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Smart and emerging nanomaterials-based biosensor for SARS-CoV-2 detection

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a primary cause of the COVID-19 pandemic. To date, various detection approaches are already present, and many other techniques are also being developed for the rapid and real-time detection of COVID-19 infection in the wake of this pandemic. Hence, this featured review will provide an overview of COVID-19, its biomarkers, current diagnostic techniques, and emerging smart nanomaterials-based biosensing approaches; apart from this, it will also extend some light on future perspectives of biosensing technologies for SARS-CoV-2 diagnosis.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a large coronavirus family; currently, the major cause of global pandemic threats to public health, and this virus belongs to the Coronaviridae family [1]. Family Coronaviridae of coronavirus contains a single non-segmented, single-stranded ribonucleic acid (ssRNA) genome of vertebrates. Further, the world health organization (WHO), after detection of rare ribonucleic acid (RNA) sequences of SARS-CoV-2, confirmed that the infection is caused by the SARS-CoV-2 virus [2]. Apart from this, it is well known that the RNA virus can be detected through real-time polymerase chain reaction (RT-PCR) techniques based on nucleic acid amplification test, which possess some very promising characteristics like low detection limits and higher sensitivity, but the major drawback of this technique is its bit longer time for detection, which needs to be figured out for developing rapid diagnostic technique. Further, looking at the current pandemic scenario, researchers have extensively worked on many aspects of the RT-PCR technique to make it highly specific towards the SARS-CoV-2 virus by determining its specific targets [3].

According to current trends in research and development, the latest growth in nanobiotechnology gave rise to excellent diagnostic and therapeutic approaches, and advancements in biosensing techniques due to the utilization of nanomaterials as a matrix for fabricating biosensors provide them higher sensitivity, specificity, and selectivity owing to unique properties of these nanomaterials, namely high adsorption capacity, high surface area, high reactivity, and quantum size, which has drawn much attention towards utilization of nanomaterials for fabricating advanced biosensors. Additionally, the shape and size of nanomaterials can easily be engineered by surface modification or immobilization via covalent and non-covalent bonding with various biological species (enzymes, antibodies, etc.), which in turn help them for biosensing applications as it offers nanomaterials high selectivity, high sensitivity, and lower detection limit towards the sample analytes [4]. Thus, a biosensor fabricated from smart nanomaterial makes the detection simple, effective, real-time, and economical, getting much attention nowadays as a rapid and effective technique for the real-time quantitative and qualitative diagnosis of infectious diseases [5]. Therefore, biosensors have added advantages for identifying RNA-viruses by utilizing aptamer-conjugated nanoparticles (for working mechanism, see Fig. 1), Au-Ag-based nanoparticles, CRISPR-Cas9 based paper strip, and surface plasmon resonance electrochemical biosensors, which serves as an efficient tool for more promising and portable diagnosis of SARS-CoV-2 [6,7]. Hence, this featured review intends to...
highlight the different smart and emerging nanomaterials used to detect SARS-CoV-2. Additionally, current diagnostic strategies, biomarkers, and future perspectives are discussed to illuminate this topic.

2. Biomarkers and current diagnostic strategies

The term “biomarkers,” a portmanteau of “biological markers” refers to objective indications of medical symptoms analyzed from the patient’s outer look, which can be measured with high reproducibility and accuracy, which help to diagnose a patient’s clinical conditions or state without affecting his body [8]. Further, as per pre-existing literature data, it is evident that enormous biomarkers can be employed for SARS-CoV-2 detection, and similarly, many different biomarkers of various viruses, namely the middle east respiratory syndrome (MERS) and influenza virus, are known to have special types of primers and may be fully expressed by RT-PCR assays with high sensitivity towards SARS-CoV-2 detection [9–11]. Moreover, the four structural proteins include, matrix (M), spike (S), nucleocapsid (N), and envelope (E), are used as antigens for the diagnosis of SARS-CoV-2. Several studies reported that assembling the structure of virus M and E proteins plays a crucial role. In contrast, S and N proteins serve as necessary biomarkers that might be used to detect SARS-CoV-2, in which S-proteins play an important role in combining with receptor-binding and host cells domains that interact with angiotensin-converting enzyme 2 (ACE2) receptors [12,13]. However, specific antibodies are also carried out for the SARS-CoV-2 detection over the patient’s serological sample. According to research, the adaptive immune response of the infected patients will develop antibodies naturally to the S proteins, then the process is known as “active immunity.” As binding occurs between antibodies and S protein, the ability of a virus to infect more cells gets neutralized, and the interaction of the virus with ACE2 gets prohibited. Thus, the progression of diseases gets limited. If antibodies develop against the spike proteins, then the process is known as “passive immunity.” S proteins enzyme-linked immunosorbent assay (ELISA) is one of the immunological assays used to measure the antibodies that can help detect the SARS-CoV-2 virus, which can help treat the SARS-CoV-2 infections [14]. Hence, the current biomarkers detection techniques for antibody detection and nucleic acid testing have evolved well, including ELISA and RT-PCR. However, these approaches still undergo some feasible drawbacks like a bit longer time for diagnosis. Therefore, compared to current biomarkers detection techniques, biosensors can serve as alternative tools, as they possess high accuracy, rapid response, enhanced sensitivity, portability, selectivity, non-sophisticated, and offer awareness of infection’s critical trends and severity [15].

3. Smart nanomaterials for biosensing technologies and their consequences

Metal and its oxides, carbon-based nanomaterials, transition metal dichalcogenide, quantum dots, polymer-based nanocomposites, and other nanomaterials are among the latest smart nanomaterials, which are being widely used for biosensing applications for combating against SARS-CoV-2 infection (various nanoparticles for combating against SARS-CoV-2, see Fig. 2) [16]. The unique properties of these nanomaterials and their composites, such as small size, signal generation, quenching, and signal amplification, are significant for biosensors fabrication. Moreover, nanomaterials’ surface, size, and shape equip biosensors with an enhanced limit of detection (LOD), sensitivity, and selectivity. Furthermore, the primary mechanism of biosensors fabricated from nano-based materials for advanced POCT (point of care tests) diagnostic techniques to detect the SARS-CoV-2 virus is demonstrated in Fig. 3, proving nanomaterials can play a vital role for biosensing application for SARS-CoV-2 detection.

3.1. Metal and its oxides-based nanoparticles

Among the different types of metal nanoparticles, the biosensing of virus infections is majorly done by the gold nanoparticles [1]. They show excellent biocompatibility and enhanced loading capacity of bioanalyte and electrocatalytic properties [2]. Moreover, significant work was done using the gold nanoparticles to detect human samples, which detected the antigen within 30 min and the obtained results were in complete agreement with WHO guidelines [3]. Another work reported by Chen et al. using polystyrene nanoparticles doped with lanthanide to detect the anti-SARS-CoV-2 IgG in human serum gave very rapid detection within 10 min; the proposed mechanism of diagnosis obtained results were comparable to the results obtained from the RT-PCR technique, making it a validated method for a clinical purpose [4].

Similarly, different metal oxides are used to detect various analytes by the fabrication of sensors and biosensors. Further, silicon (Si) and indium oxide-based nanowires are used as novel biosensing tools due to broadening the scope of detection compared to more simple optical methods, possibly due to wide bandgap [2]. Rashed et al. reported the fabrication of resistive immunosensors for SARS-CoV-2 antibody using gold (Au)-based electrodes, as Au nanoparticles are a safe choice and, when combined with various detection platforms, according to the need for analysis by utilizing as electrochemical sensors or biosensors, they are highly selective, specific, and sensitive. However, the efficiency of sensors gets affected not only by the properties of the substrate but also by the reproducibility of the deposited layer [5]. Similarly, Bajo et al. analyzed the Au chip-based sensor by manipulating the unique properties of Si substrate, functioning in three different operating modes a sensor temperature, an electrical heater, and an electrochemical sensor for nucleic acids detection [7].

3.2. Graphene and its derivatives

Graphene is an excellent nanomaterial and shows properties like

Fig. 1. The basic working mechanism of bio-nanogate bifunctional aptamer-based biosensors for SARS-CoV-2 diagnosis (reproduced with permission from V. Chaudhary et al., Nanotechnol. Environ. Eng. 6 (2021) 8 [6]).
thermally conductive, chemical stability, strength, flexibility, etc. It also provides good support for immobilizing ligands due to modifiable functional groups in its 2D plane [89]. Seo et al. fabricated a FET-based biosensor using a coating of graphene sheet for detection using specific antibodies [13].

Similarly, another study based on field-effect Au-decorated graphene nanosensors is developed to quickly identify the SARS-CoV-2 virus using clinical throat swab samples [14]. Zhang et al. fabricated an immuno-sensor using the combination of graphene-FET with antigen–antibody interaction that can give real-time detection by interacting with SARS-CoV-2 spike protein [17]. Further, it has been investigated from the current research that graphene and its derivatives are identified as essential materials because of their high conductivity and good biocompatibility, which makes them a better candidate for advanced biosensing applications for POCT [15].

3.3. Carbon nanotubes-based nanomaterials

Carbon nanotubes (CNTs) are rolled cylindrical structures made from graphene sheets with few nanometers; they show outstanding mechanical, electronic, and thermal properties [16,17][18], making them a suitable choice for the development of biosensors [19]. L. Pinals et al. developed a rapid identification system using a near-infrared mechanism by utilizing CNTs to detect the SARS-CoV-2 spike protein [20]. Another work by Aasi et al. evaluated single-walled CNTs decorated with metals for adsorption of H$_2$O$_2$ for designing inhibition surfaces to inactivate virus [21]. Additionally, due to the metallic properties exhibited by CNTs, the CNT-based sensors demonstrate excellent potential for overcoming the drawbacks of carrier migration in graphene-based sensors. Furthermore, the incorporation of metallic nanoparticles or small aromatic molecules (by covalent functionalization) in CNT-based sensors helps to enhance the stability and reproducibility of sensors [22].
3.4. Transition metal dichalcogenides based nanomaterials

Transition metal dichalcogenides (TMDCs) are known for their promising optical, electronic, mechanical, and magnetic properties [23]. Recently they are emerging as excellent materials for biosensing due to the large bandgaps and better signal strength. Among the family of TMDCs, such as molybdenum diselenide (MoSe₂), molybdenum disulfide (MoS₂), tungsten diselenide (WSe₂), and tungsten disulfide (WS₂); MoS₂ give unique properties, such as fast electron transfer rate, superior conductivity, and feasibility. They play a role in diverse applications, as it owns biocompatibility and stability [24]. One study based on the use of FET-based TMDC WSe₂ acted as a promising biosensor for the ultra-fast in-vitro detection of SARS-CoV-2. Thus, a combination of efficient fabrication methods with the unique properties of MoS₂ provides exciting opportunities for multiple applications in electronic, optical, and electrochemical biosensors [25].

3.5. Quantum dots-based nanomaterials

Quantum dots are tiny semiconductor nanocrystals and can convert light spectrum into various colors. They show excellent fluorescence, quantum confinement, and tunable band energy. The size of quantum dots ranges from 1 to 10 nm compared with tunable plasmonic nanoparticles (10–300 nm). Hence, for molecular imaging quantum dots are proved as a novel fluorescent probe because quantum dots have received great attention for fighting against viral infection [26]. Further, Loczchin et al. investigated carbon-based quantum dots and identified them as an efficient virus-inactivation agent, with 50% efficiency [27]. Another research showed that the graphitic carbon nitride-cadmium sulphide quantum dot nanocomposites could determine coronavirus 2 receptor-binding domain [28]. Moreover, carbon-quantum dots have also proved to be predominant imaging probes (chemosensors and biosensors) for detecting microbes and viral molecules. Additionally, they can be used to label the virus’s envelope, and novel fluorescent-based quantum dots may assist in developing several advanced diagnostic methods [29].

3.6. Polymer-based nanomaterials

Polymer-based nanomaterials are widely used for infectious disease diagnosis, and it’s still evolving with time in the field of diagnostics. In the field of label-free sensing, molecularly imprinted polymers (MIPs) have gained much attention. MIPs are synthetic receptors synthesized with molecular recognition cavities complementary to the target molecule. They are ultra-sensitive because of selectivity, thermal and mechanical stability, and electrical properties. According to the previous research reports, it was found that MIPs have been used to detect many types of viruses such as influenza virus, human immunodeficiency virus, hepatitis virus A and B, adenovirus, picornavirus, and dengue virus, etc. [30]. For example, Raziq et al. developed the first-time electrochemical sensor to detect SARS-CoV-2 nucleoprotein from nasopharyngeal samples of COVID patients with an 11fM LOD; the advantage of this diagnosis technique is its speed of the process of detection along with detecting vital biomarkers [31]. Thus, the MIPs based sensors are the future of upcoming sensor technology, as these sensors will be cost-effective, environmental-friendly, rapid, sensitive, selective, and specific.

3.7. Nanomaterial-based screen printed electrode

To enhance electroanalytical performances and sensitivity, screen-printed electrodes (SPE) are easily modified with nanomaterials, such as graphene, carbon black, and Au nanoparticles. According to research, screen-printed graphene electrodes (SPGE) show superior electrochemical properties because of a higher electron transfer rate and a larger electrochemical surface area than other electrode-based materials [32]. Further, a carbon-based three-electrode biosensor was developed to detect the SARS-CoV-2 virus [33]. In another study, Au nanoparticle-based biosensing was done using SARS-CoV-2 monoclonal antibodies on the screen-printed electrodes to detect the SARS-CoV-2 virus from human saliva samples, and the obtained results from the device demonstrated LOD of 90fM and 10–30 s response time [34]. Further, another work was also conducted in which the paper substrates were used for detecting the SARS-CoV-2 virus from the nasopharyngeal fluid samples, and it represented a LOD of 0.25 fg/ml. [35].

4. Conclusion and prospects

Nowadays, smart and emerging nano-based materials play a crucial role in biomedical sciences, owing to the unique properties of nanomaterials, such as the high adsorption capacity, high surface area, and high reactivity. This featured review attempts to explore the various biomarkers, indicators for SARS-CoV-2 detection, and smart nanomaterials for biosensing technologies and their consequences. Moreover, this work will also give a gist of the biological properties of SARS-CoV-2 that will enable researchers to develop novel diagnostic strategies to combat this pandemic and upcoming pandemics due to other mutating viruses/bacteria/fungus. This review is one of a kind, mainly focusing upon smart and emerging nanomaterials as biosensors for detecting SARS-CoV-2. Herein this work, we have also discussed the use of current biomarkers and indicators of the SARS-CoV-2 virus. However, from the established studies, it has been reported that, for the early and rapid diagnosis of SARS-CoV-2 infection, biosensors can serve as an analytical and powerful device that will offer more awareness of critical trends and conditions severity. Thus, this review will, in detail, provides an up-to-date literature review of smart and emerging nanomaterials as a biosensor in SARS-CoV-2 detection during this prevailing pandemic.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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