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REVIEW ARTICLE

Nanoparticles as illuminating allies: Advancing diagnostic frontiers in COVID-19- A review

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Abstract

Nanoparticles (NPs) have emerged as indispensable tools in the fight against the coronavirus disease (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-Cov2) pandemic, finding extensive utilization in both diagnosis and therapeutics. Their ability to interact with the virus and host cells in diverse manners positions them as valuable assets for detecting, treating, and preventing COVID-19. In this comprehensive review, a detailed summary of the state-of-the-art NP-based diagnostic methods for COVID-19 has been presented, particularly important classes of gold nanoparticles (GNPs), magnetic nanoparticles (MNPs), quantum dots, liposomes, silica nanoparticles (SNPs), silver nanoparticles (AgNPs), zinc oxide nanoparticles (ZnO-NPs), and carbon nanotubes (CNTs) delineating and their inherent strengths as well as limitations. Additionally, the challenges and opportunities that have been addressed lie ahead in pursuing future advancements and clinical translation of NP-based technologies for diagnosing COVID-19.

Keywords: Human, Pandemics, COVID-19, Nanoparticle.

Introduction

Nanoparticles: Promising Tool in the Battle against COVID-19

COVID-19, a global health crisis, has resulted in a substantial loss of life and widespread morbidity. Caused by the novel coronavirus SARS-CoV-2, and the disease was first identified in China in December 2019, and was rapidly disseminated to nearly every corner of the world. While COVID-19 primarily targets the respiratory system, it can impact multiple organs and systems within the body. Common symptoms include fever, cough, respiratory distress, anosmia, ageusia, and fatigue. In severe cases, individuals experience complications such as pneumonia, thrombosis, organ dysfunction, and mortality. The primary mode of transmission was through respiratory droplets, expelled during coughing, sneezing, or speaking, which infected individuals nearby or those who came into contact with contaminated surfaces and subsequently touched their eyes, nose, or mouth (Katre *et al.,* 2021). Notably, individuals infected with COVID-19 transmitted the virus even in the absence of symptoms. In the battle against COVID-19, nanoparticles (NPs) have emerged as a promising tool for both diagnosis and therapy. These minute particles, measuring less than 100 nm in size, offer diverse medical applications, including disease detection, treatment, and prevention (Campos *et al.,* 2020). NPs can be fabricated from various materials, such as metals, inorganic compounds, or organic molecules, and can be modified or functionalized to accommodate a wide array of biomolecules, such as proteins or nucleic acids (Adhikari *et al.,* 2020). By enhancing the solubility, stability, delivery, and immunogenicity of these biomolecules, NPs demonstrate the potential to interact with the virus itself, inhibiting replication or impeding its entry into host cells. This review primarily focuses on using NPs for COVID-19

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Table 1: displays various types of nanoparticles utilized for COVID-19 diagnosis, including their advantages, limitations, and mechanisms of action.

Nanoparticle Type	*Diagnostic Application*	*Advantages*	*Limitations*	*Mechanism*
Gold NPs (GNPs)	Lateral flow assays	Rapid results, simplicity of use, low cost	Limited sensitivity compared to other techniques	Antibodies attached to Gold NPs bind to viral antigens, resulting in visible color change
Magnetic NPs (MNPs)	Magnetic resonance imaging (MRI)	High sensitivity and specificity, non-invasive imaging	Expensive imaging equipment required	Magnetic NPs functionalized with antibodies bind to viral antigens, allowing detection through MRI
Quantum Dots	Fluorescence-based assays	High sensitivity, multiplexing capability	Potential toxicity of some quantum dot materials	Quantum dots emit fluorescent signals when bound to viral antigens, enabling their detection through fluorescence-based assays
Liposomes	Enzyme-linked immunosorbent assays (ELISA)	Versatile, easy to modify, increased stability	Relatively slower analysis compared to other methods	Liposomes encapsulate viral antigens and antibodies, allowing detection through ELISA
Silica NPs (SNPs)	Drug delivery, imaging, sensing, and therapy	diagnosis is their high surface area and porosity	Limited sensitivity compared to other techniques	antigen detection, antibody detection, or nucleic acid amplification
Silver NPs (AgNPs)	Detection of viral RNA	High sensitivity	Potential interference	Surface-enhanced Raman scattering (SERS); DNA hybridization
Zinc oxide-NPs (ZnO-NPs)	Developing rapid and sensitive diagnostic methods for COVID-19 detection	provide filtration and viral inactivation	Limited sensitivity compared to other techniques	antiviral activity against coronaviruses by disrupting their envelope and blocking their entry into host cells
Carbon nanotubes (CNTs)	Electrochemical biosensors	High sensitivity, real-time monitoring	Complex fabrication and limited commercial availability	Carbon nanotubes functionalized with antibodies bind to viral antigens, causing changes in electrical properties that can be measured by biosensors

diagnosis, exploring various classes of nanoparticles (NPs), gold nanoparticles (GNPs), magnetic nanoparticles (MNPs), carbon nanotubes (CNTs), quantum dots, etc., developed or tested for detecting SARS-CoV-2 (Table 1). Additionally, we will discuss the advantages and challenges associated with employing these NPs in COVID-19 diagnosis while presenting future directions and perspectives in this rapidly evolving field.

Exploring the Versatility of NPs in COVID-19 Diagnostic

In the field of COVID-19 diagnostics, NPs have been explored in various categories, including nucleic acid detection, antigen detection, antibody detection, and biosensor detection (Campos *et al.,* 2020). For nucleic acid detection, NPs can be functionalized with complementary probes to target and detect viral RNA or DNA sequences specifically. This approach enables sensitive and specific detection of the SARS-CoV-2 virus in clinical samples (Campos *et al.,* 2020). Similarly, antigen detection involves using NPs conjugated with antibodies or viral proteins to capture and detect specific viral antigens in patient samples (Karakuş *et al.,* 2021). This approach allows for the rapid identification of active COVID-19 infections. NPs can also be utilized in antibody detection assays by immobilizing viral antigens on their surfaces. This enables the detection of specific antibodies individuals produce in response to SARS-CoV-2 infection. Additionally, the integration of NPs in biosensor platforms facilitates real-time and label-free detection of viral biomarkers, offering high sensitivity and selectivity (Karakuş *et al.,* 2021). Several examples of NP-based diagnostic methods have shown promising results. For instance, GNPs have been used in lateral flow assays (LFAs) for rapid antigen detection, while quantum dots have demonstrated their utility in fluorescent-based nucleic acid detection.

GNPs: Shining Beacons in COVID-19 Diagnostics

GNPs are nanoscale particles of gold that have unique optical and physical properties that make them suitable for various biomedical applications. GNPs can be used in LFAs, which are rapid and low-cost diagnostic tests that detect the presence of COVID-19 antigens or antibodies in patient samples (Singh *et al.,* 2023). Colloidal GNPs are also used in LFAs for COVID-19 detection. They are conjugated with specific antibodies or antigens. LFAs provide rapid, cost-effective, and portable testing with minimal equipment requirements (Huang *et al.,* 2020). However, challenges include sensitivity and specificity variations, the need for optimization, standardization, and possible interference from other substances (Anik *et al.,* 2022). Gold nanorods are elongated rod-like structures with diameters ranging from 10 to 100 nm. They exhibit characteristic surface plasmon resonance, making them ideal for optical-based detection methods. Techniques like surface-enhanced Raman spectroscopy (SERS) and localized surface plasmon resonance (LSPR) sensing have utilized gold nanorods for COVID-19 diagnostics (Elsharif, 2020). These nanorods functionalize with specific antibodies or aptamers, selectively bind to target analytes, and enabled sensitive and specific detection. For example, SERS amplifies the Raman scattering signal of viral components, while LSPR sensors detect viral antigens or specific antibodies in patient samples, providing rapid and sensitive results (Goscianska *et al.,* 2022). Similarly, gold nanoshells are composed of a dielectric core surrounded by a thin gold shell. They were functionalized with specific antibodies or aptamers to bind to viral antigens or antibodies for detection purposes selectively. Gold nanoshells were used in SERS for highly sensitive detection of viral components (Lake *et al.,* 2021). They also serve as signal amplifiers in photothermal-based sensing platforms, converting near-infrared light into localized heat upon binding to viral antigens.

Furthermore, they showed potential in colorimetric assays, where color changes indicated the presence of viral components (Baidya & Hassan, 2022; Wang *et al.,* 2022). Gold nanocages, characterized by their porous structure, were functionalized with probes for sensitive and selective detection of viral components. For instance, they were coated with DNA probes that recognized the SARS-CoV-2 spike protein, allowing rapid and specific detection (Baidya & Hassan, 2022). Gold nanocages enhanced the sensitivity and specificity of PCR-based assays by acting as signal amplifiers. Lastly, gold nanostars are functionalized with specific probes for highly sensitive detection of viral components. They are used in biosensors, such as SERS, to detect the presence of the virus in patient samples (Baidya & Hassan, 2022). They can also be utilized in LFA for rapid visual virus detection, providing a simple and accessible diagnostic method.

MNPs: A Magnetic Force Unveiling COVID-19 Diagnostics

Magnetic NPs, functionalized with specific antibodies, can selectively capture viral antigens present in patient samples, enabling rapid and accurate detection (Zhong *et al.,* 2021). MNPs combined with techniques like enzyme-linked immunosorbent assay (ELISA) or magnetic relaxation-based assays to achieve a low limit of detection (Pietschmann *et al.,* 2020). Additionally, MNPs enhanced the sensitivity and specificity of PCR-based methods by selectively capturing and concentrating viral RNA. Iron oxide NPs, known for their magnetic and optical properties, offered exciting possibilities for COVID-19 detection. Functionalized with targeting agents, such as antibodies, these NPs were directed for use in magnetic resonance imaging (MRI), enhancing the identification of COVID-19-related lesions in affected tissues (Erasmus *et al.,* 2020). Iron oxide NPs were also integrated with portable biosensors, enabling rapid and sensitive detection of viral particles through changes in the magnetic field (Erasmus *et al.,* 2020). Magnetic nanobeads, composed of magnetic materials like iron oxide, were particularly suitable for nucleic acid-based diagnostic assays such as polymerase chain reaction (PCR) or loop-mediated isothermal amplification (LAMP) (Erasmus *et al.,* 2020). When functionalized with specific primers or probes, these nanobeads enhanced the separation and concentration of viral genetic material, improving the sensitivity and accuracy of diagnostic tests. They are also used in serological assays to detect COVID-19 antibodies in patient samples. Magnetic nanowires, with their exceptional properties and high aspect ratio, offer the potential to detect and diagnose viral infections. Functionalizing them with viral antigens or antibodies, they selectively capture and bound to viral particles or antibodies in patient samples (Erasmus *et al.,* 2020). The magnetic nature of nanowires enables their manipulation and separation, facilitating detection and quantification. The integration of magnetic nanowires with microfluidic systems allowed for efficient viral capture and concentration, enabling sensitive and rapid detection.

Quantum Dots: Illuminating COVID-19 Diagnostics with Optical Precision

Quantum dots, also known as semiconductor nanocrystals. Quantum dots were integrated into immunoassays, where they are functionalized with specific antibodies or viral antigens (Zhang *et al.,* 2021). The quantum dots selectively bind to their targets in patient samples, and their distinctive optical properties enable sensitive detection through fluorescence or luminescence signals. This approach allows for rapid and quantitative measurement of viral antigens or antibodies, aiding in the diagnosis of COVID-19 (Zhang *et al.,* 2021). Quantum dots were also incorporated into point-of-care devices, enabling rapid and on-site testing. By coupling quantum dots with nucleic acid amplification techniques like PCR or LAMP, the presence of viral RNA could be accurately detected and quantified (Kang *et al.,* 2022). This approach facilitated timely patient management and containment strategies. Ultrasensitive immunoassays that utilized quantum dots as labels showed excellent photostability and brightness, enabling reliable and high-throughput detection of viral antigens (Liu *et al.,* 2020).

Moreover, quantum dots have been utilized in innovative diagnostic tests such as luminescent quantum dot-based lateral flow immunoassays and quantum dot-based fluorescent immunoassays (Ahmad Najib *et al.,* 2022; Wang *et al.,* 2021). These tests leveraged the optical properties of quantum dots to offer high sensitivity, specificity, and speed in detecting SARS-CoV-2 antigens or antibodies. Additionally, quantum dot-based surface plasmon resonance assays combined the optical properties of quantum dots with the highly sensitive detection capabilities of surface plasmon resonance, allowing for accurate and rapid detection of viral markers. Finally, quantum dot-based LAMP represented a groundbreaking approach for detecting the SARS-CoV-2 virus (Wang *et al.,* 2022). This method demonstrates exceptional sensitivity, specificity, and the ability to differentiate between different coronavirus strains within a rapid timeframe.

Liposomes: Unleashing Diagnostic Potential in the Battle Against COVID-19

Liposomes are spherical structures composed of a lipid bilayer. Their versatility allows for the encapsulation of diverse molecules, including drugs, proteins, and nucleic acids, facilitating targeted delivery to specific cells or tissues (Wang *et al.,* 2022). For COVID-19 diagnosis, liposomes were employed to encapsulate viral RNA or antigens, enabling their detection using different methods (Faizal & Amin, 2022). For instance, liposomes labeled with fluorescent dyes or magnetic particles facilitating detection through fluorescence microscopy or MRI. Alternatively, liposomes are functionalized with specific antibodies that are bound to the virus or its components, providing a visual signal of infection. One notable advantage of using liposomes as a diagnostic tool is their ability to enhance the sensitivity and specificity of the assay. By encapsulating viral RNA or antigens, liposomes amplified the detectable material in the sample while minimizing background signals, ensuring accurate results (Faizal & Amin, 2022). Several liposome-based diagnostic approaches for COVID-19 have been explored, including liposome-based RNA extraction and amplification, liposome-based antigen detection, and liposome-based fluorescence assays (Ji *et al.,* 2020). Liposome-based RNA extraction and amplification involve the protection of viral RNA from degradation by liposomes during extraction, followed by amplification using reverse transcription PCR (RT-PCR) assays (Refaat *et al.,* 2021). This method aims to detect the presence of SARS-CoV-2 by amplifying the viral RNA in patient samples. Liposome-based antigen detection utilizes liposomes functionalized with specific antibodies binds to SARS-CoV-2 antigens. When liposomes encounter the antigens in patient samples, a color change occurs, providing a visual indication of the presence of viral antigens. Lastly, liposome-based fluorescence assays employ liposomes functionalized with specific antibodies and a fluorescent dye. Upon binding to SARS-CoV-2 antigens, the liposomes generate a detectable fluorescence signal that can be quantified using a fluorescent plate reader or handheld device.

SNPs: Versatile Substrates for COVID-19 Diagnostic

SNPs are nanoscale particles of silicon dioxide that have been widely explored for various biomedical applications, such as drug delivery, imaging, sensing, and therapy (Huang *et al.,* 2020). One of the advantages of SNPs for COVID-19 diagnosis is their high surface area and porosity, which allow them to load a large number of biomolecules, such as antibodies, antigens, DNA, or RNA, that can specifically bind to the viral proteins or genetic material. By functionalizing SNPs with different types of biomolecules, they can be used for various diagnostic approaches, such as antigen detection, antibody detection, or nucleic acid amplification. For example, SNPs coated with viral antigens and used as a substrate for lateral flow immunoassays, which could detect the presence of antibodies against SARS-CoV-2 in human blood or saliva samples (Zhu *et al.,* 2017). Alternatively, SNPs conjugated with antibodies against SARS-CoV-2 were used as a signal enhancer for colorimetric or fluorescent detection of viral antigens in swab samples. Moreover, SNPs modified with DNA or RNA probes that could hybridize with the viral genome and trigger a PCR or a LAMP reaction, which amplified and detected the viral nucleic acids with high sensitivity and specificity.

AgNPs: A Promising Diagnostic Tool for Efficient and Sensitive SARS-CoV-2 Detection

AgNPs are NPs with antimicrobial and antiviral properties that can interfere with viral replication, entry, and release. Several methods have been developed to detect SARS-CoV-2 nucleic acids, antigens, or antibodies using AgNPs as signal transducers or amplifiers (Orooji *et al.,* 2021). These methods exploit the optical, electrical, or magnetic properties of AgNPs, which can be altered by the binding of viral biomarkers to AgNP-based probes or labels. For example, lateral flow immunoassays use AgNP-labelled antibodies to capture viral antigens or host antibodies on a test strip, producing a visible color change (Pasparakis, 2022). Colorimetric assays use unmodified AgNPs to induce aggregation or disaggregation of DNA probes hybridized to viral RNA, resulting in a color change that can be detected by the naked eye or a spectrophotometer (Pasparakis, 2022). Electrochemical biosensors use AgNP-modified electrodes to enhance the electrical signal generated by the interaction of viral biomarkers with specific receptors. Magnetic capture assays use magnetic AgNPs to isolate viral RNA from complex biological samples and amplify it by LAMP. AgNPs have been shown to exhibit antiviral activity against various enveloped viruses, including coronaviruses. AgNPs could act as a physical barrier or a biocidal agent against SARS-CoV-2 by disrupting the viral envelope, binding to viral proteins, or interfering with viral gene expression.

ZnO-NPs: Versatile Tools for COVID-19 Diagnostics and Antiviral Applications

ZnO-NPs are emerging nanomaterials with potential applications in COVID-19 diagnostics. ZnO-NPs exhibit antiviral activity against coronaviruses by disrupting their envelope and blocking their entry into host cells. ZnO-NPs interacts with COVID-19 targets such as the ACE2 receptor, RNA-dependent RNA polymerase, and main protease, via hydrogen bond formation. These interactions were utilized for developing rapid and sensitive diagnostic methods for

COVID-19 detection. For instance, ZnO-NPs were integrated into face masks or textile materials to provide filtration and viral inactivation. ZnO-NPs also served as biosensors or nanoprobes to detect the presence of viral RNA or proteins in biological samples (Rodelo *et al.,* 2022).

CNTs: Pioneering Nanoscale Warriors in COVID-19 Diagnostics

CNTs are one-dimensional nanostructures with remarkable physical and chemical properties, such as high surface area, high conductivity, and biocompatibility. These properties make CNTs attractive candidates for various applications in nanomedicine, especially in the context of the COVID-19 pandemic. CNTs were used as biosensors for COVID-19 by functionalizing them with antibodies specific to the SARS-CoV-2 virus (Varghese *et al.,* 2022). The functionalized CNTs selectively captured and detected the virus in samples, such as saliva, blood, or nasal swabs. The interaction between the virus and the functionalized CNTs was measured through changes in electrical conductance or fluorescence, providing a rapid and sensitive detection method. However, there are still many challenges and limitations to overcome before their clinical application, such as scalability, biocompatibility, toxicity, and regulation. Further research and development were needed to fully exploit the potential of CNTs for COVID-19 diagnostics and therapeutics (Varghese *et al.,* 2022).

Conclusion

NP-based diagnostics is a powerful tool for COVID-19 detection. NPs have unique optical, electrical, and magnetic properties that can be exploited for various diagnostic applications. Their small size, large surface area, and customizable surface chemistry enable them to enhance the sensitivity and specificity of various diagnostic approaches, such as rapid antigen tests, PCR-based assays, and biosensors. NPs can also facilitate point-of-care diagnostics by integrating with smartphone-based platforms and wearable devices, allowing for decentralized testing and remote monitoring. However, challenges remain in the translation of NP-based diagnostics from the laboratory to the clinic, such as scalability, cost-effectiveness, regulatory approvals, and potential toxicity. In this article, some of the recent advances in NP-based diagnostics for COVID-19, such as LFAs, biosensors, and magnetic resonance imaging have been presented.

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