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Viral Diagnostics and Preventive Techniques in the Era of COVID-19: Role of Nanoparticles

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COVID-19 outbreak in the Hubei province of China as of December 2019 has caused massive global fatalities. Recommended preventive strategies that include the use of sanitizers and masks caused a global shortage of protective gear for the frontline health workers who were at a higher risk of infection. Implementing effective containment strategies and promoting large scale diagnosis of the general public thus forms the first line of defense in controlling the spread of the contagion as of now. The understanding of the biological identity of the SARS-CoV-2 virus has helped the researchers figure out the mechanism of infection and also helped them design efficient diagnostic kits. This review primarily provides comprehensive details of the gold standard viral diagnostic methods. With nanoparticles playing a vital role in healthcare platforms, its mode of action against other viruses and its application in COVID-19 has been elaborated. The relevance of incorporating nanoparticles in surface coatings, sanitizers, masks, and air filters have been highlighted. NP-based biosensors that can be utilized as point-of-care tests and multiplexed assay have also been discussed. Considering the ongoing threat, new research studies focus on strategically combining different diagnostic systems to enhance the sensitivity and accuracy of the detection kits. In this regard, the key details of the patents that encompass new methodologies for virus detection have been summarized.

Keywords: COVID 19, SARS-CoV-2, diagnostic, biosensor, patents

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INTRODUCTION

In 1960, coronavirus was first identified as a cause of common cold and was considered as a mild and non-fatal virus until 2002 (Yang et al., 2020). However, a mutated form of the coronavirus caused severe acute respiratory syndrome (SARS) in 2002 in Guangdong, China, and also spread to various parts of the world (Xu et al., 2004). In 2012, the virus once again reappeared in Middle East countries, where it was named Middle East Respiratory Syndrome coronavirus (MERS-CoV) (Rao et al., 2020).

In December 2019, there was an outbreak of the novel SARS virus in Wuhan, China. Beginning of this year, the world was appalled by this outbreak, and the virus was officially named as Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or COVID-19) by the World Health Organization (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). This virus has created havoc throughout the world and currently, the world has witnessed over 211,000 deaths globally (as of June 27, 2020). Identifying asymptomatic cases

remains one of the major challenges. A case study from diamond Princess cruise ship, Yokohama, Japan, 2020 pointed out that asymptomatic cases are as infectious as symptomatic cases for spreading COVID-19 infection (Mizumoto et al., 2020). Except patients having comorbidities such as hypertension, diabetes, and heart disease otherwise symptoms against COVID-19 very non-specific in nature (Udugama et al., 2020) and cannot be used for an accurate diagnosis (Pulia et al., 2020). Timely diagnosis and effective treatment are therefore very essential.

Over the last few months, healthcare personnel and researchers from different fields have been actively engaged in finding solutions to vanquish the virus A simple PubMed search on MERS-CoV which shares ∼50% genome similarity with SARS-CoV-2 show a gradual increase in publication over the last 5 years. However, an enormous spike in the publications related to SARS-CoV and SARS-CoV-2 was seen in the year 2020 (**Supplementary Figure 1**). Considering the inherent challenges associated with the development of vaccines, it may take a while before we can eliminate the deadly virus from our day-to-day lifestyle. Thus, it is necessary to focus our research on efficient preventive measures and advanced diagnostic techniques. COVID-19 or viral infections were diagnosed using nucleotide detection (Polymerase chain reaction), gene sequencing, and antigen and antibody detection (ELISA, Immunofluorescence). These methods are time-consuming and need skilled labor. In recent years, nanotechnology-based solutions have been immensely helpful in battling several viral infections. A wide range of nanoparticles (NPs) has been deployed for the treatment and detection of viruses like HIV, HSV, and Influenza (Chen and Liang, 2020). Efficient preventive strategies and robust detection kits can be developed based on the physio-chemical and anti-viral properties of NPs.

In this article, we aim to provide an overview of the mechanistic details of the gold standard viral diagnostic methods. The other key takeaways are the intervening strategies from the viewpoint of nanotechnology that can improve the current preventive and detection platforms. A strong groundwork about NP-based biosensors and patents that involve the detection of COVID-19 have been highlighted. Summarizing the mechanistic details of different prevention and detection methods can create better awareness about the ongoing pandemic.

CURRENT DIAGNOSTIC MODES: RECENT ADVANCES, ADVANTAGES, AND LIMITATIONS

Currently, the detection of COVID-19 is based on the contact and travel history of patients from the affected area as well as clinical symptoms (Kumar et al., 2020). Unavailability of a patient's contact history at all-time makes laboratory testing more difficult in the current situation. COVID-19 mainly infects the respiratory tract. Nasopharyngeal, oropharyngeal, and/or sputum or bronchoalveolar specimens are taken for diagnosing the viral load (Udugama et al., 2020). A rapid and quick diagnostic technique is still unavailable for the detection of COVID-19 although various methods have been used in the current scenario to detect with its advantages and disadvantages (Carter et al., 2020). **Table 1** compares and highlights the key features of all the diagnostic techniques that are used for COVID-19 detection.

RT-PCR (Reverse Transcriptase Polymerase Chain Reaction)

RT-PCR is the most reliable and gold standard method for the identification of COVID-19 infection. As of now, various COVID-19 RT-PCR based kits available in the market covert viral genomic RNA to complementary DNA (cDNA) by using RNA dependent DNA polymerase or reverse transcriptase enzyme and further use it for the amplification. The RNA probes that are designed from the COVID-19 genetic sequence are retrieved from the Global Initiative on Sharing All Influenza Data (GISAID) database. Probes against different target sequences of COVID-19, like spike protein, RNA dependent RNA polymerase, nucleocapsid protein are designed. In real-time RT- PCR, viral sequence-specific DNA probes are labeled with a fluorescent tag and a quencher molecule is used and the progress of the reaction can be easily monitored by observing the fluorescent tag intensity. The automated RT-PCR runs through repeated cycles of annealing and extension. While one-step RT-PCR is carried out in a single tube, where reaction mix contains forward and reverses primers together. In a two-step procedure, the forward and reverses PCR reactions are carried out in separate tubes. The one-step method is simple and quick and therefore is the preferred procedure for COVID-19 detection (Carter et al., 2020). Although it is a gold standard for the detection of COVID-19 it has the disadvantages, of requiring high equipped laboratory and skilled labor.

Reverse Transcription Loop-Mediated Isothermal Amplification (RT-LAMP)

RT-LAMP uses isothermal amplification technique at constant temperature and avoids the use of thermal cyclers, unlike conventional RT-PCR. Sensitivity is enhanced by using two to three pairs of primers against the viral gene sequence. The amount of DNA amplified in a patient specimen is measured by the turbidity formed due to the production of magnesium pyrophosphate. The approach of this method simply requires an isothermal water bath. The main drawbacks of RT-LAMP include optimizing the primer and sample run which is limited to one (Carter et al., 2020).

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) Based Assay

CRISPR represents a family of nucleotide sequences originally inferred from the prokaryotic system such as bacteria and archaea. CRISPR associated enzymes such as Cas9, Cas12, and Cas13 can recognize and cut these nucleotide sequences. Recently two companies Mammoth Biosciences and Sherlock Biosciences developed CRISPR-based technology for the detection of COVID-19 (Broughton et al., 2020). Mammoth bioscience used the Cas12 enzyme for the detection of COVID-19. In this

TABLE 1 | Comparison of the diagnostic methods used for the detection of COVID-19.

S. No.	Method	Sample type	Principle	Assay time	Advantage	Limitation	LOD
1.	RT-PCR	Nasopharyngeal and Oropharyngeal swabs	Primer and fluorescent marker based	3–4 h	Reliable/detects current viral infection	Requires sophisticated instrument/cannot detect already recovered patients	100 copies/mL (Abbott Diagnostics, Inc)
2.	RT-LAMP	Nasopharyngeal and Oropharyngeal swabs, mucus	Primer based two to three pairs of primer can be used	2–3 h	Highly sensitive/conducted at constant temperature (60–65°)	Current infected patients can be detected	80 copies of viral RNA per ml sample
3.	CRISPR- based assay	Nasopharyngeal and Oropharyngeal swabs	Gene editing tools	1 h	Highly sensitive/ low-resource settings	Many CRISPR based -kits are in development stage/need more clinical validation	RT–LAMP/Cas12 10 copies per μl input
4.	Serological assay (ELISA, Neutralizing, Chemiluminescent immunoassay etc.)	blood serum, plasma and other body fluids such as saliva and sputum	Antigen/Antibody based	30 min–4 h	Sensitive or good specificity	Depends on Host antibody response, false positive	ELISA—5IU/ml
5	Nanoparticle-based methods (Gold NPs, GO)	Gold NPs-Target DNA in nuclease free water; GO- Nasopharyngeal swabs	Gold NPs-Nucleic acid hybridization via thermoplasmonic heating; GO-Field effect transistor	Not specified	High specificity and sensitivity	Requires expertise in nanoparticle synthesis and sensor fabrication	Gold NPs–0.22pM; GO–1fg/mL

method, guide RNA (gRNA) can be designed that recognizes one of the genes found in the COVID-19. Cas12 and gRNA will search for RNA present in the sample and Cas12 will cut it without stopping. For the detection, there is an additional RNA molecule tag with fluorescein amidite and FAM which generates color. The CRISPR based assay does not require complex instrumentation for diagnosis.

Serological Assay

Serological assay means the detection of antigen and antibody present in the serum of patients. Serological assays utilize body fluids such as blood serum, plasma, saliva, and sputum. During any infection or encounter with antigen, our body immune system generates specific antibodies. Due to specificity or limited cross-reactivity, antibody detection is one of the most reliable methods to detect any infectious agents. Serological test plays a significant role in understanding antibody response, amount of antibody formation, and diversity generated by the body. The presence of immunoglobulins such as IgM indicates an early stage of infection, whereas the presence of IgG indicates the stage of current or prior infection. Some of the most commonly utilized serological test during COVID-19 include ELISA (Enzyme-Linked Immunosorbent Assay), Neutralizing test, chemiluminescent immunoassay (CLIA), and Rapid diagnostic test (RDT).

ELISA (Enzyme-Linked Immunosorbent Assay)

An ELISA is a microwell plate-based assay designed for detecting antigen or antibody. The indirect ELISA used for COVID-19 determines the total antibody concentration in a sample. For microwell plate coating, different proteins of SARS-CoV-2 mainly the structural proteins N and S (highly immunogenic and prolifically expressed during infection) are used. Viral antibodies present in the samples bind to the antigen and forms an antibody-protein complex, later detected by secondary antibody and colorimetric method. The ELISA-based serological tests entirely depend on host antibody response to the virus and it is suggested to do tests after 1-week post symptom (Carter et al., 2020).

Neutralizing Test

Plaque reduction neutralizing tests use a subset of antibodies produced against a virus that independently block viral entry. Performed under the BSL3 facility, it requires the use of live viruses. In this test, the patient's serum is mixed with a suspension of the infectious virus here COVID-19 particles. Affected patient serum containing antibody against COVID-19 will bind to virus particles and prevent them from further invading the cells in the culture, finally neutralizing the virus (Carter et al., 2020). Limitations of this test include its restriction to the BSL3 facility only and it takes 3–5 days for the viral neutralization so it is very time-consuming.

Chemiluminescent Immunoassay

Chemiluminescent immunoassay is a variation of the standard enzyme immunoassay (EIA) work. This test is a quantitative, lab-based technique where antigens can be identified in an affected sample by using an enzyme that converts a substrate to a reaction product, which emits a photon of light. Mixing the COVID-19 patient sample and a specific enzyme-linked antibody gives a light-based luminescent signal. Antibodies present in the sample against COVID-19 react with the viral protein and forms a complex inducing a chemical reaction that produces light which is directly proportional to the amount of antibodies in the sample (Vashist, 2020). The disadvantages of chemiluminescent

immunoassay are high cost, less sensitivity, and requirement of a closed analytical system.

Rapid Diagnostic Test (RDT)

RDT is typically a qualitative lateral flow assay that detects antigens/antibody (IgM or IgG) in patients sample (blood sample, saliva, and nasal swab fluids). Herein, COVID-19 viral antigen is present in the sample binds to specific antibody encoded in the paper strip providing results within 15 to 30 min. False-negative results may occur due to cross-reactivity from other endemic infections. Compared to molecular diagnostic tests they are fast and easy to perform and can serve for point of care testing (POC).

ROLE OF NANOTECHNOLOGY IN COVID-19 PREVENTION AND DETECTION

NPs due to their high surface-area-to volume-ratio easily binds either with the viral membrane proteins or to the viral replication system (DNA/RNA) eventually hampering it's potential to infect the cells. Metal NPs such as gold, silver, and copper have been strategically used for inhibition of viral growth (Ravishankar Rai, 2011). Copper being a cheaper alternative to silver and gold has often been examined for its wide anti-microbial activities. Inactivation of the virus on copper surfaces after 4 h suggests the possible application of copper in destructing the virus (van Doremalen et al., 2020). CuI NPs destructs the influenza A virus (Fujimori et al., 2012) and also reduce the infectivity of Feline calicivirus (FCV) (Shionoiri et al., 2012). Copper composite NPs were also reported to inactivate 50% of virus-like particles (VLPs) in 10 min (Broglie et al., 2015). **Supplementary Table 1** summarizes a few of the applications of NPs against a range of viruses.

Scope of Nanotechnology in the Prevention of COVID-19

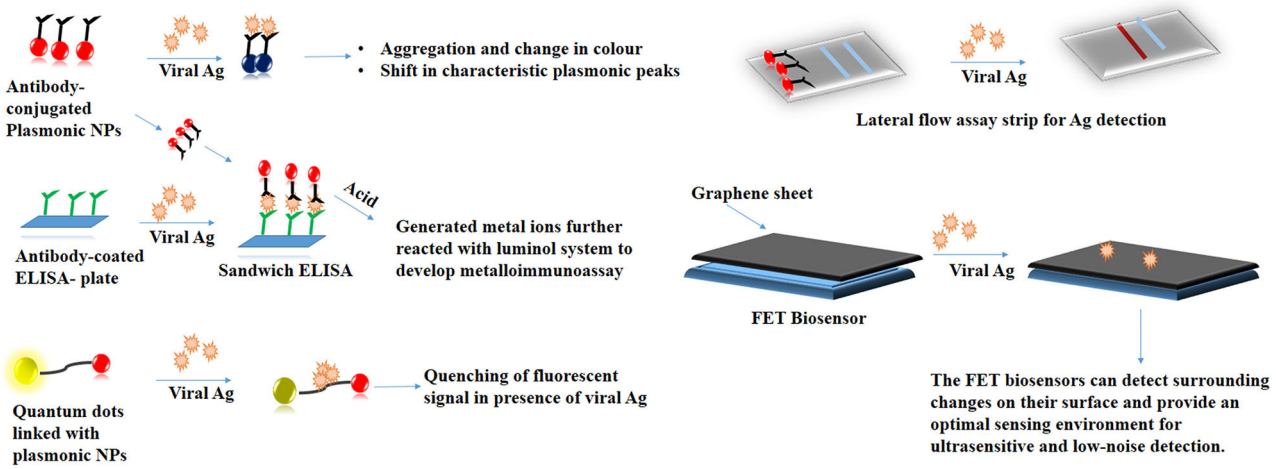
Since the COVID-19 pandemic, extensive research has been focused mainly on the fabrication of efficient vaccines and drugs. However, the first line of safety from the viral infection mainly depends on an individual's awareness and hygiene practices. In this section, we highlight a few of the aspects wherein, the use of nanomaterials to manage COVID-19 can be beneficial (Kaushik, 2019; Mujawar et al., 2020). Surface contact and/or droplet-based transmission of the virus can be carefully eliminated by incorporating anti-viral NPs in surface coatings, sanitizers, filters, and respiratory cloth masks.

Silver and copper-based NPs have long been used in surface coatings, paints for their anti-microbial properties. ROS generation and viral cell destruction by these metal NPs can be put into use by incorporating them in a different matrix. PEI-coated model surfaces with AgNPs and CuNPs successfully reduced the viral titer by changing the viral membrane permeability and/or by electrostatically binding the virus to the cationic surface (Sinclair et al., 2019). In another study perhydrolase-immobilized carbon nanotubes (CNTs) paints generated peracetic acid (PAA) effectively reducing influenza A titer values (Grover et al., 2013). NPs can also be incorporated in disinfectants. Currently, most of the disinfectants contain either hypochlorite or 70–80% alcohol. Recently, a disinfectant formulation containing nano-TiO_2 and AgNPs were used for sanitizing public places in Milan, Italy (Nanotech Surface Coronavirus, 2020). In another interesting study, mesoporous silica protected AgNP-based composite was synthesized as an efficient disinfectant with controlled Ag^+ release and easy magnetic removal post-treatment (Wang et al., 2019). At this time, dentists are at a much higher risk due to the inherent nature of the practice that is involved in the treatment of the patients. The use of positively charged imidazolium-based ionic liquid-protected silver nanoparticles serves as a promising anti-bacterial disinfectant. Considering the involvement of AgNPs, the concept can be extended for viral inhibition (Abbaszadegan et al., 2015).

Introduction of NP-based high-efficiency particulate air-filters (HEPA) in health-care centers, airports, and other closed places can effectively eliminate the viral spread. SiO_2-Ag NPs coated antiviral air filters with a coating density higher than 2.0×10^8 cm^2 were reported to reduce the viral infection by 99.9% (Joe et al., 2014). AgNPs-coated filters with nano-TiO_2 were established as an advanced air purifying system in hospitals (Le et al., 2015). A hybrid composite comprising AgNPs and CNTs synthesized using aerosol nebulization and thermal evaporation/condensation processes were used as antimicrobial air filter (Jung et al., 2011). Anti-viral NPs embedded onto fabrics can resolve the issue of viral contamination related to masks and PPE kits (Adams and Walls, 2020). Anti-viral textile was manufactured by a Swiss company named HeiQ by combining vesicle technology and the anti-viral property of AgNPs. The vesicle system entraps the virus and the AgNPs inhibit the viral replication (Materials, 2020). The impregnation of CuO NPs in respiratory masks can efficiently reduce the risk of viral contamination (Iyigundogdu et al., 2017). The problems of improper handling of PPE can be solved by treating them with graphene oxide (GO) grafted-metal NPs (Perreault et al., 2015). Interestingly, fluorescent virus-like NPs with a size range nearly that of SARS-CoV-2 can track the filtration efficiency of different fabrics that are currently in use (Lustig et al., 2020). Preventive measures in combination with nanotechnology can serve as a productive platform for research studies related to virology in the future. **Supplementary Scheme 1** summarizes the role of nanotechnology in the prevention of COVID-19.

Nanotechnology-Based Viral Diagnostics in the Era of COVID-19

NPs with their tunable physiological properties have served as a promising tool in several biosensing applications (Mejía-Salazar and Oliveira, 2018). It is necessary to address the problems associated with RT-PCR wherein, the genetic drift of the viral strains that tend to compromise the assay performance. Earlier, mutations in the highly conserved region of the Influenza A virus had reduced the sensitivity of numerous RT-PCR kits (Stellrecht, 2018). Bottlenecks in such classical detection techniques can be solved with the help of nanotechnology. Colorimetric assays based on the principle of aggregation of antibody-conjugated



SCHEME 1 | Summary of NPs-based viral detection systems.

plasmonic NPs in the presence of viral proteins can serve as an inexpensive tool for viral detection (Yadavalli and Shukla, 2017). Virus-mediated fluorescence quenching of peptide-linked nanocomposite consisting of QDs and AuNPs achieved a detection limit of 17.02 fg/mL (Nasrin et al., 2020). AgNPs-based chemiluminescent Did you mean: radioimmunoassay metalloimmunoassay has high sensitivity toward the detection of H1N1 Influenza virus without involving the complexity of antigen amplification (Li et al., 2013). The colorimetric changes in these NPs following their interaction with the target analyte can be easily tracked by cameras in smartphones. Such an approach makes sensitive diagnostic platforms more portable and user-friendly (Dong et al., 2017). Photothermal effect (PTT) and localized surface plasmon resonance (LSPR) was utilized to synthesize a sensitive dual-functional gold nanoisland (AuNIs)-based sensor with a detection limit of 0.22 pM. The sensor showed a precise detection of a specific gene sequence (Qiu et al., 2020). Fabric-based sensor synthesized by incorporating antibody-coated GO has been used to detect the presence of the Influenza virus with a detection limit of 10 ng/mL (Kinnamon et al., 2018). A graphene-based field-effect transistor (FET) has been for on-site detection of the SARS-CoV-2 virus (Seo et al., 2020). NP-based point-of-care detection kits mainly the lateral flow assays (LFA) with enhanced sensitivity can be explored for detection for several viral analytes (Soh et al., 2020). **Scheme 1** summarizes the NP-based detection strategies that are employed in viral diagnostics.

CURRENT PATENTS INVOLVING DETECTION OF COVID-19

Tremendous effort has been put forward by several research groups to find a possible solution for the ongoing pandemic, more than 500 patents have been filed during this time that discusses the potential strategies of preventing and treating the infection (Liu et al., 2020). In this section, we discuss a few of the patents related to COVID-19 diagnosis. Detection methods based on the principle of antigen binding to antibody-coated NPs were used for biosensor fabrication. For instance, a colloidal gold-based immunochromatography device (LOD-1000 pg/mL) (CN111239400A, 2020) and a dual antigen kit (CN111239394A, 2020) was patented. Europium microspheres coated with specific novel coronavirus NP protein mAb (LOD-10 pg/mL) (CN111060691A, 2020) was patented. Fluorescent nanostrips-based bedside detection technique was fabricated using immunoglobulin conjugated Up-Conversion Nanoparticles (UCNPs) (CN111190012A, 2020). Other nucleic acid-based detection techniques include the use of RT-PCR in combination with RPA reaction on the reversed cDNA (CN111074008A, 2020). RPA reaction system in combination with multi-component deoxyribozyme (MNAzyme) was used for the generation of non-specific linear DNA that can emit light for a relatively long time. The method tends to overcome weak signals generated by target nucleic acids (CN111187863A, 2020). Digital PCR-based technique that involves designing a primer pair and probe for ORF1ab region of COVID-19 has been patented which claims to have high sensitivity and eliminates signal interference (CN111270017A, 2020). Inventions such as these that can benefit the public health at this unforeseen emergency situation.

DISCUSSION

The current COVID-19 pandemic has created a global emergency crippling both the developed and the developing nations. With the unavailability of the vaccine and the virus spreading rapidly it is necessary to develop robust, sensitive, and advanced, detection tools. Nanomaterials can be readily applied to modify the available detection platforms to improve their sensitivity. The review aimed to brief about the methodologies of viral diagnostics that are in use and also other NP-based sensing systems. Disinfectant formulations and textiles with anti-viral

NPs can be utilized to reduce the long-term viability of the SARS-CoV-2. Advanced smartphone and/or LFA strip-based detection techniques that can be performed at the bedside can prove to be indispensable for the healthcare community who are already overworked. The present situation establishes scope for new research developments, helping us handle similar pandemics in the future in a much-controlled fashion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AM conceived the original idea and designed the review paper. SK gave conceptual ideas. DC wrote the manuscript in consultation with AM and SK. NC gave critical inputs. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnano.2020.588795/full#supplementary-material

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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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