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REVIEW ARTICLE

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Nanotechnology for SARS-CoV-2 diagnosis

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ABSTRACT

As the first cause of death in the last three years, SARS-CoV-2 infection gained lots of interest. In light of this, several studies have been done to fabricate novel, high-speed detection methods for different virus variants. Indeed, the high mortality rate that could result from the late detection and the probable false results of conventional tests used to detect infection led to the introduction. Among the most interesting of them are -based biosensors fabricated from inorganic-based nanomaterials to diagnose SARS-CoV-2. Accordingly, this review paper presents an overview of recent nanotechnology advances in fabricating biosensors for diagnosing SARS-CoV-2 infections.

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1. Introduction

Viruses are among the leading causes of immunodeficiency and acute respiratory infections worldwide that harm health and socio-economic development [1, 2]. Viruses typically consist of a particular genetic material and constructional viral proteins that are assembled as "capsid" and cover the nucleic acids [2]. Based on the genome type, viruses can be classified into two main categories: DNA-based and RNA-based viruses. Their genome could be in a single-stranded form or double-stranded and linear or circular [3].

Although they cannot live without a host, viruses are present worldwide, and there is rarely a place where they would not be found. They could affect humans, animals, and even plants and could lead to a global pandemic causing a high mortality rate, like what happened due to the spread of the COVID-19 virus in 2019. Despite the advancements in diagnostic and treatment of viral infections in the past two decades, there is a noticeable shortcoming in our ability for that. Indeed, there is an urgent need to develop novel methods for detecting viral infection and their treatment, as seen recently in the case of the COVID-19 outbreak [4-6].

Nanomaterials have been employed in the industrial and biomedical sectors for various purposes [7-11]. In fact, the remarkable properties of nanomaterials, such as tunable surface charge, extensive surface area, and high functionalizing capacity, make them one of the best candidates for novel viral detection and treatment methods [12-14]. It has been shown that nanomaterials can be employed as diagnosis agents with high sensitivity and specificity to detect and trace various types of infections [15-18]. Indeed, they could be functionalized with different probes simultaneously and provide the feasibility of fabricating cheap, highly stable, non-invasive, straightforward, and reusable sensors with excellent selectivity, high specificity, and rapid response [19]. Accordingly, different types of nanomaterials, such as organic and inorganic nanomaterials, were applied in the structure of biosensors to detect viruses via different approaches [20-22]. Nanomaterials like metal and metal oxide nanoparticles, carbon-based, quantum dots, silica-based, etc., with different physicochemical features (like optical and electrochemical properties), in various shapes, could improve the performance of biosensors for viral detection [23, 24].

Since the emergence of the COVID-19 outbreak, various diagnostic strategies have evolved. In this review paper, some of the recent developments in inorganic-based biosensors about the ongoing pandemic of COVID-19 have been presented and discussed. We aim to draw attention to technologies and methods that can increase the sensitivity of the currently available detection methods for COVID-19 detection.

2. SARS-CoV-2 respiratory system infections: An overview

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) relates to the Coronavirinae subfamily that with Torovirinae from the Coronaviridae family in the Nidovirales order, have spherical envelope; they contain a 5' capped, single-strand RNA genome [25].

While the respiratory region is the most influential infection district, some other organs, such as the brain, have been shown to contain a virus or viral products [26]. Their envelope contains at least three proteins, the envelope protein, the spike protein, and membrane protein. Some coronaviruses also include a hemagglutinin esterase (HE). The envelope and membrane proteins are involved in virus construction, and the spike protein is the mediator of virus entry. The connection of the spike protein starts virus entry with specific proteins on the surface of a cell. After beginning attachment, enveloped viruses fuse with the organism cell membrane to release their nucleocapsid to the purpose cell. The spike protein plays a double function in the entrance by membrane fusion and interfering with receptor binding [27, 28].

SARS-CoV invades human cells with surface spike protein to achieve its purpose; spike protein binds to its human receptor, human angiotensin-converting enzyme 2(hACE2), by its receptor-binding domain (RBD) and is activated by human proteases. SARS-CoV-2 RBD has a more powerful hACE2 binding than SARS-CoV RBD. The virus binds to a cell surface receptor, enters endosomes, and fuses viral and lysosomal membranes [29, 30]. The spike protein has three components.

SARS-CoV S1 contains a receptor-binding domain (RBD) that identifies angiotensin-converting enzyme 2 (ACE2) as its receptor. Subsequently, SARS-CoV entry stimulates cell surface protease TMPRSS2 and lysosomal proteases cathepsins [31, 32].

Coronaviruses (CoVs) are enveloped positive-sense single-stranded RNA viruses (+ssRNA) with the largest genome among RNA viruses (length of up to 32 kilobases in size). CoVs belong to the order Nidovirales, suborder Coronavirineae, family Coronaviridae, and subfamily Orthocoronavirinae. This subfamily is subdivided into four genera: *Alphacoronavirus* and *Betacoronavirus* (α- and β-CoV), infecting mammals, *Gammacoronavirus* and *Deltacoronavirus* (γ- and δ-CoV), primarily infecting avian species [33]. While most human CoVs (hCoVs) cause relatively mild infections of the upper respiratory tract (common cold), three of the β-CoVs of zoonotic origins, namely severe acute respiratory syndrome coronavirus (SARS-CoV then termed SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused severe respiratory disease outbreaks respectively occurred in China in 2002-2003, in Saudi Arabia in 2012, and in Wuhan (China) in late 2019 [34].

The CoV particle carries four major structural proteins, including the trimeric spike (S), nucleocapsid (N), membrane (M), and envelope (E) proteins (**Fig. 1**). Some β-CoVs also express the membrane-anchored hemagglutinin-esterase (HE) protein [35]. The S protein is the major glycoprotein forming peplomers on the viral surface, and it is responsible for viral attachment, fusion, and entry into target cells [36]. The protein consists of S1 and S2 subunits. CoV infection

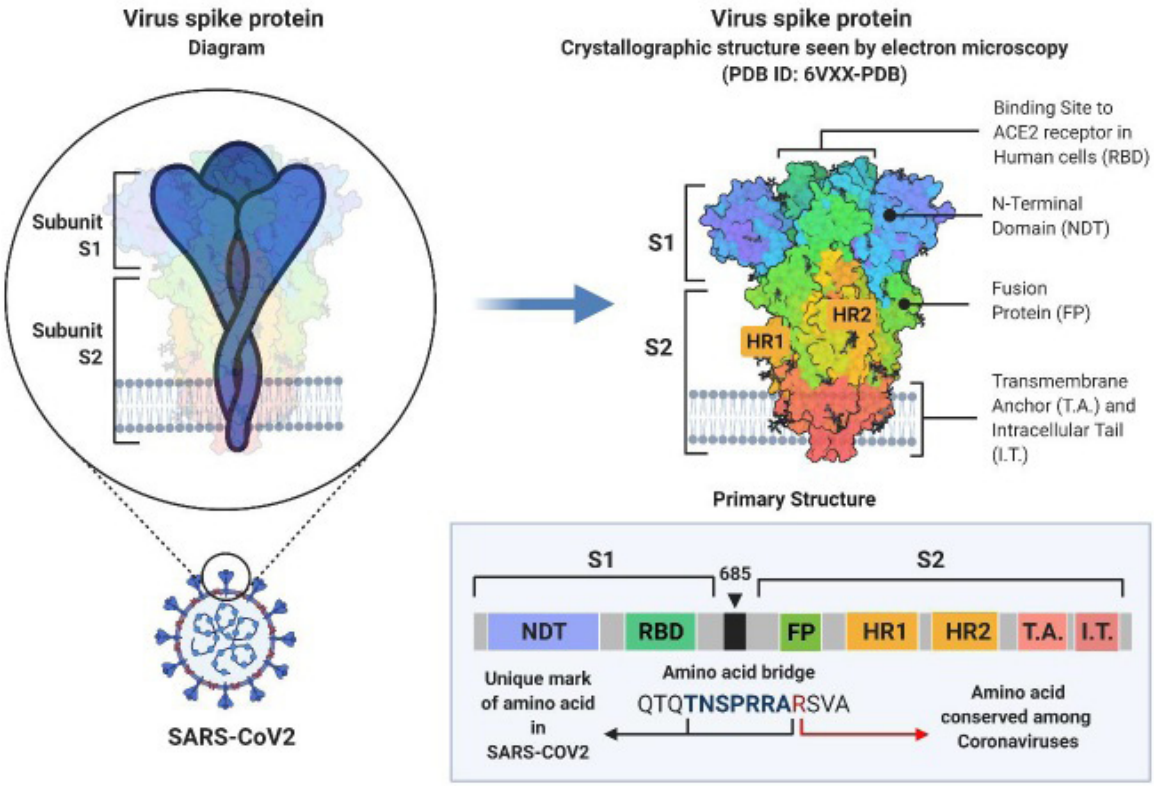

Figure 1. An in-depth look into the structure of the SARS-CoV2 spike glycoprotein. The S glycoprotein of the SARS-CoV2 is composed of two subunits, S1 and S2, and is commonly represented as a sword-like spike. The real structure of this protein, however, can be observed using crystallography. The Protein Data Bank (PDB) model of this glycoprotein reveals how the subunits are comprised of different regions that are fundamental to the infection process. S1 and S2 are linked together by a polybasic amino acid bridge, which may be important in studying viral targeting. Figure is created with BioRender.com.

initiates when the S protein binds to a host receptor through the receptor-binding domain (RBD) in the S1 subunit and then mediates viral cell membrane fusion through the S2 subunit [37]. The angiotensin-converting enzyme 2 (ACE-2) protein has been identified as the cell entry receptor for SARS-CoV-1 and SARS-CoV-2. In contrast, the MERS-CoV S protein engages dipeptidyl peptidase-4 (DPP-4, also known as CD26) receptor to mediate viral entry [38].

Recent bioinformatics approaches have revealed a high potential affinity of SARS-CoV-2 S RBD to DDP-4, with RBD E484 residue critical for DPP-4 binding [38]. Additionally, neuropilin-1 (NRP1) and CD147 are host factors for SARS-CoV-2 infection, potentially enhancing the viral entry by endocytosis [39]. Various human tissues express ACE2 receptors emphasizing lungs, heart, and vasculature. ACE2 is heterogeneously expressed in the human respiratory tract, highest within the Sino nasal cavity and pulmonary alveoli. Clinical effects of viral infection in respiratory and cardiovascular tissues are shown in **Fig. 2.** Reduction of ACE2 is recognized to be linked to diabetes, hypertension, coronary artery disease, and heart failure [40, 41]. DPP-4 has been detected in the lung and is also widely expressedin epithelial cells of the kidney, liver, intestine, thymus, and bone marrow [42].

Besides engagement of functional receptors, proteolytic cleavage of CoV S protein at the S1/S2 boundary and 'S2' site by host cell proteases is essential to promote successful conformational changes in S that lead to viral fusion at the cellular or endosomal membrane. SARS-CoV and MERS-CoV employ the cell surface serine protease TMPRSS2 (transmembrane serine protease 2) and endosomal cysteine cathepsins B and L (CTSB/L) proteases for S priming/activation and entry [43, 44]. TMPRSS2 and lysosomal cathepsins can activate SARS-CoV-2 S protein, playing an important role in SARS-CoV-2 cell entry [31, 45, 46]. Depending on protease availability at the plasma membrane, upon engagement of the host receptor, CoV can enter target cells either by "early pathway" or "late pathway" [36] and fuse at the cellular or endosomal membrane, releasing the viral genome into the cytosol (**Fig. 3**).

CoVs express and replicate their genome during the intracellular life cycle to create newly infecting CoV virions [48]. Upon CoV infection, viral RNA can be sensed and detected by pattern-recognition receptors (PRRs), including toll-like receptors (TLRs), and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs). Signaling mediated by TLRs and RLRs leads to the production of type I interferons

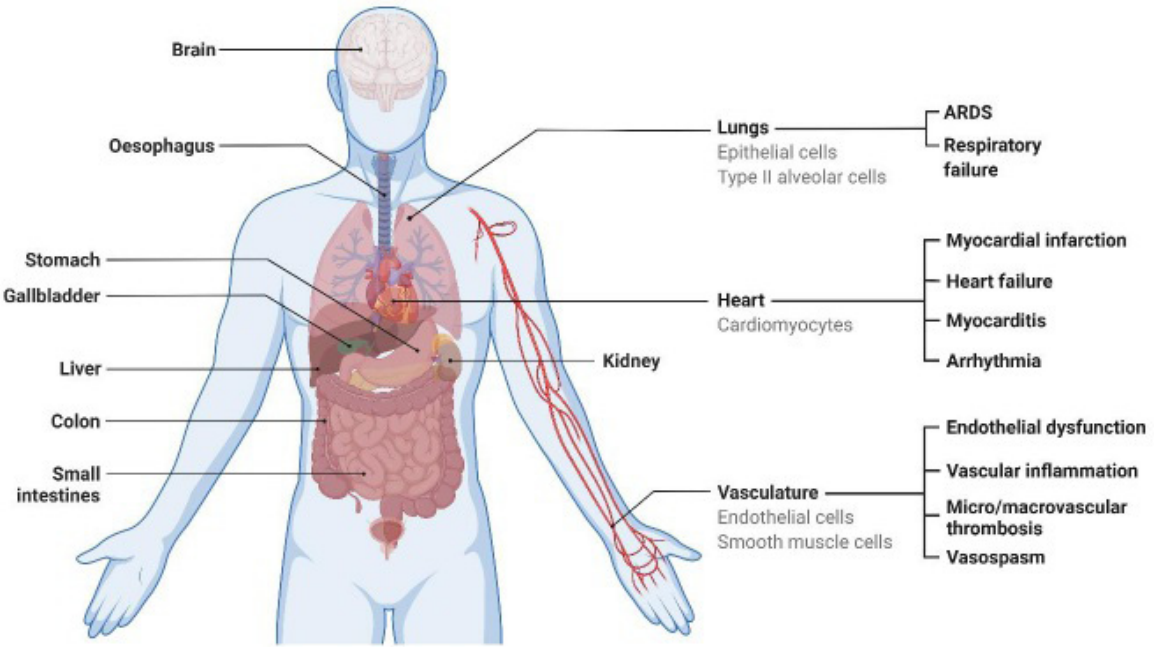

Figure 2. Expression of ACE2 receptor in human host tissues, highlighting lungs, heart and vasculature.

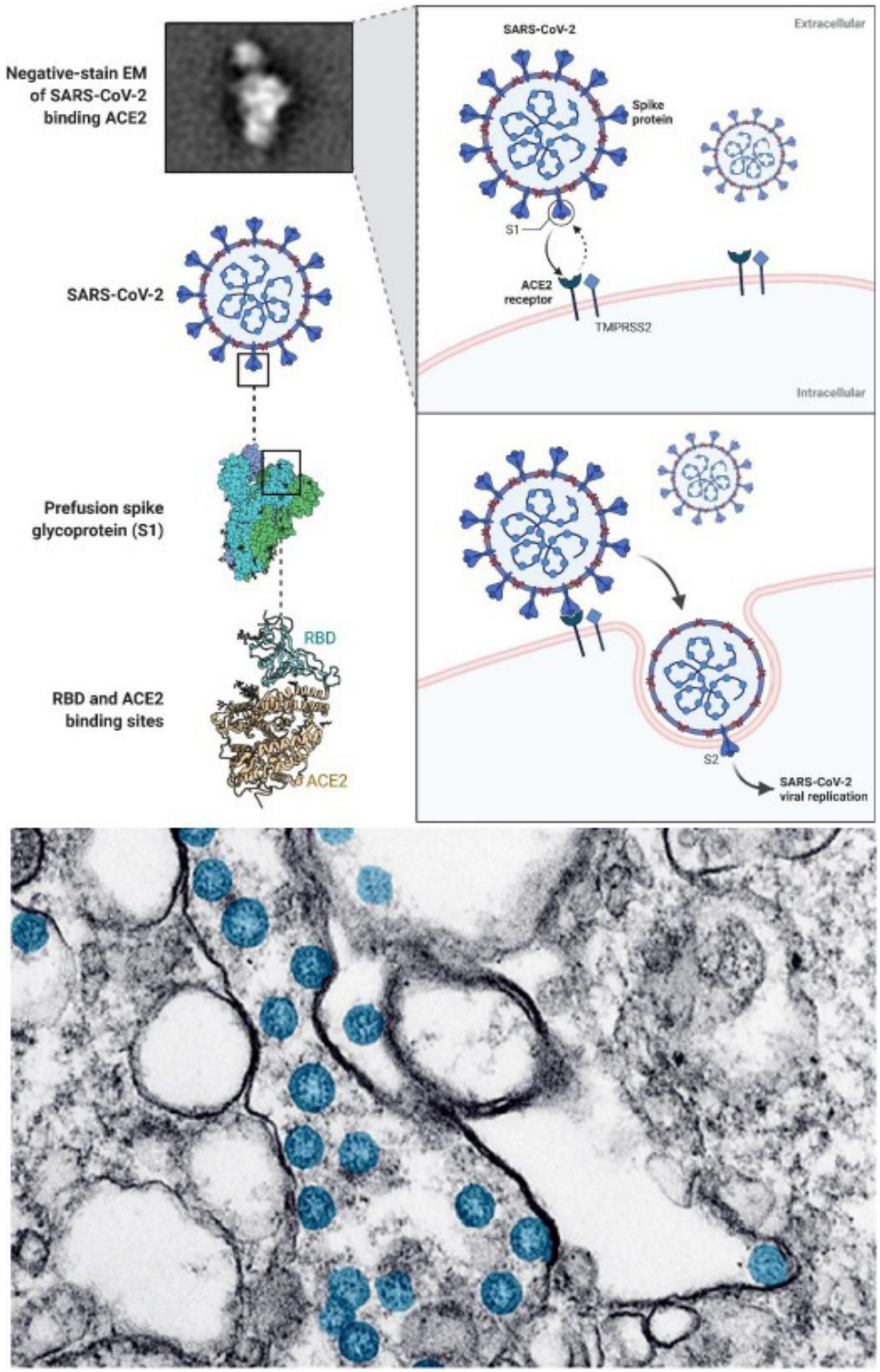

Figure 3. Electron microscope and schematic illustration of coronavirus (CoV) entry mechanism into infected cells. The presence of cell surface serine proteases, such as TMPRSS2, triggers the "early fusion pathway" of viral entry. TMPRSS2 activates CoV S protein, promoting subsequent fusion of the viral membrane with the plasma membrane and release of CoV genome into the cytosol. A transmission electron microscope image of SARS-CoV-2 spherical viral particles in a cell. The virus is colorized in blue. Reproduced with permission from [47].

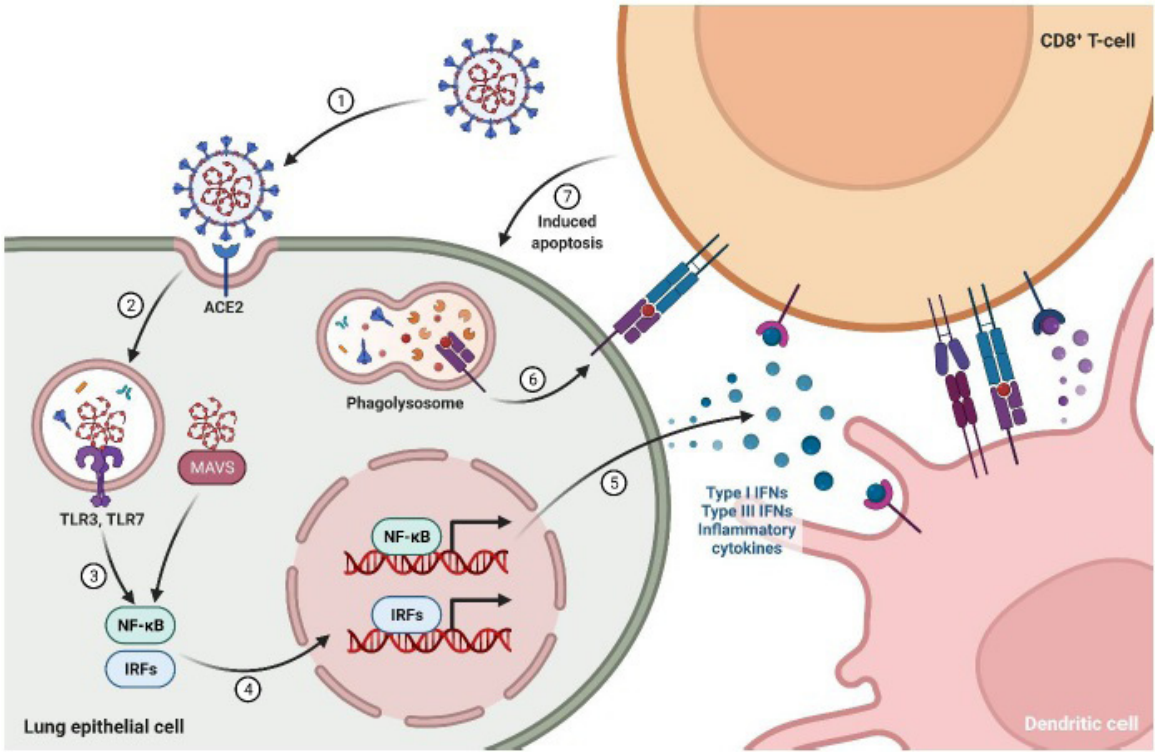

Figure 4. Acute Immune responses to coronaviruses. Some coronaviruses can infect human lung epithelium via the receptor ACE2(1). After endocytosis (2), viral RNA activates endosomal and cytoplasmic sensors, TLR3/7 and MAVS, respectively (3). These receptors activate interferon regulatory factors (IRFs) and NFκB (4) to induce inflammatory cytokines (5), including interferons (IFNs). Dendritic cells (DCs) sample antigen and migrate to lymphoid organs to prime adaptive immunity. $CD8^+$ T-cells recognize antigens on DCs or infected cells (6) and induce apoptosis in affected lung epithelial cells (7) [52].

(IFNs) and proinflammatory cytokines that recruit immune cells to trigger innate and adaptive immunity (**Fig. 4**) [49-51].

CoV infection can additionally trigger assembly and activation of NLRP3 (NLR family pyrin domain containing 3) inflammasome to activate caspase-1 and drive secretion of IL-1β and IL-18 proinflammatory cytokines. SARS-CoV, MERS-CoV and SARS-CoV-2 can also activate caspase-8 and caspase-3 to initiate PANoptosis, a unique inflammatory cell death pathway [49]. An exacerbated systemic inflammatory response contributes to the cytokine storm that might cause severe inflammation, tissue damage, and acute respiratory distress syndrome (ARDS), eventually leading to death [53].

Since the emergence of coronavirus 2019 (COVID-19), several mutations have occurred in the genome of the virus, resulting in the emergence of various types of viruses with different power of infection including alpha, beta, delta, and omicron. Due to the high infectivity and quickly spread, such alterations have resulted in a high fatality rate [54]. In November 2020, Alpha (B.1.1.7), the first coronavirus mutation, occurred in the UK, leading to an increase in the number of infections in December of that year due to the elevation in the invasiveness feature of the virus [55]. Beta, also known as B.1.351, was the second variant of the COVID virus discovered in South Africa in late 2020 and then spread to other countries [56]. Delta (B.1.617.2), the most aggressive form of COVID, was discovered in India in late 2020. It quickly expanded worldwide and became the most common coronavirus strain. Delta is thought to have infected more than twice as many people as of earlier strains [57]. After that, at the end of November 2021, the Network for Genomics Surveillance in South Africa identified a new SARS-CoV-2 mutation, omicron

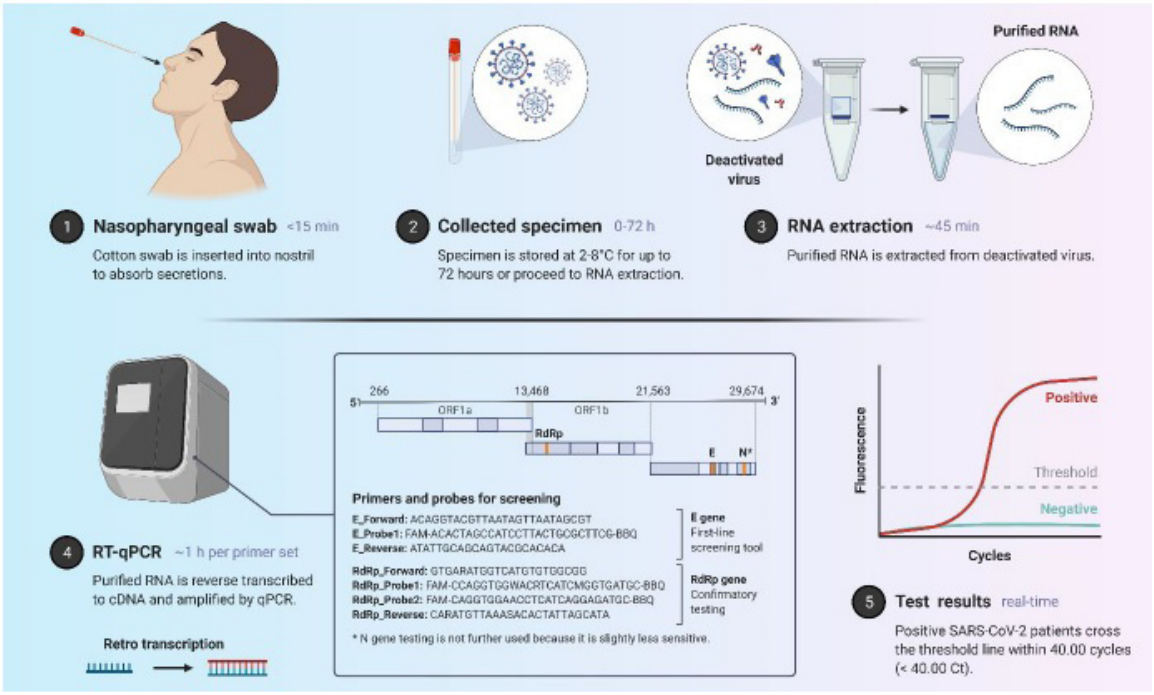

Figure 5. COVID-19 Diagnostic Test through RT-PCR.

(B.1.1.529), which is much more transmissible than delta virus variants. This intensity level is linked to more mutations in the omicron-SARS-CoV-2 spike protein receptor binding site. The lethal and infectious of this variant are lower than others, and its symptoms are primarily like cold; however, this may also be related to the widespread global vaccination [58].

3. Diagnostics

Diagnosing is a critical weapon in the argument against the COVID epidemic because it is essential to isolate infected people as soon as possible and prevent the spread of the virus [59]. Effective diagnosis of viruses recreates a vital role in the treatment and general health, as well as in biodefense and bio-industry. Studies of the course of "filterable agents" small adequately to press through sub-micron permeable filters verified the contagious character of these so-called "viruses" and confirmed their role in infections [60].

Since the innovation of polymerase chain reaction (PCR) and immunoassays in the early 1980s, virus detection has seen crucial improvements [61, 62]. Thus, the rapid development of a vast range of molecular and serological diagnosis methods makes it possible for laboratory examination and the clinical detection of viruses (**Fig. 5**).

Instead of PCR test, point-of-care (POC) lateral flow immunoassay test, enzyme-linked immune-sorbent assay (ELISA), hematology parameters examination, and CT-imaging are the other common tests used for the detection of COVID. Despite their effectiveness, all the mentioned methods suffer from some limitations. For instance, most of them are slow and need a long turnaround time to provide the results. Moreover, they need sophisticated equipment and trained person and also suffer from poor sensitivity that could lead to false results in some cases [63]. Accordingly, it is important to fabricate other diagnosis methods that could decrease the time of detection and enhance the accuracy of detection even in the presence of minimal amounts of viruses.

Improvements in nanotechnology and its application in medicine lead to meliorating the current viral diagnostics methods or introducing novel detection ways. In other words, nanomaterials with a high surface-to-volume ratio could produce appreciatively surface interactions between the analyte and the detector, creating it feasible to detect the virus faster and more reliable. Moreover, their

capability to be modified with different functional groups and their cost-effectiveness introduced them as ideal agents that could be applied in the structure of biosensors with high accuracy. Among the most widely used nanomaterials that have been employed in the structure of biosensors for the diagnosis of the pathogenic virus are inorganic nanomaterials like carbon-based nanomaterials (such as carbon nanotube (CNTs), graphene, graphene oxide, etc.), metal nanoparticles, silica-based nanoparticles, and quantum dots [64, 65].

In general, the available testing kits work based on enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR), which are expensive and time-consuming [65, 66]. In contrast, a large-scale and rapid diagnosis of SARS-CoV-2 could reduce its spread and prevalence in communities. Biosensors, especially nano biosensors, can fulfil this requirement due to their high sensitivity, specificity, detection speed, and cost-effectiveness [67].

In the following part of this study, we first introduce different analytical agents that could be used to fabricate nanobiosensors. Then, in the second part, we describe different biosensors thathave been fabricated so far for the detection of COVID-19 viruses.

3.1. Biological agents used for the detection of COVID viruses

3.1.1. Aptamer based biosensors

Aptamers are single-stranded or double-stranded nucleic acid compounds (DNA or RNA) with high specificity that could be functionalized on the surface of different nanosensors for the detection of a specific virus. These nucleic acid compounds have high affinity to a specific ligand or protein on the surface of their targeted agent. Different types of aptamer-based biosensor were fabricated to rapidly detect COVID infectious [68-71]. For instance, aptamer functionalized silver nanoparticles were used to detect viruses that acted based on the surface-enhanced Raman spectroscopy (SERS) technique [72].

3.1.2. Antibody-based biosensors

Antigen detection is one of the other main groups of materials used to fabricate nanobiosensors for the detection of viral antigen nucleocapsid protein. In detail, the N and S proteins are the antigens that could be used as a biomarker for detecting COVID-19. These types of nanosensors are fabricated based on the interactions between antibodies immobilized on the surface of nanomaterials and the antigen of virus present in the samples that could change ,for example, the electrical conductivity of the sensor [69, 73].

3.1.3. Receptor based biosensor

In this group, the amounts of antibodies (IgG and IgM) presented in the samples were detected to identify the probable infection. Despite the beneficial benefits of these biosensors, they could notn't be used for detecting viruses in their early and asymptomatic stages. This results from the antibody response of the patients that generally occurs after ten days of symptoms' onset [74, 75].

3.2. Nanobiosensors and COVID-19 detection

So far, different types of nanobiosensors have been fabricated for the detection of SARS-CoV-2 viruses. Compared to the conventional methods used for the detection of COVID, nanobiosensors could provide a more sensitive detection method in a shorter time with lower cost that could lead to a better reaction in the appropriate time [19, 68, 76].

Seo *et al*. fabricated a field-effect transistor (FET) immunological biosensor in which the surface of graphene oxide nanosheets was functionalized with a specific antibody used to detect SARS-CoV-2 spike protein. The fabricated biosensor showed high selectivity and sensitivity with the detection limit of about 1.6×10^1 pfu/mL and 2.42×10^2 copies/mL in culture media and real samples, respectively, and a linear range between 1.6×10^1 - 1.6×10^4 pfu/mL (**Fig. 6**) [77].

Carbon nanotube (CNT) was also used in the structure of an electronic biosensor for the selective detection of SARS-CoV-2. CNTs were produced on a flexible Kapton substrate functionalized with 2-mercaptopyridine via applying polydimethylsiloxane (PDMS). Then RNA aptamers, which was the reveres sequence of the virus RNA, were immobilized on it. The fabricated FET biosensor showed good sensitivity (with a detection limit of about 10fM) and selectivity in real-time conditions [78].

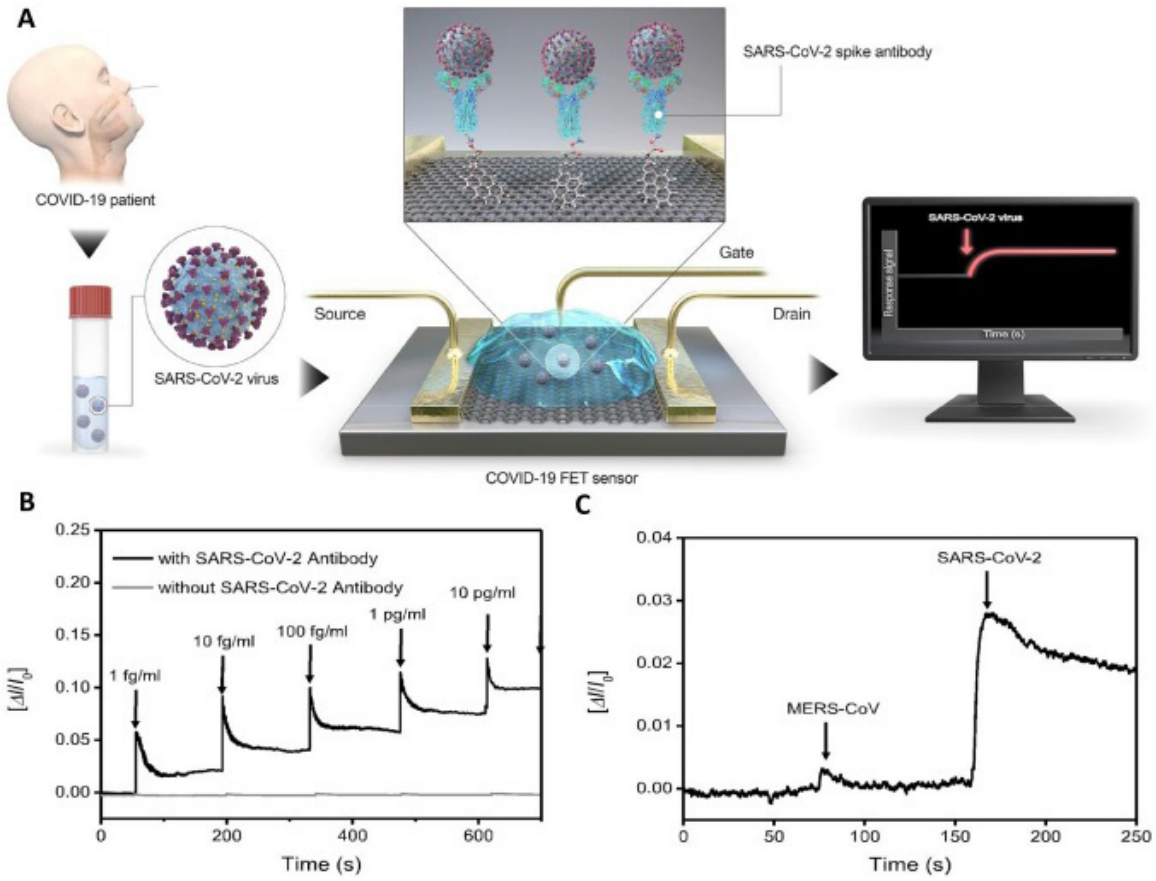

Figure 6. **(A)** Schematic diagram of COVID-19 nano-based sensors for detecting SARS-CoV-2 spike protein using graphene-based FET sensors. **(B)** The responsibility of the biosensor in the presence/absence of SARS-CoV-2 antibody. **(C)** Selective detection of COVID-19 in the presence of MERS-CoV protein and SARS-CoV-2 antigen protein. Reproduced from [77] with permission from the American Chemical Society.

In addition to the electrical biosensors, other types of sensors were also used to detect COVID by utilizing inorganic nanomaterials. Optical biosensors are one of the different types of biosensors used to detect SARS-CoV-2. Due to several recombinations in the spike antigen of SARS-CoV-2, some new nanosensors have been introduced to detect this antigen. A highly sensitive optical sensor was fabricated using metal-organic framework (MOF) nanoformulation. It was a safe, low-cost, and highly sensitive biosensor synthesizedly sensitive based on MOF-5/$CoNi_2S_4$ functionalized by porphyrin. It showed high performance against recombinant SARS-CoV-2 spike antigen with a 5 nM detection limit (**Fig. 7**) [79].

Gold nanoparticles functionalized with antisense oligonucleotides were applied for the colorimetric detection of SARS-CoV-2 via targeting the nucleocapsid phosphoprotein (N-gene). This type of biosensor acted based on the surface plasmon resonance (SPR) method and could detect viruses for 10 min with the detection limit of 0.18 ng/μL. This biosensor also provides the capability of naked-eye detection due to the change in the solution colour after adding 1 ng/μL of SARS-CoV-2 RNA [80].

SPR method was also used to fabricate a label-free aptasensor composed of thiol-modified niobium carbide MXene quantum dots (Nb_2C-SH QDs). A kind of aptamer was attached on the surface of Nb_2C-SH QDs that can interact with the N-gene of SARS-CoV-2. This biosensor acted based on the conformational changes resulting from the binding of aptamer and N-gene that could alter the SPR signal of the chip. 4.9 pg mL^{-1} detection limit toward N-gene in the concentration range of 0.05 - 100 ng mL^{-1} confirmed the high sensitivity of this sensor. Moreover, it showed high

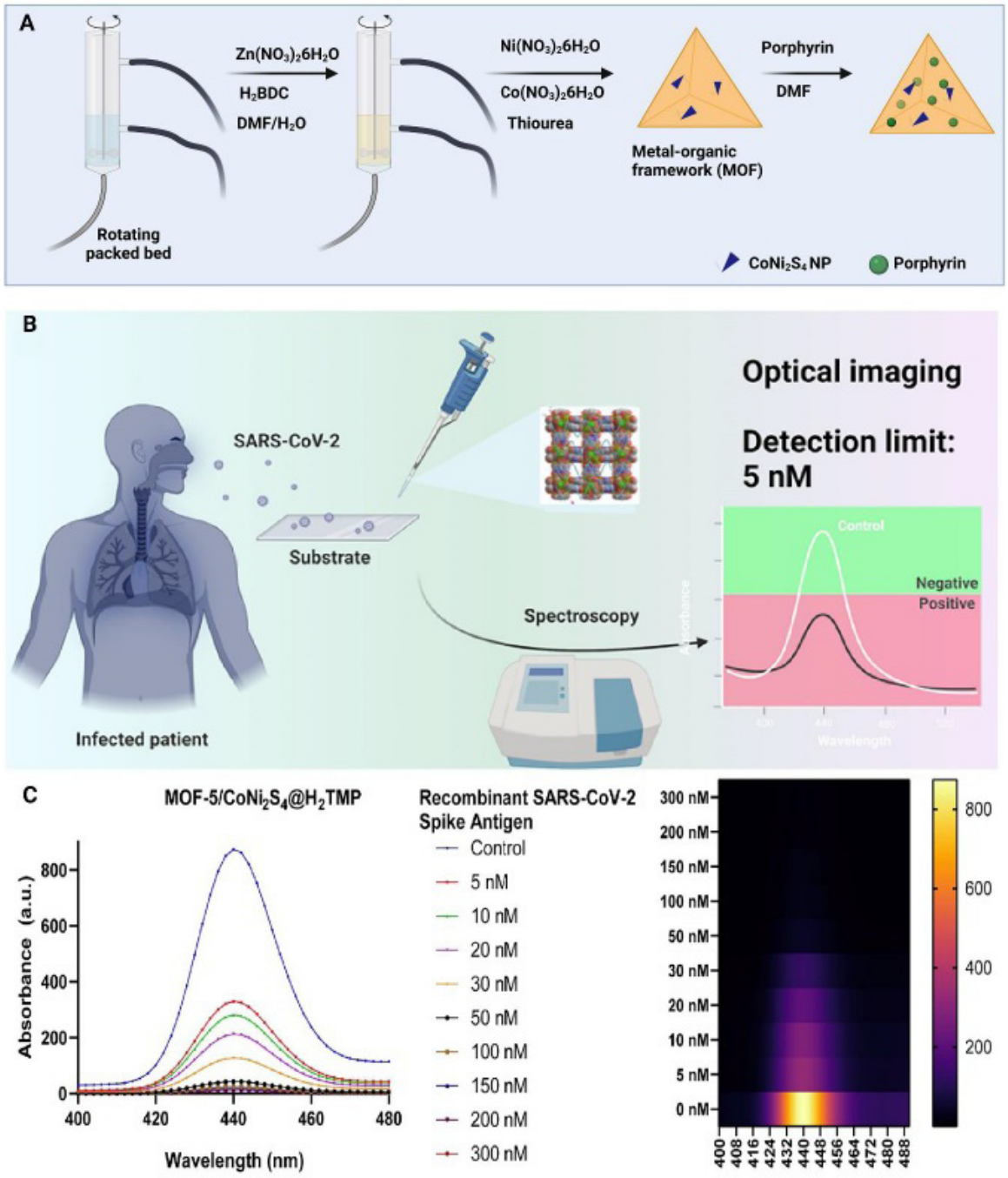

Figure 7. **(A)** Schematic illustration of the one-pot synthesis of MOF-5/CoNi2S4 nanocomposites and nanomaterial fabrication for recombinant SARS-CoV-2 spike antigen assay. **(B)** Schematic representation of MOF-5/$CoNi_2S_4$ nanostructures for optical imaging. **(C)** The fluorescence spectra of the optical probe in the presence of different concentrations of recombinant SARS-CoV-2 spike antigen and the heat map of the changes. Reprinted with permission from [79].

selectivity against SARS-CoV-2 in the presence of other types of respiratory viruses and serum proteins [81].

Among different biosensors, electrochemical biosensors are more sensitive than other biosensors and ideal for detecting specific virus proteins and nucleic acids [82]. A label-free paper-based electrochemical biosensor was fabricated to detect SARS-CoV-2 immunoglobulins without any need to apply an antibody. This new type of biosensor was worked based on the square-wave voltammetry (SWV) method and contained three main parts: closing ePAD, counter ePAD, and working ePAD. Graphene oxide nanosheets were used in the working ePAD of the biosensor and were functionalized with SARS-CoV-2 spike protein. This protein has a receptor-binding domain (SP RBD) that could bind and capture the SARS-CoV-2 antibodies, which exist in actual samples. Fabrication of this immunocomplex led to a decrease in the SWV response. The results of this study showed a fast and high sensitive detection with 0.14 and 0.96 ng/mL detection limit for SARS-CoV-2 IgM and IgG, respectively, and a linear range between 1 to 1000 ng/mL that acted better than other lateral flow immunoassays (**Fig. 8**) [83].

A highly activated graphene-based nanoplatform functionalized by Au nanostar was also used to fabricate a high-speed electrochemical biosensor. This biosensor could detect the monoclonal IgG antibodies produced against the S1 protein of SARS-CoV-2 in real samples. The specificity of this biosensor can be further confirmed by showing a wide detection limit (0.18 × 10−19%V/V) and sensitivity (2.14 μA.%V/V.cm^{-2}) in the

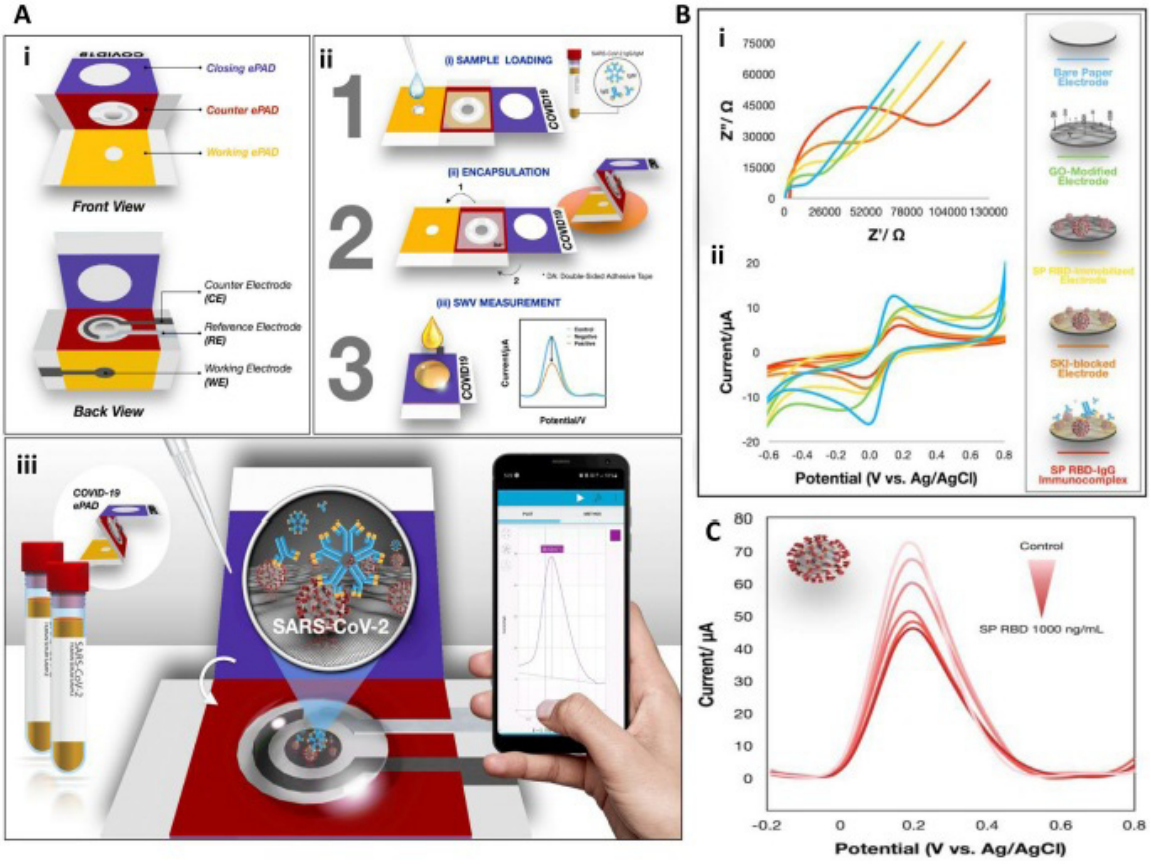

Figure 8. **(A)** Schematic representation of paper-based electrochemical sensor. **(i)** Different parts of the biosensor. **(ii)** The detection process of the biosensor. **(iii)** Working ePAD part of the biosensor. **(B)** Electrochemical impedance spectroscopy (EIS) **(i)** and cyclic voltammetry (CV) **(ii)** results of biosensor after each functionalization. **(C)** The results of SWV response of the biosensor after exposure to the different concentrations of SARS-CoV-2 spike protein. It is reprinted from [83] with permission from Elsevier.

presence of several components and antibodies in blood samples [84].

The combination use of point-of-care diagnostic tests and nanobiosensors leads to introducing novel biosensors with interesting features like high-speed detection, on-site results, reducing the time of action, and prevention of infectious disease transmission. These features not only could facilitate the further treatment, but also reduce the number of probable death and the prevalence of infectious [85]. For instance, graphene oxide nanosheets covered the surface of a double-interdigitated capacitive (DIDC) to fabricate a biosensor for detecting spike (S1) proteins of SARS-CoV-2. Anti-SARS-CoV-2 antibodies were functionalized on the surface of graphene oxides via EDC-NHS functionalizing method. This biosensor could be used as a biochip for the POC monitoring of COVID viruses in with scaling-up ability and portability. It showed a rapid detection with wide range from1.0 mg/mL to 1.0 fg/mL, low detection limit (1 fg/mL), high sensitivity of (1.0 fg/mL), and ideal linearity (18.56 nF/g) [86].

4. Perspective

The COVID-19 pandemic has brought with it self-many challenges, and today more than ever, we require novel therapeutic and diagnostic methods to combat viral diseases efficiently. At the time of writing this article, the Sars-CoV-2 Omicron Variant BA.2 is dominating the world, especially in Europe; a new outbreak is in continuation of that of the predecessor BA.1 Omicron variant, which was identified first in southern Africa in late November. Several laboratory studies on BA.2 suggest its rapid ascent can be attributed to its greater transmissibility over the BA.1. variant. Preliminary studies indicate that the virus can readily overcome immunity from vaccination and previous infection with earlier varieties. Multiple laboratories are working on identifying the differences between BA.1 and BA.2 mutations to overcome this problem. Currently, the most prevalent method for detecting COVID 19 is utilizing the PCR test, which is time-consuming, a little expensive, and may be accompanied by false results. So, it is critical to introduce novel methods that could detect in real-time with high performance and good sensitivity to detect different variants of this virus.

It is believed that nanotechnology may overcome current methods' limitations and provide high-performance detection devices. Also, their capability to functionalize with several materials, especially aptamers and antibodies, could produce highly sensitive biosensors for real-time monitoring of viruses. The other interesting feature about the nanomaterials is their capability to fabricate theranostic platforms simultaneously, with the ability of diagnosis and therapy. This could be a promising approach that could eliminate the detected infection time, which is very important, especially in the case of COVID infection. Indeed, in most cases of COVID, patients have died due to the late detection and treatment, which could be overcome via nanotheranostics materials shortly [87].

Internet of medical things (IoMT) assisted point-of-care testing (POCT) systems are the other technique that could be combined with nanomaterials to prepare artificial intelligent systems that could provide us wireless data about the diagnosis of infections, their propagations, and treatment efficiency. IoMT are computational medicinal devices that could promote the real-time data collections from patients and transfer them to a central database to prepare a large set of databases for each patient [85]. These are worked via smartphones and are the focus of developing the next generation of biosensors that could be used for real-time monitoring of patientsin their homes. The smartphone-based microchips containing nanosensors could fabricate ideal diagnostic agents for rapid and highly sensitive detection of COVID viruses [88]. Data Transfer and Automation (IoT) is another technique that could be used for the POC diagnosis of infection diseases like COVID. It is a rapidly growing technology, including sensors and cyber systems that use the internet and connect different devices (including sensors, electronics, actuators, software, and networks) to keep patients' data updated. This technique, artificial intelligence (AI) technology and nano-based biosensor could provide ideal methods for managing the COVID-19 pandemic via fabricating intelligent healthcare monitoring devices [89].

Nanomaterials could also be used for the prevention of viruses' propagation. Nano-coating filter technology could be a good idea for preventing human-to-human transmission of viruses via removing the viruses in the air

by utilizing nano-enable photoelectrochemical oxidation method (PECO). This technique showed high performance with more than 99% virus trapping and destruction and could be used for future air purification of public places [90].

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