

SPECIAL ISSUE ARTICLE

Insight of smart biosensors for COVID-19: A review

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Abstract

The review discusses the diagnostic application of biosensors as point-of-care devices in the COVID-19 pandemic. Biosensors are important analytical tools that can be used for the robust and effective detection of infectious diseases in real-time. In this current scenario, the utilization of smart, efficient biosensors for COVID-19 detection is increasing and we have included a few smart biosensors such as smart and intelligent based biosensors, plasmonic biosensors, field effect transistor (FET) biosensors, smart optical biosensors, surface enhanced Raman scattering (SERS) biosensor, screen printed electrode (SPE)-based biosensor, molecular imprinted polymer (MIP)-based biosensor, MXene-based biosensor and metal-organic frame smart sensor. Their significance as well as the benefits and drawbacks of each kind of smart sensor are mentioned in depth. Furthermore, we have compiled a list of various biosensors which have been developed across the globe for COVID-19 and have shown promise as commercial detection devices. Significant challenges in the development of effective diagnostic methods are discussed and recommendations have been made for better diagnostic outcomes to manage the ongoing pandemic effectively.

KEYWORDS

biosensors, COVID-19, point of care devices, rapid detection, smart sensors

1 | INTRODUCTION

COVID-19 is caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) and has spread worldwide drastically, causing an emergency pandemic to be declared on March 13, 2020. This virus has not only caused high morbidity and mortality but has also caused a severe unexpected socio-economic burden.^[1,2] Since the outbreak hit, millions of people became infected in early December 2019 in Wuhan and thousands died. Offices, schools, and many institutes were closed which created economic crisis in many countries.^[3] The spread of the virus was initially detected through breathing, aerosol

particles and direct contact with surfaces which had virus on it. The virus was also evidenced to be transmitted through feces since this virus was also detected in fecal matter. The transmission of the virus from patients who were carriers and had no symptoms were also observed in many cases.

Some studies revealed the relation between COVID-19, air pollution and climate change.^[4] Numerous studies have demonstrated an increase in COVID-19 mortality rates due to a number of air pollutants, including particulate matter (PM) up to 2.5 µm in diameter (PM_{2.5}), PM up to 10 µm in diameter (PM₁₀), carbon monoxide (CO), nitrogen dioxide (NO₂), sulfur dioxide (SO₂), and ozone (O₃). However,

some studies contend that the indirect impact of COVID-19 may aid in lowering air pollution. An increase in COVID-19 events has been connected to PM. Although CO and SO₂, which are both adversely and favorably linked with SARS-CoV-2 transmission, are not sufficiently supported by the current investigation to allow for definitive conclusions. In many regions of the world, current research has found both a negative and a positive association between NO_x and COVID-19. Ozone (O₃) was discovered to be a key COVID-19 and air pollution-related infection marker for SARS-CoV-2. While there has been no definitive evidence of the effect of climate change on COVID-19, which is often a long-term phenomenon. A few studies suggested that SARS-CoV-2 has a greater airborne survival and transmission rate than the influenza virus in tropical locations. By 2030, a pandemic-driven response will result in a reduction in global temperature. The association between the atmosphere and COVID-19 incidents can be supported by the relationship between temperature, humidity, and wind speed.

The World Health Organization (WHO) motivated the scientist and investigators worldwide to undertake enormous amount of testing to control the spread of the virus and also understand its epidemiology.^[5,6] Rapid diagnostics became very critical in deciding the treatment and management options. The isolation if infected, made it possible for the spread to slow down as it became less transferrable when people stayed in quarantine.^[6] The people who tested false-negative in tests could transfer the infection in healthy individuals without adequate infection curbing and management. Many diagnostic tests were used like computerized tomography (CT) scan, reverse transcription polymerase chain reaction (RT-PCR) which are laborious and time consuming and were not able to give accurate results fast enough, therefore, there was an urgent need for a faster and reliable diagnostic method.^[5,7]

Development and utilization of point-of-care system tools facilitates a quick diagnosis to the disease thereby bypassing the complex, time-consuming conventional methods. The advantage that with smart biosensing application (nanoparticle-based) and their composites includes clear signal amplification, signal generation, significant limit of detection (LOD), higher sensitivity, smaller in diameter and selectivity that are important for biosensor development and demonstrating the capability of smart biosensing application in SARS-CoV-2 detection.^[8,9]

2 | BIOSENSORS

Biosensors are analytical tools used for simple and effective devices for detection of many kinds of infectious diseases specifically COVID-19. Biosensors were invented almost a decade ago by biotechnologists for the detection of bacteria, viruses and various biomolecules using biomarkers which are characteristics of the intended targets. Bioreceptors can sense elements owing to their biochemical characteristics which make them more sensitive and selective for the detection of biomarkers with least interference with other microorganisms or the molecules which are present in the tested sample. Biosensors

consist of three main components, namely, the bioreceptor, the transducer and processing system of signals.^[10] Biosensor based testing comprises of a biological recognition component specific for detecting biological analytes.^[11–13] The binding between these two components is detected and with the help of a transducer measurable signals are produced on the basis of which sensors are classified, examples include impedance signals, surface plasmon resonance (SPR), field effect transistor (FET)-based, electrochemical (EC), surface enhanced Raman scattering (SERS)-based biosensors or labeling via enzymes or optical compounds.^[14,15] Highly sensitive biomarkers and biochemical indicators for diagnosis in COVID-19 are highly recommended.

The innovation and novelty in biosensors can speed up the early diagnosis and open new therapeutic access to COVID-19.^[16] The bioreceptor part of biosensors can be monoclonal antibodies, nucleic acids, enzymes as well as glycans, tissue or whole cell interactions which specifically bind along a biomarker. The transducer converts these connections with each other in a measurable signal^[17] aiding in qualitative as well as quantitative identification of pathogens. For SARS-Cov-2, the targets are viral RNA (nucleic acid testing), surface antigens like spike protein or nucleocapsid protein (S and N proteins, antigen testing), or immunoglobulin M (IgM) and immunoglobulin G (IgG) (antibody testing). The data is visualized, reported, and subsequently analyzed.^[18,19] The stability, sensitivity and the LOD are the most important features while choosing a biosensor.^[18] Figure 1 represents the working of biosensors.

2.1 | Types of biosensors used in COVID-19 detection

There are various types of biosensors through which COVID-19 is being detected. Biosensors are proficient ways of monitoring the biomarkers for diagnosis of COVID-19 patients having symptoms ranging from mild to critical which helps in development of anti-inflammatory therapies.^[20] The nucleic acid and antibody based testing using RT-PCR and enzyme-linked immunosorbent assay (ELISA) respectively, are considered gold standards but these tools still have some shortcomings.^[21] Biosensors are the ideal tool because of being rapid in analysis, high fidelity, good sensitivity with early diagnostic ability mainly by approaches involving smart phones as a diagnostic aid.^[22]

There are various kinds of biosensors which are used for detection like fluorescence-based biosensor, colorimetric, quartz crystal as well as FET-based biosensors and EC-based sensors for COVID-19 detection.^[23–25] However, the most widely used ones for COVID-19 detection are SPR, SERS, FET-based biosensor and EC biosensors as shown in Figure 2.

2.1.1 | Smart and intelligent based biosensor

Development and utilization of point-of-care system tools facilitates a quick diagnosis to the disease thereby bypassing the complex, time-consuming conventional methods. The advantage that withholds

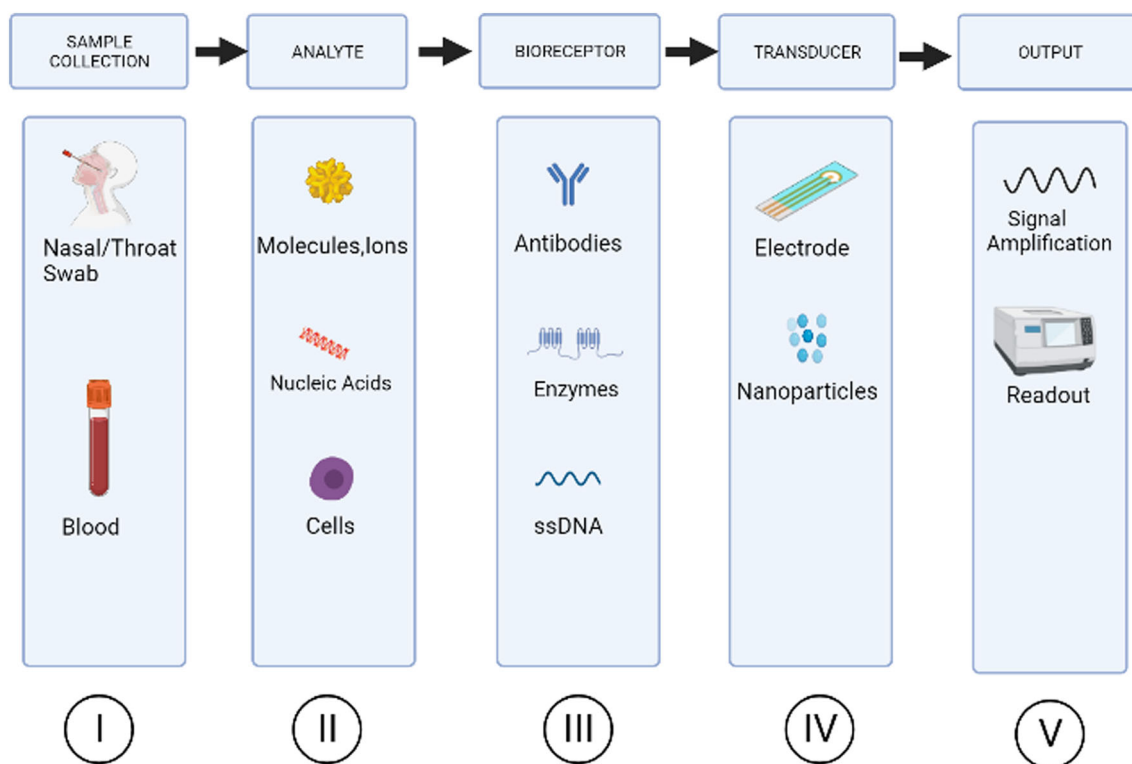


FIGURE 1 Working principle of biosensors

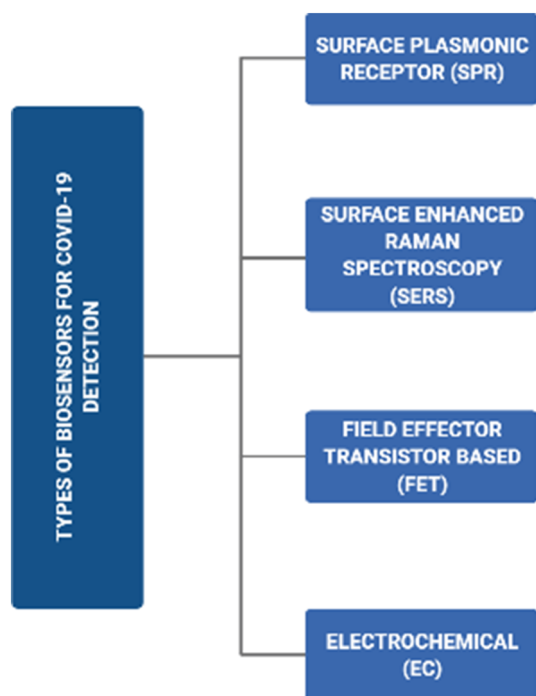


FIGURE 2 Different types of biosensors

smart biosensing application (nanoparticle-based) and their composition includes clear signal amplification, signal generation, significant LOD, higher sensitivity, smaller in diameter and selectivity that are important for biosensor development and demonstrating the capability of smart biosensing application in SARS-CoV-2 detection.^[26]

Carbon nanotubes (CNTs) are formed from graphene sheets with smaller nanometer and have shown to possess excellent electrical, mechanical and thermal characteristics thereby making them suitable candidates to be developed into a biosensor. Pinals et al., developed a single-walled carbon nanotube (SWCNT) that is similar in functionality with angiotensin-converting enzyme 2 (ACE2) receptor of SARS-CoV-2 and it was observed that the presence of SARS-CoV-2 excites a two-fold nano-sensor fluorescence when exposed to spike protein of virus within 1 h and 30 min^[27] and it was reported that this biosensing application indicated a 73% fluorescence indication in response to 5 s exposure to 35 mg/L of SARS-CoV-2 virus particle thus developing a rapid tool for SARS-CoV-2 detection.^[27] Aasi et al., also evaluated CNTs in conjunction with hydrogen peroxide (H₂O₂) concluding that with strong adsorption and their longer shell life made them a feasible candidate for sensor development.^[28] CNTs overcome the problem of migration owing to their metallic properties that are faced by graphene-based biosensor and due to the utilization of metal particles in the compound structure CNTs enhancing reproducibility and stability.^[26]

In the recent decade, quantum dots have received attention due to their ability to fight against vital infections. Quantum dots are small semi-conductor nanocrystals that transform the light spectrum into a variety of colors and range from 1 to 10 nm that showcases efficient fluorescence, quantum property and changeable band energy.^[29] Łoczechin et al., investigated anti-viral activity of carbon-based quantum dots against SARS-CoV-2 and by experimenting on 4-aminophenylboronic acid saw the inhibition of HCoV-229E due to interaction between functional groups and its receptors and the

presence of boronic acids with its anti-viral property proved crucial for this finding.^[30] Amouzadeh Tabrizi et al., designed a photochemical aptasensor based on carbon nitride (C_3N_4) and cadmium sulfide (CdS) quantum dots and its LOD was obtained as 0.12 nM and this sensing system was used to detect SARS-CoV-2.^[31]

MNP (magnetic nanoparticles) dependent biosensors have been utilized to diagnose respiratory viruses in the past, these MNPs are used for the nucleic acid detection when used in conjunction with homogeneous circle-to-circle amplification (HC2CA) and iron oxide nanoparticles (IONPs).^[32,33] Herein the single-stranded DNA (ssDNA) of a sample is identified in a mechanism where either detection probes of IONPs are either individually or combined with HC2CA and under external magnetic field influence utilized properties such as adsorption or scattering to detect the ssDNA and this method was able to differentiate the gene sequence of SARS-CoV and SARS-CoV-2.^[32,33] It was also discovered that when coated with carboxyl polymer magnetic nanoparticles (pcMNP) they were effective towards SARS-CoV-2 viral detection through RNA extraction and it is also worth noting that magnetic nanosensor-based devices were manufactured for COVID-19 detection by T2 Biosystems, Inc.^[32-34]

Due to their unique possession of large, sharp emission band and larger luminescence that is utilized to detect highly sensitive molecules the lanthanide-doped polystyrene nano-particles were used for COVID-19 detection^[35] along with a lateral-flow immunoassay (LFIA) built using lanthanide-doped nano-particles was developed using mini-emulsion polymerization to detect COVID-19, as it is able to detect anti-COVID-19 IgG from human serum in a span of 10 min thus providing additional equipment for SARS-CoV-2 detection.^[36,37]

Gold-based nanoparticles have often been utilized for virus detection and also for SARS-CoV-2 detection. A successfully designed gold nanoparticle (AuNP)-based biosensor is a thiol modified antisense-oligonucleotide (ASO), an AuNP-ASO colorimetric biosensor for COVID-19 detection was used due to its distinctive method to detect nucleocapsid phosphor protein (N-Gene) in RNA that was derived from the oral part of the pharynx and this developed technique is able to detect RNA-dependent RNA polymerase (RdRp) gene found in SARS-CoV-2 virus taken from nasopharyngeal sample.^[38,39] An AuNP coupled with LFIA detection device was developed that can detect both IgG and IgM antibodies of SARS-CoV-2 from human blood sample with a specific accuracy of 90.63% and sensitivity of 88.66% in a simultaneous way.^[40]

2.1.2 | Plasmonic biosensors

The SPR are biosensors which have now gained importance in detecting and quantifying biological targets in a wide variety of areas.^[41] These type of biosensors are free of labels, highly sensitive and can be easily applied to different analytes for clinical testing.^[42] SPR biosensors have also been used for identifying SARS-COV-2 antibodies with the help of proteins created by genetically fusing the polypeptides, which are bounded by gold to a surface antigen of SARS-COV-2.^[43]

Recently, an SPR biosensing technology-based study was conducted in which undiluted serum samples from humans was used for the detection of nucleocapsid antibodies which are quite precise against SARS-COV-2.^[43] The monolayer of the specific peptide was then effectively coated on the surface of the SPR biosensor and was then further functionalized with virus nucleocapsid protein. This set-up was found to be capable of SARS-CoV-2 antibody detection at a nano-molecular level. This convenient SPR instrument was widely used for carrying out bioassays.^[8] Exposure to SARS-CoV-2 causes an immune response, which leads to antibody production. These antibodies are detected and monitored. Antibody analysis helps in assessing patient's immunity and is helpful in vaccine development studies.^[44] Accurate antibody detection allows for vaccine development support and SARS-CoV-2 immunity testing of individuals. Wang's research group has also demonstrated a dual functional biosensor which is plasmonic and constructed by the combination effect of plasmonic photothermal (PPT) and can provide localization of surface plasmon response (LSPR) which in the reviewed research provides promising positive diagnostic results.^[45,46] Two-dimensional gold nanomaterial combined with complementary DNA receptors are able to identify a selective sequence from SARS-COV-2 by the hybridization of nucleic acids. This type of detection was further enhanced by the help of plasmonic heat generation on the surface of AUNIs when they began to illuminate at the frequency of plasmonic resonance.^[47] The heat generated by plasmonic photo-thermal heat has the ability of increasing the temperature in situ which consequently helped in distinguishing between gene sequences. The dual functional LSPR biosensor can sense superbly with a very low LOD of 0.22 pM and the determination was also very specific among^[48] many gene targets.^[43]

The SPR-based biosensors are reliable, sensitive and can be achieved in real-time.^[49] SPR-based biosensors can be miniaturized with low cost and are user friendly.^[50] However, the SPR is not that useful for small analytes. This is because SPR measures the mass of the material which then binds the surface of sensor. In SPR-based biosensors small amounts of analyte provide quite small responses.^[51]

2.1.3 | FET-based biosensor

Another most important biosensor used in the detection of SARS-CoV-2 as a rapid diagnostic technique is FET-based biosensor. The promising benefits of this biosensor are its sensitivity and the ability to detect in a very small time. This kind of biosensor has the capability to be used in clinical analysis. As well as on site diagnosis and tests which are point of care for the patients. Graphene-based FET biosensors can be used to carrying out specific diagnosis with good quality and sensitivity. In a study, Seo and his colleagues have developed a diagnostic biosensor for the quick identification of SARS-CoV-2 in clinical aspects. The sheets of graphene having FET have conjugated with specific antibodies in contrast to SARS-CoV-2 spike protein for constructing the biosensors.^[48,52] A study done by Parvin and his colleagues present a promising biosensor for the quick and accurate

detection of SARS-CoV-2 in vitro that is based on FET and semiconducting transition metal dichalcogenide (TMDC) WSe₂. The sensor has a detection limit of 25 fg/L in phosphate-buffered saline and is made by functionalizing WSe₂ monolayers with a monoclonal antibody against the SARS-CoV-2 spike protein.^[53] Additionally, Zhang et al. created a graphene-based FET (GFET) sensor with a minimal detection limit of 0.2 pM for the 2-min detection of SARS-CoV-2.^[54] Recent studies depicts the use of bimetallic nanoparticles of platinum and palladium added to graphene oxide (GO-FET) biosensor. The COVID-19 spike antigen in phosphate-buffered saline has a LOD of 1 fg/ml in an internally built biosensor. The outcome of the overall studies show that a promising FET biosensor for COVID-19 diagnosis was successfully fabricated.^[55]

2.1.4 | Smart optical biosensor

Optical biosensors are another type of biosensors that can be applied for the detection of the SARS-CoV-2 virus.^[56] Optical biosensors are preferred over conventional analytical techniques as they provide real-time results, eliminating the need for nucleic acid amplification. It is a highly specific and sensitive biosensing technique. And one of its major advantages includes its compact apparatus that is easily portable.^[56–60]

An optical biosensor is a compact analytical device that contains a biorecognition sensing element that is integrated with an optical transducer system. The basic objective of an optical biosensor is to produce signals that are proportionate to the concentration of the analyte.^[61] The optical biosensor can utilize several biological materials as biorecognition elements, including enzymes, antibodies, antigens, receptors, nucleic acids, and even whole cells and tissues.^[61] Optical biosensors present an alternative method for virus detection due to their safe, straight-forward use, and cost-effective technology.

Optical biosensing combines detection and visualization which provides an in-depth understanding of the virus in addition to detecting it in biological samples.^[62] Optical bioimaging combines advanced optical methods with pathogen-specific tracers, that allow targeting as well as detection of abnormalities in a disease pathway at the molecular level.

These optical biosensors can be vital in optimizing COVID-19 tests in terms of cost, rate of testing, and sensitivity. Despite the fact that imaging-based biosensing techniques are a costlier and more complicated method for virus detection, they prove to be very useful in providing better information on the virus replication pathway and can also help in developing treatment options.^[63] Biosensors possess a unique property for surface modification to create targeting sensors by the attachment of biomolecules that detect specific viral sequences. The hybridization of SARS-CoV-2's DNA-RNA that is used in RT-PCR amplification can be induced by setting the temperature slightly lower than the melting temperature of the nucleic acid strand.^[64] Qiu et al. implemented this phenomenon to develop a dual-functional gold nano island-based biosensor by using thermos plasmonic heating (for signal amplification) and SPR imaging for the detection of RdRp, which is a closely related nucleic acid sequence of SARS-CoV-2, at a 0.22 pM

detection limit.^[65] At this concentration, a 200 µl of analyte solution contained $\sim 2.26 \times 10^7$ copies of the RdRp-COVID sequence, which is higher than the viral load of the SARS-CoV-2 virus.^[66] This biosensor was comprised of a thiol-complementary DNA (cDNA) functionalized gold surface which on heating up to 41°C immobilizes RdRp. Being rapid and efficient, this biosensor is a single-use apparatus and also requires the preparation of a sample prior to the analysis. All the information regarding different advantages and disadvantages of biosensors are depicted in Table 1.

2.1.5 | SERS-based biosensors

The SERS-based biosensors are another most efficient kind of biosensors used in COVID-19 detection. The SERS-based biosensors have captivated immense attention of researchers around the globe because of its high sensitivity and quantitative determination of analyte by using the SERS-encoded nanoparticles. For sensitive and simultaneous quantitative determination of respiratory viruses magnetic strips are used by various researchers.^[58]

A study proposed by Zhang et al., developed a COVID-19 biosensor based on SERS for the highly sensitive detection of the SARS-CoV-2 virus in untreated saliva. The SARS-CoV-2 spike protein was detectable by a SERS-based biosensor at concentrations of 6.07 fg/ml in untreated saliva and 0.77 fg/ml in phosphate-buffered saline. Without sample pretreatment, the developed SARS-based biosensor demonstrated great specificity and sensitivity for the SARS-CoV-2 virus, offering a possible option for the early diagnosis of COVID-19.^[62,67,68] Researchers also use SERS and disposable electrospun micro/nano-filter membranes or integrated microchannels functionalized with vertically aligned gold/silver coated CNTs in microfluidic devices. These tools may effectively capture viruses from a variety of bodily fluids and secretions, such as saliva, nasopharyngeal secretions, tears, etc.^[69] Yang and coworkers in 2021 presented a gold “virus traps” nanostructure functionalized with human ACE2 as an incredibly sensitive SERS biosensor that can quickly and accurately detect S-protein expressed coronaviruses, like the current SARS-CoV-2, in contaminated water down to the single-virus level. Such a SERS sensor has remarkable 106-fold virus enrichment due to high ACE2

TABLE 1 Advantage and disadvantages of biosensors

Biosensors	Advantages	Limitations
Surface plasmon receptor (SPR)	Label free, reliable, low cost, sensitive	Not suitable for small analytes
Field effect transistor (FET)	Fast response, low-cost, and ease of use	Low sensitivity and response time.
Electrochemical (EC)	Widely-used, easy to modify, compatible, sensitive	Highly susceptible to temperature fluctuation
Surface enhanced Raman scattering (SERS)	Sensitive and provides accurate results	Difficult to fabricate

protein affinity as well as “virus-traps” made of oblique gold nanoneedles and 109-fold enhanced Raman signals due to multi-component SERS effects.^[70]

2.1.6 | Metal-organic framework-based smart sensor

Metal-organic frameworks (MOFs) are an efficient tool due to their crystalline structure with surface potential, providing porous activity and possessing exceptional characteristics.^[71] MOFs exhibit properties such as high stability, greater surface region and good biocompatibility, therefore utilizing these advantages leads to the development of biosensing technologies, bioimaging, etc.^[71] Some of the recently reported techniques on MOF are designing a two-dimensional (2D) MOF nano-enzyme to detect *Staphylococcus aureus* using an EC biosensor^[72] and a nanostructure developed by combining MOF, nickel, AuNP and CNTs for HIV detection using DNA hybridization, thus suggesting the utilization of MOF for viral infectious agent detection.^[60] Therefore, a MOF-5 was coated with CoNi₂S₄ nanoparticles since these nanostructures can enhance the selectivity of the biosensor due to their unique spatial shaping structure and this complex was enhanced by H₂TMP (porphyrins) and was experimented to detect SARS-CoV-2 spike antigen protein using optical methods.^[72] It was also reported that nanocomposite particles have significant sensitivity activity towards spike protein of COVID-19.^[73] This study also reported with a LOD around 5 nM that is very adaptive and consistent with other studies regarding cost-effective optical nano-sensing technology.^[74]

2.1.7 | Screen printed electrode-based smart sensor

Screen-printed electrodes (SPEs) are emerging platforms with outstanding potential for their use as transducers in EC biosensors.^[75] Their superior advantages, including disposability, portability, low-volume loading, make them ideal for on-site detection in clinical, environmental, and argo-food areas. Additionally, their further modification with functional biomolecules broadens the wide range of EC biosensor designs. The high potential of SPE-based biosensors is worthy of much attention.^[76] Also, the combination of such miniaturized EC transducers, cheap and portable EC detection instruments, and the modification with functional biomolecules make for an ideal system for sensing applications in various areas, even in the current fight for the detection of COVID-19.

2.1.8 | Molecular imprinting polymers (MIPs)-based smart sensor

Molecularly imprinted polymers (MIPs) are synthetic materials that mimic biological recognition. Molecular imprinting technology offers a self-assembled monolayer on the surface of the electrode and the

further fixation of a target molecule into the dedicated architecture of cavities embedded in the polymer matrix.^[77] MIPs are even used in combination with magnetic materials, ionic liquids, chiral and nano-sized detection strategy. MIPs have already been used for the diagnosis of cancer and drug residue monitoring and it could also be vital for the diagnosis of SARS-CoV-2.

2.1.9 | MXenes-based smart sensor

Another type of 2D synthetic nanomaterial-based MXenes are used as transducer substrates and/or interfaces in the development of EC biosensors in diagnostics. This new type of 2D metal carbides or nitrides are represented by a general formula $M_n + 1X_nT_x$, where M is the transition metal, X is a carbon or nitrogen atom and T is the functional group (-OH, =O, Cl or F). By forming MAX phases, that are closely-packed alternating layers of M and A where A is an A-group element, that are usually an atom that belongs to the groups 13, 14 or 15 of the periodic table,^[67] MXenes possess unique chemical, physical, electric and mechanical properties owing to the layered structure of the strong M-X (metallic-covalent) bond and a comparatively weak M-A bond. The modification of exfoliated MX layers with terminal functional groups mentioned earlier has a major effect on the electron transfer processes that occur at the biosensor interface, especially in the case of biomacromolecules like enzymes and proteins when the direct electron transfer is not possible because of the deeply rooted location of their redox-active centers. MXenes offer a rich surface for binding the biomolecules of interest. Their biocompatibility and dispersibility in aqueous solutions represent one of the most prominent features for fabricating the advanced biomedical sensing platforms. MXenes-based biosensors have been employed in various applications, namely, biomedical detection of gene mutation-based diseases and now it can be applied in the detection of COVID-19 virus.

3 | EXAMPLES OF DEVELOPED BIOSENSORS FOR COVID-19 DETECTION

Many innovative biosensors have been developed for the detection of COVID-19. We have compiled a comprehensive list of such reported sensors which show promise for commercial applications. These sensors are classified on the basis of sample type, target, turnaround time, LOD, and specificity. Different types of biosensors developed in the laboratory for COVID-19 are represents in Table 2.^[46,48,65,78-86,87,88]

4 | CHALLENGES AND OPPURTUNITIES

The most commonly faced issue for constructing a compatible biosensor is to capture a signal of very low magnitude that takes place between the biological species (bio-receptor and analyte. To tackle this problem, nanomaterials can be employed as labels to obtain a remarkable improvement in the signal, high enough to be easily

TABLE 2 Some examples of developed biosensors for covid-19 detection

Type	Analyte	Sample	LOD	Time	Reference
CRISPR–fluorescence detection system	RNA	Saliva	0.38 copies/ μ l	15 min	[48]
Plasmonic photothermal biosensors	RNA	—	0.22 $\pm$ 0.08 pM		[78]
eCovSens (FTO/AuNPs/nCovid-19Ab sensor)	Antigens	Spiked saliva	90 fM	10–30 s	[79]
Electrochemical immunosensor	Antigens	Saliva	19 ng/ml and 8 ng/ml	30 min	[80]
Multiplexed grating-coupled fluorescent plasmonics biosensor	Antigens	Serum and dried blood		30 min	[81]
Field effect transistor (FET)-based biosensor	Antigen	Swab	2.42 $\times$ 10 ² copies/ml	—	[82]
Electrochemical biosensor	Antibody	Serum	0.96 (IgG) and 0.14 ng/ml (IgM)	30 min	[83]
Plasmonic biosensor	Antigens	Serum	19.9 ng/ml		[84]
Electrochemical biosensor	N protein	—	8.33 pg/ml		[85]
Electrochemical biosensor	Genes		0.972 fg/ μ l (RdRP gene) and 3.925 fg/ μ l (N gene)	<20 min	[86]
Optical biosensor		Swabs	—		[65]
Reverse transcription loop-mediated isothermal amplification	Opening reading frame and nucleoprotein in genes	Swabs		1 h	[46]
Field-effect transistor (FET)-based biosensor	Antigen (spike protein)	—	25 fg/ μ l	—	[87]
Reverse transcription multiple cross displacement amplification labeled nanoparticles biosensor	Open reading frame and nucleoprotein gene	Feces, nasal, pharyngeal and anal swabs		1 h	[88]

detectable, for example metallic nanomaterials (e.g., gold or silver nanoparticles) and quantum dots can also be analyzed and employed for labeling by attaching them onto the targeted DNA/bio-recognizing probe. This would lead to a synergetic effect owing to the nano-labeling consequences to significantly amplify the EC signal, and make it possible to design ultrasensitive and selective labeled-biosensing strategies. Very limited tests have been performed to create these nanomaterials-based biosensors for SARS-CoV-2 detection.^[68] This technique can replace PCR-based testing for COVID-19, with the advantages of simplicity, cost-effectiveness, fast response and real-time diagnostic procedures. These nanomaterial-enabled biosensors primarily rely on the nucleic acid and protein (antigen/antibody) mediated detection of SARS-CoV-2, although they have not yet yielded 100% accuracy owing to the contamination of these highly sensitive bio-receptors, and ultrasensitive, rapid, and portable SARS-CoV-2 sequence detection methods are highly demanded.

5 | FUTURE PROSPECTS

The ongoing pandemic has caused a lot of death and disruption worldwide. Healthcare infrastructure is overburdened and crumbling in

many countries. Since there is no definite cure, we must rely on rapid testing and isolation to flatten the curve. Thus, there is a need for rapid diagnosis and monitoring of the disease. COVID-19 infection develops into cytokine storm causing acute respiratory distress syndrome (ARDS) which is fatal. Multiplex sensors will prove to be an important element in monitoring multiple biomarkers and parameters at once such as respiratory health, inflammatory factors and cytokine levels. This is especially useful since in a lot of cases the disease deteriorates rapidly. Wearable monitors and patches can also be of significant help in disease monitoring and management as treatment can be administered before the symptoms progress to ARDS or pneumonia. There is a strong need to have faster and possibly single step diagnostic device which eliminates the need for trained personnel and expertise in order to carry out tests. This in turn eliminates problems such as crowded testing centers and simpler mass-testing. This situation can be further resolved by the use of smartphone-aided testing.

6 | CONCLUSION

COVID-19 is the current global problem. To keep the pandemic outbreak under control, urgent action is required due to the epidemic's

billions of infected cases. It is impossible to exaggerate the significance of early detection and treatment in halting the spread. There is a lot of interest in the creation of new COVID-19 biosensors that are quick, dependable, and sensitive. There are a few articles on the new biosensors for COVID-19 diagnosis, but there are few studies on the biosensor based on use of different materials. The uniqueness of this article also stems from the viewpoint on material and sensor selection based on clinical concern for the ongoing COVID-19 outbreak. The biosensors would be a one-step identification or sensing technique. In instances where traditional laboratory techniques are not readily available, biosensors have already shown that they can deliver affordable, accessible diagnoses.

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AUTHORS CONTRIBUTIONS

All the authors participated in the study design and coordination and prepared the manuscript. All authors have read and approved the last article.

CONFLICTS OF INTEREST

Authors declares on conflict of interest among others.

DATA AVAILABILITY STATEMENT

NA.

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