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A Review on Biosensors for COVID-19

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ABSTRACT

The global spread of the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) has altered people's lives and had a significant influence on economies and communities. It has created an insatiable demand for advanced diagnostic tools for rapid and accurate diagnosis, investigations, and quarantine techniques, particularly because vaccine or therapies are unavailable. Presently, quantitative real-time polymerase chain reaction (qRT-PCR) is commonly utilised for detecting corona virus disease 2019 (COVID-19), however this method is time-consuming, labor-intensive, and may not be quickly deployable in remote or resource-constrained situations. This could make it more difficult to obtain reliable statistics on SARS-CoV-2 infection rates and communal spread in the populace. This paper covers the present state of diagnostic approaches, their drawbacks, and the use of biosensors for SARS-CoV-2 diagnosis. Electrochemical biosensors, optical biosensors, and surface plasmon resonance are examples of emerging biosensing devices being employed for the detection of ribonucleic acid (RNA) viruses. They might be useful instruments for a faster, more accurate, mobile, and more hopeful diagnosis in the present epidemic.This paper also discusses current problems and recommendations for developing robust biosensors for the efficient, affordable, and precise detection and monitoring of COVID-19.

Keywords: Biosensor, Covid-19, Diagnosis, Nanobiosensor, RT-PCR, SARS CoV-2.

1. INTRODUCTION

A febrile sickness characterised by fever with extreme respiratory infections first appeared in China in December 2019, and an emerging scenario involving infection with a new coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was described. A novel RNA virus was discovered during metagenomic rinonucleic acid (RNA) sequencing of the patients infected with SARS-CoV-2' bronchoalveolar lavage fluid. Phylogenetic and genomic investigations subsequently indicated that the virus is genetically similar to the SARS-like corona virus. The World Health Organisation (WHO) has labeled the SARS-CoV-2 outbreak a Public Health Emergency of International Concern (PHEIC) from March 12, 2020. More than 15 million incidents have been reported worldwide so far. Aside from the health catastrophe, the SARS-CoV-2 epidemic has wreaked havoc on the global economy. Until recently, no particular therapeutic options or vaccinations, such as those currently under investigation, have been developed to control the outbreak. As a result, massive diagnostics are required to halt the unusual transmission of the virus and to help in the early detection of corona virus disease 2019 (COVID-19) and understanding its epidemiology in order to enhance therapeutics. Before the commencement of the infection, SARS-CoV-2 has a 2 to 7 day of incubation phase. This period is largely symptomless and infectious, as the virus may transfer from person to person. Owing to problems in estimating or diagnosing the illness, the number of infected individuals and the exact case fatality ratio (CFR) of COVID-19 infected individuals are currently

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unknown. As a result, the pandemic's true scope remains unknown. Bio sensing of the presence of viral nucleic acids (Deoxyribo Nucleic Acid and Ribo Nucleic Acid), intact viral particles, antibodies and viral proteins, produced in patient's body in response to the virus is used to screen individuals for any viral illness.[1]

COVID-19 is now identified via RT-PCR, and computed tomography (CT) scans have been used to confirm it, but each method seems to have its own set of disadvantages. Three problems have developed as a result of RT-PCR, to begin with, the supply of PCR reagent kits has not maintained pace with its demand, furthermore, medical centres outside of major cities do not have the necessary PCR facilities to handle large volumes of samples, finally, the appearance of recognizable SARS-CoV-2 in patient's sample is required for RT-PCR. When an asymptomatic individual who had previously been infected with SARS-CoV-2, has subsequently recovered, PCR cannot detect the virus, and precautions would not be implemented. Meanwhile, CT scanners are costly, demand technical skill, and are unable to detect COVID-19 precisely. To remedy these flaws, other approaches must be developed to detect SARS-CoV-2.[2]

Another suitable strategy regarding the molecular detection, Loop Mediated Isothermal Amplification (LAMP), does have the capability to replace the traditional RT-PCR technique. Two enzymes are involved in this technique, one that converts RNA of virus to DNA and the other that copies that DNA. A set of six primers unique to a viral gene sequences is also necessary, in addition to enzymes. The assay's usefulness is limited by the possibility of varied findings owing to primer mutation.

However there are a variety of alternative approaches for identifying virus particles, they are limited in their practical application due to a number of issues. These restrictions include the following: Reduced precision and sensitivity; preparation and purification of sample are required; time-consuming; instrument, accessory, and maintenance costs are higher; widespread accessibility; instruments' intricate functioning; need for highly skilled technical professionals; not appropriate for on-the-spot analysis.[3]

As a result, innovative, more effective approaches for the quick detection of viral proteins or genetic materials are needed, taking into account the diversity of viruses as well as their reproduction habitats. These methodologies must be implemented in a way that ensures better precision, mobility, and wide-scale availability to evaluate a large population. The goal of this review is to gain understanding of the various types of biosensing devices used in the detection of SARS Cov-2 virus, and the future of biosensors in stopping the virus from spreading in large population.[4]

2. BIOSENSORS FOR THE DETECTION OF COVID-19

In latest generations, the biosensors industry has seen significant growth, particularly in the healthcare sector. The primary motivator for this advancement is a pandemic that has spread over the world owing to poor health care system and a lack of accountability for the danger of epidemic monitoring; thus, we must address this area of concern. A biosensor consists of three primary parts; a bioreceptor, a transducer, and a digital output detector.[5] Figure 1 represents the steps involved in the detection of SARS CoV-2 using biosensors.

The purpose of biosensors is to detect physiological and metabolic sources that are very specific physiologically. Following the COVID-19 epidemic, researchers have concentrated on designing a sensor that detects the infectious virus in the air. The devised sensor may be utilised to make a clinical diagnosis as well as quantify the virus's content in the atmosphere.[6] Data from a molecular biosensor can be related to cell biology, environmental sensing, or research.[7]

2.1. Optical Biosensors

Changes in the refractive index (RI) with in sensor surface's locale are used to power optical biosensors.[8] To detect SARS-CoV-2, Jing Wang and colleagues developed a novel sensor in the guise of an optical biosensor. For detecting the virus, this sensor combines two types of effects: an optical effect and a thermal effect.[9] Because their genomes include single-stranded RNA, the new SARS CoV-2 is an RNA virus. As a result, the biosensor's receptor works as a complimentary sequence for the virus's RNA sequence, allowing the virus to be

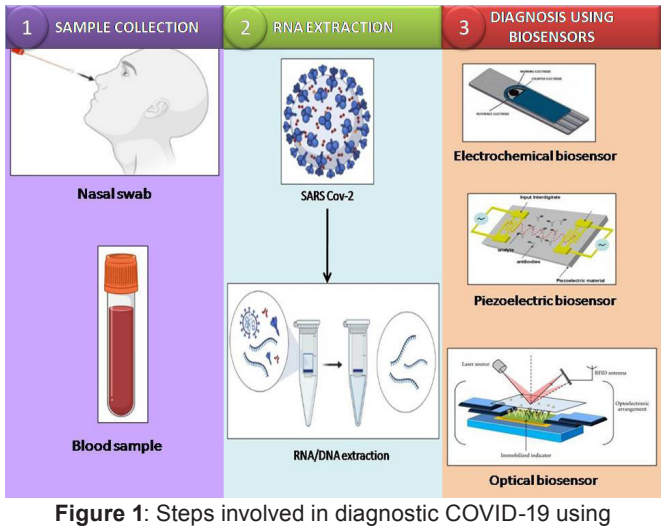

Figure 1: Steps involved in diagnostic COVID-19 using biosensors

detected. It detects the target analyte in real time, quickly, and without the need of labels.[10]

2.2. Electrochemical Biosensors

Scientists throughout the globe have been striving to design robust and sustainable innovative biosensor-based techniques for timely identification of SARS-CoV-2 in the present pandemic crisis. High sensitivity, high precision, simplicity of handling, cost-effectiveness, compactness, and quick testing are just a few of the benefits of electrochemical biosensors. They also offer an extreme low detection limit with a small sample size and no need for sample preparation, rendering them the most suited diagnostic instruments available. Furthermore, these biosensors may be readily combined with the microfluidic substrate and multiplexed, enhancing the device's sensitivity.[11] Mahari et al. have designed a pair of electrochemical biosensors for detecting SARS CoV-2 spike protein antigen. The electrodes can remain intact for up to four weeks, allowing the diagnostic technique to be used in far-flung locations without compromising sensitivity. Furthermore, these biosensors may be employed directly in individual's saliva samples and offer findings in 10–30 seconds.[12]

2.3. Piezoelectric Biosensors

A piezoelectric biosensor has been developed for immediately detecting COVID-19 specimens without the need for any prior processing. The biosensor which serves as a transducer is blanketed with an specific antibody. A surface tension is induced owing to the mass shift, when the SARS-CoV-2 antigens attach to the upper surface of the microcantilever via their spike proteins, resulting in observable tip bending and floating voltage. Various forms and piezoelectrics have been evaluated in order to develop a biosensor with optimal characteristics.[13]

2.4. Other Types

2.4.1. Plasmonicphotothermal Biosensor

The attachment of proper complementary sequences to the DNA nucleotide strands on the sensor in plasmonicphotothermal (PPT) biosensors is accomplished by providing heat to the nanostructures using a laser of a certain wavelength. The SARS CoV-2 genome is single-strand RNA, as previously stated. Hybridization is the procedure by which single-strand RNA binds with their corresponding sequence to generate double-stranded RNA. Denaturation is the breakdown of double-stranded RNA. At a specific temperature, i.e. melting temperature, denaturation can occur. Because the surface temperature in the biosensor is lesser than the melting point, DNA sequences can attach to non-complementary nucleotide sequences. As a result, PPT is utilised to keep the ambient temperature below the melting temperature, allowing only complimentary strands to bond.[14]

2.4.2. Cell-Based Biosensors (CBBs)

Cell-based biosensors (CBBs) have been employed for the detection of particular species' analytic information and its conversion into an electrical and optical signal using a processor.[15] Living cells are directly integrated into the biosensing devices to build CBBs systems. SARS-CoV-2 may spread via air and can be found in the air sample inside the aerosol for 3 hours, according to experimental research. SARS-CoV-2 is lethal to people and causes multiple illnesses. SARS-CoV-2 virus might be detected in the air using cell-based biosensors. Unfortunately, these biosensors are still to be demonstrated in real-world applications.

2.4.3. Nanosensor

COVID-19 is unquestionably combated by nano-technology.[16] To develop a successful sensor, use of sensing technologies is required.[17] Nanomaterials are being used by Chinese scientists to regulate SARS-COV-2, and the virus›s strength is reduced by 96.5 percent to 99 percent.[18] The recognition of viral RNA is done using nanomaterials, and RNA-based detection is a quick diagnosis method.[19] The fast infection of COVID-19 is revealed by a nanomedicine.[20] Nano biosensors are being developed in current technology to learn more about advanced COVID-19 identification.[21-23] Hybrid nanomaterials are being used to quickly identify SARS CoV-2.[24] The advantages and limitations of the existing nano biosensors are summarized in Table 1.

3. RECENT ADVANCEMENTS IN BIOSENSORS FOR POINT-OF-CARE (POC) DIAGNOSIS OF SARS COV-2

Biocompatibility, simplicity of bioconjugation, durable, quick, and ultrasensitive detection with reduced sample volume is all advantages of nanoparticles in the development of PoC diagnostic platforms. Metal nanoparticles (Au and Ag), magnetic nanoparticles, and fluorescent nanoparticles are all often employed as biosensor labels.[30]

Due to its superior electrical conductivity, huge surface area, and durable handling, graphene has recently gained popularity as a promising substrate for biosensing applications. By immobilising spike antibody on the graphene surface with the help of a crosslinker, a graphene-based Field Effect Transistor (G-FET) biosensor was observed to identify the SARS-CoV-2 spike protein, which provides great precision over other coronaviruses

Table 1: Currently available nanobiosensors, their advantages and limitations

Nanobiosensor	*Advantages*	*Limitations*	*References*
Paper-based biosensor	cost-effectiveness, biodegradability as well as easeof-fabrication, functionalization and modification	Lack of quantification	[25]
Chip-based biosensor	biocompatibility, high transparency and cost-effectiveness	Complex fabrication process Requires skilled personnel Clean room is usually required for fabrication	[26]
DNA-based biosensor	low cost, simplicity, small dimensions, high sensitivity and compatibility	Highly expensive and not portable	[27]
Film-based biosensor	Low cost easy fabrication and is userfriendly	Complex fabrication process	[28]
Thread-based biosensor	Cost-effective simple-to-fabricate and highly sensitive	Lack of quantification	[29]

because of complexity of nucleic acid sequence of the virus.[31]

Wearable sensors are gaining popularity for their ability to provide constant monitoring, non-invasive readings, and the ability to bypass the time-consuming sample collecting processes used in typical laboratory screening procedures. Furthermore, when compared to blood, biological materials such as perspiration and tears allow for more specific detection. As a result, wearable sensors provide point-of-care diagnosis and are effective in mass screening, which is critical for controlling disease transmission.[32]

Jeong and his colleagues devised a patch sensor that can measure precise respiratory characteristics, crucial factors linked to cardiac activity, and body temperature. The early phase testing demonstrated a link between changes in respiratory characteristics, which aided in understanding the outlook of COVID-19 viral infection. Furthermore, the patch sensor is durable, resulting in reduced patient suffering and increasing its utilization for mass level testing.[33]

Cell phones and nanotechnology have merged to create smart nanobiosensors that might let the general people utilise their smartphones as optical, physical and electrochemical nanobiosensors. Smartphones are being employed for biosensing purposes in two ways: as a sensor for detecting variations in biochemical events, and as a data analytics platform for developing a database, thus supporting eHealth.[34]

4. CHALLENGES IN THE APPLICATION OF BIOSENSORS FOR COVID-19 DETECTION

Effective diagnostic strategies based on biosensors have the ability to reduce the spread of viral infections. Because early diagnosis of viral illness informs health care providers, the infected individual may be isolated for a timeframe until the virus is treated. A few researchers acquired important lessons from prior SARS-CoV and Middle East Respiratory Syndrome (MERS) crises in terms of the possible development of pharmaceutical interventions against these viruses, but better planning is necessary for dealing with the present pandemic. However, with regard to diagnostic approaches, the road to preparation appears to be underperforming thus far.

Sample collection, extraction of viral RNA, reverse transcription, replication of complementary DNA (cDNA), signal transduction, and output are the steps normally required for biosensing of SARS-CoV-2 RNA sequence. Nevertheless, before a biosensor becomes completely ASSURED and Point-of-care (PoC) compliant, there are hurdles at each phase. The most typical way of sample collection is to take a swab from a patient's nose or throat because thats where a significant viral load is suspected.[35] However, it is natural for people to feel uneasy. Non-invasive samples such as saliva, mucus and exhaled breath can be utilised to avoid uneasiness.[36] The immunological response of the host to SARS-CoV-2 infection could generally be identified after a week or later.[37] Because it takes so long to acquire an identifiable antibody or viral protein, antibody-based biosensing approaches have a hard time identifying, separating, and treating individuals quickly. As a result, asymptomatic individuals might transmit the virus to other people before further confirmatory tests can appropriately diagnose them.[38]

5. RECOMMENDATIONS FOR DEVELOPING AN IDEAL BIOSENSING DEVICE

The following recommendations are required for designing of ideal biosensing equipment used to test infectious diseases: They must be: Disposable, enabling for bulk manufacturing; convenient and economical, enabling for screening large population; simple to use, even by unskilled users or patients; without the need for any equipment or with the use of a cheap and mobile output unit; quick, allowing for fast sample-to-result

timeframes (less than an hour); competent to operate with small sample quantities and samples that are conveniently accessible (for e.g., blood from a finger prick); extremely specific and sensitive (without target amplification if feasible), producing precise results in agreement with central laboratory results; having a sample preparation system that is integrated; flexible and scalable enough to identify several targets on the same system (like CRISPR (clustered regularly interspaced short palindromic repeats)-based technologies), and multiplexing capability, allowing simultaneous detection of several analytes, including standard group.

6. CONCLUSION

In the context of today's SARS-CoV-2 outbreak, when millions of people throughout the world are constantly at risk of severe respiratory disease, quick, cost-effective, and early diagnostic methods are critical. Recent research has combined sample-to-answer procedures in a unique biosensor to detect viral nucleic acids and human antibodies produced by immune response, which might be helpful in detecting SARS CoV-2 infections. The nanobiosensing area is constantly changing due to technological advancements, and newly established sophisticated biosensors have the ability to prevent current pandemics. Several affordable diagnostic kits for SARS CoV-2 have been devised, and the validation procedure for FDA (Food and Drug Administration) certification is being carried out. Restricted sensitivity, multiplexing, repeatability, real-time operability, miniaturisation, sampling, and patient compliance are among the challenges associated with the effective diagnosis of SARS CoV-2. Before they reach the commercial sector and function in decentralised conditions, these obstacles must be tackled. As a result, along with modern electronics, connectivity, and data analytics, the PoC diagnostic systems might effectively face and battle future pandemics.

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