Biosensors in diagnosing COVID-19 and recent development

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Abstract

The outbreak of Coronavirus was first reported from Wuhan, Hubei, China on the end month of 2019. Due to its rapid outbreak and quick transmission, the World Health Organization (WHO) declared it as an ongoing pandemic. Presently, available medicines for viral influenza are found to be ineffective in treatment and there is immediate need of strong technology to detect and monitor public health [91]. Early, notification on symptoms of disease is necessary and can be control up to some extent from this dreadful disease. If monitored in early stage, the infected person can undergo different therapeutic approaches. In order to scan the early symptoms of covid-19 different system has been applied. Use of sensor is considered as one of the method. Sensors when combine with a systematic device, it is utilized to detect the chemical compound and further combines with a biological
component with a physicochemical detector. This biosensing system can be included in smart band, optical sensor, plasmonic photothermal sensor, wearable sensor, cell-based sensors, and nano-sensor which can be used to diagnose the COVID-19. Therefore, it is discussed thoroughly in this review with its recent development and future scope on detecting COVID-19.

**Keywords** Biosensor, Covid-19, Diagnose, Sensors, Nanosensors

**INTRODUCTION**

Sensors are tools used to determine the events or variations in an environment that also assist in delivering data to other electronics, usually to a computer processor. The physical data are collected and transformed into a signal that is appropriate for processing and this give a readable result [1]. A systematic tool that helps in recognition of chemical compound which further merge the organic element with a physicochemical indicator is known as Biosensor [2, 3, 4]. It shows a great potential in identifying and diagnosing of many diseases and also on this happening pandemic Covid-19 [87]. The components of biosensor include a bioreceptors/bio-recognition element (BREs) (enzyme/antibody), transducer (nanomaterials), an electronic system that is comprised of processor and display [5]. The parts like transducer and electronics can be merged, for example, in complementary metal oxide semiconductor [6, 7]. The recognition substance, generally termed bioreceptor, uses biomolecules through organisms that are further modeled next to biological systems that interrelate with an interesting analyte. This relationship is calculated by the biotransducer that gives the result of a measurable signal that is equivalent to the existence of the target analyte in the specimen. The main focus of biosensor is to allow fast, appropriate testing at the point of interest [8, 9]. On the basis of biotransducer, the biosensors are categorized accordingly. Some general types of biotransducers that are utilized in chemical canaries are as follows: electrochemical biosensors, optical biosensors, etc. The proper arrangement of chemical canaries depends on their area of application that can be classified biotechnology, agriculture, food technology, and biomedicine [10].

**COVID-19:**

COVID-19 is an infectious disease which can spread widely in a short period if precautions are not taken up. Before the epidemic began in Wuhan, China, in December 2019, nobody got to know about this new virus and disease. Now, this COVID-19 pandemic got spread all over the world [11]. There are different kinds of Coronavirus for examples
severe acute respiratory syndrome Coronavirus (SARS-CoV) 2003, Middle East respiratory syndrome Coronavirus (MERS-CoV) 2012, Swine acute diarrhea syndrome Coronavirus (SADS-COV) 2016, newly discovered novel Coronavirus (2019-nCoV), out of all the above the nCoV in china emerged as big threat to human and animal well-being [13]. It has already claimed that coronavirus is air borne and transmitted from an infected person to another person if have physical contact [80]. The first case of novel coronavirus was detected by Metagenomic sequencing [83]. For diagnostic propose polymerase, chain reaction is developed.

**SMART BAND WITH BODY TEMPERATURE SENSOR**

**Sensor:**

To determine the events or variations in an environment, a tool called sensor is used that also assist in delivering data to other electronics, usually to a computer processor. To obtain a physical amount and transforming that amount into a signal that is appropriate for processing. At present, an electrical signal is obtained from the transformation of physical phenomena to an electrical signal [1].

**Biosensor:**

A systematic tool that helps in recognition of chemical compound which further merge the organic element with a physicochemical indicator is known as Biosensor [3, 4, 5]. The components of biosensor include a bio-reactor (enzyme/antibody), transducer (nanomaterials), an electronic system that is comprised of processor and display [6]. The parts like transducer and electronics can be merged, for example, in Complementary metal oxide semiconductor [6, 7]. The recognition substance, generally termed bioreceptor, uses biomolecules through organisms that are further modelled next to biological systems that interrelate with an interesting analyte. This relationship is calculated by the biotransducer that gives the result of a measurable signal that is equivalent to the existence of the target analyte in the specimen. The main focus of biosensor is to allow fast, appropriate testing at the point of interest [8, 9]. On the basis of biotransducer, the biosensors are categorized. Some general types of biotransducers that are utilized in chemical canaries are as follows: electrochemical biosensors, optical biosensors, etc. The proper arrangement of chemical canaries depends on their area of application that can be classified biotechnology, agriculture, food technology, and biomedicine [10].

**The function of smart band as body temperature sensor**
The rapid transmission nature of Covid-19 has disturbed all the regular activities of human kind and makes everyone extremely fear. To control the panicking state, different techniques are evaluated to detect the virus [88,89], but it takes a longer period of time. Generally, the affected patient acquires different symptoms that help in the detection of viruses. Technology acts as an essential element in the prevention of Coronavirus getting spread. The contact tracing “Aarogy Setu” app is the best example of technology which helps during the crisis. Generally, it is a bluetooth and location data which helps to warn the users coming in contact with an infected person [9].

The temperature differs depending upon the assessment area from which the skin temperature can be controlled. Further, the temperature is being measured with the help of thermoelectric effects, etc. [10]. The calculation of body temperature perfectly becomes a crucial agenda. The temperature of the skin is less than the body temperature that is measured by a wrist-wearable device. According to the environmental temperature, the skin temperature differs; apart from that, the body temperature remains less than 10°C [11]. The low thermal reach in the middle of the skin and the sensor, along with the evaporation of sweat, can be affected in decreasing connection in the middle of the skin and body. To calculate the exact body heat, a specific domain is added in the smart band [12]. To calculate stress and emotions, measurement of Skin temperature together are used. The skin heat is inversely proportional to the stress [13, 14].

![FIG 1: Diagrammatic Representation on action of Smart band (Vital 3.0)](image-url)
Vital 3.0 smart band is one of the latest products from Goqii. It is fitness wearable band with different features of measuring heart rate, blood pressure, and sleep. Moreover, it has the capability to track body temperature. Hence, it is believe that it can be used for detecting early COVID-19 symptoms. As we know, changes and rise in body temperature is one of the major early indicator COVID-19. This smart band is waterproof and a single charge can be use up for 1 week. The additional information of this band is it can track activities such as steps, distance, and calories burned. The key to success of this band is the thermal sensor.

COVID-19 VIRUS DETECTION IN THE ENVIRONMENT USING BIOSENSOR

A novel Coronavirus called SARS-CoV-2 identified in china in 2019. This type of viruses can grow in epithelial cells and usually causes respiratory infection. It shows symptoms like nausea, fever, cold, diarrhoea [15]. The suffering patients of COVID-19 of about 2-35% has found showing symptoms of gastrointestinal problems like diarrhoea, vomiting, and abdominal pain, which leads to the detection of viral RNA in sewage and faeces. Also, the presence of Coronavirus in faeces and wastewater were also examined [16, 17]. Hand washing, sputum, and vomit are too some sources of containing Coronavirus in wastewater [18]. Mainly, through RT-PCR, the virus was detected from the faecal sample, which was accepted worldwide to detect viral RNA in many clinical samples. The waste water-based epithelial technique is an inexpensive and potentially robust tool for tracking COVID-19. It requires the consideration of the temperature to find the perfect data [19]. The aim of biosensing is to detect the biological and biochemical sources which derived biologically in a highly specific way. In January, China developed PCR- based testing, which is helpful in diagnosing COVID-19 and accepted worldwide [20]. Jing Wang, with his fellow researcher, studied the air-born pollutants and analyzed them. From January after the outbreak of COVID-19, they have focused on developing a sensor that can detect the virus in the air. The developed sensor can be used as a clinical diagnosis and to measure the concentration of the virus in the air [21]. Molecular based biosensor provides data that are linked to cell physiology, environmental monitoring, or research. Cell-Based Biosensor is used to detect the pollutant occur in air and plays a role in environmental monitoring [22].

OPTICAL SENSOR FOR RNA SAMPLE

In the early outbreak of the novel Coronavirus (COVID-19), RT-PCR is used for the detection of COVID-19 diagnosis, but this technique causes frequent errors and reported false negative or positive cases as well as takes a lot of time [23]. Therefore, scientists focus on
developing a new sensor that can speedily and authentically recognize SARS-CoV-2. The optical biosensors are carried out by the changes that occur in the refractive index (RI) in the locality of the sensor surface [24]. Jing Wang, along with fellow researchers, approached a new sensor in the form of an optical sensor for the detection of SARS-CoV-2. This sensor is designed by combining two kinds of effect: an optical effect and thermal effect for the detection of a virus [25].

On a glass substrate, the biosensor is consisting of gold nanoislands, which are based on the tiny gold structures. The gold nanoislands are grafted with the artificially synthesized DNA receptors and the complementary RNA sequences of SARS-CoV-2 [25, 26]. The novel coronavirus is an RNA virus as their genomes contain a single-stranded RNA. Therefore, the receptor of the sensor acts as complementary sequences for the RNA sequence of the virus that can detect the virus.

Localized surface plasmon resonance (LSPR) is used to detect if the RNA sequence binds to the sensor. LSPR occurs in metallic nanostructures, based on an optical phenomenon. These metallic nanostructures, when excited, the incident light changes to definite wavelength by the nanoislands and produce a near plasmonic field around the nanostructures. Upon binding, the molecules to the surface of the biosensor, the local refracted index inside the plasmonic near field changes. An optical sensor is used to measure these changes, present on the backside of the sensor, and determine if the sample contains RNA strands or not [26].

**PLASMONIC PHOTOTHERMAL BIOSENSOR**

The DNA strands on the sensor bind to the complementary RNA strands of SARS-CoV-2, but in ambient temperature, the RNA strands that are not complementary bind to the DNA strands, hence displaying false reading [25]. To overcome this problem, biosensors with plasmonic photothermal (PPT) effect is used to increase accuracy. In PPT biosensors, for the binding of correct complementary strands to the DNA strands on the sensor is done by applying heat to the nanostructures with a laser of a particular wavelength. As mentioned earlier, the genome of the Coronavirus is single-strand RNA. Upon binding with their complementary strand, the single-strand RNA form double-stranded RNA; this process is called hybridization. The splitting of double-stranded RNA is called denaturation. Denaturation can happen at a certain temperature, i.e., melting temperature. In the biosensor, the DNA sequences can bind to the non-complementary sequences due to the much lower ambient temperature than the melting temperature. Therefore, PPT is used to maintain the ambient temperature moderately lower than the melting temperature, so that only
complementary strands can bind [25]. Thermoplasmonic effect is the converted form of plasmonic photothermal (PPT) heat energy that is highly present around the nanoparticles, which act as in situ heat source for the manageable and constant thermal processing [27-30]. A dual functional LPSR biosensor is developed by combining the photothermal effect and transduction of plasmonic sensing for the detection of SARS-CoV-2 viral nucleic acid. The nanoabsorbers (AuNI) localized in the plasmonic chip are capable of producing local PPT heat and help in the detection of SARS-CoV-2 by transducing in situ hybridization.

![FIG 2: Diagrammatic Representation of Plasmonic Photothermal Biosensor (PPT)](image)

**Advantages**

- Inhibit the binding of non-complementary sequences to the DNA strand of the sensor by promoting local temperature.
- By enhancing hybridization kinetics of fully matching strands, PPT effect shows quick and sensitive detection of nucleic acid.
- Lower false-positive or false-negative rate and increases the accuracy in genetic diagnosis.

**WEARABLE SENSORS FOR COVID-19**

Nowadays, COVID-19 is characterized as a pandemic by WHO. Wearable sensors distinguish the physiology and history of COVID-19. For the recognition of COVID-19,
about 1.3 billion wearable sensors are used. Wearable sensors are very advanced to detect COVID-19. The wearable sensors that are used to check COVID-19 are smartphones, apple watch, fit bit, and bio harness. These are the digital level of diagnosis tools for human health [31]. The sensors do not only trace the virus COVID-19 but also give information about the patient's health, disease symptoms, and recovery. Wearable sensors also detect body conditions [32]. Respiration monitoring is the most effective way to know about the presence of COVID-19. This virus affects the respiratory tract [33]. Remote like wearable system track the symptoms of COVID-19, and it also reduces the spread of the disease [34]. These sensors indicated symptoms of COVID-19 like fever, cough, and physiological methods detect cold. Wearable sensors are used to give information about the common health problem of the people [35,96]. Huami wearable device is used to detect the resting heart rate, cardiac rhythm, fever [36]. Fit bit detects the heart rate for the good management of public health. RADAR-base is a mobile system for health that is used to regulate the information that comes from multiple sensors [37]. RADAR-base system is used as a remote to detect the central nervous system, multiple sclerosis [38]. Smartphones and smartwatches not only detect the body temperature but also useful for the education and transport system during the lockdown period [39]. Wearable devices are more useful for tracking the health system and a good concept to maintain social distancing. Temperature guns are used to detect the temperature in communal areas [40]. Contact tracing most useful to check the severe acute respiratory syndrome. GPS is needed for contact tracing and to check the changing of individual health steadily [41]. Now Germany gives us the method to collect the health data of the people in a digital way. That can reduce the health problems, and advanced detection of the disease is possible [42].
BIOSENSOR ON CELL FOR COVID 19

Cell-based biosensors (CBBs) are used to detect certain species analytic information and amplification of those species into an optical and electrical signal through a processor [43]. CBBs devices are created by direct integration of living cells onto the biosensor platform. Cell-based biosensors associate with the downstream process for the detection of pathogens [44]. As the cells are made up of naturally developed receptors, enzymes, and ion channels can target biologically active analytes [43].

Molecular based biosensors are sensitive to the changes that occur in the environment as compare to CBBs, but these biosensors are used to detect the complex responses inside a living cell by modifying them applying simple genetic engineering protocols [43]. These biosensors also provide data that are not provided by molecule-based biosensors; those data are linked to cell physiology, environmental monitoring, pharmacology, and toxicology. Cell-based biosensors worked in a wide range of conditions like pH values and temperature. They are sensitive to the changes occurring in the environment or in the electrochemical state of tissue samples [44-47]. This biosensor plays a key role in environmental monitoring, food
analysis, drug screening, and pharmaceutical industry or research [45-49]. Generally, the CBBs have the ability to study the physiological condition of a living cell when they are subjected to stimulus. From the analytic point of view, the analytic function is evaluated by CBBs [22]. However, these types of biosensors also have the ability to perform real-time bioassays positively and speedily. Experimental studies show that SARS-CoV-2 can transmit through the air and can occur in the air sample within the aerosol for the 3 hours, which is fatal to humans and causes numerous infections. Cell-based biosensors might detect the SARS-CoV-2 virus in the air. However, these biosensors have not been proven yet for practical uses. As mention earlier, a cell-based biosensor is used to detect the pollutant that occurs in the air. On contact with the toxic pollutants, the sensor reports to the cellular response and emerging cellular signals transduced by secondary transducer producing electrical outputs along with the appropriate readouts.

**NANOSENSOR FOR COVID-19**

Nanotechnology assuredly fights against COVID-19 [50]. Sensing technology is very necessary to create an effective sensor [51]. Graphene is a nonmaterial’s used in sensor technology because it contains electrical characteristics [52]. In modern technology, nanomaterials are used to find nanomedicine. These are used to detect, treat, and recovery of various diseases [53]. Nanomedicines are also used in chemical sanitization [54]. Dendritic nanochips are used for determination of hydrogen peroxide in blood samples [97]. Chinese scientists use nanomaterials to the control of SARS-COV-2, and it decreases 96.5%-99% of virus potency [55]. Nanomaterials are used in the identification of RNA, and RNA based detection is a rapid diagnosis process [56]. Nowadays, researchers used iron oxides and gold nanoparticles in testing kits [57]. Nanotechnology is very important for viruses and infectious disease detection [58]. Nanoparticles based diagnostic kits contain 2D materials, graphene, and carbon [59]. A nanomedicine gives information about the rapid infection of COVID-19 [60]. Theragnostic is a nanomedicine research place that identifies the viruses by nanomedicine [61]. The best part of nanomedicine is it can affect only the damaged part, but part is not harmed by this [62]. Thomas Webster introduces iron oxide nanoparticles by chemical engineering Department, North East University; it contains magnetic properties that are used in haemoglobin synthesis in the human body [63]. Using photodynamic therapy, nano-virus can also be inhibited [64]. Graphene nonmaterial is mostly used to control the viral infection due to its negative charge [65]. In modern technology, nano biosensor is developing to know about the advance identification of COVID-19 [92,93,95]. For speedy identification of Coronavirus, hybrid
nanomaterials are used [66]. Hydroxy chloroquine, ribavirin, and lopinavir are the drugs used as medicine for treatment of COVID-19 till now [67].

**IMMUNOSERSOR FOR COVID-19**

Immunosensor is a multiplex small wireless object which can detect covid-19 rapidly. It helps in detection of viral antigen nucleocapsid protein, IgM and IgG antibodies [85]. Also it is use for inflammatory biomarker C-reactive protein on basis of mass producible laser engraved graphene electrodes [86]. For the quantitative detection biomarkers specific to COVID-19 in both blood and saliva includes SARS-CoV-2 nucleocapsid protein (NP), specific immunoglobulins (Igs) against SARS-CoV-2 spike protein (S1) (S1-IgM and S1-IgG), and CRP, within physiologically related ranges [85]. With the help of this platform, we can check the progression of an infection and scanning of infectious individual based on vulnerable and immune [94]. Some of the main advantages of this new technique are high sensitivity, low cost, ultra-fast detection, wireless remote, and multiplexed sensing.

**FIG 4: Different Ways of Using Nanosensors (Graphene)**

**RECENT DEVELOPMENT OF CORONA VIRUS**

Many researchers all over the world are trying to develop a possible drug obtained from plants, animals or other microorganism or repurposing existing drugs or medication or vaccine that can cure COVID-19 [98,99]. A positive development has been shown by Bharat
Biotech International Limited while developing the vaccine, which points out that the month afterward to be the most crucial stage by the researchers. By isolating the spike protein, the vaccine is being developed and reduce the percentage of spread [68]. India is listed as the third miserably affected country hit by this COVID-19 of about 1.8 million cases. Many companies and medical groups are coming together for the development of the COVID-19 vaccine. In which 30 separate Indian companies are working on the production of vaccines to fight to cure the infection. WHO has approved seven companies that are in the process of testing and studies [69]. The names of some vaccines that are carried out under progress are COVAXIN, ZyCoV-D, Mynvax, Astra Zeneca [69]. The first country to finish clinical trials of the COVID-19 vaccine on humans in Russia. There are two types of probable Covid-19 trails allowed by Russia, which is developed by the Gamaleya National Research Centre for Epidemiology and Microbiology in the month of June 18 [70]. The Burdenko Military Hospital developed the 1st vaccine, which forms the solution for intramuscular administration. The volunteers were advised to stay in isolation in hospital premises for about 28 days after the vaccination process [70].

Table1: Representing other uses of nanoparticles in treatment of diseases

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<tr>
<th>NANOPARTICLES</th>
<th>DISEASE</th>
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<tr>
<td>Liposome containing si-RNA</td>
<td>EVD (Ebola virus disease)</td>
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<tr>
<td>Silver nanoparticles</td>
<td>HPIV (Human para influenza virus)</td>
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<td>Lipid based nanosystem</td>
<td>HAV (Hepatitis A virus)</td>
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<td>Liposome and Oseltamivir silver nanoparticles</td>
<td>Influenza</td>
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<td>ARVdrug with nonosystem</td>
<td>HIV</td>
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<tr>
<td>Nanozymes</td>
<td>HCV (Hepatitis C virus)</td>
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<tr>
<td>Nanoparticles loaded with Acyclovir</td>
<td>HSV (Herpes Simplex virus)</td>
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CONCLUSION AND FUTURE SCOPE

The flared up of COVID-19 throughout the globe has terrified people and attract more attention towards health. It made a challenge to the researchers in development of medicines
and vaccines or advanced methods to prevent the spreading out of the virus. A thermal scanner is used to detect the body temperature but unable to detect the virus. RT-PCR is also used to detect the COVID-19 diagnosis, but it was also marked as useless as it gives false results. A biosensing device too utilized in form of a smart band and have the functional properties to detect body temperature. An optical sensor which is designed by combining two different kind of effect i.e., a visual and a thermal is use to detect the virus. A powerful biosensor like cell-based biosensor have the ability to detect some species and amplification of those species, molecular biosensors to monitor the virus in the environment and also plays a vital role in the pharmaceutical industry, environmental and monitoring of food analysis etc. As a matter of fact, scientists have focus on working of new technology and produce a rapid diagnostic sensor that can detect the SARS-CoV-2 within a minute. Jing Wang, along with his fellow researchers, developed a new sensor in the form of an optical sensor whose receptor acts as a complementary sequence for the RNA sequence and detect the virus. Biosensor with plasmonic photothermal effect also developed, which inhibits the binding of non-complementary sequence to the sensor's DNA strands by promoting local temperature. Cell-based biosensors are also used to detect the species and their amplification into an optical and electrical signal through a processor. It also used in wide range conditions like pH values and temperature. An app named ‘Aarogya Setu’ has been developed to warn the user of coming in contact with an infected person. More other theories emphasis on smart phone-based sensing systems have brought attention and developed within a smartphone. It is designed with a system of detecting any locations. This method may result into an alternative form against other expensive technologies [81]. Another recently developed method for COVID-19 diagnosis is practice of Nano bio engineered analytical clinically [82]. Engineered nanomaterial assisted for signal-amplification are also use as strategies for improving analytical performance of electrochemical biosensors [90]. Studies also revealed that SARS-CoV-2 could transmit through the air, and the cell-based biosensor may detect it, but these sensors have not been proven till now. Focusing on the non-PCR based method, many molecular tests were developed, which include Nucleic Acid sequence-based Amplification Techniques and loop-mediated isothermal amplification to detect SARS-CoV-2 RNA. Many more techniques should develop to diagnose the virus at less cost. Thus, tools like biosensor which can diagnose rapidly are necessary to prevent the rapid spreading of the virus. Biosensor and other technology should improve with high sensitivity, reproducibility, etc.

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**Conflict of Interest**
Authors declares there is no conflict of interest

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Conflict of Interest and Authorship Conformation Form

Please check the following as appropriate:

- All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

- This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.

- The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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