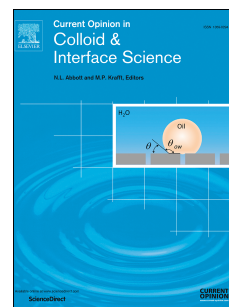


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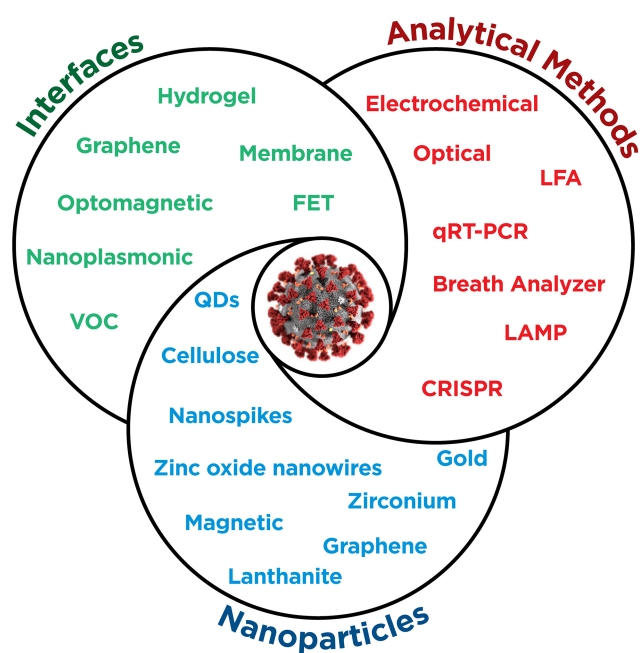
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State of the art of colloidal particles and unique interfaces-based SARS-CoV-2 detection methods and COVID-19 diagnosis

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Abstract

In March 2020, SARS-CoV-2 based infections were declared ‘COVID-19 pandemic’ by the World Health Organization (WHO). Pandemic raised the necessity to design and develop genuine and sensitive tests for precise specific SARS-CoV-2 infections detection. Nanotechnological methods offer new ways to fight COVID-19. Nanomaterials are ideal for unique sensor platforms due to their easy manufacturing, chemically versatile properties. In this context, selected examples for integrating nanomaterials and distinct biosensor platforms are given to detect SARS-CoV-2 biological materials and COVID-19 biomarkers, giving researchers and scientists more goals and a better forecast to design more relevant and novel sensor arrays for COVID-19 diagnosis.

Keywords: SARS-CoV-2, COVID-19 biomarkers, colloidal nanoparticles, interfaces

1. Introduction

Coronaviruses (CoVs) are large enveloped non-segmented single-stranded RNA viruses responsible for causing respiratory tract disorders in humans. A new coronavirus (SARS-CoV-2) named (COVID-19) emerged in Wuhan, China, in 2019 (1). SARS-CoV-2 is a beta-coronavirus family member and causes mild upper respiratory diseases together with four ubiquitous family members, namely 229E, OC43, NL63, and HKU1 (2). SARS-CoV-2 pathogenic strain is a combination of SARS-CoV and MERS-CoV viruses. The metagenomic analysis revealed that the SARS-CoV-2 has approximately 80% similarity with SARS-CoV and two other SARS-like coronaviruses recognized in bats (bat-SL-CoVZC45 and bat-SL-CoVZXC21) (2). The appearance of new coronaviruses in humans depends on primary factors

for the frequent emergence of the coronaviruses related to the wide distribution, high prevalence, high genetic diversity, frequent genome recombination, and human-animal interface activities (3).

Although COVID-19 showed a low fatality rate in humans, it was highly infectious, with raw reproduction number (R_0) ranges from 1.4 to 6.47 (4). The primary clinical symptoms in these studies are fever, cough, shortness of breath, and myalgia (5). Soon after infection, acute respiratory distress syndrome (ARDS) was observed in patients, followed by a severe cytokine storm, which frequently accounted for COVID-19- related deaths (3). Due to the severity of infection as a pandemic, highly sensitive, precise, distinctive, and specific biosensor platforms should be developed by the researchers.

Nanotechnology offers various *in vitro* and *in vivo* solutions to combat SARs-CoV-2-based infections. Nanomaterials are a critical component in these technologies and crucial in detecting or transforming biochemical interactions (6). In this review, various nanomaterial-based particular biosensor arrays are given in a select platform.

2. Biological materials and indicators of Covid-19 diagnosis

2.1. Biological materials for SARS-CoV-2 testing

The whole SARS-CoV-2 itself, as well as its structural proteins, such as spike (S) glycoprotein, nucleocapsid (N), matrix (M), and a small envelope (E), are used as antigens in several testing methods. According to previous reports, S-protein is crucial for the adhesion to host cells, in which the S-protein mediates the interaction of the angiotensin-converting enzyme-2 (ACE2) with its receptor-binding domain (RBD). S and N proteins are invaluable antigen biomarkers for serological testing in the detection of COVID-19. The produced IgM, IgG, and IgA against S and N proteins are mostly used to develop various serological assay methods (7).

Typically, preferred targets for SARS-CoV-2 genetic assays are Spike glycoprotein S gene, Envelope protein E gene, Nucleocapsid protein N genes, Non-structural RNA-dependent RNA polymerase RdRp gene, and Open reading frame of the 1a/bc ORF1a/b gene. E and

ORF1a/b genes are most frequently used in molecular tests to detect SARS-CoV-2 infections (8).

2.2. Indicators of COVID-19

According to Ponti and his coworkers (2020), many biochemical, hematological, and inflammatory-based indicators are found to be accompanying COVID-19 infections. The leading hematological indicators in COVID-19 infections are counts of lymphocytes and neutrophils and their ratios (9). Several studies reported lymphopenia in COVID-19 patients in severe cases (10,11). As other biomarkers, several biochemical indicators such as troponin, creatine kinase, and D-dimer are present. According to Yao and coworkers (2020) and Tersalvi and coworkers (2020), the disease severity is directly related to the D-dimer levels (12,13). Garg and coworkers (2021) postulated that elevated levels of inflammatory biomarkers such as procalcitonin (PCT), C-reactive protein (CRP), ferritin (FT), and Interleukin-6 (IL-6) are indicators of the severity of COVID-19 infections (14).

3. Standard test methods for SARS-CoV-2

Detection of the virus is a crucial weapon in combating the COVID-19 pandemic and plays a decisive role in isolating infected individuals early to avoid the risk of transmission. Early, affordable, and accurate diagnosis of SARS-CoV-2 is an urgent need to ease the early intervention efforts and slowing down the transmission of this pandemic disease. The standard test for COVID-19 is quantitative reverse transcription-polymerase chain reaction (qRT-PCR) (15) as a gold standard. Also, nanoparticles get their importance in nucleic acid-based methods with their usage in RNA purification techniques. With this in mind, a simple and modern magnetic nanoparticle protocol is proposed for assisted SARS-CoV-2 RNA extraction by using zinc ferrite MNPs with carboxyl-containing polymers functionalized surface (16). In another approach, a simplified three-step method for the production of large quantities of magnetic nanoparticles for RNA extraction in response to developing countries' needs. Poly-NH₂-MNPs are optimized and scaled for high-quality SARS-CoV-2 RNA extraction (17). Due to the simple and inexpensive nature of magnetic nanoparticle-based extraction methods, these can be a suitable substitute for traditional techniques.

The neutralizing antibody (IgM and IgG) detection based on enzyme-linked immunosorbent assay (ELISA), which depends on their interactions with antigenic compounds of virus ligand, is another traditional technique for the detection of Covid-19 neutralizing antibody testing.

However, unwanted false-negative results, long response time, and low sensitivity are their main drawbacks. The development of serological tests to accurately show the previous infection and followed immunity to SARS-CoV-2 will be critical for epidemiological research and monitoring tests (18).

Due to the straight need for fast, sensitive, and low consumption diagnosis of COVID-19, nanotechnology can play a crucial role in detecting SARS-CoV-2. Mechanical, electronic, and magnetic properties of nanoparticles are fundamental in diagnostics endeavors (19).

4. Nanoparticle-based detection strategies of COVID-19

Diagnostic methods are essential strategies that could be used to tackle COVID-19, isolating the infected patients and prevent dissemination (20). Several techniques are available to detect SARS-CoV-2, such as ELISA or RT-PCR from nasopharyngeal swabs obtained from noses and throats of patients (7). These techniques rely on their interaction with the detection of ligand complementary strands. The main disadvantage of these methods is their false-negative results and low sensitivity (21).

Nanomaterials are the most current components in SARS-CoV-2 testing since they have distinct properties, such as their large surface-to-volume ratios. Extensive surface interactions of the nanomaterials and the sensor and the analyte, these materials allow rapid and reliable detections with high sensitivity (19).

SARS-CoV-2 virus infection triggers many inflammatory, biochemical, and hematological biomarkers. Various inflammation markers, such as (PCT), (CRP), (FT) and (IL-6) have been intricately linked to this infection. Detection of these markers can also help to understand the level of disease. By monitoring these biomarkers, infections with low SARS-CoV-2 RNA are also predicted in patients where traditional tests miss. In this area, nanoparticles are also used to develop several COVID-19 diagnosis methods (14). Several types of nanoparticles used in SARS-CoV-2 detection methods are given in Figure 1.

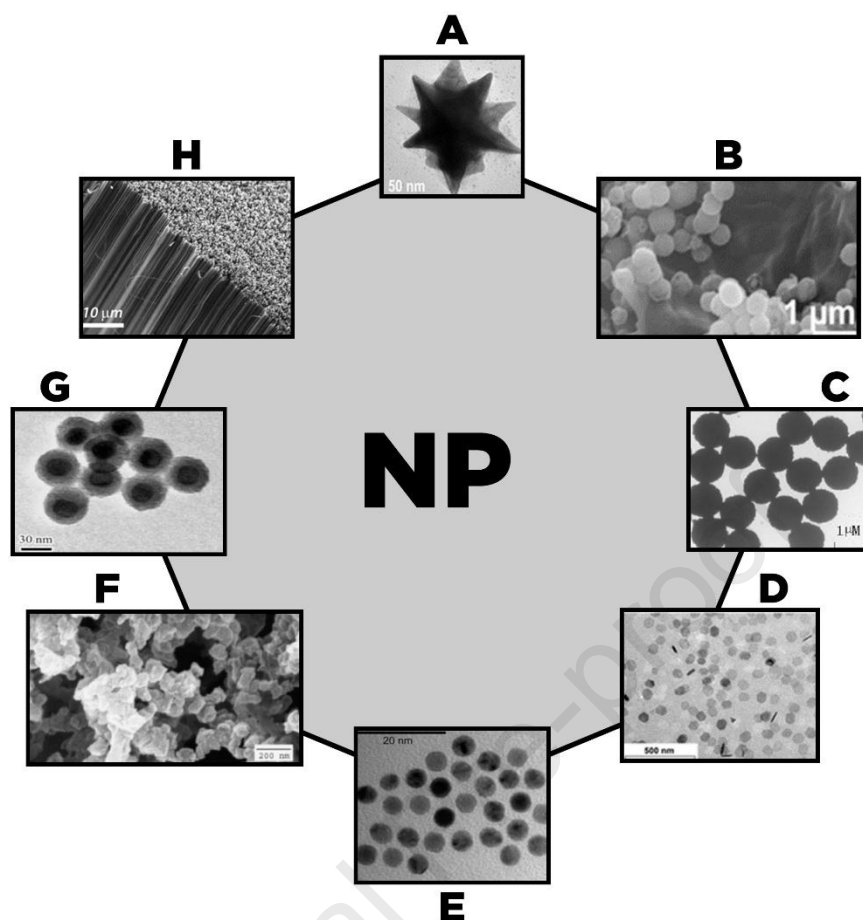


Figure 1. Distinctive colloids and nanoparticles used in SARS-CoV-2 detection and COVID-19 diagnosis. (A) Transmission electron micrographs of gold nanospike, Reprinted with permission (22); (B) Scanning electron microscopy (SEM) images for CuWO₄@rGO hybrids, Reprinted with permission (23); (C) Transmission electron microscopy (TEM) of the superparamagnetic beads, Reprinted with permission (24); (D) TEM image of single-crystalline graphene quantum dots, Reprinted with permission (25); (E) TEM image of size distributed AuNPs, Reprinted with permission (26); (F) SEM image of aggregated cellulose nanoparticles with an average diameter of 80 nm, Reprinted with permission (27); (G) TEM image of lanthanide nanoparticles with lanthanide complexes doped in the silica shell, Reprinted with permission (28); (H) Field emission-scanning electron microscopy (FE-SEM) image of a single-walled carbon nanotubes (SWNTs) forest, Reprinted with permission (29).

4.1. Gold nanoparticles

Within nanoparticles, gold nanoparticles are universally used in testing strategies due to their unique features. These are easy synthesis, stability in time, size variability, biocompatibility,

enhancement of catalytic size by silver deposition, conductivity, electrochemical properties, and ability to quench fluorescence. Therefore, nanoparticles become highly effective materials for developing fluorescent sensors (30). Gold nanoparticles have peculiar optical properties, which is named Localized Surface Plasmon resonance (LSPR). LSPR is used in biosensors because of its light adjustability and scattering of wavelengths in the visible spectrum. LSPR spectra of gold nanoparticles change as a function of the refractive index of their surrounding media. Thus nanoparticle aggregation degree is considered a decisive factor for their applicability in biological detection (31). Alafeef and his coworkers (2020) reported a fast, inexpensive, easy-to-apply, and quantitative paper-based electrochemical sensor chip that enables digital detection of SARS-CoV-2 genetic material by using gold nanoparticles coated with highly specific antisense oligonucleotides that target the viral nucleocapsid phosphoprotein gene with a limit of 6.9 copies/ μl . Sensor probes are immobilized on a paper-based electrochemical platform to provide a nucleic acid tester with a screen that can be registered with a simple handheld reader (32).

~~Yadavalli and Shukla (2017) developed a simplified test to detect viral proteins relying on the color change of gold nanoparticles when they are bound to antibodies [31].~~

Broughton and coworkers (2020) utilized the powerful genome editing techniques of CRISPR/CAS9 for detecting viral RNA of SARS-CoV-2 from nasopharyngeal swabs in a lateral flow assay using AuNP as a label (33). Ventura and coworkers (2020) recently developed a colorimetric biosensor for the mass testing of COVID-19 with a sensitivity and specificity higher than 95% for more than 90 samples (34). In another application, conjugated colloidal gold nanoparticles with streptavidin are used for an RT-LAMP combined with a flow-through assay for CoV detection (35). Biotin/FITC-labelled amplicons bind to streptavidin-functionalized gold nanoparticles, and by using an antibody-coated strip, the color formation can be detected. The assay takes 35 minutes to detect LOD 10 copies/ μl of MERS-CoV RNA. Also, this approach produced high specificity without cross-reactivity for other CoVs (35). In another research, gold nanoparticles were conjugated with thiol-modified antisense oligonucleotides (ASOs) to detect the RNA coding for the N-protein of the SARS-CoV-2, calorimetrically. Results were seen within 10 minutes with a LOD less than 0.18 ng/ μl (36).

One of the most frequently used techniques to detect neutralizing antibodies of SARS-CoV-2 is the lateral flow immunoassay technique. The technique is used in several tests developed for Covid-19 antibodies, virus antigens, and nucleic acid-based methods (37). Roda and his coworkers (2021) developed a dual optical/chemiluminescent type of an LFIA immunosensor for IgA in serum and saliva, which depends on capturing SARS-CoV-2 antibodies with a recombinant nucleocapsid antigen (38). A simple device utilizing a smartphone camera measures the color signal provided by anti-human IgA labeled nanogold particles. For ultrasensitive chemiluminescence transduction, they used a portable contact imaging device based on cooled CCD and measured the light signal that resulted from the HRP-labeled anti-human IgA reaction with an H_2O_2 /luminol/enhancer substrate (38).

Gold nano spikes are a promising class of molded nanoparticles since these multi-branched nanoparticles with sharp tips have exciting plasmonic properties with a broad plasmon band in the near-infrared region (NIR) (22). Funari and coworkers (2020) utilized the Localized Surface Plasmon Resonance (LSPR) LSPR to design an Opto-microfluidic sensor with gold nano spikes for detecting SARS-CoV-2 spike protein in human plasma less than 30 min. This label-free method achieves the LOD of $\sim 0.08 \text{ ng/mL}$ (39).

Gold NPs are also used in the detection of COVID-19 biomarkers several times. For this purpose, an ultrasensitive sandwich electrochemical immunosensor was developed for procalcitonin (PCT) detection (40). The immunosensor is formed using delaminated-sulfur doped- MXene ($\text{dS-Ti}_3\text{C}_2\text{TX}$ MXene)-modified carbon electrode (GCE) containing the PCT antibody-conjugated AuNPs were used as an immunosensor array. Carboxylated graphitic carbon nitride (c-g- C_3N_4) was then conjugated with PCT Ab2 as a signal amplifier. Electrochemical impedance spectroscopy and cyclic voltammetry are performed to detect c-g- C_3N_4 catalytic activity against H_2O_2 and are used directly as a redox probe. The linearity range and LOD results were calculated as $0.01\text{-}1.0 \text{ pg mL}^{-1}$ and 2.0 fg mL^{-1} , respectively (40).

An optical assay-based aggregation of AuNPs coated with two complementary aptamers for different IL-6 target fragments in a sandwich-type was developed for IL-6 detection. Recognition and binding of the complementary pair of aptamers caused the corresponding functionalized nanoparticles to be aggregate. The aggregation of AuNPs gives a visible color, which is changed from red to pink with a difference in absorbance 520-540 nm. The test

works in a concentration range from 3.3 to 125 $\mu\text{g ml}^{-1}$ IL-6, and the detection limit is 1.95 $\mu\text{g ml}^{-1}$ (41).

An origami paper-based electrochemical immunoassay for detecting C-reactive protein (CRP) was developed with multiple electrode modification steps onto a graphene-modified screen-printed carbon electrode (G/SPCE). Gold nanoparticles electrodeposited a self-assembled monolayer of L-cysteine modifies G/SPCE. A capture anti-CRP does CRP measurement on the modified electrode by using hexacyanoferrate as a redox probe. The increase in impedance in the concentration range of 0.05–100 $\mu\text{g ml}^{-1}$ CRP, and the LOD is found as 15 ng ml^{-1} (42).

4.2.Magnetic nanoparticles (MNPs)

Magnetic nanoparticles are indispensable tools for the development of several diagnosis and analysis methods. MNPs have been used in several methods in COVID-19 diagnosis and development of detection tests against SARS-CoV-2. The prominent use of a magnetic nanoparticle is to separate the viral RNA for diagnostic purposes, of which iron oxide nanoparticles are highly used due to their high magnetic capability and easy manufacturing procedure (43). It was recently demonstrated that a carboxyl group attached polyaminoester (PC)-coated magnetic nanoparticle could detect SARS-CoV-2 RNA with high purity performance within 30 minutes. The PC-coated magnetic nanoparticle proved high binding capacity with viral RNA, and the pcMNP–RNA complexes were amplified by Real Time-PCR (44).

Direct virus detections are also shown recently (45). The study shows the detection of SARS-CoV-2 by measuring the magnetic particle spectroscopy (MPS) signal of magnetic nanoparticles (MNPs) functionalized with the SARS-CoV-2 spike protein-antibody with a detection limit of 0.084 nM (5.9 fmol). An MPS system was used to measure the MPS signal from functionalized MNPs. Also, AC sensitivity spectra (ACS) were measured with a rotating magnetic field system (RMF) to evaluate the Brownian relaxation time (45).

A carbon-based SPE as a sensor combined with an MB-based electrochemical test with a 19 ng/mL detection limit was reported for SARS-CoV-2 in saliva. SARS-CoV-2 proteins, S-and

N were used as the target analyte to develop a sandwich experiment with antibodies immobilized on MBs for S or N proteins from nasopharyngeal swab samples (46).

On the other hand, magnetic bead-based methods are developed for detecting COVID-19 biomarkers. A new electrochemical lab-on-chip magnetoimmunoassay was proposed for the determination of procalcitonin (PCT). The method depends on the online presence of the biorecognition event and detection on a microfluidic thin-film gold electrode chamber operating at $E = -0.20$ V, compared to Au in less than 15 minutes with a detection limit and quantification at 0.02 ng/ml and 0.05 ng/ml, respectively (47). The same group, this time, developed an electrochemical immunoassay based on magnetic beads in a sandwich format with two different approaches: The first approach consisted of disposable screen-printed carbon electrodes (SPE-C) and microfluidic chips (EMC-Au) with integrated Au electrodes. This approach offers good sensitivity with LOD of 0.1 and 0.04 ng mL⁻¹ for SPE-C and EMC-Au, respectively, with a total test time of fewer than 20 minutes (48).

4.3. Quantum Dots (QDs)

Quantum Dots (QDs) possess unique optical and electrical properties, so they have been used to detect several viruses (49). As the QDs also have an excellent plasmonic property, a star-shaped chiroplasmonic gold nanoparticle is conjugated with it to develop an optical biosensor to detect the influenza virus (50). For this Anti-HA and anti-NA, the influenza virus antibodies are immobilized on the gold nanoparticle on quantum dots' surfaces, respectively. Once the recombinant protein of the respective virus is mixed to form a nanohybrid complex was formed with the gold nanoparticle and QDs, after that, a plasmon-excitation interaction is created on the nanohybrids, which enhance the chiral optical response of the solution. In this way, the viral recombinant protein is detected with the measured circular dichroism response of the solution. By these techniques, a group of researchers achieved a LOD of less than 1 pg/ml for influenza virus and coronavirus (50). A similar method was developed to aid a magnetoplasmonic fluorescent biosensor depending on the zirconium Quantum Dots and Fe₃O₄-Au core-shell magnetoplasmonic nanoparticles. Once the virus is added to the mixture, the conjugated zirconium Quantum Dots and magnetoplasmonic nanoparticles formed magnetoplasmonic-fluorescent nanohybrid structures. The virus presence is showed by the nanohybrids complexes' photoluminescence properties in which LOD was 79.15 EID/50 µl in blood samples (51). The possibility of QDs ability to increase the sensitivity of SPR-based

fluoroimmunoassay for the detection of norovirus virus was established (52). Such types of novel fluorescent-based quantum dots can be used to develop a practical method of COVID-19 detection (53).

A spike recombinant receptor binding domain conjugated with fluorescent quantum dots was used to develop an imaging probe. Energy transfer quenching with ACE2-conjugated gold nanoparticles in solution is used to monitor the interaction. Neutralizing antibodies and recombinant human ACE2 blocks quenching with a specific binding interaction within nanomolar potency. The QD probe can then be used to study the inhibitors of SARS-CoV-2 spike and ACE2 receptor binding proteins in human cells (54).

In a novel study, QDs from biosurfactant stabilized/functionalized tungsten disulfide (WS₂-B) and its effect on a ferritin immune sensor were described (55). Extensive characterization is done using analytical techniques to investigate further possible screen-printing electrodes (SPE) applications, functionalized with WS₂-B-QDs. Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques are combined for electrochemical immunosensing of ferritin with detection limits of 3,800 ng/ml in DPV and 6,048 ng/ml in CV (55). The same group also tested ferritin detection by hexagonal boron nitride quantum dots (hBN QDs). Electrochemical impedance spectroscopy is used in a platform where hBN QDs are a functionalized detection platform for screen-printed electrodes. The developed immune sensor has a linear range from 10 to 2000 ng/ml⁻¹ ferritin concentration with a detection limit of 1.306 ng/ml⁻¹ (56).

Wu and his co-workers (2018) report an LFIA for quantitative and rapid detection of CRP based on CdSe/ZnS QDs by measuring the fluorescence intensity immediately afterward with a fluorescence immunoassay analyzer. QDs are synthesized using the "green" phosphine-free method with a wide detection range between 0.5 ng ml⁻¹ and 1 µg ml⁻¹, and the analytical detection limit is 0.3 ng ml⁻¹ (57).

4.4. Graphene nanoparticles

The two-dimensional hexagonally arranged carbon has a promising future due to its high ultrasensitive characteristic of surface area, electrical and ionic mobility (58). A field-effect transistor (FET) sensor to detect SARS-CoV-2 in human nasopharyngeal swabs was reported

recently (59). In this wet transfer method, graphene is placed onto the SiO₂/Si substrate using the photolithographic method. The graphene surface is coated with SARS-CoV-2 spike protein antibody to prepare the FET-based analytical system. The clinical samples of COVID-19 patients are applied on the FET-based biosensing device, and LOD is reported as 1 fg/mL (59).

4.5. Carbon nanotubes

In a new approach, reactive oxygen species (ROS), harmful to many viruses, including coronaviruses, are used to detect COVID-19 diagnosis (46). Recently, metal-decorated single-walled carbon nanotubes (SWCNTs) adsorbed with hydrogen peroxide (H₂O₂) were investigated for their possible use in the design of inactivation of viruses on surfaces (60). Pt, Pd, Ni, Cu, Rh, or Ru decorated SWCNTs are tested for detecting SARS-CoV-2. The detection of separate H₂O₂ molecule adsorption on bare and metal-functionalized SWCNTs is based on Density Functional Theory (DFT) (60). Based on H₂O₂ production and adsorption on the CNTs, an electrochemical sensor to detect the ROS concentration in the sputum sample was developed (61). The accuracy and sensitivity of the sensor are found at 97% and 95%. The COVID-19 ROS detection approach contains an electrochemical ROS/H₂O₂ system. It consists of a portable automatic electrochemical reader and a single-use sensor for detection. The sensor is made by growing multi-walled carbon nanotubes (MWCNTs) on the tip of steel needles (61).

An optical nanosensor based on non-covalently functionalized SWCNTs with ACE2 proteins was developed recently (62). The nanosensor principle depends on the SARS-CoV-2 spike protein presence, which leads to an increase in nanosensor fluorescence within 90 minutes of exposure to the spike protein. Sensor responded in the salivary samples and virus transport environments. It is shown that ACE2-SWCNT nanosensors retain detection capability in a modified surface with a 73% fluorescence turn-on response within 5 seconds of exposure to 35 mg / L SARS-CoV-2 virus-like particles (62).

4.6. Specialized nanoparticles

Lanthanite complexes and nanoparticles are excellent fluorescent probes in a wide variety of biomedical research due to their unique fluorescence emission peaks, bright and

monochromatic emissions, high quantum efficiency, large Stokes drift, and long fluorescence lifetimes (63). Immense research has been conducted to improve the credibility and sensitivity of POC tests for SARS-CoV-2 by using lanthanide nanoparticles. A recent study reported the utilization of lanthanide-doped polystyrene nanoparticles and detection with a portable fluorescence reader obtained from RT-PCR (64).

Whang and coworkers (2020) offered an LFA (Lateral flow assay) test kit based on SARS-CoV-2 nucleoprotein modified with selenium nanoparticles to detect anti-SARS-CoV-2 IgM and IgG in human serum (65). The results were visible to naked eyes within 10 minutes. Selenium nanoparticles are synthesized by L-ascorbic acid reduction of selenic acid and conjugated with the nucleoprotein. The IgM and IgG detection limits are 20 ng mL^{-1} and 5 ng mL^{-1} , respectively. No cross-reaction with other anti-nuclear antibodies and influenza viruses is observed using the designed test kit (65).

A specific LFIA-based biosensor for COVID-19 was developed using a cellulose nanosphere (CNB) platform. SARS-CoV-2 nucleocapsid protein (NP) -specific single-chain variable fragment crystallizable fragment (ScFv-Fc) fusion antibodies are generated by phage display technology. ScFv-Fc antibodies are specific to SARS-CoV-2-NP antigen with high affinity, and three specific antibody pairs are used on the cellulose nanosphere (CNB)-based LFIA kit. The detection limits for the best pair are found as 2 ng of antigen protein and 2.5×10^4 pfu of the cultured virus (66).

Individual nanoparticles are also used in COVID-19 biomarker detections. A conductive nano-hybrid material consisting of Au-NPs and molybdenum disulfide, functionalized with an ionic liquid (Au-NPs/IL-MoS₂), was produced and used to immobilize primary CRP antibodies. Later, 1,5-diaminonaphthalene (DN) was adsorbed via p-p stacking on graphene oxide (GO), which is modified with iridium nanoparticles (Ir-NPS) as a label for labeling secondary CRP antibodies. Immunosensor shows a linear detection ranging from 0.01 to 100 ng mL^{-1} and LOD of 3.3 pg mL^{-1} (67).

A photoelectrochemical procalcitonin (PEC-PCT) immunosensor platform based on photoactive CuWO₄ nanospheres, grown on reduced graphene oxide layers (CuWO₄ @ rGO) was constructed (23). The immunosensor is used for PCT detection based on an

electrocatalytic mechanism. The recorded reduction of the photocatalytic oxidation signal was observed within the concentration range varying from 10 pg mL^{-1} to 50 ng mL^{-1} (23).

A label-free electrochemical immunosensor was developed to detect PCT using toluidine blue-functionalized-NiFe-Prussian blue analog nanocubes (NiFe PBA-nanocubes @ TB) as signal amplifiers. NiFe PBA nanocubes were synthesized with a selective method. The electrochemical performance of nanocubes is increased by functionalization with TB. The developed immune sensor showed a linear detection range of 0.001 to 25 ng mL^{-1} and a LOD of $3 \times 10^{-4} \text{ ng mL}^{-1}$ (68).

A quantitative Eu-Np combined LFIA method for the detection of IL-6 is created by Huang and his co-workers (2020) in serum. To develop the quantitative IL-6 detection kit, a double antibody sandwich immunofluorescence assay is tested on LFIA with a wide linear range (2 - 500 pg/mL) and good sensitivity (0.37 pg/mL) (69).

5. Recently developed exclusive interfaces-based biosensors for SARS-CoV-2 testing and Covid-19 diagnosis

Nanobiosensors are a valuable alternative to conventional laboratory devices for clinical and environmental analysis. They can combine the unique electrical and optical properties of nanomaterials with biological or synthetic molecules that are used as receptors for the selective detection of all types of analytes (70). In figure 2, distinct nanobiosensor platforms are given in the detection of SARS-CoV-2.

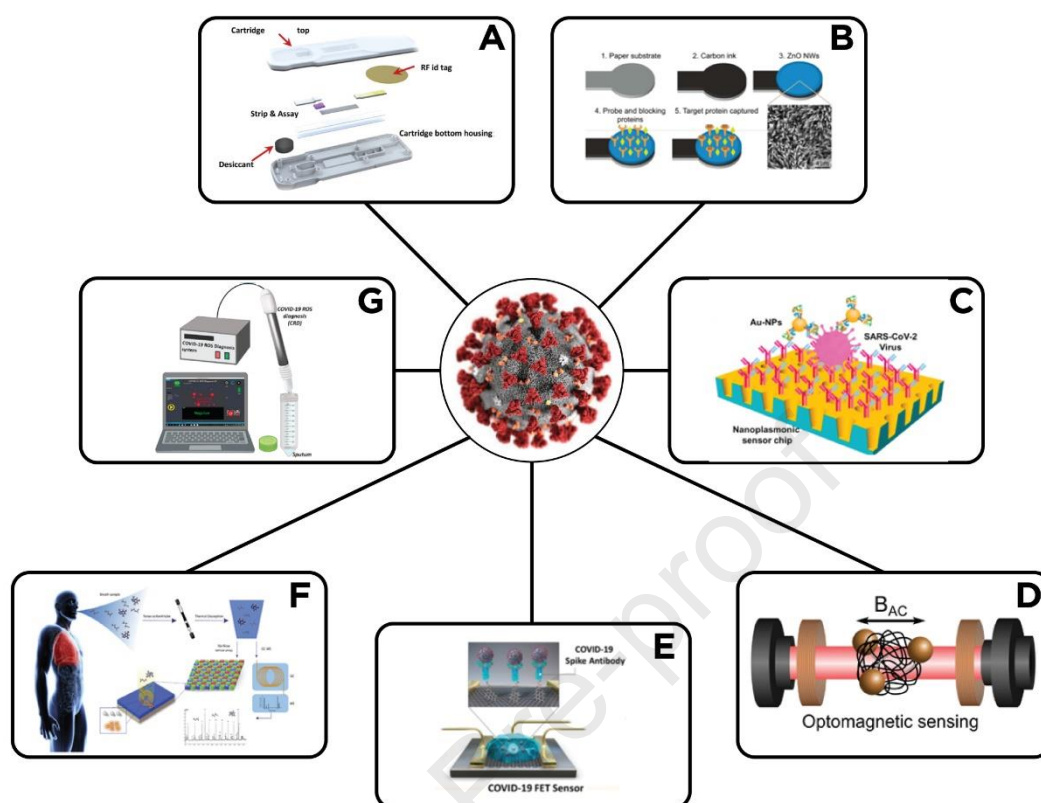


Figure 2. Fascinating nanobiosensor platforms in the detection of SARS-CoV-2. (A) Lateral flow test platform, Reprinted with permission (71); (B) Paper-based electrochemical impedance spectroscopy nanobiosensor, Reprinted with permission (72); (C) Nanoplasmonic sensor in generic microplate reader and point-of-care device, Reprinted with permission (73); (D) Real-time optomagnetic detection of SARS-CoV-2, Reprinted with permission (74); (E) Field-Effect Transistor-Based Biosensor for SARS-CoV-2 detection, Reprinted with permission (59); (F) Exhaled breath sampling and analysis procedure, Reprinted with permission (75); (G) The COVID-19 ROS diagnosis system with three electrodes coated by functionalized multi-wall carbon nanotubes, Reprinted with permission (61).

5.1. Breath analyzers

Two recent reports showed that the potential volatile organic compounds (VOC) marker contain higher ethyl butyrate levels than healthy control (76,77). The markers used by breath analyzers are reported to be related to COVID-19 disruption of respiratory biochemistry resulting from ketosis, inflammatory processes, and gastrointestinal effects (78). A multiplex

sensor was designed based on nanomaterials linked with organic ligands, which created a versatile sensor layer that can change its structural properties when exposed to VOCs and cause electrical resistance changes (79). Inorganic nanomaterials were responsible for electrical conductivity within the sensor, and the organic film element provided sites for VOC adsorption. When exposed, VOCs spread to the sensor layer and reacted with functional groups covering organic segments or inorganic nanomaterials. The interactions caused a change in volume via swelling or shrinkage in the nanomaterial film. The nanomaterial layer's, exposure to VOCs, caused a rapid charge transfer to/from the inorganic nanomaterial, resulting in fluctuations in the measured conductivity even if no structural changes occurred in the sensor layer. The presence of aenosis was used for distinguishing COVID-19 surgery-patients from non-infected participants based on VOC patterns in two exhaled samples (80).

5.2. Plasmonic Nanosensors

Nanoplasmonic biosensor technologies based on surface plasmon resonance (SPR) and local surface plasmon resonance (LSPR) are now available and commercialized in different areas (81). Also, the acquisition of real nanoplasmonic Point of Care (POC) biosensors includes and enhances microfluidic systems that minimize or automate sample processing and easy-to-use readings SARS-CoV-2 detections (81).

Recently, a fast and online nanoplasmonic resonance sensor for detecting SARS-CoV-2 without sample preparation was developed in a single step. Within 15 minutes, only 370 vp/ml is detected, and the linearity is ranging from 0 to 107 vp/ml. The measurements obtained from a generic microplate reader and a handset combined with a smartphone showed that cheap and fast detection methods could be applied quickly in normal clinical conditions and resource-constrained settings (73).

As an alternative to RT-PCR, a plasmonic biosensor combined with a plasmonic photothermal (PPT) effect and surface plasmon resonance was recently developed (71). Gold nanomaterials linked with complementary DNA sequences to detect hybridized cDNAs of SARS-CoV-2 is used. This device can detect cells using a cell surface protein reaction with specific antibodies conjugated to Au NPs (82).

A multilayer grid-linked fluorescent plasmonic (GC-FP) biosensor platform is being developed to measure antibodies against COVID-19 in human blood serum and dried bloodstain samples (83). The array gives antibody-antigen binding interactions by showing 100% selectivity and 86.7% sensitivity in serum IgG levels against Spike S1, Spike S1S2, and N protein COVID-19 antigens. The test was repeated on other sample matrices, such as dried bloodstain samples, to demonstrate the effectiveness of the test. The test also successfully detects IgM, IgG and IgA antibody-antigen interactions and multiple immunoglobulin isotypes (83).

Novel plasmonic biosensor platforms are also developed to detect COVID-19 biomarkers. A novel plasmonic biosensor platform was developed (84). The study presented a label-free method for the quantitative detection of interleukin 6 (IL-6). Cobalt ferrite/CoF and magnetite nanoparticles are combined in a hydrogel matrix by applying an external magnetic field, and detected antibodies are conjugated on their surfaces. The interaction of IL-6 with the antibody created a blue shift in the resonance wavelength after CoF addition and magnetite-based MPC at a 50 pg/ml concentration, and the reflection intensity increased up to 50% and 44%, respectively (84).

Procalcitonin detection is achieved with an uncoated segment of glass fiber conjugated with an anti-PCT captured antibody to obtain a fiber sensor, and then the anti-PCT detection antibody is conjugated to AuNPs to provide nanoplasmonic probes. A comprehensive linear response range is achieved from 1 pg/ml to 100 ng/ml and LOD of 7.3 fM for PCT within 15 minutes (85).

5.3. Electrochemical sensors

Various non-SARS CoV-2 electrochemical biosensors were developed using potentiometric or amperometric readings. A Screen-printed carbon electrode (SPCE) biosensor device (eCovSens) using screen printing and compared to a commercial fluorine-doped tin oxide electrode (FTO) consisted of a potentiostat (86). Researchers tested their new device for sensitivity, specificity, detection time, sample volume, portability, and Covid-19 antigen detection. The ECovSens device consists of a biosensor element (nCovid-19 Ab), a transducer (carbon electrode), and an internal device to detect voltage changes. Conjugated gold

nanoparticles recognize virus particles and catalyze the electrochemical signal by improving the electrical conductivity. Covid-19 particles trapped on the modified electrode caused current changes proportional to the interested analyte concentration. Virus particles were successfully captured and detected at 90 fM (LOD) using prickly saliva samples and found within 10 to 30 seconds (86).

Researchers developed a quantitative paper-based electrochemical sensor for digital detection of SARS-CoV-2 genetic material with fast, inexpensive, and user-friendly properties. The principle depends on AuNPs coated with highly specific antisense oligonucleotides (ssDNA) targeting the viral N gene. Sensor probes are immobilized on a paper-based electrochemical array to provide a nucleic acid test with a simple handheld reader. The sensor's sensitivity is $231 (\mu\text{L}^{-1}\text{-copies})^{-1}$ and a detection limit of 6.9 in less than 5 minutes, with 100% accuracy, sensitivity, and specificity [84].

A fast and sensitive method for detecting and measuring D-dimer, a COVID-19 biomarker, present in high concentrations in patients, was developed (87). The method relies on an immunosensor, based on a single-chain antibody (ScAb) immobilized on the transducer surface. The redox activity of an N-alpha-bis (carboxymethyl) -1-lysine (ANTA)/Cu²⁺ complex-bound to a polypyrrole skeleton is taken as the signal. D-dimer presence is monitored with a linear ranging from 0.1 ng mL⁻¹ and 500 ng mL⁻¹. A LOD of 100 pg mL⁻¹ in PBS is measured by Electrochemical Impedance Spectroscopy (EIS) (87).

A simple, inexpensive, and label-free electrochemical immunoassay was developed to measure serum C-reactive protein (CRP) concentrations with an immunosensor strip put on an anti-CRP functionalized AuNPs modified screen-printed carbon electrode (SPE). The measurement is based on the reduction in the redox indicator Fe³⁺/Fe²⁺ oxidation current, resulting from the immune reaction between CRP and anti-CRP with a linear range of 0.4 to 200 with a detection limit of 0.15 nM (88).

An entropy-based enhanced electrochemiluminescence (ECL) method was developed by Fan and coworkers (2021) to detect the RNA-dependent RNA polymerase (RdRp) gene of SARS-CoV-2. DNA tetrahedron (DT) on the surface of the electrode is modified for the design of the biosensor. Biosensor shows an "ECL on" state with LOD up to 2.67 fM (89).

5.4. Field-effect transistors (FET)

Field-effect transistor biosensors show high sensitivity and selectivity through biorecognition on the conducting channel. A FET device is functionalized with an anti-SARS-CoV-2 spike protein antibody to detect the SARS-CoV-2 where graphene sheets were used. A detection limit of 1 fg/mL in phosphate-buffered saline and 100 fg/mL in clinical transport medium. Changes in surface charge upon binding lead to transducible differences in source-drain current measurements (59).

A label-free immunosensor, based on a single-walled carbon nanotube-field-effect transistor (NTFET) device, was developed to detect CRP. The immune reaction principle relied on direct adsorption of CRP-specific antibodies (anti-CRP) onto single-walled carbon nanotube networks (SWCNTs) with a linear range of 10^{-4} - 10^2 µg/ml (90).

Conclusion

Unlike the traditional sensing platforms, nanomaterial-based biosensors offer much-required selectivity, sensitivity, reliability, reproducibility, and robustness while being cost-effective in sample measurements. Biosensor platforms based on nanomaterials are becoming more critical to a clinical diagnostic approach. Extensive studies are dedicated to displaying the applicability of various nanomaterial-based sensors against a wide variety of RNA viruses. Based on these findings, it is safe to say that nanotechnology will play an efficient and particular role in the effective surveillance of COVID-19 in the future. Therefore, it is clear that nanomaterials can be used more effectively in the management of SARS-CoV-2, which can be achieved by developing various nanomaterial-based sensor arrays such as plasmonic-based, paper-based, FET-based, and electrochemical-based, LFA-based methods. Also, significant challenges are not given for the usage of quantum dots and VOC biosensors. This can be a real future perspective of the nanomaterial and distinct interface-based nanotechnological methods for the detection of SARS-CoV-2 and COVID-19 diagnosis. In further reliable and cost-effective biomedical devices are expected to provide affordable, practical, and easy-to-use products accessible to all countries. Usage of the Internet of Telephone (IOT) and smart technologies are outstanding tools that must be used to monitor, control, and predict the evolution of COVID-19 pandemics.

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Author contribution: Both authors contributed equally.

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Journal Pre-proof

Highlights

- Extraordinary nanoparticles in SARS-CoV-2 detection
- Specialized interface-based detection methods for SARS-CoV-2
- Unique nanoparticle-based detection methods for COVID-19 biomarkers
- Nanobiotechnology-based biosensing technologies for SARS-CoV-2 detection and COVID-19 diagnosis

Declaration of interests

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

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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