

Biosensor Element

Various types of substances are used as bio elements in biosensors which include

- Nucleic acid
- Plant proteins or lectins
- Protein such as enzymes and antibodies
- Complex materials like tissue slices, microorganisms, and organelles slice.

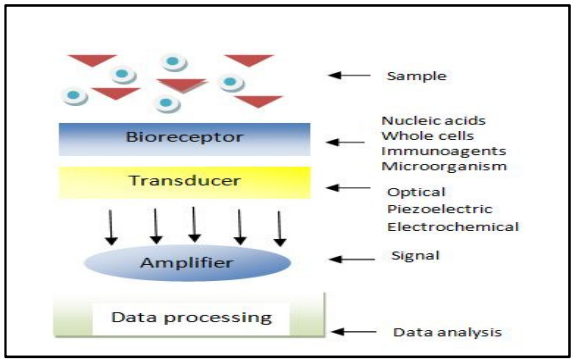

Fig.1 principle of biosensor, where the analyte binds specifically to a bioreceptor that leads to generating a signal which can be amplified to be read by data processing.

Biosensor consists of four main components: bioreceptor, transducer, amplifier, and data processing system. Bioreceptor recognition substances such as a monoclonal antibody, enzyme, nucleic acid, glycan, lectin, tissue, or whole-cell interact specifically with biomarkers. All these biomolecules interrelate with an interesting analyte. This relationship is calculated by the transducer that gives the result of a measurable signal, then the qualitative and quantitative identification of pathogens is obtained by recording and displaying the signal [20 ,21]. Along with these components, biosensors need to comply with certain characteristics.

IV. ESSENTIAL CHARACTERISTICS OF BIOSENSORS

The essential parameters to boost biosensor output performance when manufacturing is described. However, these parameters rely on the analysis method, the configuration set-up, materials deposited as thin films, and even how sensible the instrumentation is [22]. There are bound static and dynamic attributes that each biosensor possesses. The optimization of those properties is mirrored in the performance of the biosensor.

A. Selectivity:

Selectivity is maybe the foremost vital feature of a biosensor. Selectivity is the capability of a bioreceptor to notice a particular analyte in a sample containing alternative admixtures and contaminants. The simplest example of selectivity is portrayed by the interaction of an antigen with the antibody.

B. Reproducibility:

Reproducibility is the ability of the biosensor to come up with identical responses for a duplicated experimental set-up. The reproducibility is characterized by the preciseness and accuracy of the transducer and electronics in the biosensor.

 ©IJSRED: All Rights are Reserved

Exactitude is the ability of the device to produce similar results each time a sample is measured and accuracy indicates the sensor's capability to provide an average value near to the actual value when a sample is measured more than once.

C. Stability:

Stability is the degree of susceptibility to surrounding disturbances in and around the biosensing system. These disturbances can cause a drift within the output signals of a biosensor under measurement. This could cause a slip in the measured concentration and might affect the exactness and accuracy of the biosensor

D. Sensitivity:

The minimum quantity of analyte which will be noticed by a biosensor defines its limit of detection (LOD) or sensitivity. During a range of medical and environmental observation applications, a biosensor is needed to detect analyte concentrations of as low as ng/ml or maybe fg/ml to substantiate the presence of traces of analytes in a sample. For instance, a prostate-specific antigen (PSA) concentration of 4 ng/ml in the blood is related to adenocarcinoma for which doctors recommend biopsy tests. Hence, sensitivity is taken into account to be a very important property of a biosensor.

V. BASIC CONCEPTS IN BIOSENSORS

A biosensor includes a bio-element and a sensor-element. The bio-element can be an enzyme, antibody, live cells, or tissue. The sensing element can be electric current, electric potential, and so on. A specified list of various viable bio-elements and sensor elements different mixtures of bio-elements and sensor-elements represent numerous forms of biosensors to fit a considerable pool of applications. The bio elements and the sensor elements may be coupled collectively in one of the 4 viable methods i.e., a) membrane entrapment, b) physical adsorption, c) matrix / porous entrapment and d) covalent bonding:

a) In the membrane entrapment case, a semi-permeable membrane separates the analyte and the bio-element; the sensor is connected to the bio-element.

b) The physical adsorption case depends on a mixture of Vander Waals forces, hydrophobic forces, hydrogen bonds, and ionic forces to connect the biomaterial to the surface of the sensor.

c) The porous entrapment case is based on forming a porous encapsulation matrix across the biological material that facilitates binding it to the sensor.

d) In the case of the covalent bonding, the sensor surface is handled as a reactive group to which the organic substances can bind.

The commonly used bio-element enzyme is a massive protein molecule that acts as a catalyst in chemical reactions, however, it stays unchanged at the cease of the reaction. An enzyme, upon interaction with a substrate, forms a complex molecule that, under suitable conditions, produces the ideal product molecule liberating the enzyme at the end. The enzymes are extraordinarily unique in their action. This extraordinarily unique action of the enzymes is the basis of biosensors [24].

VI. TYPES OF BIOSENSORS

Based on various modes of detection, the biosensors are classified into different types. Here we describe a few rapid methods of detection.

A. Electrochemical Biosensors

Electrochemical biosensors are biosensing gadgets containing electrochemical transducers that transform biochemical records and have benefits such as simple instrumentation, great sensitivity, cost-effectiveness, and the opportunity of miniaturization. In this review, we will focus on the

 ©IJSRED: All Rights are Reserved

recent improvement of impedance-based electrochemical strategies and immuno-sensors for the detection of numerous viruses lately reported. An electrochemical biosensor can display the activities of living cells or enzymes by measuring the interplay between an analyte and the bioreceptor.

B. Electrochemical Impedance Spectroscopy

Electrochemical impedance spectroscopy (EIS) is referred to as a cost-effective and efficient technique that even detects any very small changes which occur in the solution–electrode interface [25]. Therefore, EIS is mainly used to sense devices and to monitor binding. Santos et al. identified the first dual marker dengue electrochemical assay and proved that dengue antigen assay times could be reduced to a few seconds in serum by moving to an immittance assay from capacitance. Research thinks to the design of specific SARS CoV 2 DNA primers by modifying this dengue RNA detection platform with a specific hybridization between the probe (DNA primers) and spike surface glycoprotein (S)/ small envelope protein (E)/ matrix protein (M) or nucleocapsid protein (N) can play a significant role in the diagnosis of COVID-19 virus. The method of Impedimetric detection of SARS CoV 2 is at an initial stage. Due to rapid detection, label-free detection, low LOD, cost-effectiveness, and point of care monitoring of the samples, the EIS method could be the future for the detection of COVID-19 [26]. For example, for viral RNA detection, functionalized graphene-wrapped silica electrode materials have been developed. For hybridization with viral (dengue) RNA, specific DNA primers were immobilized. The EIS test also looked into the considerable difference in interfacial RCT between non-complementary and complementary DNA hybridization [27]. Antibodies against SARS-CoV-2 are also detected by EIS. Generally, it is detected using either the recombinant spike protein or the smaller RBD portion of the spike protein. This study only tested detected binding of antibodies to RBD but similar results would be expected with the recombinant spike protein as well [26].

C. Electrochemical Immunosensors

Immunosensors are biosensing devices in which an immunochemical reaction is coupled to a transducer and used to detect specific antigens or antibodies in bodily serum and other media via immunochemical reactions. It is a useful technique for the detection of pathogens because of the main principle of immunosensor to detect an antigen or antibody. Whereas antibodies are naturally bound with antigen to form an antigen-antibody complex. Here, an electrochemical immunosensor has been developed by researchers for the detection of highly pathogenic SARS CoV 2 associated with the MERS-CoV. The concept of the immunosensor is to detect the signal after binding of the antigen during 45 min of incubation with a sample and perturbation obtained from Ferri/ferrocyanide measurements. The detection range of the spike protein was determined by measuring the absolute change in the [Fe (CN)6]3/4 current as antigen concentrations on the immunosensor surface increased. The sensor was able to detect a particular signal of recombinant spike protein subunit 1 over 260 nM (20 g/mL) [28]. Scientists developed a smart immunosensor for SARS-CoV-2 detection in saliva by combining the use of magnetic beads as support for immunological chains and carbon black-based Screen-Printed Electrodes for sensitive and reliable detection. When tested with seasonal H1N1 influenza virus and the 2009 pH1N1 influenza pandemic, this sensor configuration demonstrated the ability to detect S and N proteins in untreated saliva with detection limits of 19 ng/mL and 8 ng/mL, respectively, as well as SARS-CoV-2 in saliva clinical samples and cultured SARS-CoV-2, all without cross-reactivity. The adequate analytical Characteristics found in terms

 ©IJSRED: All Rights are Reserved

of accuracy, sensitivity, and selectivity with the time of examination (30 min), easiness to use, and the requirement of convenient instrumentation to improve this biosensor to achieve a good position in SARS-CoV-2 detection, taking into account the ease of saliva sampling. Its efficacy was achieved using the nasopharyngeal swab specimens tested with Real-Time PCR using the cultured virus in biosafety level 3 and saliva clinical samples comparing the data. The data agreement, the low detection limit obtained, the speedy analysis (30 min), the compactness, and portability of the instrument, as well as its ease of use and non-invasive sampling, all contributed to the instrument's success [29].

D. Calorimetric/ thermal Biosensor

In our day-to-day life, a large number of biological reactions take place that are particularly interconnected with heat, and this makes the base for the invention/formation of thermometric biosensors [30]. All chemical and biological reactions involve the trade of heat. Thus, the overall concept of generation and absorption of heat has contributed to the start of calorimetric-based biosensing devices [31]. Thermometric biosensors take advantage of the essential assets of biological reactions (exothermic or endothermic), i.e., absorption or evolution of heat which in turn changes the temperature of the medium wherein the reaction occurs [23 ,24 ,32,34]. Usually, these types of sensors that address heat are known as thermal (heat) biosensors [30]. This is pondered as a change in the temperature in the reaction medium [32]. Thermal transduction relies on the ideas of calorimetry which requires the measurement of temperature changes in the reaction among biorecognition elements and a suitable analyte [23 , 31 ,35]. Initially, calorimetric transduction has been employed for enzyme-based sensors and has eventually been implemented in DNA/cell and immunosensors [31]. They are combined by combining immobilized enzyme molecules with temperature sensors [34,36]. When the analyte comes in contact with the enzyme, the overall heat evolution or absorption is proportional to the molar enthalpy and the total quantity of product molecules created in the biochemical reaction [24, 31, 32]. In the calorimetric device, the heat change is generally measured using either a thermistor i.e., temperature-based resistors, (commonly metal oxide) or thermophile (commonly ceramic semiconductor) as the detector unit [23], [31]. The primary thermal biosensor was referred to as an ‘‘enzyme thermistor’’[24, 35]. Thermistors rely upon the changes in the electric resistance with temperature. From this, the absolute temperature may be determined. Thermopiles measure the temperature difference between 2 regions [33, 37].

The predominant benefits of this kind of thermal detection are the long-term stability, accuracy, and opportunity of miniaturization. This approach is used for label-free screening of biomolecule interaction. The calorimetric method can rapidly detect DNA hybridization [31]. There are multiple application possibilities of the thermal biosensors, it is utilized in diverse bioprocess industries because of its easy design and it is simple to operate and maintain. It additionally increases the robustness and sterile sampling [37].

Still, thermal biosensors have not often been used for biosensor measurements. One reason for this can be the issue to cope with nonspecific temperature changes, e.g., arising from dilution or solvation effects, requiring extra means, such as reference channels [35]. Calorimetric devices for ordinary use were restricted by the price of operation and comparatively long experimental procedures. Its poor popularity is likewise because of its complex thermostat and its very vulnerable sensitivity. It additionally has non-particular heating effects, there is no direct way to

 ©IJSRED: All Rights are Reserved

discriminate among particular and non-particular heat changes. And hence it is not employed in pandemic situations [33, 37].

E. Optical Biosensor

An optical biosensor is made up of an analytical device comprising a biorecognition sensing element amalgamated with an optical transducer system. The main aim of an optical biosensor is to produce a signal which is proportional to the concentration of a measured substance (analyte). The optical biosensor can be used in the detection of various biological materials, such as antibodies, antigens, enzymes, nucleic acids, receptors, whole cells, and tissues as biorecognition elements. In the construction of optical biosensors, huge numbers of variations occur, and here we are going to explain a few biosensors that are useful in the detection of the SARS CoV 2 virus [38].

The optical biosensors are detecting the changes which occur in the refractive index (RI) in the Vicinity of the sensor surface [20]. Jing Wang and his fellow researchers developed an optical sensor for the detection of SARS-CoV-2. This sensor is designed by integrating two kinds of operations: an optical effect and a thermal effect for the detection of a virus [39]. A glass substrate biosensor consists of a tiny structure of gold, which is known as nanoislands. The gold nanoislands are artificially implanted with the synthesized DNA receptors and the complementary RNA sequences of SARS-CoV-2. The novel SARS CoV 2 is an RNA virus as their genomes contain an ssRNA. Therefore, the receptor of the sensor acts as complementary sequences to the RNA sequence of the virus that can accurately identify the virus [40]. The technology the researchers use for the detection of an RNA virus is called localized surface Plasmon resonance (LPSR). Based on the optical phenomenon LPSR occurs in metallic nanostructures. This metallic nanostructure gets excited when incident light of a specific wavelength range produces a near plasmonic field around the nanostructures. When molecules in the sample bind to the surface of the sensor the local infracted index inside the plasmonic near-field changes. An optical sensor is used to detect this change and thus assess whether the RNA strands in the sample are present or not [39].

F. Plasmonic Biosensor

Plasmonic fiber optics is a U-bent optical fiber probe that is a diagnostic device [8]. This device is Cost-effective and sensitive. P-fab detects various molecules with gold nanoparticles [41]. This biosensor can detect patients suffering from Covid 19 Infection. It has proven to be a convenient one where the saliva sample is taken and the presence of N protein is checked. But before using this biosensor for covid-19 detection it needed to be modified a bit [42]. This has optical, magnetic, and electrical properties which are responsible for detection. This can also detect various others like influenza and tuberculosis [8].

G. Piezoelectric Biosensor

Piezoelectric sensors are also called acoustic sensors, work on the piezoelectric effect. The piezoelectric effect is the capability of a material to produce voltage when it is mechanically stressed and vice versa. Sometimes when the alternating voltage is given to the piezoelectric material, it causes mechanical stress (or Oscillations). The working principle of the sensors is, the alternating voltage is given on the surface of two electrodes which causes oscillations of the piezoelectric material. The frequency of the material is measured when it is put into an oscillation circuit [43]. Piezoelectric materials are usually anisotropic crystals, which are crystals without a center of

 ©IJSRED: All Rights are Reserved

symmetry. The change in the oscillations of the material is dependent on the mass bound on it [44].

The piezoelectric immunosensors are the biosensors used for the detection of different macromolecular compounds and microorganisms, as they contain antibodies as biorecognition elements [45]. The specificity of this immunosensor depends upon the specificity of the antibody. They can be used for analytes that are higher in molecular weight as they cause a higher decrease in the oscillation frequency. The magnetic nanoparticles covered with antibodies were also for the detection of the tumor necrosis factor-alpha. The number of oscillations decreases when the antigens get attached to the antibodies on the Piezoelectric crystal, decreasing the frequency of oscillations, then the nanoparticles coated with the antibodies get attached to the same antigen bringing the frequency of oscillations to the lowest [46].

The molecularly imprinted polymers are used as the biorecognition element in the biosensor instead of antigen or antibodies. These polymers are artificially synthesized in the presence of the template(analyte). Acrylates and acrylamides, sol-gels, chitosan, dextrin, and organo-metallic composites prove to be great materials for the synthesis of good molecularly imprinted polymers. The piezoelectric biosensors containing molecularly imprinted polymers react directly with the template by affinity reaction and cause a decrease in the oscillation frequency [46]. Genetic information like DNA and RNA are used as Biorecognition elements. Here, the sample or analyte DNA is denatured and one of its strands hybridizes with the complementary strand immobilized on the piezoelectric sensor resulting in a lessening of the frequency of oscillations [46].

Piezoelectric sensors are used in a wide variety of detection-based applications, like detection of cancer, detecting specific cancer biomarkers, determining drug effectiveness, DNA hybridization detection, Comparing DNA strands, Detection of the hepatitis C virus. This proposed the idea of biosensors that can detect at an early stage with high sensitivity and low cost. Piezoelectric and magnetostrictive biosensors can be preferred. These sensors can detect the viruses from frequency changes by directly using the output voltage. In addition, they should be combined with piezoelectric and magnetostrictive energy-harvesting devices, with the possibility to identify viruses by monitoring mechanical vibration. They can also be attached or embedded in smart clothing. However, none of these is commercially available on the market, and cannot be used for pandemic diseases such as COVID-19.

Along with these five basic types of biosensors, a new innovative technique i.e., paper-based immunosensor has been developed.

H. Paper-based Immunosensor

The new conception demonstrates a paper-based chemistry platform as a screening tool to notice SARS-CoV-2 immunoglobulins (represented by IgG and IgM). Paper, as a substrate material, was the main element because it has several benefits (such as low value, natural abundance, and portability [10]. Further, paper is often simply and safely disposed of by combustion. The strategy comprises 3 components (working ePAD, counter ePAD, and shutting ePAD), that have different functions. Specifically, within the zone of the operating ePAD, the SARS-CoV-2 spike macromolecule containing receptor-binding domain (SP RBD) is immobilized to capture incoming SARS-CoV-2 antibodies [13].

For the diagnostic step, the electrochemical signals are monitored using the square-wave voltammetry (SWV) technique. In this view, the SWV response is attenuated upon immunocomplex formation. Particularly, several assays were also carried out in real patient sera (both SARS-CoV-2-

 ©IJSRED: All Rights are Reserved

infected and -uninfected patients), and to demonstrate the approach's potential usefulness in real-world sample testing, the results were compared to an ELISA method. Finally, the projected platform was to be extended to the detection of antigen (SARS-CoV-2), exhibiting glorious sensing ability for COVID-19 point-of-care (PoC) testing.

Construction of COVID 19 e-PAD

The device was designed by Adobe creative person CC (Adobe Systems, USA) and printed using a wax printer [13]. The reprint pattern was heated in an oven at 150 ◦C for 2 min to make a three-dimensional wax barrier. During this work, one sheet of the COVID-19 ePAD consists of 3 folding layers: a working ePAD, a counter ePAD, and a shutting ePAD (see Fig. 1A). The hydrophilic center of every zone was restricted by a wax barrier, where the solution could flow through to the test zone at the bottom. Three electrodes were then screen-printed at the back of the device and dried in an oven at 55 ◦C for 30 min.

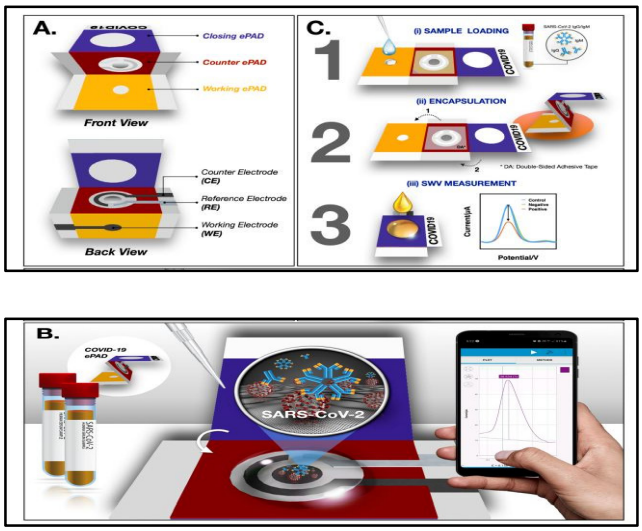

Fig. 2. Schematic representation of the diagnosis of COVID 19 sample via e-PAD where: (A) device components, (B) detection principle, and (C) detection procedure of the COVID-19 ePAD. [13]

To construct the COVID-19 e-PAD for SARS-CoV-2 antibody detection, the spike protein receptor-binding domain (SP RBD) of SARS-CoV-2 was immobilized on the test zone of the working e-PAD (front view) (Fig. 1B)[47]. Here, the Graphene Oxide (GO) solution was implanted in a very porous structure of a test zone of the operating e-PAD and allowed to dry at room temperature. Activation of a carboxylic group (–COOH) of GO with 20 mM EDC/40 mM NHS for 1 h and paired with the SARS-CoV-2 SP RBD for 1 h after washing with Milli-Q water. After a washing step with 0.01 M PBS (pH 7.4), the check zone was blocked using skim milk for 30 min at RT. The device was kept in the refrigerator at 4 ◦C until use. Then, the device was ready to use. To prepare a COVID-19 ePAD for SARS-CoV-2 spike protein detection was utilized, with a change from SARS-CoV-2 (SP RBD) immobilization to SARS-CoV- 2 IgM immobilization. There is an activation of a carboxylic group (–COOH) of Graphene-oxide.

For the diagnostic step (Fig1C), 10 µl of a human serum sample containing targeted antibodies is applied to the test zone of the operating ePAD and incubated at room temperature (i). After the first step, the test zone is washed with 0.01 M PBS (pH 7.4) to get rid of unbound antibodies. Then, to enable paper folding, the plastic cover of double-sided sticky tape affixed on both sides of the counter ePAD was removed. For additional investigation, the counter ePAD was manually folded to the functioning e-PAD and layered with the closing ePAD. (ii). Particularly, this configuration can minimize direct contact with the biohazardous fluid and prevent exposure to the environment. For electrochemical detection (iii), On the closing e-PAD, a redox indicator solution ([Fe (CN)6]3-/4-) will be administered. Following that, the electrochemical response will be measured with the square-wave voltammetry (SWV) technique.

 ©IJSRED: All Rights are Reserved

Remarkably, a similar procedure was applied to the detection of the SARS-CoV-2 spike protein [13].

and in 8 pt Regular font with Small Caps. Every word in a table caption must be capitalized except for short minor words as listed in Section III-B. Captions with table numbers must be placed before their associated tables, as shown in Table 1.

Table 1. Comparison of Biosensors

Methods	Working principle	Advantages	Time required	Disadvantages
Electronic biosensor	It works on the principle of field electric transistors (FET)	1.Simple & ready to use 2.Low cost	20 to 25 min	1.Sample sorting in initial phases is required 2.Chances of false results are high
Optical biosensors	When the light of a particular wavelength is incident on a metallic surface, atoms are excited and LSPR occurs, leading to the detection of virus	1.enable the direct, real-time, and label-free detection of many biological and chemical substances. 2.Their advantages include high specificity, sensitivity, small size	20 min	1.Sterilized environment is necessary 2.High cost of Instrumentation.
Electrochemical biosensors	Its response is proportional to the analyte concentration by comparison of its activity to the reference electrode	1.robustness, easy miniaturization, excellent detection limits, 2.also with small analyte volumes, and the ability to be used in turbid biofluids with optically absorbing and fluorescing compounds	40 mins	1.Narrow or limited temperature range. 2.Short or limited shelf life 3.Cross-sensitivity of other gases. 4.The greater the exposure to the target gas, the shorter the life span.

 ©IJSRED: All Rights are Reserved

Piezoelectric sensors	The piezoelectric effect is the capability of a material to produce voltage when it is mechanically stressed and vice versa.	It is small in size. It has a good frequency response. It has a negligible phase shift.	20 to 30 min	1.Highly temperature sensitive 2.High moisture sensitive

VII. ADVANTAGES OF BIOSENSORS

Due to the constraints and issues associated with antique and cutting-edge techniques, the improvement of biosensors in recent years has acquired a greater interest of researchers. Findings from numerous researches indicate that biosensors are equipment with excessive sensitivity and specificity in addition to rapid overall performance that may be an awesome opportunity to develop strategies of coronavirus detection. The biosensor era may be concerned with electrochemical impedance spectroscopy, electrochemical immunosensors, paper-based immunosensors, P-fibre optics, and nano-sensors which may be implemented to diagnose the COVID-19 [15].

Due to their paper-based signal generation design, the immunosensors have a low detection limit of 10*3 pg mL-1 on PBS. But semi-quantitative measurements can be performed over a wide dynamic range of five orders of magnitude. This type of biosensor could be adapted to detect other cytokines, such as TNF-* and IL-8, by substituting the antibodies surrounding the nanoparticles with others capable of recognizing these targets specifically. All materials in the tests are filter paper, which allows them to be light, easy to transport and distribute, and to be easily disposed of or incinerated. In addition to being especially useful for home testing, the app cannot be controlled by any lightbox or accessory [48].

While using a PMO-functionalized G-FET nanosensor, the RNA from SARS-CoV-2 is directly detected in clinical throat swab samples, potentially leading to PCR-free detection of COVID-19. This method has advantages over other methods as The detection limit of this platform is as low as 0.37 FM, which is lower than the other reported biosensing platform. It provides a well-defined distinction between SARS-CoV-2 and SARS-CoV. It has the excellent anti-interference capability and high precision in detecting undiluted biological samples (throat swab/serum samples). It is outstandingly reliable and with accuracy for trying out RNA extracts from actual scientific specimens and excessive settlement with the consequences of RT-PCR [49].

In the case of Fibre optics, by using diverse bioassay formats, scientists have effectively completed the restriction of detection right down to an attomolar (10–18 M) attention of protein. It also displays good specificity and sensitivity (but multi-layered). There are a variety of shortcomings

 ©IJSRED: All Rights are Reserved

encompass coping with the labeled reagent one after the other and lots of surprising bottlenecks in putting in the chemical strategies and device fabrication.

Biosensors working on the principle of the electrochemical assay are ultra-sensitive and have brief instruction time. The evolved sensor ought to lessen the false-bad ratio. Being so correct it additionally doesn't have cross-reactivity with MERS-COV. Evaluation of saliva and oropharyngeal swab samples is Simple and speedy whilst those biosensors are used.

VIII. CONCLUSION

As the signs and symptoms expressed in COVID 19 aren't always very precise, molecular testing is more accurate to locate the infection. Viral assessments verify the presence of the virus at the time of detection and accordingly identify the individuals with lively infection. Although these testing strategies are of exceptional value, time consumption, tedious sample making, and the requirement of expertise and complex, steeply-priced optical imaging gadgets positioned them down. The contamination rate and contagiousness of SARS-CoV-2 are a great deal in comparison with different SARS infections. Therefore, fast and point-of-care diagnostic techniques are enormously required to conquer the constraints of traditional strategies. Thus, scientists are searching for an inexpensive, reliable, facile manner for the apt detection of SARS-CoV-2 with excessive accuracy. Biosensors can be used to detect various infections and diseases which is possible due to its ideal characteristics like specificity, linearity, etc. the infection or disease is detected by its sensing element and bio element enzyme commonly used is protein molecule. Various types of biosensors are also able to detect the novel coronavirus like electrochemical impedance spectroscopy where recognition is done with recombinant spike protein or the smaller RBD portion of the spike protein. Electrochemical immunosensors work by collecting the saliva samples and then testing them with real-time PCR. An optical biosensor can detect antibodies, receptors. In this, Covid 19 is detected by knowing whether it has the presence of RNA strands or not. Plasmonic Biosensor is one of the types of Optical biosensor where the presence of N protein is checked from saliva sample for covid19 detection. Paper-based immunosensor is a new concept that is derived, used in the detection of covid-19. It is a safe immunosensor as the paper is a cheap source and can be easily disposed of. Here e-Pad is constructed to detect various viruses which are then also beneficial to detect SARS-CoV-2 spike protein.

IX. FUTURE ASPECTS

Biosensors are devices with magnificent properties and applications. As biosensors have played a significant role in the detection of Covid-19, they also play important roles in various fields like biomedicine, food technology, and packaging, Environmental protection, Pharmaceutics, Healthcare, etc. Recently they were used in tissue engineering and regenerative medicine in the forms of enzymes, antibodies, and receptors. In the field of healthcare, they were used in the early detection of various diseases like Epilepsy and cardiovascular diseases [50]. Recently, they were also used in the protection of the environment by detecting deleterious algae. They play a very significant role in the food industry for quality analysis purposes. This abundant number of applications of biosensors leads to proliferation in demand for them. Thus, many top industries like Abbott (US), Roche (Switzerland), Medtronic (Ireland), Bio-Rad Laboratories, Inc. (US), and others have shown interest in the production of biosensors.

In the future scientists will be trying to model more specific, sensitive, non-toxic, and cost-

 ©IJSRED: All Rights are Reserved

effective biosensors [51]. According to research the combination of biosensing and bio-fabrication can make powerful biosensors [52]. Researchers from Stanford University have shown the use of biosensors for the early detection of Diabetes. According to recent research at the University of California, the number of accidents can be reduced by using the technology named "Biosensor tattoo" by detecting the alcohol level in blood. An era of "autonomous" biosensors is evolving [53].

REFERENCES

[1] J. Bedford *et al.*, "COVID-19: towards controlling of a pandemic," *Lancet*, vol. 395, no. 10229, pp. 1015–1018, 2020, doi: 10.1016/S0140-6736(20)30673-5.

[2] S. Chen, J. Yang, W. Yang, C. Wang, and T. Bärnighausen, "COVID-19 control in China during mass population movements at New Year," *Lancet*, vol. 395, no. 10226, pp. 764–766, 2020, doi: 10.1016/S0140-6736(20)30421-9.

[3] B. Udugama*et al.*, "Diagnosing COVID-19: The Disease and Tools for Detection," *ACS Nano*, vol. 14, no. 4, pp. 3822–3835, 2020, doi: 10.1021/acsnano.0c02624.

[4] D. Chakraborty, S. Kumar, N. Chandrasekaran, and A. Mukherjee, "Viral Diagnostics and Preventive Techniques in the Era of COVID-19: Role of Nanoparticles," *Front. Nanotechnol.*, vol. 2, 2020, doi: 10.3389/fnano.2020.588795.

[5] P. Mehrotra, "Biosensors and their applications - A review," *J. Oral Biol. Craniofacial Res.*, vol. 6, no. 2, pp. 153–159, 2016, doi: 10.1016/j.jobcr.2015.12.002.

[6] S. M. Azab and A. M. Fekry, "Electrochemical design of a new nanosensor based on cobalt nanoparticles, chitosan and MWCNT for the determination of daclatasvir: A hepatitis C antiviral drug," *RSC Adv.*, vol. 7, no. 2, pp. 1118–1126, 2017, doi: 10.1039/c6ra25826c.

[7] R. Kumar, S. Nagpal, S. Kaushik, and S. Mendiratta, "COVID-19 diagnostic approaches: different roads to the same destination," *VirusDisease*, vol. 31, no. 2, pp. 97–105, 2020, doi: 10.1007/s13337-020-00599-7.

[8] D. Murugan, H. Bhatia, V. V. R. Sai, and J. Satija, "P-FAB: A Fiber-Optic Biosensor Device for Rapid Detection of COVID-19," *Trans. Indian Natl. Acad. Eng.*, vol. 5, no. 2, pp. 211–215, 2020, doi: 10.1007/s41403-020-00122-w.

[9] J. Sengupta and C. M. Hussain, "Graphene-based field-effect transistor biosensors for the rapid detection and analysis of viruses: A perspective in view of COVID-19," *Carbon Trends*, vol. 2, p. 100011, 2021, doi: 10.1016/j.cartre.2020.100011.

[10] S. Tiwari, V. Sharma, M. Mujawar, Y. K. Mishra, A. Kaushik, and A. Ghosal, "Biosensors for epilepsy management: State-of-art and future aspects," *Sensors (Switzerland)*, vol. 19, no. 7, 2019, doi: 10.3390/s19071525.

[11] A. E. Dhamad and M. A. AbdalRhida, "COVID-19: Molecular and serological detection methods," *PeerJ*, vol. 8, pp. 1–18, 2020, doi: 10.7717/peerj.10180.

[12] I. H. Alsohaimi, "Analytical detection methods for diagnosis of COVID-19: developed methods and their performance," *Biotechnol. Biotechnol. Equip.*, vol. 35, no. 1, pp. 196–207, 2021, doi: 10.1080/13102818.2020.1865838.

[13] A. Yakoh, U. Pimpitak, S. Rengpipat, N. Hirankarn, O. Chailapakul, and S. Chaiyo, "Paper-based electrochemical biosensor for

 ©IJSRED: All Rights are Reserved

diagnosing COVID-19: Detection of SARS-CoV-2 antibodies and antigen," *Biosens. Bioelectron.*, vol. 176, p. 112912, 2021, doi: 10.1016/j.bios.2020.112912.

[14] A. Aziz, M. Asif, G. Ashraf, U. Farooq, Q. Yang, and S. Wang, "Trends in biosensing platforms for SARS-CoV-2 detection: A critical appraisal against standard detection tools," *Curr. Opin. Colloid Interface Sci.*, vol. 52, p. 101418, 2021, doi: 10.1016/j.cocis.2021.101418.

[15] A. Mobed and E. SepehriShafigh, "Biosensors promising bio-device for pandemic screening "COVID-19"," *Microchem. J.*, vol. 164, no. December 2020, p. 106094, 2021, doi: 10.1016/j.microc.2021.106094.

[16] I. El Jaddaoui*et al.*, "A review on current diagnostic techniques for COVID-19," *Expert Rev. Mol. Diagn.*, vol. 21, no. 2, pp. 141–160, 2021, doi: 10.1080/14737159.2021.1886927.

[17] Y. Shen, T. Bin Anwar, and A. Mulchandani, "Current status, advances, challenges and perspectives on biosensors for COVID-19 diagnosis in resource-limited settings," *Sensors and Actuators Reports*, vol. 3, no. December 2020, p. 100025, 2021, doi: 10.1016/j.snr.2021.100025.

[18] A. Yakoh, U. Pimpitak, S. Rengpipat, N. Hirankarn, O. Chailapakul, and S. Chaiyo, "Paper-based electrochemical biosensor for diagnosing COVID-19: Detection of SARS-CoV-2 antibodies and antigen," *Biosens. Bioelectron.*, vol. 176, no. December 2020, p. 112912, 2021, doi: 10.1016/j.bios.2020.112912.

[19] S. Robertson, "Sally-Robertson @ Www.News-Medical.Net." 2019, [Online]. Available: https://www.news-medical.net/medical/authors/sally-robertson.

[20] S. A. Abid *et al.*, "Biosensors as a future diagnostic approach for COVID-19," *Life Sci.*, vol. 273, no. October 2020, p. 119117, 2021, doi: 10.1016/j.lfs.2021.119117.

[21] S. Behera *et al.*, "Biosensors in diagnosing COVID-19 and recent development," *Sensors Int.*, vol. 1, no. November, p. 100054, 2020, doi: 10.1016/j.sintl.2020.100054.

[22] B. A. Taha *et al.*, "An Analysis Review of Detection Coronavirus Biosensor Application," *Sensors*, vol. 2019, pp. 1–29, 2020.

[23] P. Rakesh, P. Pramod, and P. Sujit, "Biosensors: Current tool for Medication and Diagnosis."

[24] P. Bhalinge, S. Kumar, A. Jadhav, S. Suman, P. Gujjar, and N. Perla, "Biosensors : Nanotools of Detection- A Review," *Int. J. Healthc. Biomed. Res.*, vol. 04, no. April, pp. 26–39, 2016.

[25] M. Z. H. Khan, M. R. Hasan, S. I. Hossain, M. S. Ahommed, and M. Daizy, "Ultrasensitive detection of pathogenic viruses with electrochemical biosensor: State of the art," *Biosens. Bioelectron.*, vol. 166, no. July, p. 112431, 2020, doi: 10.1016/j.bios.2020.112431.

[26] Mohamed Z. Rashed, "Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information," no. January, 2020.

[27] S.-A. Jin, E. E. Marinero, L. A. S. Stanciu, S. Poudyal, and R. J. Kuhn, "Impedimetric Zika and Dengue Biosensor based on Functionalized Graphene Oxide Wrapped Silica Particles," in *APS March Meeting Abstracts*, Mar. 2017, vol. 2017, p. E5.010.

[28] B. Mojsoska, S. Larsen, D. A. Olsen, J. S.

 ©IJSRED: All Rights are Reserved

Madsen, I. Brandslund, and F. A. Alatraktchi, "Rapid SARS-CoV-2 detection using electrochemical immunosensor," *Sensors (Switzerland)*, vol. 21, no. 2, pp. 1–11, 2021, doi: 10.3390/s21020390.

[29] L. Fabiani*et al.*, "Magnetic beads combined with carbon black-based screen-printed electrodes for COVID-19: A reliable and miniaturized electrochemical immunosensor for SARS-CoV-2 detection in saliva," *Biosens. Bioelectron.*, vol. 171, p. 112686, Jan. 2021, doi: 10.1016/j.bios.2020.112686.

[30] G. Palani, K. Kannan, and D. Radhika, *The Impact of the COVID-19 Pandemic on Green Societies*. Springer International Publishing, 2021.

[31] C. Karunakaran, R. Rajkumar, and K. Bhargava, *Introduction to Biosensors*. Elsevier Inc., 2015.

[32] K. Ramanathan and B. Danielsson, "Principles and applications of thermal biosensors," *Biosens. Bioelectron.*, vol. 16, no. 6, pp. 417–423, 2001, doi: 10.1016/S0956-5663(01)00124-5.

[33] V. Naresh and N. Lee, "A review on biosensors and recent development of nanostructured materials-enabled biosensors," *Sensors (Switzerland)*, vol. 21, no. 4, pp. 1–35, 2021, doi: 10.3390/s21041109.

[34] R. Kazemi-Darsanaki, A. Azizzadeh, M. Nourbakhsh, G. Raeisi, and M. AzizollahiAliabadi, "Biosensors: Functions and Applications," *J. Biol. Today's World*, vol. 2, no. 1, pp. 20–23, 2013, doi: 10.15412/j.jbtw.01020105.

[35] F. J. Gruhl, B. E. Rapp, and K. Länge, "Biosensors for Diagnostic Applications. A Biosensor, Detection, Diagnostics and Test format," 2011, doi: 10.1007/10.

[36] S. Mohanty, "Biosensors: A Survey Report," *Univ. South Florida, USA*, 2001.

[37] Ra. Dharshni, Rd. Dharshini, and N. Sivarajasekar, "Thermal Biosensors and Their Applications," *Am. Int. J. Res. Sci.*, no. March, p. 50, 2019, [Online]. Available: http://www.iasir.net.

[38] P. Damborský, J. Švitel, and J. Katrlík, "Optical biosensors," *Essays Biochem.*, vol. 60, no. 1, pp. 91–100, 2016, doi: 10.1042/EBC20150010.

[39] Hannah Balfour, "41f5049b917db3e1f3ecd03c0203a30d1b93a5cd @ www.europeanpharmaceuticalreview.com," *European pharmaceutical review*.

[40] Global biodefense staff, "6d76c4bf2b77994dfa57e79dd9a76ab4078789d6 @ globalbiodefense.com," *global biodefense*.

[41] X. Lv*et al.*, "Label-Free Exosome Detection Based on a Low-Cost Plasmonic Biosensor Array Integrated with Microfluidics," *Langmuir*, vol. 35, no. 30, pp. 9816–9824, 2019, doi: 10.1021/acs.langmuir.9b01237.

[42] M. Srivastava, N. Srivastava, P. K. Mishra, and B. D. Malhotra, "Prospects of nanomaterials-enabled biosensors for COVID-19 detection," *Sci. Total Environ.*, vol. 754, p. 142363, 2021, doi: 10.1016/j.scitotenv.2020.142363.

[43] G. García-Martinez *et al.*, "Development of a mass sensitive quartz crystal microbalance (QCM)-based DNA biosensor using a 50 MHz electronic oscillator circuit," *Sensors*, vol. 11, no. 8, pp. 7656–7664, 2011, doi: 10.3390/s110807656.

[44] C. Zhang, N. Liu, J. Yang, and W. Chen, "Thickness-shear vibration of AT-cut quartz plates carrying finite-size particles with rotational degree of freedom and rotatory inertia [Correspondence]," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control*, vol. 58,

 ©IJSRED: All Rights are Reserved

no. 3, pp. 666–670, 2011, doi: 10.1109/TUFFC.2011.1851.

[45] G. A. Campbell, J. Uknalis, S. I. Tu, and R. Mutharasan, "Detect of Escherichia coli O157:H7 in ground beef samples using piezoelectric excited millimeter-sized cantilever (PEMC) sensors," *Biosens. Bioelectron.*, vol. 22, no. 7, pp. 1296–1302, 2007, doi: 10.1016/j.bios.2006.05.028.

[46] M. Pohanka, "Overview of piezoelectric biosensors, immunosensors and DNA sensors and their applications," *Materials (Basel).*, vol. 11, no. 3, 2018, doi: 10.3390/ma11030448.

[47] A. Yakoh, S. Chaiyo, W. Siangproh, and O. Chailapakul, "3D Capillary-Driven Paper-Based Sequential Microfluidic Device for Electrochemical Sensing Applications," *ACS Sensors*, vol. 4, no. 5, pp. 1211–1221, 2019, doi: 10.1021/acssensors.8b01574.

[48] C. Adrover-Jaume*et al.*, "Paper biosensors for detecting elevated IL-6 levels in blood and respiratory samples from COVID-19 patients," *Sensors Actuators, B Chem.*, vol. 330, no. December 2020, 2021, doi: 10.1016/j.snb.2020.129333.

[49] J. Li *et al.*, "Rapid and unamplified identification of COVID-19 with morpholino-modified graphene field-effect transistor nanosensor," *Biosens. Bioelectron.*, vol. 183, no. December 2020, 2021, doi: 10.1016/j.bios.2021.113206.

[50] M. Pal and R. Khan, *Biosensor platforms for detection of cardiovascular disease risk biomarkers*. Elsevier Ltd., 2019.

[51] S. Vigneshvar, C. C. Sudhakumari, B. Senthilkumaran, and H. Prakash, "Recent advances in biosensor technology for potential applications - an overview," *Front. Bioeng. Biotechnol.*, vol. 4, no. FEB, pp. 1–9, 2016, doi: 10.3389/fbioe.2016.00011.

[52] J. R. Windmiller, A. J. Bandodkar, S. Parkhomovsky, and J. Wang, "Stamp transfer electrodes for electrochemical sensing on non-planar and oversized surfaces," *Analyst*, vol. 137, no. 7, pp. 1570–1575, 2012, doi: 10.1039/c2an35041f.

[53] F. W. Schelle*et al.*, "Future of biosensors: A personal view," *Adv. Biochem. Eng. Biotechnol.*, vol. 140, no. November 2013, pp. 1–28, 2014, doi: 10.1007/10_2013_251.

 ©IJSRED: All Rights are Reserved