



Innovative Nanotechnology a Boon for Fight Against Pandemic COVID–19

Ibrahim Aminu Shehu^{1*}, *Nura Mustapha Auwal*¹, *Muhammad Kabir Musa*²,
*Abubakar Mukhtar*¹, *Mashahudu Sha'arani Yusuf*¹, *Anees Ashir Yau*¹, *Murtala Muhammad*¹,
*Yusuf Baba Dala*¹, *Salisu Abdullahi Sani*¹, *Mahmoud Seed Ahmad*¹ and *Mojahidul Islam*¹

¹Sharda University, Noida, India, ²Ahmadu Bello University, Zaria, Nigeria

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*Correspondence:

Ibrahim Aminu Shehu
ibrahimaminushehu@gmail.com

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COVID – 19 is a contagious disease caused by severe acute respiratory syndrome (SARS-CoV2). The rate at which COVID – 19-virus spread from epidemic to pandemic within a short period is quite alarming. As of July 2020, the Dashboard of the World Health Organization (WHO) recorded over 15 million COVID – 19 cases across 213 countries, with mortality of over 620,000. The governments and healthcare agencies responsible for mitigating the virus's spread have adopted several strategies to end the pandemic. However, all hands were on deck to establish the standard treatment modalities of SARS-CoV-2 through inventing new drugs, vaccine candidates, or repurposing the existing medicines and robust diagnostic tools, in addition to other technological innovations. Therefore, nanotechnology's employment would play a vital role in bringing multidisciplinary ways of developing affordable, reliable, and powerful tools for diagnosis, in addition to personal protection and effective medicines. Additionally, nanosensors' application would significantly aid the diagnoses of the COVID–19 even on asymptomatic patients, and thus would be an essential means for determining its prevalence. Likewise, nanoscale fibers can optimize personal equipment protection and allow their reusability for medical and economic benefits. Accordingly, the literature was intensively reviewed by searching for the combinations of the research keywords in the official scientific databases such as Science Direct, PubMed, and Google Scholar. Hence, this research highlighted the perspective contributions of nanotechnology in the war against the COVID-19 pandemic.

Keywords: COVID-19, diagnosis, nanoparticles, nanomaterials, vaccines, nanomedicines

INTRODUCTION

June Almeda first identified the coronavirus family in 1963 while working at the Ontario Cancer Institute in Toronto, Canada. The Scottish scientist saw some greenish dots embedded in a spike-like structure under an electron microscope called corona in the Latin term, which means crown in English (History and Culture, 2020). Viruses have been characterized by their pathogenicity and rapid transmission from zoonotic to human beings, which has caused a wide range of diseases. However, it was not confirmed whether or not the virus was zoonotic (Shereen et al., 2020). Severe Acute Respiratory Syndrome (SARS-CoV) was the first outbreak of coronavirus in Spain in 2003 (Xie and Chen, 2020). While the Middle East Respiratory Syndrome (MERS) was the second pandemic that broke out in Saudi Arabia in 2012. Where it causes a serious range of illnesses in the Middle East part of Asia (Cao et al., 2020). Recently, the outbreak of the COVID-19 pandemic in China's Wuhan market in December 2019 was first diagnosed as a pneumonia of unknown etiology (Biomedical and

Pharmaceutical Sciences, 2020). However, the genomic sequence investigation revealed its 80% genetic resemblance to SARS-CoV. Consequently, the “International Committee on Taxonomy of Viruses” (ICVT) named it SARS-CoV-2 (Siordia, 2020). Moreover, COVID-19 identified as a single-stranded RNA virus with an oval like shape and enveloped within a crown-like structure of 60–140 nm in diameter (Woo et al., 2009; Walls et al., 2020).

At present, the actual mechanism through which COVID-19 transmit is under investigation (Majumdar et al., 2020). However, Liu J et al. reported the transmission from person to person by direct body contact or droplet nucleus (aerosols) of the infected person. Indirect transmission by contact with contaminated surfaces is possible under certain conditions. Similarly, the possibility of fecal-oral infection was evident following the detection of COVID-19 in fecal swabs of both positively and negatively testes people (Zhang et al., 2020a; Chan et al., 2020; Liu et al., 2020; Xiao et al., 2020). Perhaps, some reports have suggested that respiratory droplets are the primary sources of transmission; in this instance, even asymptomatic patients could be able to transmit the COVID-19 virus without their consent. The droplet size may alter the means of the viral spread; the droplets of 20 μm and more might be influenced by gravity, making it falls to the objects. While the smaller ones that have a diameter of less than 5–10 μm may evaporate to air and suspend for more than 12 h, potentiating the possibility of airborne transmission (Ge et al., 2020; WHO, 2020). Therefore, Jayaweera M et al., reported that the infected person’s coughs or sneezes could transmit airborne particles to a distance of more than 20 feet (Bahl et al., 2020; Jayaweera et al., 2020; Yen et al., 2020).

Currently, the treatment of COVID-19 remains challenging in a global healthcare setting (Rojas et al., 2020).

Moreover, scientists have been working around the clock to develop either novel or repurpose drugs and vaccines that could treat the virus entirely or provide prophylaxis against it (Zhang et al., 2020b) since there are no approved clinical protocols and vaccines or medications to treat the infection (Wu et al., 2020). Therefore, establishing a reliable assay that can accurately diagnose SARS-CoV-2 in a suspected sample within a short period is equally needed (Ozma et al., 2020). World Health Organization (WHO) recommended the international community to be conducting a wide-range of COVID-19 diagnostic tests to reduce the number of undetected cases (WHO, 2011). However, setting up the proper testing protocol of COVID-19 is essential for better understand the disease, its prevalence, and preventive measures (Joshi and Bhansali, 2008; Dicker et al., 2018). In this challenging time, nanotechnology’s employment can significantly open pipelines that will provide a breakthrough in the diagnosis, mitigation, prevention, and management of SARS-CoV-2 infection (Sivasankarapillai et al., 2020). According to the available literature, nano-formulations of various metallic and metallic oxides have been used to inactivate and prevent the transmission of different virus species (Li et al., 2015). Nowadays, Synthetic nanofibres are used to make reusable facemasks and Personal Protective Equipment PPE with the highest protection affinity (Moin, 2020). Besides, several rapid

diagnostic tests of high precision and accuracy have been developed using different nanomaterials to detect viral presence within a few minutes (Zainol Rashid et al., 2020). Also, theranostic NPs and optical biosensors can reliably trace the viral genome present at a minute in the sample. Similarly, nano-bio-interaction can serve as a powerful tool to elucidate the viral life cycle in the host cell, facilitating the identification of new molecules that could interfere with vital viral targets (Morse et al., 2020). Researchers have developed small and ultra-sensitive single nanowire biosensors that have gained much attention due to their ultra-sensitive efficacy in pathogen detection (Joshi and Bhansali, 2008). Silver-based nanoparticles (AgNPs) have several biomedical applications ranging from drug delivery optimization to low toxicity antimicrobial properties (Naqvi et al., 2013; Burduşel et al., 2018). Therefore, the concept of nanotechnology can serve as an alternative way to adopt in the global fight against the COVID-19 pandemic (Kim et al., 2020a). However, more research is needed on nanotechnology to explore its full potentiality in fighting the virus. This research highlighted the significant contributions of nanotechnology in preventing, diagnosing, and treating the pandemic COVID-19 infection.

Cellular Bio-Interaction of SARS-COV-2

All coronaviruses contain a specific region in ORF1 downstream that encodes viral replication, spikes formation, and nucleocapsid. These spikes-glycoprotein located at the outer part of the virus are responsible for the virus’s attachment with the host’s cells (Yan et al., 2020). It also contains a receptor-binding domain (RBD), which acts as a binding pocket that enables the virus to bind to several sections at a time. Other coronaviruses are recognized and bind to carbohydrates or aminopeptidases as a critical receptor for entry into the human body, while SARS-CoV-2 binds to ACE2 with the help of exopeptidases, which catalyzes the reaction (Baig et al., 2020). However, the mechanism depends on the cellular proteases like human airway trypsin-like protease (HAT), transmembrane protease serine 2 (TMPRSS2), and cathepsins. The SARS-CoV-2-spike protein exhibits van der Waals force of attraction with the RBD and the lysine residue of angiotensin-converting enzyme ACE-2 recognizes the glutamate residue in the host’s RBD region (ACE-2) (Tahir ul Qamar et al., 2020). The life cycle begins when the Spike protein of the virus binds to the cellular receptor of ACE2 (Devaux et al., 2020). A conformational change occurs, which facilitates viral fusion with the cell membrane through the endosomal pathway. The virus releases RNA into the host’s cell and then translated it into the viral replicas pyrophosphatase (inorganic)-1a (pp1a) and pyrophosphatase (inorganic)-1b (pp1b), which cleaved into tiny pieces by viral proteinases (Elfiky, 2020). The enzyme polymerase produces a series of subgenomic and mRNA discontinuous transcription and then finally translated into relevant viral protein. The proteins are assembled into the Golgi apparatus’s virions and endoplasmic reticulum. The replicated viruses were then transported into vesicles and subsequently released out of the

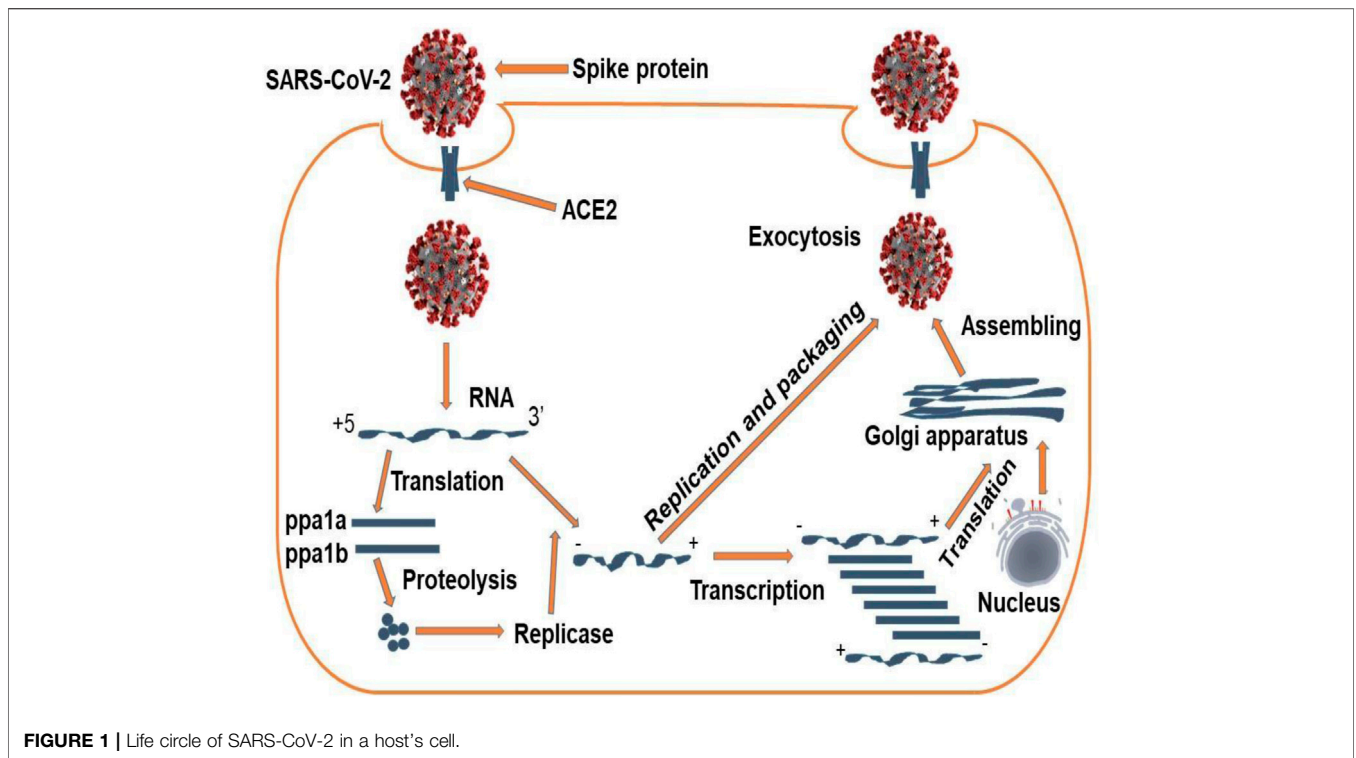


FIGURE 1 | Life circle of SARS-CoV-2 in a host's cell.

TABLE 1 | Illustration of antiviral nanoparticles that inactivate different types of Viruses.

| Composition | Shape | Size (nm) | Coating | Virus | References |
|----------------|-----------------------------|------------------------|---|---|---|
| AgNPs | Spheroid | 2.08 | BSA | HIV-1 | Lara et al. (2010) |
| | Spheroid | 25, 55, 80 | Chitosan | Monkeypox | Rogers et al. (2008) |
| | Not available | 10, 15 | Not available | Hepatitis | Chen et al. (2013) |
| | Spheroid | 10, 25 | Polysaccharide | Tacaribe | Speshock et al. (2010), Xiang et al. (2013) |
| | Spheroid | 35 | PVP | RVFV | Borrego et al. (2016) |
| | Spheroid | 9.5 | Organic | H3N2 | Xiang et al. (2013) |
| | Spheroid | 3.5, 12.9 | Chitosan | H1N1 | Chen et al. (2016a) |
| | Spheroid | 5–25 | Graphene oxide | Coronavirus | Lin et al. (2017a) |
| | Branched chitosan structure | 21.2 ± 1.3, 2.2 to 3.6 | Polyethylenimide Hybrid of chitosan-polyarginin | H1N1 influenza Influenza A | Petrova-Brodskaya et al. (2017) |
| | TiO2 NPs | Poly-shape | 52.9 | - | H9N2 |
| C. Fullerene | - | Not available | - | H1N1 | Ji et al. (2008) |
| Peptide-NPs | Dendritic | 2.4 and 29.8 | - | Influenza A | Zhao et al. (2016) |
| Ivermectin-NPs | Spheroid | 60–140 | IVM | Zika | Ketkar et al. (2019) |
| FeONPs | Spherical | 9, 12, and 32 | - | Antimicrobial agent | Santoshi et al. (2015) |
| (CuONPs | Crystalline | 1 to 25 | CuONPs-coated cotton fabric | Inhibit replication of HIV-1 and herpes simplex Virus | Ishida (2018), Sathiyavimal et al. (2018) |

cell. (Dhama et al., 2020; Yan et al., 2020). The schematic illustration of this mechanism has been summarized in **Figure 1**.

APPLICATIONS OF NANOTECHNOLOGY FOR THERAPY AND DIAGNOSIS OF COVID - 19

Nanotechnology is a powerful weapon for mitigating the fatality and mortality of coronaviruses (Zhou et al., 2020). It could exert

its applicability both externally and internally of the host body. Many evidence-based studies have previously proved the antiviral effectiveness of many forms of nanotechnology-based formulations, especially on the respiratory tract and Human Immunodeficiency Virus (HIV) infections (Jackman et al., 2016; Yadavalli and Shukla, 2017). Nanotechnology and nanomaterials have been widely explored as diagnostic and therapeutic agents in managing infectious diseases and could be applied to COVID-19 treatment (Adesina and Akala, 2015). The application of nanotechnology in diagnosing, mitigating, and

managing many SARS-CoV-2 related viruses has been summarized in **Table 1**.

Plasmonic Photothermal Effect on COVID-19

Ag and AuNPs or nanotubes have been reported to induce a “Plasmonic photothermal effect” that could be achieved by subjecting metals to intense solar irradiation, which makes them emit light capable of viral inactivation at an optimum wavelength (Govorov and Richardson, 2007). The AuNPs are preferable to be used as a Plasmonic photothermal in-activator because of their lesser toxicity than AgNPs (Loeb et al., 2018). However, the concept of “Pulsed-laser irradiation systems” was found to have shown the desirable selectivity in viral inactivation. Loeb et al. demonstrated the case study that examined photonic gold nanorods’ effectiveness in “Murine Leukemia Virus” inactivation by striking the 250 μ L viral sample with 805 nm fs pulses at the energy of 7.5 mJ at a repeated rate of 1 KHz for 10 s under the temperature of 22°C. The result showed that photonic gold nanotubes significantly reduced viral infectivity to less than 3.7-log, reducing the virus’s selectivity with high precision by inducing no effect on co-inoculated antibodies (Nazari et al., 2017).

Nano-Biosensors and Their Applications in COVID-19 Diagnosis

The proper diagnosis is critical in tackling COVID-19 pandemics infection (Zhuang et al., 2020). The vigorous testing operations of approximately 20,000 people run daily in some countries, including South Korea conduct (Morales-Narváez and Dincer, 2020). While the German laboratories run about 400,000 coronavirus tests every week (Richardson et al., 2020). This comprehensive testing possibly attributes to their emergence among the most prosperous countries that record the lowest COVID-19 mortality rate worldwide (Hussain et al., 2020). However, the biosensor device is the technology behind this massive testing ability. Moreover, understanding the sensing mechanism in nano-dimensions is essential in developing efficient biosensors (Das et al., 2016). Biosensors have currently been employed to analyze the microorganism’s biological structure or detect biomolecules present at a minimum concentration in the sample (Polizzi, 2019). These biosensors are made up of three components, namely (A) a “sensing bioreceptor” (signal producer) (B) “signal transducer,” and (C) a “reader device” (Li et al., 2020a; Aminu Shehu and Mukhtar, 2020). Perhaps, among the latest biosensing diagnostic devices, a field-effect transistor (FET)-based biosensor offers many benefits. Including the ability to conduct extremely responsive and rapid tests using small amounts of analyses (Li et al., 2020a), and it became beneficial for medical diagnosis (Hsiao et al., 2009). Nevertheless, graphene shows the extraordinary properties of having a wider 3-D area, high carrier mobility, and electronic conductivity (Cooper et al., 2012) that make it a suitable means for various sensing platforms (Geim and Novoselov, 2007). However, Graphene-based (FET) biosensors can detect minute changes in the environment and create an ideal sensing atmosphere for ultra-

sensitivity. Therefore, graphene-based FET-technology is very appealing for sensitive immunological diagnostic applications (Lei et al., 2017; Zhou et al., 2017). The surface receptors of biosensors are similar to the specific RNA sequence of COVID-19, making it easier for the biosensors to recognize the presence of SARS-CoV-2 in the suspected sample. (Seo et al., 2020; Aminu Shehu and Mukhtar, 2020) As a result of the inconvenience associated with the real-time polymerase chain reaction (RT-PCR) assay, this includes the possibility of a false result. Scientists have conducted several studies to find the right alternatives, among others; Swiss scientists have developed a “dual-functional plasmon biosensor” that works by applying two-dimensional (2-D) gold nanoislands (AuNIs) and plasmonic photothermal (PPT) effects. The sensor detects COVID-19 at a low concentration (0.22 pM) in the suspected sample (Singh, 2014; Nguyen and Sim, 2015). However, the sensor recognizes the SARS-CoV-2 RNA in high precision by measuring the refractive index’s change because of the interaction between the SARS-CoV-2-RNA and the DNA receptors incorporated in gold nanoislands of the biosensors, following the temperature changes due to the plasmonic photothermal effect (American Chemical Society, 2020; Qiu et al., 2020). Besides, J. Wang et al. have shown that SARS-CoV-2 can be detected precisely and quickly using a dual-functional Plasmon system. Therefore, the “localized surface Plasmon Resonance” (LSPR)-based biosensors could be a reliable tool for COVID-19 diagnostics. The researcher also demonstrated that SARS-CoV-2 could be detected precisely and quickly using a dual-functional Plasmon system. Therefore, the “localized surface Plasmon Resonance” (LSPR)-based biosensors could be a reliable tool for COVID-19 diagnostics (Jin et al., 2020a). Moreover, attention has been paid to paper-based biosensors’ point of-care testing’ in “point-of-care testing” because of their cheapness, practicality, and excellent biopharmaceutical properties compared to chip-based biosensors (Hu et al., 2017; Böhm et al., 2018; Choi et al., 2019). However, V.X. Ting et al. have developed a Gold NPs based biosensor for rapid detection of COVID-19; the biosensor uses colorimetric techniques and enables the detection of SARS-CoV-2 nucleic acid present at a minute (100 fM) in a particular sample within 5 min (Aldewachi et al., 2018; Zhao et al., 2020a). S.A. Layqah, et al. designed the Au-NP immunosensor to detect COVID-19, and the biosensor was found to have used the spike protein as a biomarker. The biosensor was shown to accurately identify the COVID-19 in less than 20 min (Layqah and Eissa, 2019). Graphene oxide nanoparticles (GO-NPs) have been determined to inhibit the cellular entrance of COVID-19 by blocking the viral spike protein (Ahmed et al., 2020a). Some studies have shown the inhibitory effect of silver-graphene nanoparticles against SARS-CoV-2 (Weiss et al., 2020). against the virus COVID-19 (Lin et al., 2019; Choi, 2020). As summarized in **Table 2** and **Figure 2**.

COVID-19 Rapid Testing Using Different Nanoparticles

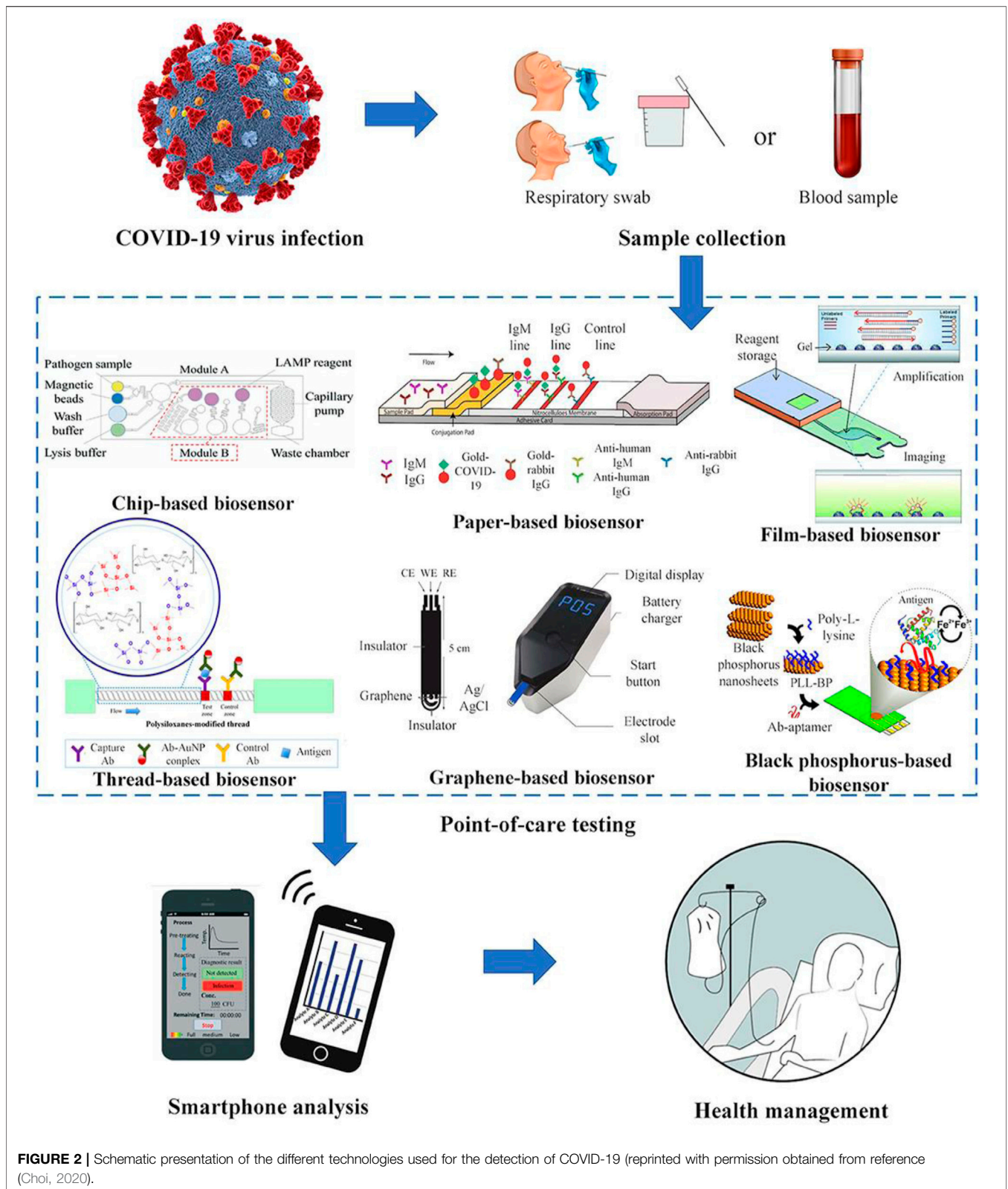
Real-time polymerase chain reaction (RT-PCR) is the conventional procedure for laboratory diagnosis of COVID-19, as per the WHO guidelines (Jin et al., 2020b). This approach does

TABLE 2 | Summarized the application of various nanomaterial in the sensing system of SARS-CoV and other related viruses.

| Biosensors | Nanomaterial | Viruses | Mechanism for detection | Limitations | References |
|--|--|---|---|---|---|
| Electrochemical bio/ immunosensor | Au/Ag nanoparticle | Influenza a virus M1 parainfluenza Rhinovirus the middle east respiratory syndrome (MERS) SARS-CoV-2 | To determine the variation of electrical conductivity by detecting the virus in the saliva sample | Large-scale availability and it require technical know-how | Mizuta et al. (2016), Zhang et al. (2018), Liu et al. (2019) |
| Optical Bio/ Immunosensor | Gold nanoparticles Au NPs | SARS-CoV; H5N1 influenza virus; Human Adenovirus; Respiratory Syncytial virus (RSV); influenza | Optical Immunosensor uses the transduction of the light signal to recognize the analytic sample | The devices are expensive. The fluorescent signal gets weak quickly — | Chen and Yin (2014), Pereira et al. (2014), Sharifi et al. (2019) — |
| Thermal biosensor | Quantum dots/Au nanoparticles | SARS-CoV, MERS SARS-CoV-2 | To measure the heat energy released or absorbed from a given sample | The biomolecule turned into a colloid, then to nanocrystal's | Campuzano et al. (2019), Faria and Zucolotto (2019), Choi et al. (2020) |
| Piezoelectric immunosensor | Gold nanoparticles (AuNPs) | SARS-CoV, influenza Virus; adenovirus; Rsv; MERS MERS | Based on sound vibration called acoustics biosensor | It is challenging to determine the substance in a given solution | Wu (2007), Raghav and Srivastava (2016), Suresh et al. (2018) |
| Plasmonic | Gold nanoparticles (AuNPs)/carbon nanotube | COVID-19 | To detect the nucleocapsid (N) protein in the saliva sample, an essential protein of the COVID-19 | It requires substantial financial support, BSLIII laboratory infrastructure, and industrial partner | Murugan et al. (2020) |
| Fiber-optic Absorbance Biosensor (P-FAB) | — | — | — | — | — |
| Colorimetric paper-based biosensor | Gold nanoparticles (AuNPs) | MERS SARS-CoV, SARS-CoV-2 | To convert signals from pathogen to produce an amplified colorimetric readout | The presence of low sensitivity, instability in the environment, and high cost of production | Yusuf et al. (2020) |
| Chip-based biosensors | Gold nanoparticles (AuNPs) | SARS-COV-2 | Based on nucleic acid detection by the colorimetric signal of loop-mediated isothermal amplification (LAMP) | It has a complicated fabrication process. It requires highly skilled personnel. There is a lack of quantification | Tymm et al. (2020), Jin et al. (2020b) |

not offer solutions to nonsuit ability for on-site detection and procedure for the Isolation of lengthy nucleic acids. In addition to this, a fake-negative report is also unavoidable due to many factors, like faulty reagents, inaccurate sampling techniques, as well as the lower sampling viral load (Li et al., 2020b). Scientists have currently developed a novel COVID-19 testing protocols that can visually detect coronavirus presence within a period of 10 min (Balfour, 2020). However, some researchers from the University Of Maryland, School of Medicine (UMSOM), United States, analyzed the samples obtained from the suspected patient's nasal swab and saliva, using a highly sensitive molecule incorporated with gold nanoparticles (AuNPs) to detect the COVID-19 viral RNA. On examination, the samples that contained the viral antigen reacted with gold nanoparticles (AuNPs) and changed the color of the liquid reagent from purple to dark blue, while the negative viral-antigen samples retain their purple colors (Balfour, 2020). In addition, these visual color changes could be the simplest means of COVID-19 detection, just as they were used in the diagnosis of HIV, influenza viruses et al. Similarly, the reaction complex that occurs between AuNPs-coupled

antibodies and the enzyme-linked immunosorbent assay (ELISA) in the presence of viral antigen results in a visual color change from red to blue, and could therefore be a promising alternative for coronavirus 2019 detection (Lagier et al., 2020). Chao Huang et al. performed a rapid diagnostic test using colloidal gold nanoparticle-based lateral-flow "AuNP-LF" strips. They have tested the samples of both positive and negative COVID - 19 and compared the results with the conventional diagnostic approach of real-time polymerase chain reaction (RT-PCR) (Huang et al., 2020a). The study concluded that a colloidal gold nanoparticle-based lateral-flow (AuNP-LF) assay had owned an excellent IgM detection property from a minute sample quantity (10–20 µL) shows high specificity to COVID -19 detection within a short period of about 15 min (Huang et al., 2020a). Moreover, the techniques became a breakthrough for longer diagnostic procedures and being simple, easy to handle, and reliable to confirm the presence of SARS-CoV-2 (Huang et al., 2020a). Meanwhile, J. Ying et al., have demonstrated an immuno-chromatographic assay using AuNPs of varying sizes (14, 16, 35, and 38) nm, and assess their conjugation affinities to antibodies under different



environmental PH. In conclusion, the author discovered that the size of AuNPs, optimum PH, and antibody concentration in the sample are the factors that determine the effectiveness of the

diagnosis (Lou et al., 2012). Therefore, desirable antibody-labeled-AuNPs could serve as a standpoint for the clinical diagnosis of COVID-19. Nevertheless, the South Korean

TABLE 3 | Nanotechnology-based vaccines.

| Sponsor | Vaccine | Description | Stage | Ct number | Expected date of completion | References |
|--|------------------------------------|--|------------------------|--------------------------------------|-----------------------------|---|
| Modern, national institutes of health | mRNA-1273 | mRNA encapsulated in lipid NPs, the trial was conducted on 18–55 years healthy volunteers for 63 days | Phase 1 | NCT04283461 | April 16, 2020 | Amanat and Krammer (2020), Moderna (2020b) |
| Pfizer/BioNTech and CureVac | INO-4800 | A randomized clinical study involved 3 age groups (65–85, 18 to 55 and 18–85 years of age) conducted in 3 stages, each consist of 15 participants in which the vaccine administered in low moderate and high doses, respectively | Phase I/II trials | NCT04368728, NCT04380701 | Jan. 23, 2023 | Ahmed et al. (2020b) |
| The university of oxford and AstraZeneca | ChAdOx1 | ChAdOx1 has been administered to 6 rhesus macaques exposed to heavy doses of COVID-19. The chimpanzee adenovirus vector vaccine is dependent on the vaccine. The vaccine should not be used infection avoidance, even if it decreased the severity of the diseases | Phase I clinical trial | NCT04324606 | April 2020 | Author Anonymous (2017), Novavax (2020) |
| CanSino biological inc. and Beijing institute of biotechnology | Ad5-nCoV | “mRNA-1273” produced antibody titers more than the levels observed in convalescent once, in every 8 initial participants between the 25–100 µg dose cohorts of the phase I trial | Phase I/II trials | NCT04398147, NCT04341389, NCT0431312 | May 18, 2020 | U. S. National Library of Medicine, (2020b) |
| | ChiCTR2000031809, ChiCTR2000032459 | | | NCT04383574, NCT04352608 | | |

(Continued on following page)

TABLE 3 | (Continued) Nanotechnology-based vaccines.

| Sponsor | Vaccine | Description | Stage | Ct number | Expected date of completion | References |
|---|---------|---|------------|-----------|-----------------------------|-----------------------------------|
| China national pharmaceutical group (sinopharm), in association with the “wuhan institute of biological products” and “beijing institute of biological products | | The latest investigation on live attenuated vaccines provide partial or complete protection in macaques rhesus and now being tested clinical trials | Phase I/II | | April 11, 2020 | Among et al. (2020), Reiss (2020) |

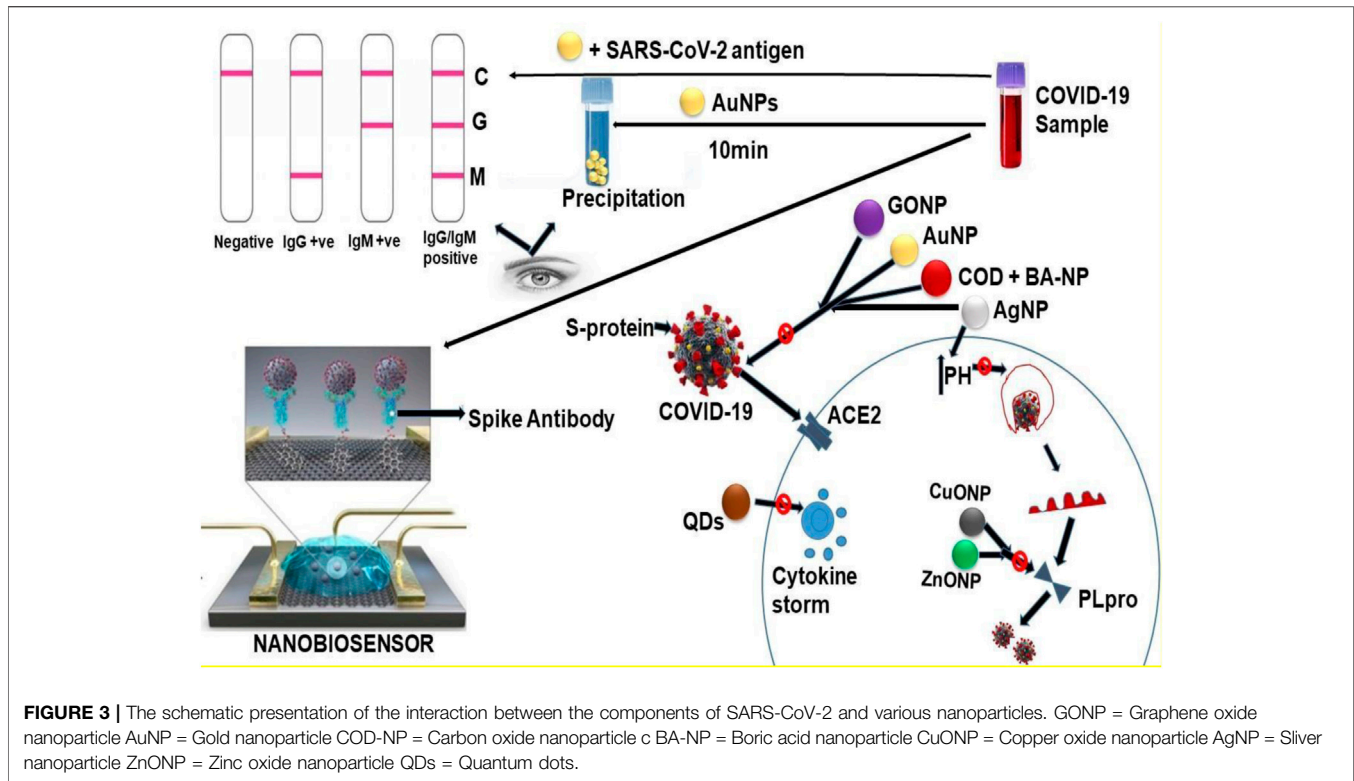
TABLE 4 | Status of some nanomedicine and vaccines in a clinical trial against COVID19.

| S/ No | Candidate | Clinical trial | Sponsor | References |
|-------|---------------------------------------|----------------|--|---|
| 1 | AV-COVID- 19 | Phase I/II | AIVITA biomedical, inc | Sheng and Christopher (2016) |
| 2 | BNT162a, BNT1621b, BNT162b2, BNT162c2 | Phase I/II | Biotech RNA pharmaceuticals GmbH | Chauhan et al. (2020) Thanh Le et al. (2020) |
| 3 | Ad5-nCoV | Phase1 | CanSinoBiologics | Hua and Wu (2018) |
| 4 | NVX-CoV2373 | Phase I/II | Novavax | Moderna (2020b) |
| 5 | CTII-nCoV | Phase I/II | Institute of biotechnology, “academy of military medical sciences”, PLA of China | Huang et al. (2020b) |
| 6 | ChAdOx1 | Phase I/II | Jenner institute—the university of oxford | |
| 7 | INO-4800 | Phase I | Inovio pharmaceuticals | |
| 8 | SCB-2019 trimeric S-subunit protein | Phase I/II | Clover biopharmaceuticals AUS pty ltd | |
| 9 | INO-4800 | Phase I | Inovio pharmaceuticals | Tebas et al. (2021) |
| 10 | Oral bacTRL- spike | Phase I | Symvivo corporation | Lara et al. (2011) |
| 11 | mRNA | Phase III | Pfizer and BioNTech (approved for emergency used) | Thi et al. (2015) |
| 12 | mRNA-1273 | Phase III | Moderna (approved for emergency used) | Nam et al. (2003) |
| 13 | LV- SMENP- DC | Phase I | Shenzhen geno- immune medical institute | Gupta and Jain (2010) |
| 13 | Pathogen-specific aAPC | Phase I | Shenzhen geno- immune medical institute | Skirtach et al. (2006) |

company (Sugentech IVD) has recently developed “SGTi-flex” kit for COVID-19 IgG/IgM detection in suspected samples using the AuNPs-based immuno-chromatographic technique. The kit has visually shown the presence of COVID-19 within the period of not more than 10 min. Hence, it provides the medium for the screening of both symptomatic and asymptomatic patients (Nano the Magazine for Small Science, 2020; South Korean Government, 2020).

AL Tomas et al., has invented two types of “strip lateral flow immunoassays” (LFIA) in 2019 for the diagnosis of pneumocystis pneumonia (*P. jirovecii*). These tools detect the presence of *P. jirovecii* antibodies with the help of AuNP- recombinant, synthetic antigens (RSA) conjugation reaction. During the demonstrations, both the kits have performed efficiently and were found to have formed redlines in positive samples (Nagatani et al., 2006). Moreover, these Kits are handy and could be conducted at the bedsides, train stations, and airports. Meanwhile, the samples were collected conveniently by fingertip pricking (Storhoff et al.,

1998; Nano the Magazine for Small Science, 2020). However, it was evident that the sample collected via vein does not prioritize those gathered using fingertip pricking, thus affirming the system’s reliability and convenience (Nano the Magazine for Small Science, 2020). Nevertheless, such a kind of antibody test can detect SERS-CoV-2 accurately within a few minutes (Tanaka et al., 2006). Z. Zhao et al., Developed carboxyl groups-coated magnetic nanoparticles (pcMNPs)-based viral RNA extraction system for the detection of COVID-19 (Zhao et al., 2020b). Conversely, excellent water disparity is the most promising feature of pcMNPs, making it widely applicable for COVID-19 viral RNA diagnosis in direct RT-PCR (Gan et al., 2020). Henceforth, the extraction procedure will significantly reduce the time consume and specific requirements in current COVID-19 diagnosis, particularly for early clinical diagnosis (Zhao et al., 2020b). And this could resolve the problems associated with RT-PCR based diagnosis technique. Zhenhua



Chen, et al., has reported the efficiency of “lateral flow immunoassay” (LFIA) in the detection of IgG antibodies produces in human serum in response to COVID-19 infection using “lanthanide-doped polystyrene nanoparticles” (LNPs). The mouse of human anti-IgG antibody incorporated with self-assembled lipid nanoparticles set to produce fluorescence when the SARS-CoV-2 recombinant protein mix with specific IgG on “nitrocellulose membrane” in a short period of 10 min (Chen et al., 2020). However, this technique could also provide a promising breakthrough for the rapid diagnosis of anti-COVID - 19 IgG in the suspected samples. Similarly, Lateral flow test strips designed to detect IgG and IgM in the blood samples have been widely used to detect COVID-19 (Li et al., 2020c). Tian Wen et al., developed a lateral flow immunoassay strip (LFIAs) that selectively detects IgG antibodies against COVID-19’s nucleocapsid protein in less than 20 min. The clinical evaluation of this point of care POC assay shows a satisfactory and cost-effective result that could serve as alternative means of confirming SARS-CoV-2 suspected infections (Development of a lateral, 2020).

COVID - 19 TRANSMISSION PREVENTION AND CONTROL USING DIFFERENT NANOPARTICLES

Nanoparticles are single structure with at least one of their three dimensions that exist as less than 100 nm in size. Moreover, the chemical compositions of the nanoparticle can be organic or

inorganic. Recently, nanoparticles have become increasingly essential and extensively utilized in the biopharmaceutical field due to their unique biocompatibility, biochemical reactivity, conductivity, and reduced toxicity (Vance et al., 2015). Nevertheless, nanoparticles and nanomaterials have a broad scope in healthcare and biopharmaceutical fields. As such, they have been used in the optimization of drug delivery systems, diagnosis, imaging tools, anticancer, antivirals, protective and medical consumables, et al. (Pelaz et al., 2017; Dilnawaz et al., 2018; Sim et al., 2018)

Virus Entry Prevention Using Nanoparticles

The treatment of specific viral strains is becoming increasingly difficult because of the viruses’ frequent evolutions and mutations. On the other hand, nanoparticles can play a vital role in killing and preventing viral entry into the host’s cells due to their unique characteristic of interfering with multiple antigens or their surroundings. Nanoparticles such as carbon quantum dots (CQD) and gold nanoparticles (AuNPs) were reported to have been promising tools for preventing viral-cellular entry (Szunerits et al., 2015). The study conducted by Loczechin A. et al., have shown that boronic acid nanoparticles ligands conjugated with carbon quantum dots (CQDs) have interfered with the functions of COVID-19 Spike-proteins and found to have been able to stop its cellular fusion mechanism significantly. Moreover, inhibition of HIV entry using conjugated boronic acid NPs was found to be efficient and successful (Fahmi et al., 2016). Achraf A. et al. demonstrated an experiment by adding nanoparticles to the coronavirus culture medium. Upon

examination, a considerable reduction in the cell-viral infection and replication rate remarkably reduce. Therefore, nanomaterials can now be employ as a powerful tool to prevent the replication of the viral genome, owing to their nano size of 10nm, excellent hydrophilicity, and high penetration efficiency (Itani et al., 2020). A characteristic spheroid shape of antiviral nanoparticle has an aspect ratio close to 1, with a range between 1–50 nm and an average range of 23 nm smaller than that of SARS-Cov-2 viral particles. Consequently, nanoparticles have gained a great privilege to contest with the COVID-19 surface spike proteins.

Applications of Nanomaterials

Brabazon D et al. have extensively investigated the use of nanomaterials in textiles and textiles. Fabrics coated with nanoparticles could be used to enhance the protective effect of Personal Protective Equipment (PPEs), such as lab coats and reusable facemasks. These nanomaterials have been used for UV protection, self-cleaning, fire-resistant clothing, antimicrobials, antivirals (Brabazon et al., 2017) (Figure 2). Therefore, the outbreak of the COVID-19 pandemic raises the need to exploit such nanoparticles due to increased demand for highly protective PPEs and facial masks. As a result, global consumption of Ag nanoparticles increased to 350 tones per year. (Siddiqi et al., 2018). Besides, wearable smart textiles for detecting and sensing biomolecules have been studied, particularly in the healthcare sector (Libertino et al., 2018). However, numerous nanomaterials based coatings are being used currently for various products. Silver, Bismuth, and titanium nanomaterials have been employed for coating surfaces to provide significant protection against microbial invasions (Brabazon et al., 2017). Nowadays, silver base disinfectant is readily available for sanitization purposes of healthcare-related facilities, and they have been found to have inhibited the SARS-Cov-2 contaminated surfaces significantly (Hebalkar et al., 2011). Furthermore, nanomaterials have been used extensively for the protective optimization of air filters in the health setting (Joe et al., 2016; Vaze et al., 2019) and wound dressing materials' production due to their ability to hasten the wound healing process (Mishra et al., 2008; Ali and Ahmed, 2018).

NANOPARTICLES AND MECHANISM OF ANTI- SARS-COV INFECTION

SARS-CoV related viruses, like all viruses, rely on host cells to reproduce and obtain basic metabolic systems for survival. For example, they use the host cell's cellular machinery to replicate their genetic materials. The investigation of nano systems and their possible interaction mechanisms with viral components may be advantageous for drug delivery enhancement by allowing for surface charge modification of materials (Uskoković, 2020).

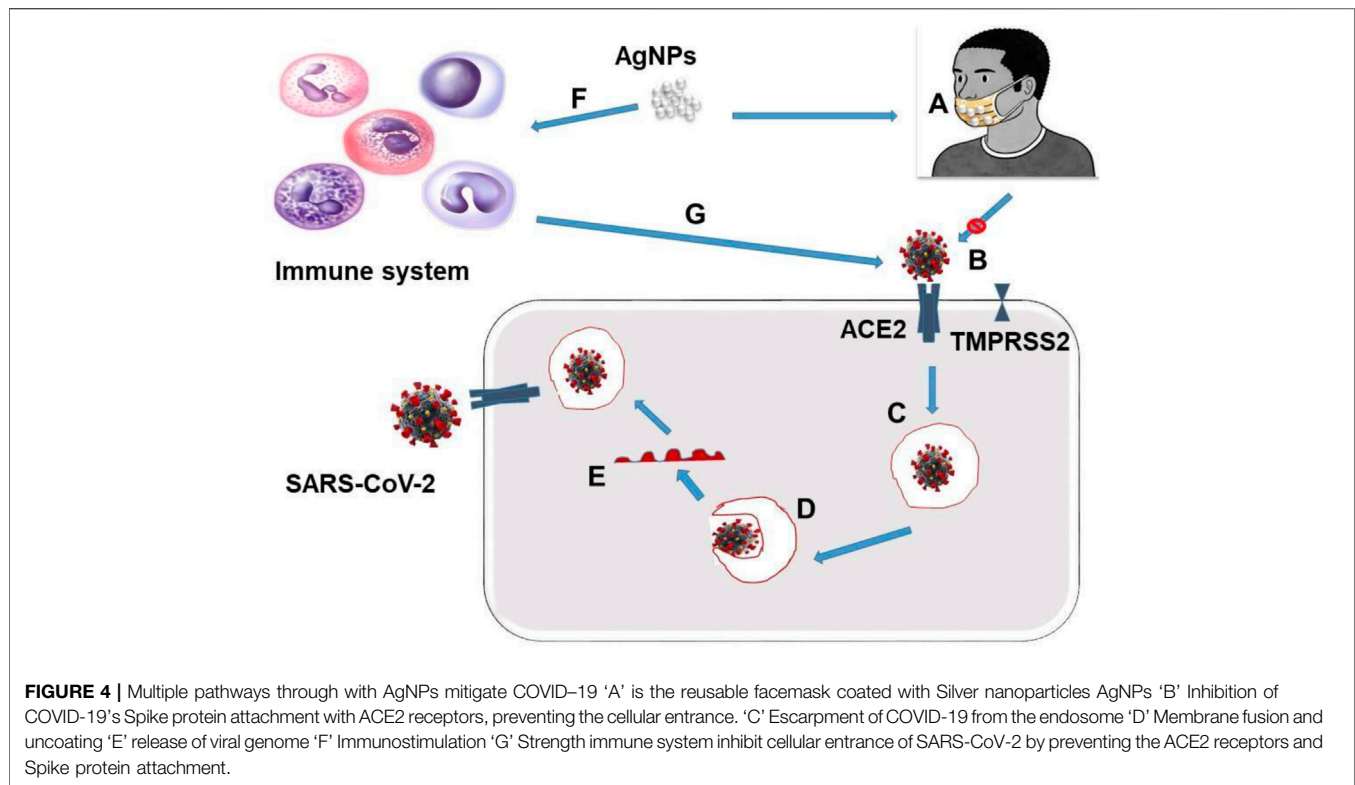
Blockage of Viral-Cellular Entry and Attachment

All viral infections require cellular attachment and entry. Similarly, SARS-CoV 2 infection begins with S-protein binding

to the host's ACE2 receptor. The attachment and fusion into the cell are carried out by the two S-protein subunits (S1 and S2) using its C and N-terminal domains. The S₁ subunit is primarily responsible for attaching the virus to the human ACE2 receptor (Hoffmann, 2020). The S₂ subunit, on the other hand, mediates the fusion of virus across the cell membrane and endocytosis. The S₂ subunit's function is aided by the proteins potential fusion peptide (pFP), transmembrane domain (TM), and heptad repeat N and C (HR-N and HR-C) (Ou et al., 2020). As a result, inhibiting this mechanism could be a potential target for anti-SARS-CoV2 drug development as well as treatment with repurposed drugs, as in the case of chloroquine (Wang et al., 2020). However, various NPs have the potential to interfere with the viral-cellular interaction as demonstrated by Ting et al. The author reported that cationic carbon dots (CDs) of approximately 1.6 nm size could interfere with the cellular fusion mechanism of the prototypic 'porcine epidemic diarrhoea virus' SARS-CoV2 (PEDV) (Hu et al., 2020). The effectiveness of CD inhibition is suggested to be due to viral charge neutralization caused by electrostatic interaction between negatively charged PEDV and positively charged cationic CDs. Furthermore, CDs may slow cellular apoptosis by reducing cellular accumulation of reactive oxygen species (ROS). Curcumin-modified AgNPs (cAgNPs) were also tested for their ability to prevent viral-cellular entry more effectively and safely. The cAgNPs have a significant advantage of high surface area due to their nanosized form, allowing them to interfere with the cellular entry process of viral enveloped protein d. (Huang et al., 2019). Similarly, GO in combination with AgNPs has demonstrated a high potential for viral inhibition of cellular entry of both feline COV (FCoV) and enveloped viruses (Yang et al., 2016). Huang et al. also demonstrated that the mechanism of antiviral activity of AuNPs is similar to that of GO-AgNPs (Chen et al., 2016b). Porous silicon NPs (SiNPs), according to Osiminka et al., have an affinity for inhibiting the cellular fusion mechanism of many enveloped viruses, including the nCOV superfamily (Osminkina et al., 2014).

Sekimukai, H. Et al. reported that gold nanoparticles AuNPs act as both an adjuvant and an antigen carrier for immunization. It is believed to be a major adjuvant in the SARS-CoV vaccine that inactivated by ultraviolet radiation. Nasrollahzadeh M et al. performed preliminary tests on mice by immunizing them with a dose of 0.5 µg of spike protein after being infected with the mouse-adapted virus. The adjuvant protein of gold nanoparticles contributes to a strong IgG reaction but does not improve the vaccine's efficacy or reduce eosinophilic infiltration. The result obtained in this study of the gold nanoparticle-adjuvant S protein can lead to a promoted antigen-specific IgG response against SARS-CoV (Nasrollahzadeh et al., 2020; Salleh et al., 2020).

Schlecht S, et al. discovered that AuNPs functionalized with sialic acids could inhibit the cellular entry of the Influenza A virus. The mechanism of inhibition involved the blocking of the viral surface protein (hemagglutinin), which is responsible for the recognition of sialic acid on host cells. According to Stone JW study, functionalized AuNPs with a diameter of 14 nm are more efficient in blocking the influenza A virus than those with a



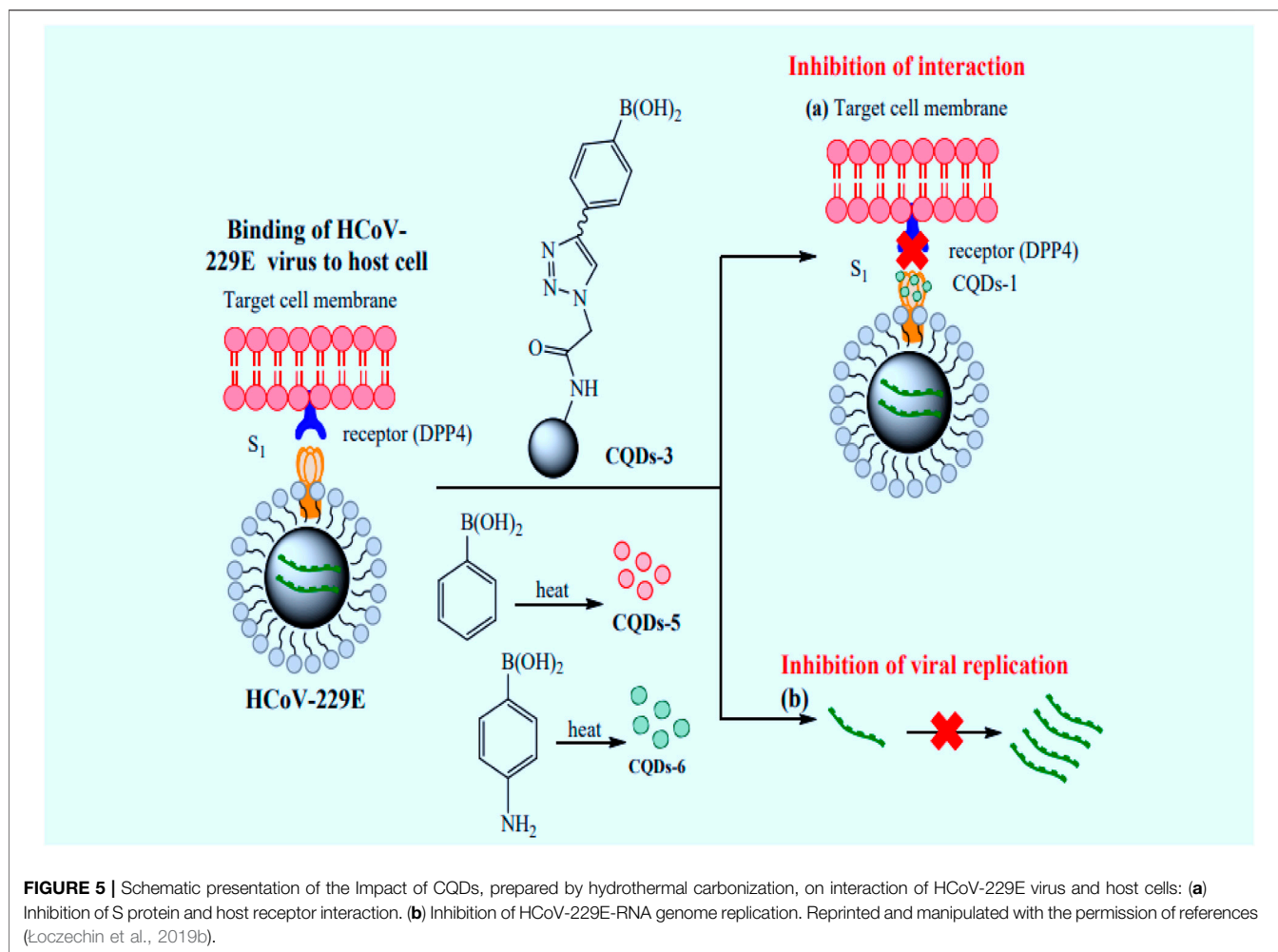
diameter of 2 nm, which have a less significant outcome (Kim et al., 2020b). Fujimori et al. investigated the antiviral potential of copper iodide nanoparticles (CuINPs) against the 2009 pandemic Influenza A virus. CuINPs can generate reactive oxygen species (ROS), which cause viral degradation and inactivation by acting on essential viral proteins such as neuraminidase and hemagglutinin (Abo-Zeid et al., 2020).

Inhibition of Viral Replication

The copper surface is very susceptible to modern SARS-CoV-2, which is responsible for the current COVID-19 pandemic. Copper nanoparticles (CuNPs) have antiviral properties that act by blocking papain-like protease-2, a protein that requires replication of severe acute respiratory coronavirus syndrome (SARS-CoV). Oxidized Cu oxide (CuO) nanoparticles (CuONPs) are commonly used as catalysts to improve the ability of CuONPs to minimize the use of viruses (Sekimukai et al., 2020). On the other hand, Ting Dut et al. reported that turmeric-based cationic carbon dots nanoparticles interact with coronavirus by inhibiting viral proliferation; Curcumin-based cationic carbon dots may inhibit the synthesis of negative-stranded RNA and virus budding as well as the aggregation of reactive oxygen species by viruses. The structure of the surface protein in viruses has been altered to prevent viral entry. It may also inhibit viral replication by promoting pro-inflammatory cytokines and interferon-stimulating genes (ISGs) (Du et al., 2018a; Raha et al., 2020). Meanwhile, Jiangong Liang et al. observed that Treatment with Ag₂S NCs prohibited the viral budding and negative-strand RNA formation. The formation of

IFN-stimulating genes (ISGs) and the expression of pro-inflammatory cytokines are positively regulate the inhibition of viral infection and coronavirus proliferation (Lin et al., 2017b). the positive surface charge of carbon-based QDs could be used for sequestering the S protein of SARS-CoV-2. Besides, cationic surface charges of QDs interact with the virus's negative RNA chain, contributing to reactive oxygen species formation in the COVID - 19. The introduction of desired functional groups with quantum dots may effectively interact with COVID - 19 entry receptors and affects genomic replication (Du et al., 2018b). The schematic presentation of these interactions was presented in **Figure 3**.

Silver nanoparticles (AgNPs) are used as effective antiviral therapy for SARS-CoV-2 with fewer adverse reactions. The mechanism by which AgNPs interact with COVID-19 is minimal because of the complexity of the COVID-19 structure. Silver nanoparticles interact with COVID-19 in two ways: 1) They bind to the virus's outer layer, thereby inhibiting the attachment of the virus to the receptor cells. 2) They attach to the DNA or RNA virus, thereby inhibiting viral replication within the host cells. Some studies suggested that AgNPs act by binding to the spike glycoprotein virus, thereby inhibiting the virus's attachment to the cells. The release of silver ions could reduce the ambient pH of the respiratory epithelium, where the COVID-19 virus tends to become more acidic and hostile to the virus (**Figure 4**; Manivannan and Ponnuchamy, 2020). Because CoVs mutate so quickly, treating human infections remains difficult. In this regard, oczechin, A. et al. developed carbon quantum dots nanoparticles (CQDs-NPs) of approximately 10 nm size from a citric acid/



ethylene diamine precursor and modified them with boric acid. They were discovered to inactivate the HCoV-229E virus in a concentration dependent manner (EC₅₀ of 52- 8-g/mL1) (Łoczechin et al., 2019a). Furthermore, the author synthesized CQDs-NPs directly from 4-aminophenylboronic acid with no post-synthetic modifications. The CQDs synthesized using the direct method have the potential for viral inactivation at much lower concentrations, with an EC₅₀ of 5.2 0.7 g mL1 compared to the modified one. The author proposed that the interaction between the functional groups of CQDs and the host's receptor could be a mechanism for both viral inactivation and replication inhibition. (Łoczechin et al., 2019b). As illustrated schematically in **Figure 5**.

NANOTECHNOLOGY-BASED DRUGS AND VACCINES FOR COVID - 19 TREATMENT

The absolute genomic similarity between the previous pandemic coronaviruses and SARS-COV2 could greatly help achieve success in vaccines and drug development against the pandemic COVID -19 (Sharma et al., 2019). Nanoparticles are loaded with a range of

antigenic moieties using physical or chemical entrapment. Perhaps they have better loading and delivering precise antigen efficiency to the targeted cell than conventional approaches (Pearson et al., 2017). More importantly, nanocarriers' nanosized structure enhances their delivery efficiency, bypasses the biological barrier restrictions, and improves their tissue targeting specificity. Furthermore, they provide flexible administration routes such as oral, intranasal, subcutaneous, and intramuscular routes (Pati et al., 2018). Currently, nanotechnologies have played a significant role in developing four vaccines approved for emergency use against COVID-19 satisfactory completion of phase 2 clinical trials. However, Moderna and Pfizer/BioNTech vaccines were designed by encapsulating the mRNA of SARS-CoV-2 in Lipid Nanoparticles (LNP). Similarly, the Russian Scientist developed the two vaccines received emergency licenses from the Russian Ministry of Health to be used against COVID-19. These vaccines have been reported to achieve higher stability and safety for human use (**Table 3** and **Table 4**; Raha et al., 2020; Du et al., 2018a; Lin et al., 2017b; Du et al., 2018b; Manivannan and Ponnuchamy, 2020; Łoczechin et al., 2019; Sharma et al., 2019; Pearson et al., 2017; Pati et al., 2018; U. S. National Library of Medicine, 2020a; Moderna, 2020a).

TABLE 5 | Antiviral nanomaterials, applications, and limitations.

| S/ NO | Nanoparticles | Anti-antiviral activity | Application | Limitations | References |
|-------|--|---|--|---|--|
| 1 | Hydrogen peroxide. H ₂ O ₂ nanoparticles | Stopping the active of SARS-COV-2 BY breaking down the structure of the virus | Reduce oxidative stress | Generate radicals of highly reactive hydroxyl | Ghaffari et al. (2019) |
| 2 | Ag (silver) nanoparticles | Cell membrane destruction and DNA damage | Virucidal agents | The mechanism of inhibition is not yet understood | Huh and Kwon (2011) |
| 3 | Lipid-based nanoparticles | SIRNA ebola virus | Inhibition of viral replication | Production is costly | |
| 4 | Manganese | Human immunodeficiency virus (HIV) | Maintain the balance of redox reaction Increase the rate of mutation of HIV | Unrecorded | Antoine et al. (2012) |
| 5 | Solid lipid nanoparticles | Hepatitis B virus | Decrease toxicity, with the improved drug-release profile | Poor loading capacity and high cost of production | Savrasova et al. (2011), Ingle et al. (2014) |
| 6 | Gold nanoparticles | Inhibit and destroy viral particles directly. Attenuating infectivity of influenza a virus | Detection of the virus. High specificity in drug release to target site | Formation of protein binding complex called "corona" | Trends in IT Value (2008), Jeyaraj et al. (2019) |
| 7 | ZnO-NPs | H1N1 influenza virus inhibition | Biosensing, antigenic, bio imaging, and tissue engineering | Biodegradable and immunogenic "PEGylated with ZnO-NPs" is alternative | Dehghan et al. (2013), Sulkowski et al. (2013) |
| 8 | Silver (ag) | Inhibit replication of viruses. E.g. simple harpies' virus. Hepatitis B | Cancer treatment, biosensor, biomolecules, and labels of the cell | Induced cytotoxicity in a mammalian cell | Mohajer et al. (2014) |
| 9 | FeO, and CUO | Detection of influenza virus | Antiviral, biosensors | Low detection limit | Heidari et al. (2017) |
| 10 | Platinum nanoparticles | Detection of influenza virus | Antioxidant, antiviral | <i>In vivo</i> toxicity | Bimbo et al. (2013), Pierantoni et al. (2015) |
| 11 | PEGylated IFN and ribavirin nanoparticles | Hepatitis c virus | Liver cirrhosis | Low limit of tolerance | Faria and Zucolotto (2019), Lynn et al. (2015) |
| 12 | Nano spheres nanoparticles | Hepatitis B, herpes simplex virus, and influenza | Inhibition of viral replication, high drug loading capacity. Neuroprotective function | High dose requirements Handling requirements | Dash et al. (2011) Lee et al. (2018) |
| 13 | Silicon nanoparticles | HIV, Herpes simplex virus, monkey poxvirus respiratory syncytial virus, and hepatitis B virus | High delivery of antiviral to infected cells Immunosensors Bioanalytical research | Cytotoxicity | Liu et al. (2015), Cai et al. (2017) |
| 14 | Chitosan | HIN2 influenza H1N1, H3N2, H5N1 influenza | Micro molecules delivery. Include vaccines and protein across the nasal mucosa and oral system | Low aqueous barrier properties | Dash et al. (2011) |

Benefit and Challenges of Using Nanomedicines in Mitigating COVID – 19

Generally, nanomedicine changes the paradigm of healthcare delivery owing to its potential therapeutic effectiveness. Moreover, they have a wide range of applications in therapeutics, diagnosis, and overall healthcare delivery (Singh et al., 2018). The developmental aspects of nanotechnology and its clinical applications are understudying. Perhaps, there are enormous challenges that need to be addressed in exploring their clinical significance. Therefore, specialists' hands need to be on deck to optimize their full potentiality in all aspects of medical space (McNamara and Tofail, 2017). We summarised the clinical benefits and challenges associated with the use of nanomaterials were for the management of viral infections in **Table 5**.

CONCLUSION

This study suggested that nanotechnology could serve as a promising alternative to reduce the spread of COVID-19 across multiple techniques. Besides, it greatly optimizes viral diagnosis by making it possible to detect viral genome presence in a minute sample quantity

within a short period. It is also possible to diagnose COVID-19 in asymptomatic patients. It can, therefore, reduce the chances of viral transmission. Several nanoparticles and nanomaterials have also been found to possess the unique properties of viral inactivation, block its entrance mechanism, and inhibit several vital proteins responsible for viral attachment and intercellular replication. However, Nanotechnology has potentially accelerated the process of novel drugs and vaccine designation and delivery against COVID-19.

AUTHOR CONTRIBUTIONS

AM: COVID - 19 transmission prevention and control using different nanoparticles. MA: Specific applications of nanosensors for the detection of COVID - 19. NA: Rapid testing of COVID - 19 using other NPs. MM (7th author): Application of nanoparticles in vaccines and drug delivery against COVID - 19. AY: How a COVID - 19 infects cells. MY: Challenges in the phase of nanomedicines use against COVID-19 and their prospective solutions. SS: Latest updates on the status of nanotechnology-based drugs and vaccines in clinical trials

against COVID -19. MM (3rd author): Nanoradiations: either a diagnostic test or curable means or against COVID- -19 virus. IS: Drawing of figures and manuscript writing. YBD: Antiviral nanoparticles/nanomaterials. MI: Approving the final version of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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