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Review

Nanostructures for the Prevention, Diagnosis, and Treatment of SARS-CoV-2: A Review

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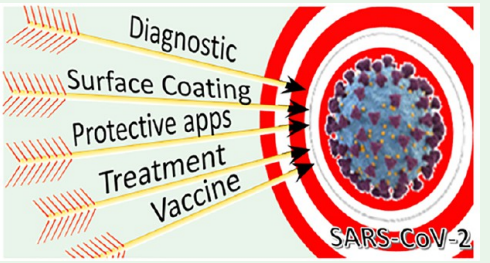
ABSTRACT: Scientists, doctors, engineers, and even entire societies have become aware of the seriousness of the COVID-19 infection and are taking action quickly, using all the tools from protection to treatment against coronavirus SARS-CoV-2. Especially in this sense, scientific approaches and materials using nanotechnology are frequently preferred. In this review, we focus on how nanoscience and nanotechnology approaches can be used for protective equipment, diagnostic and treatment methods, medicine, and vaccine applications to stop the coronavirus SARS-CoV-2 and prevent its spread. SARS-CoV-2, which itself can be considered as a core−shell nanoparticle, can interact with various materials around it and remain bound for variable periods of time while maintaining its bioactivity. These applications are especially critical for the controlled use of disinfection systems. One of the most important processes in the fight against coronavirus is the rapid diagnosis of the virus in humans and the initiation of isolation and treatment processes. The development of nanotechnology-based test and diagnostic kits is another important research thrust. Nanotechnological therapeutics based on antiviral drug design and nanoarchitecture vaccines have been vital. Nanotechnology plays critical roles in the production of protective film surfaces for self-cleaning and antiviral masks, gloves, and laboratory clothes. An overview of literature studies highlighting nanotechnology and nanomaterial-based approaches to combat SARS-CoV-2 is presented.



KEYWORDS: *COVID-19, SARS-COV-2, nanotechnology, nanomaterials, protective equipment, diagnostics, treatment*

1. INTRODUCTION

As Albert Einstein said, "In the midst of every crisis lies great opportunity." The COVID-19 pandemic has dramatically altered the progression of our lives. As of the beginning of 2022, there have been more than 5 million deaths due to COVID-19, according to the records of the World Health Organization. Considering the high rates of infection together with the absence of absolute medical treatments, the prevention of the transmission of the SARS-CoV-2 virus appeared to be the only viable solution. As the most dominant mechanism of virus spreading involves respiration droplets, preventative measures involved mask wearing and social distancing. These preventative measures have themselves resulted in significant negative effects on the economy and social life. Collectively, the COVID-19 pandemic has shown the inability of the "developed" world to fight against a virus with a nanoscale dimension.

Nanostructures have presented a range of unique solutions to different challenges that are revealed by the COVID-19 pandemic. Nanostructures are typically defined based on the use of materials with at least one dimension being at a small length scale. In a practical sense, nanostructures have critical dimensions smaller than 500 nm.[1] In addition to the outstanding properties of nanostructures, a notably important characteristic of nanotechnology is its interdisciplinary nature. A broad range of scientific communities from health sciences to engineering disciplines work on nanomaterials. This breadth translated into the potential of developing solutions to the different challenges of the COVID-19 pandemic. This potential has been effectively highlighted at the beginning of the COVID-19 pandemic by several perspective and review articles.[2−4] As a result, in a relatively short amount of time, researchers across the world have made significant progress in fundamental and applied studies regarding the COVID-19 pandemic. Despite the difficulty of translating these developments into real-world products in a short amount of time, the attained knowledge will be extremely valuable in preparing for other pandemics. This review aims to provide a survey of the most recent efforts on the use of nanostructures in this rapidly growing field. Nanostructure-based solutions in the fight against COVID-19 are shown in Figure 1.

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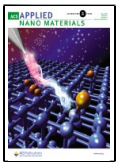

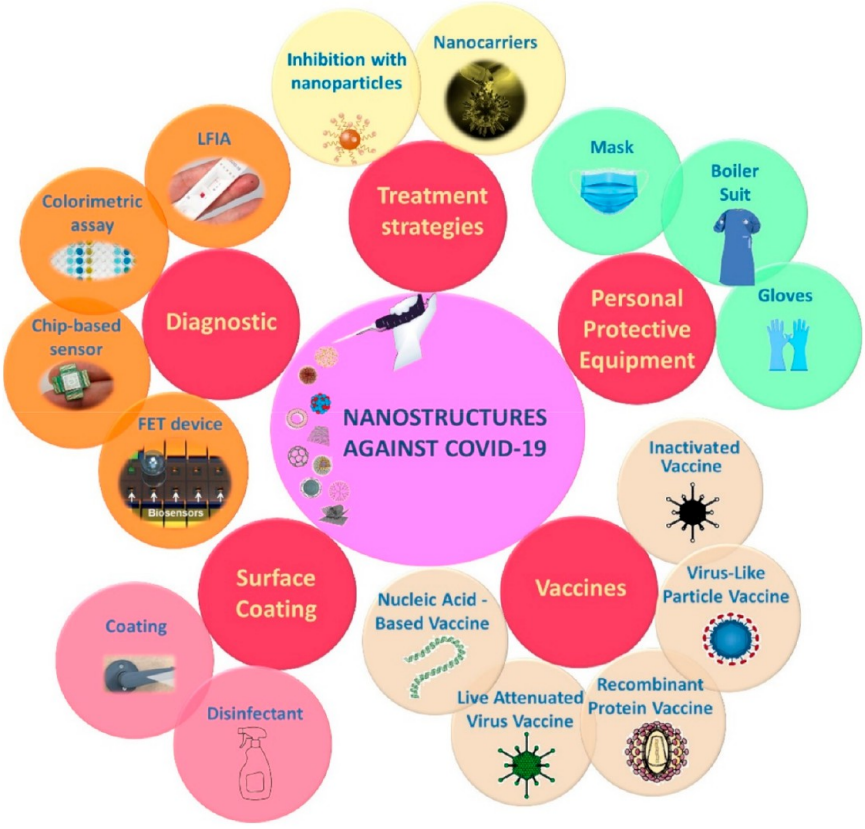

Figure 1. Applications of nanostructures in the fight against COVID-19.

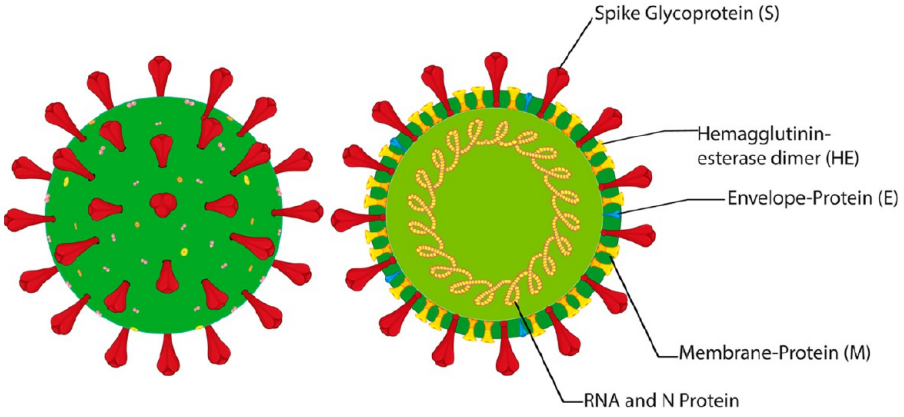

Figure 2. Structure of coronavirus.

In the following, we present a comprehensive review of recent literature on the use of different forms of nanomaterials in the fight against COVID-19. In section 2, we start by summarizing the structure of the coronavirus, its ways of infecting, its reproduction mechanism, and its dangers to humans. In section 3, we focus on the employment of nanomaterials in the diagnosis and detection of COVID-19. Section 4 presents a brief but detailed discussion of the mechanism of traditional and nanoenabled vaccines developed for the treatment of COVID-19 and the importance of nanomaterials and nanotechnology in these vaccines. In section 5, treatment strategies other than vaccines for COVID-19 and the role of nanomaterials that make these strategies effective are discussed. Section 6 particularly focuses on developing nanomaterials-based protective equipment. A summary of coating technologies for minimization of the SARS-CoV-2 virus transmission is presented in section 7. Our perspective and possible future directions are covered in the final section.

2. SARS-CoV-2 STRUCTURE AND MODE OF INFECTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the agent of "coronavirus disease 2019 (COVID-19)" with severe respiratory failure, is a new species in the Coronavirus family.[5,6] Coronaviruses belong to the Coronavirinae subfamily in the Coronaviridae family, and the subfamily

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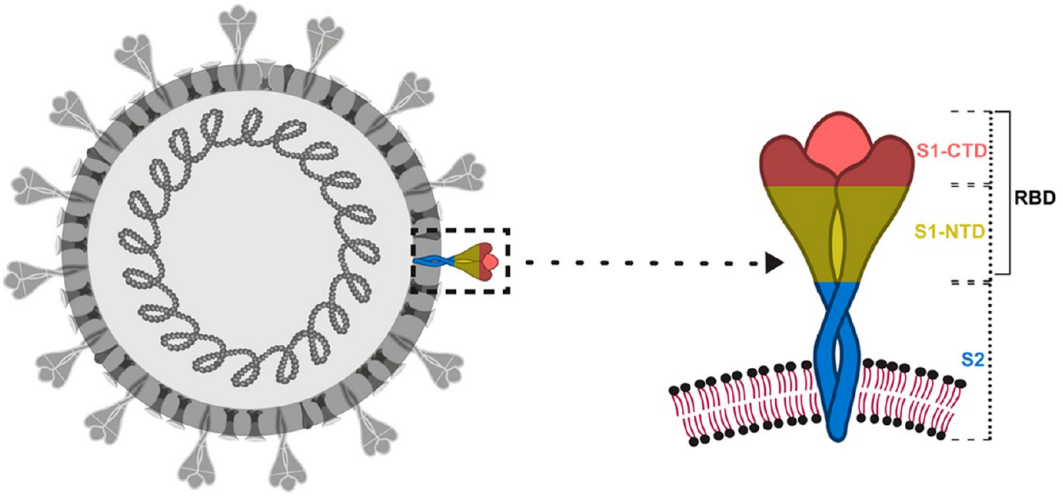

Figure 3. Schematic representation of the spike-receptor binding mechanism (RBD: receptor binding domain).

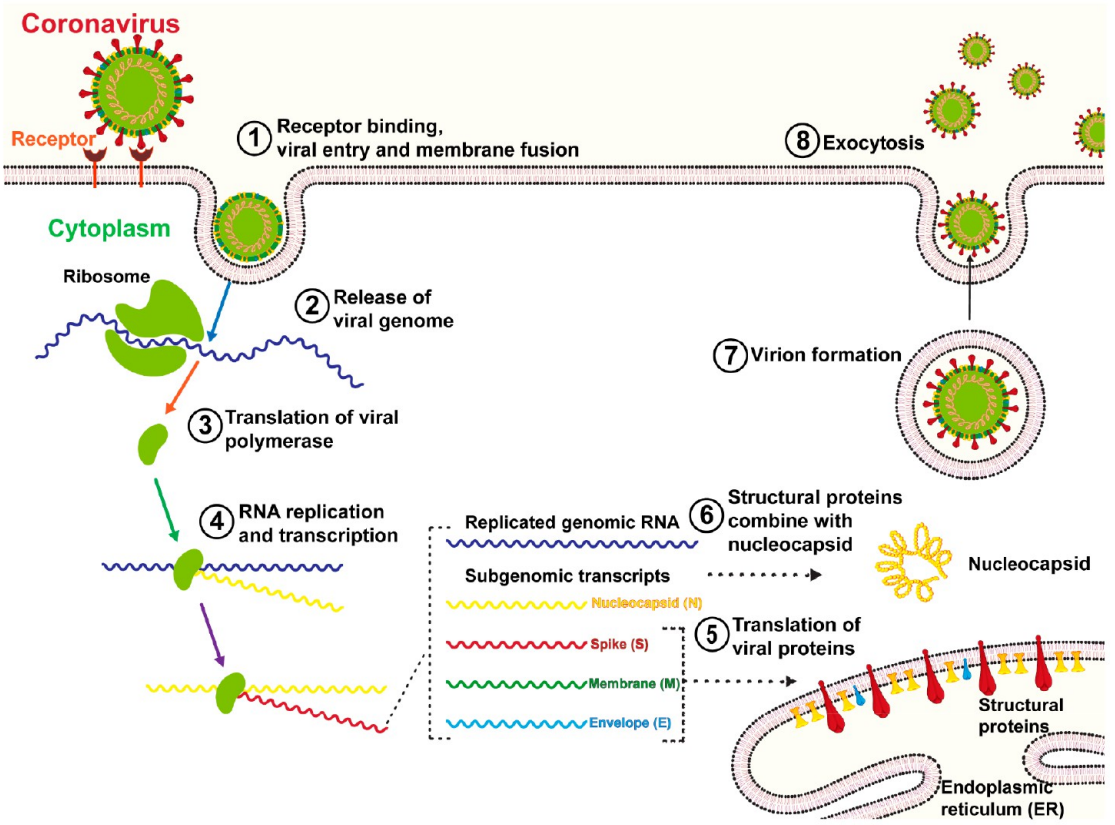

Figure 4. SARS-CoV-2 replication cycle.

includes four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus.[7,8]

Subgroups of the coronavirus family are alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus.. There are six coronaviruses that have been reported to cause illness in humans. SARS-CoV-2 is the seventh coronavirus reported to infect the human species after SARS-CoV and MERS-CoV.[9−11] This new type of coronavirus has been reported to be a member of the β coronavirus group such as SARS-CoV and MERS-CoV. The international virus taxonomy committee named this virus SARS-CoV-2 and the disease caused by the virus COVID-19.[12]

2.1. Virus Structure and Cell Incorporation. SARS-CoV-2 is a positive-sense RNA β coronavirus. These viruses contain single-stranded RNA as the genome material. All coronaviruses have a spike (S), membrane (M), envelope (E), viral genome, nucleocapsid (N) structure. As shown in Figure 2, SARS-CoV-2 is also in the typical coronavirus structure; this virus has an S protein and other polyproteins, nucleoproteins, and membrane proteins.[13]

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M protein is abundant in viral structures. It is the main protein that provides control of the virus as it fuses with the host cell to make new virus particles. Studies show that the M protein interacts through the viral ribonucleoprotein (RNP) and S glycoproteins in the budding region, promoting fusion with the host cell.[14,15] E protein is responsible for the pathogenesis of the virus. N protein protects the viral genome by wrapping the ribonucleoprotein complexes in a helical structure. This protein also regulates transcription and translation events, which are important processes for viral genome replication.[16] S proteins are in the crown structure that gives the name to the coronavirus. What makes S proteins important is that they lead to entry into host cells. This stage is the leading step for the virus to reproduce itself. Therefore, researchers generally target this crown structure in studies of bringing new vaccine and drug candidates to treatment.[17]

The S protein is in the form of homotrimers that form protrusions on the surface of the virus. It facilitates binding of envelope viruses to host cells by interacting with angiotensin converting enzyme 2 (ACE2) in lower respiratory tract cells. The S protein is cleaved by the furin-like protease in the host cell into two subunits, S1 and S2. There is a furin cleavage zone (PRRARS of V) at the boundary between S1 and S2 subunits.[13,18] Furin is highly expressed in the lungs and plays a role in viral infections. It has the potential to increase viral fusion to the host cell membrane by cleaving envelope glycoproteins. This situation increases pathogenicity and plays a role in host selection. Segment S1 is responsible for the binding of the host cell and the virus. Segment S2 mediates virus fission with the host cell.[19,20]

The S1 part consists of two parts, the S1 subunit N-terminal domain (S-NTD) and the S1 subunit C-terminal domain (S-CTD), which serve as receptor binding. These areas are important in viral pathogenesis (Figure 3).[21,22]

Human angiotensin converting enzyme 2 (ACE2) and CD209L have been identified as cellular receptors for SARS-CoV. ACE2 is the dominant receptor and CD209L has a lower affinity. The genomic length of the new coronavirus consists of nearly 30 000 nucleotides. All viral genome sequences obtained show more than 99% sequence similarity.[23−25]

ACE2 is a membrane-bound aminopeptidase. ACE2 is a physiologically important enzyme that affects the cardiovascular and immune systems. ACE2 catalyzes the production of vasodilator peptides, including angiotensin I, and is responsible for balancing the potent vasoconstrictor effects of angiotensin II. ACE2 is the main receptor for the coronavirus that causes SARS. When coronavirus (SARS-CoV), which is the main cause of SARS, binds to the enzyme, it enters the pulmonary endothelial cells by combining with the membrane. This interaction is mediated by the SARS-CoV spike protein.[26,27]

2.2. Replication of Virus in Host Cell. Replication cycle steps of SARS-CoV-2 in the host cell are summarized in Figure 4. The S1 subunit of the S unit responsible for binding of the virus binds with the ACE2 and CD209L receptor of the host cell. Thus, the conformational change of the S protein in the trimer structure takes place. This protein enters the host cell, after which the viral and cellular membranes fuse. The endosome, which carries the virus, is formed. Viral RNA is released into the cytoplasm.[28]

In addition to the membrane fusion, clathrin-dependent and -independent endocytosis also plays a role in the entry of the virus into the cell. The viral genome released into the host cell acts as a template, encoding enzymes and proteins required for replication and subgenomic mRNA synthesis. Two polyproteins and structural proteins are synthesized from viral RNA. Following this, the viral genome begins to replicate. First, RNA polymerase is synthesized, and RNA is split into small pieces to form negative polarity RNAs. As a result of transcription, mRNA is produced and translated into viral proteins.[29]

Most of the nonstructured proteins join the replication-transcription complex (RTC) for RNA synthesis. These proteins are responsible for RNA replication and transcription of subgenomic RNAs. After replication and subgenomic RNA synthesis, S, E, and M proteins are translated. Synthesized viral RNA and other proteins are brought together in the endoplasmic reticulum. The virions are then moved to the cell surface in the vesicles formed in the shade. Virions inside the vesicle are released from the cell by exocytosis.[30−32]

In summary, coronavirus attaches to receptors and enters the host cell. The viral genome is released into cytoplasm. The translation of the viral polymerase occurs through the ribosome. Then, there is RNA replication and transcription. Translation of structural and nonstructural viral proteins occurs. Proteins are assembled. It is enclosed in a vesicle, which combines with the membrane and is removed from the host cell.[33]

2.3. Immunopathology/Immune response. COVID-19 patients generate both cell-mediated and humoral immune responses. Biomarkers related to the infection increase in these patients. T cells (CD4+ and CD8+), B cells, and natural killer (NK) cells are reduced. Tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6) and IL-8 levels increase in COVID-19 disease. These are proinflammatory markers that are an important part of the immune system.[34,35]

Macrophage inflammatory protein-1 alpha (MIP-1α), interferon gamma-induced protein-10 (IP-10), granulocyte colony-stimulating factor (G-CSF), IL-10, IL-7, IL-2, and monocyte chemoattractant protein-1 (MCP-1) proinflammatory cytokines levels increase. The immune system is activated. All of this causes a cytokine storm. The body creates this mechanism to protect itself. This phenomenon can cause major damage to cells and tissues and increase mortality.[36]

Viral replication damages endothelial and vascular cells. It induces cell death. While increasing proinflammatory cytokine expression, noninfected immune cells migrate to the infection site. The accumulation of uninfected monocytes/macrophages and neutrophils at the site of infection creates a strong inflammatory response. This immune response causes tissue damage and widespread inflammation.[37,38]

During the cytokine storm in COVID-19 patients, lymphopenia accompanies the picture. SARS-CoV-2 infects T lymphocytes through its S proteins. Thus, a decrease in lymphocyte levels is seen.[39] Some patients have atrophy of lymphoid tissues.[40,41] It is necessary to understand this cytokine storm and lymphocyte subsets well when planning treatment in COVID-19 disease because the balance of the immune response is of major importance for the prognosis of the disease.

2.4. SARS-CoV-2 Challenge. As it is known, the coronavirus family is quite broad. The first coronavirus in the human respiratory system was detected in the 1960s.[16,42] Since those years, different coronavirus strains have been detected in humans and animals. These usually cause respiratory or gastrointestinal diseases. The most dangerous coronaviruses detected in the 2000s are SARS-CoV and

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Table 1. Nanoparticle-Based Diagnostics for Coronavirus Detection

virus	detection platform	nanostructure	analyte	sensitivity (%)	specificity (%)	detection limit	detection time (min)	ref
SARS-CoV-2	LFIA	AuNP (40 nm)	IgM and IgG	88.66	90.63	N.A.	15	50
SARS-CoV-2	LFIA	AuNP (40 nm)	IgM and IgG	95.85	97.47	N.A.	15	51
SARS-CoV-2	LFIA	AuNP (30 nm)	IgG	69.1	100	N.A.	15−20	52
SARS-CoV-2	LFIA	AuNP (30 nm)	IgM	100	93.3	N.A.	15	53
SARS-CoV-2	LFIA	SiO_2@Au@QD nanobeads	IgM and IgG	100	100	N.A.	15	54
SARS-CoV-2	LFIA	selenium NPs	IgM and IgG	93.33	97.34	N.A.	10	55
MERS-CoV	paper-based colorimetric assay	AgNPs (19 nm)	DNA strand	N.A.	N.A.	1.53 nM	N.A.	56
SARS-CoV-2	colorimetric assay	AuNP (<60 nm)	SARS-CoV-2 RNA	N.A.	N.A.	0.18 ng/μL	10	57
MERS-CoV	chip-based sensor	Au NPs on carbon electrodes	antibody	N.A.	N.A.	1.0 pg/mL	20	58
SARS-CoV-2	FET device	graphene nanosheets	antibody	N.A.	N.A.	1.6×10^1 pfu/mL	real-time detection	59
SARS-CoV-2	FLISA	IgG-coupled QDs	IgM and IgG	N.A.	N.A.	4 pg/mL	15	60

Middle East respiratory syndrome coronavirus (MERS-CoV).[43] Although the mortality of SARS-CoV-2 is not higher than these two viruses, it has posed a bigger problem for humanity since its contagiousness is very high. The adherence rate of SARS-CoV-2 with spike proteins to the ACE2 receptor is much higher than that of SARS-CoV. The S protein structure of SARS-CoV-2 is similar to MERS-CoV. However, since SARS-CoV-2 has a higher affinity for ACE2 receptor, it is more contagious.[44] In addition, since SARS-CoV-2 is constantly mutating, the danger is constantly increasing. The genetic code of the RNA reproducing in the host of living or nonliving organisms is constantly changing. Since RNA consists of a single strand, it does not have a self-repair mechanism like DNA. This further increases the tendency for mutation.[45]

3. DIAGNOSIS AND DETECTION OF COVID-19 BASED ON NANOSENSORS

Diagnosis is the key point in the fight against COVID-19 because of isolating infected people as early as possible and reducing the chance to spread this pandemic. Therefore, nanomaterial-based approaches are being developed for SARS-CoV-2 tagging and rapid detection (Table 1). The comparable sizes of nanomaterials and viral particles make the interactions between these structures very strong. This length scale overlap provides high selectivity and improved sensitivity.[46−49]

One of the easiest methods to use nanostructures for detection of viruses is localized surface plasmon resonance (LSPR) using metallic NPs, especially gold. The free electrons in the NP oscillate at a certain frequency with the oscillation of the electric field vector of external light. As a result of this oscillation, LSPRs are formed near the particle surface.[61,62] In addition to the special optical properties revealed by this effect, it has found wide applications in biomedical fields due to its interesting properties including excellent stability, chemical tunability, biomolecule conjugation, and biocompatibility.[63−65] In addition, these nanostructures have high selectivity because their surfaces can be modified with structural proteins, viral antigens or antibodies, etc.

Many research groups have shown that the diagnosis of SARS-CoV-2 can be made effectively using lateral flow immunoassays (LFIAs). The basis of these methods is to detect IgM antibodies that appear after 7 days and the IgG antibodies that appear after 10 days in the blood. Antibodies were detected by LFIAs from blood serum samples from infected patients.[66] Li et al. reported that the recombinant receptor binding domain of S protein (MK201027) was fixed on gold NPs and was used as an antigen. In this way, they developed a strategy to create a rapid diagnostic kit (Figure 5-I).[50] According to WHO diagnostic guidelines, rapid tests to be used for detection of SARS-CoV-2 should provide sensitivity and specificity above 80% and 97%, respectively.[67] Therefore, sensitivity of diagnostic kits should be improved. Using a similar design, Liu et al. increased the sensitivity and specificity of the assay by 95.85% and 97.47%, respectively, using Au NPs (hydrodynamic size, 40 nm) conjugated to ncov-ps-Ag8 (a recombinant nucleocapsid antigen) (Figure 5-II).[51] The difference in sensitivity between these two test kits can be attributed to the types of antigens immobilized on the nanoparticles.

In addition to the LSPR properties, the colorimetric properties of Au and Ag metallic NPs have the potential to be used for responsiveness for the existence/absence of the analyte. Here, two ways are used for Au NPs for the detection.[68] The first method is the appearance of a red color as a result of the interaction of the labeled Au NPs with the analytes.[69] The second one is that a bluish color appears due to the change in the wavelength of the light absorbed by the NPs as a result of the aggregation (after matching of the probe and targets) of the Au NPs.[70] Fabricating colorimetric sensors using probe molecules that detect viral genetic materials obtained by pre-extraction is considered an effective strategy. Therefore, Teengam et al. developed a colorimetric assay method that can detect the complementary DNA of the virus using Ag NPs and a pyrrolidinyl peptide nucleic acid (acpcPNA) probe (Figure 6).[56] Ag NPs are negatively charged because they are stabilized with citrate. Therefore, Ag NPs aggregate with the addition of positively charged acpcPNA. Since the DNA analyte is not complementary, the color on the sensor shifts toward red. In the other case, since the DNA forms a double-stranded structure with the probe molecule, there is no aggregation between the Ag NPs, and the Ag NPs dispersed well and exhibited their yellow color. In another study, Moitra et al. developed a diagnostic kit using Au NP modified with antisense oligonucleotides to detect the gene of the SARS-Cov-2 N protein (Figure 7).[57] Modified Au NPs were obtained by binding thiol-modified antisense oligonucleotides to Au NPs from the thiol end. When the relevant viral

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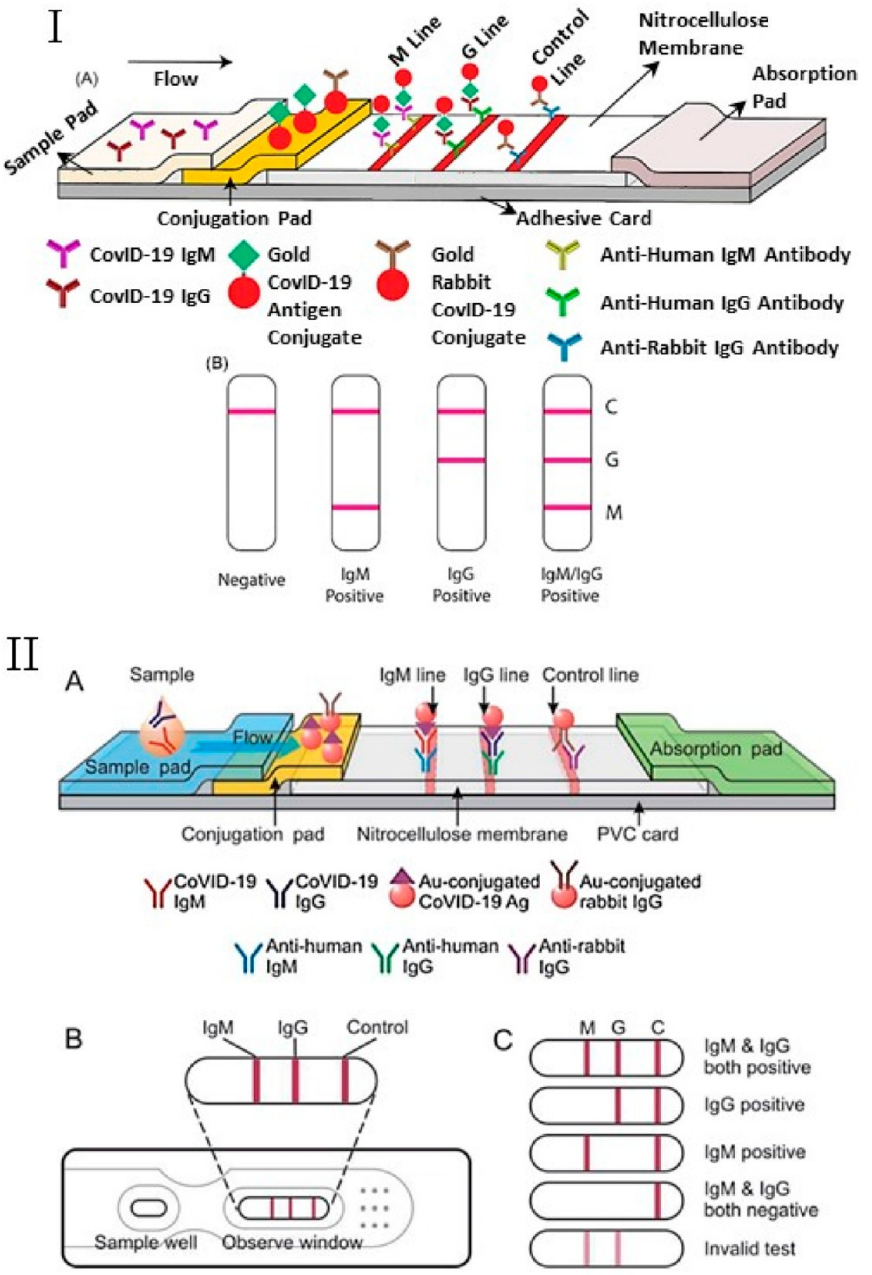

Figure 5. I. Schematic illustration of rapid SARS-CoV-2 IgM-IgG combined antibody test. (A) Schematic diagram of the detection device; (B) an illustration of different testing results.[50] Reprinted with permission from ref 50. Copyright 2020, John Wiley and Sons. II. Schematic view of the COVID-19 IgM/IgG rapid test strip. (A) Preparation and principle of the COVID-19 IgM/IgG rapid test strip; (B) assembled products.[51] Reprinted with permission from ref 51. Copyright 2020, Royal Society of Chemistry.

RNA is in the environment, RNA−DNA hybrids begin to form. As a result, changes in SPRs were observed as Au NPs agglomerated. Moreover, when RNaseH was added to the hybridized sample, cleavages appeared within the RNA sequence. Aggregated Au NPs can be seen by the naked eye without any device.

Different colorimetric methods have been developed for the detection of SARS-CoV-2 without using genetic materials. One of them is a diagnostic kit developed by Ventura et al. that rapidly detects the presence of virus from throat and nose samples.[71] Using 20 nm Au NPs conjugated with antibodies against S, E, and M proteins of SARS-CoV-2, the presence of virus in the samples could be detected. The shift toward a reddish color that occurs in the presence of the virus allows diagnosis within minutes. Thanks to this method, a rapid diagnosis was made only in the presence of viral particles, without the need for viral genome extraction or amplification. The sensitivity and specificity of the sensor, which is over 95%, also meet the WHO standards, making it interesting. For the rapid and reliable diagnosis of the virus, it may be possible to confirm the NPs with appropriate antibodies by a photochemical immobilization technique (PIT). NPs can be rapidly and extensively modified with antibodies by PIT.[72]

In addition to LFIA systems, nanomaterials-based platforms can detect the coronavirus in a sensitive, fast, and selective manner. Nanomaterial-based biosensors have good potential

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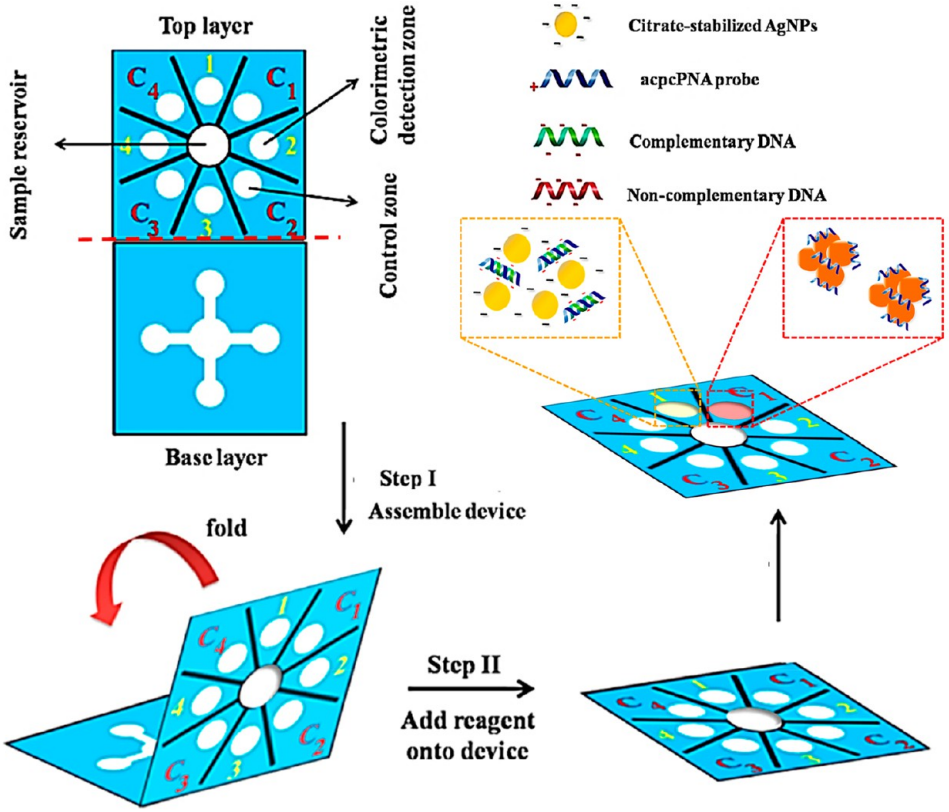

Figure 6. Design and operation of a multiplex paper-based colorimetric device.[56] Adapted with permission from ref 56. Copyright 2017, American Chemical Society.

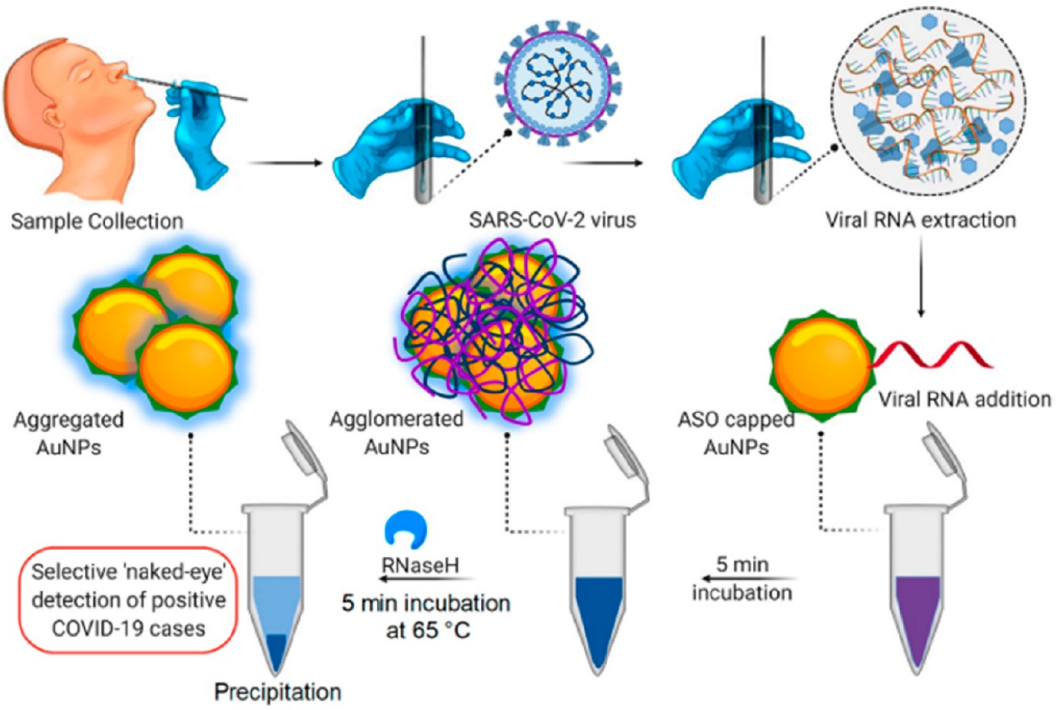

Figure 7. Schematic representation for the selective naked-eye detection of SARS-CoV-2 RNA mediated by the suitably designed ASO-capped AuNPs.[57] Reprinted with permission from ref 57. Copyright 2020, American Chemical Society.

for detecting viral infections and are competitive alternatives to PCR-based diagnosis as they takes less time (<100 min). Layqah et al.[58] aimed to detect the recombinant S1 protein for the diagnosis of coronavirus (Figure 8-I). They reported that

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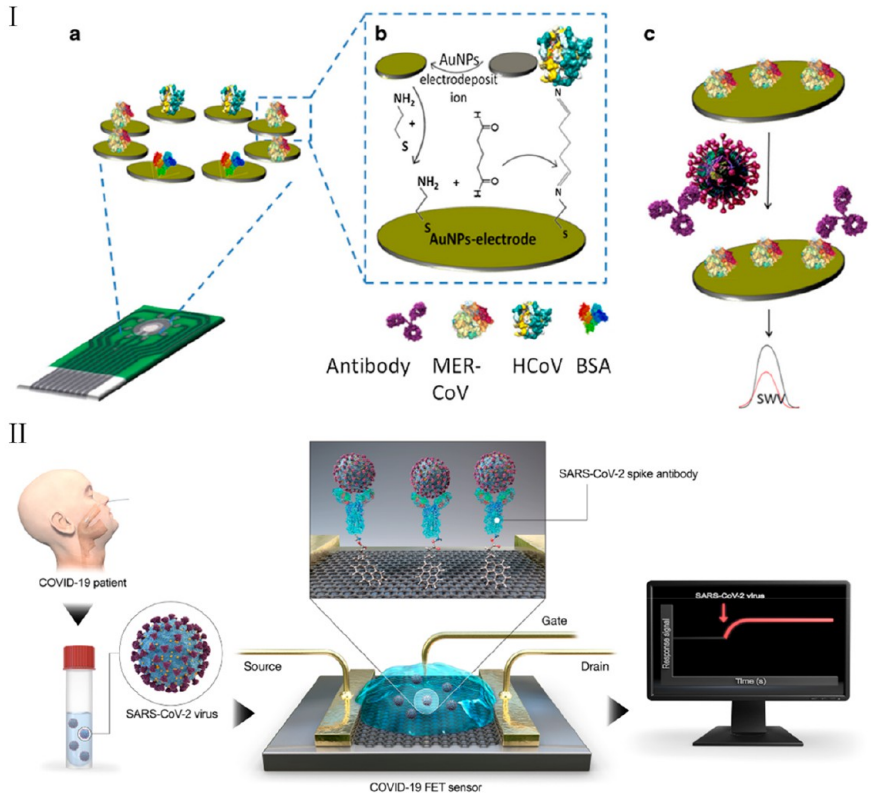

Figure 8. I. COV immunosensor array chip (a). The immunosensor fabrication steps (b), the detection process of the competitive immunosensor for the virus (c).[58] Reprinted with permission from ref 58. Copyright 2019, Springer Nature. II. Schematic diagram of the COVID-19 FET sensor operation procedure.[59] Reprinted with permission from ref 59. Copyright 2020, American Chemical Society.

an electrochemical immunosensor designed using Au NPs modified carbon electrode. Seo et al.[59] reported that they detected SARS-CoV-2 in humans by designing a field effect transistor (FET) prepared with graphene nanosheets to work as a FET-based biosensor (Figure 8-II). Graphene sheets deposited on SiO_2 interacted with specific antibodies against the spike glycoprotein (S protein) of SARS-CoV-2.

Guo et al.[60] reported a fluorescent-linked immunosorbent assay (FLISA) in which they used quantum dots (QDs) to detect human anti-SARS-CoV-2 IgG. A sandwich identification technique was used with mouse antihuman IgG-conjugated Fe_3O_4 nanospheres and rabbit antihuman IgG-linked QDs (Figure 9). For fluorescence intensity analysis, first, a nanoparticle-based sandwich complex is formed in the presence of Anti-SARS-CoV-2 human IgG, and then magnetic separation is performed. In conclusion, it showed a detection limit of 4 pg/mL and did not differ significantly from the results of a conventional enzyme-linked immunosorbent assay (ELISA). Compared to Au NP-based LFA and colorimetric tests, FLISA showed greater sensitivity. The readers are referred to a recent review article for a more detailed discussion of sensing technologies based on nanoscale materials.[73]

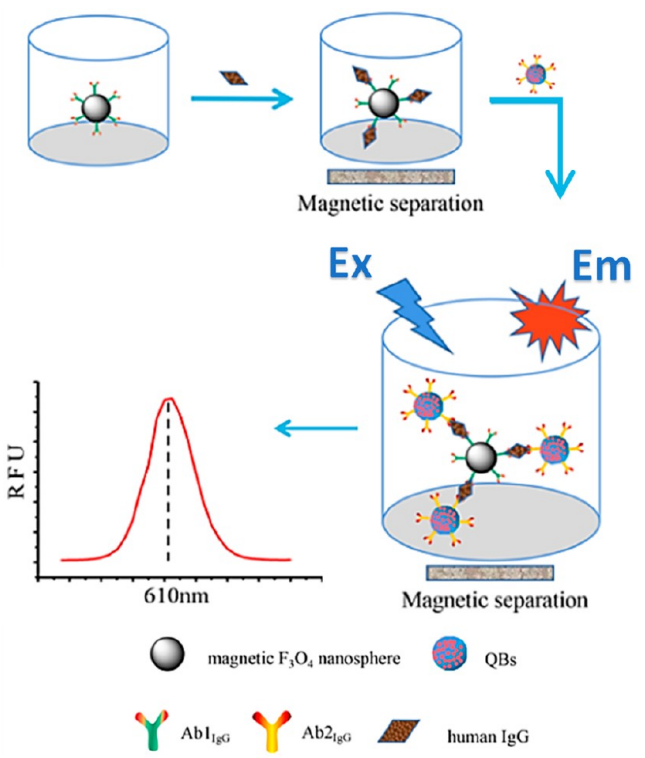

Figure 9. Schematic presentation of the determination of human IgG based on FLISA.[60] Reprinted with permission from ref 60. Copyright 2020, American Chemical Society.

4. TRADITIONAL AND NANOENABLED VACCINES AGAINST SARS-COV-2

The humanitarian and economic impacts of the COVID-19 pandemic necessitate the evaluation of next-generation vaccine technology platforms and the acceleration of vaccine development studies. Platform diversity of vaccine development

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technology for COVID-19, nucleic acid (DNA and RNA), virus-like particles, peptides, viral vectors (replication and nonreplication), recombinant proteins, live attenuated virus, and inactivated virus approaches are being widely pursued.[74]

The S proteins of the coronavirus fuse to the membrane and bind to host cells via the ACE2 receptor, releasing viral RNA. Viral RNAs are detected by toll-like receptor TLR 3, TLR 7, TLR 8, and TLR 9 recognition receptors. These receptors detect viral RNA and DNA in the endosome. A key advantage of all virus vaccines is that they can stimulate TLRs, including TLR 3, TLR 7, TLR 8, and TLR 9.[75] However, extensive additional testing is often required to confirm the safety of live virus vaccines. Close monitoring of increasing infection findings after vaccination with live or killed whole virus is very important, especially for coronavirus vaccines. Live attenuated or inactive all virus vaccines are the classic strategy for viral vaccines.[76]

Various vaccine platforms are being developed, and various technologies are used for the SARS-CoV-2 vaccine. It has been shown that recombinant subunit vaccines are safe and stimulate the immune system without live virus, increasing T cell response and neutralizing antibody levels. DNA vaccines produce a broad immune response by direct injection of antigen-encoding plasmids by electroporation with the addition of adjuvant.[77]

The main purpose of mRNA vaccines against SARS-CoV-2 is to provide both humoral (B cell response) and cellular (cytotoxic T cell response) immune responses with antigenic stimulation that occurs with S protein production. While their cheap and rapid production is an important advantage, there is no risk of vaccine-related infection.[78] The need for an error-free cold chain, especially in the vaccine transport phase, is a matter that needs special attention. Newly developed technologies are used in mRNA vaccines. These vaccines do not require genome integration, stimulate the immune response, and have rapid development and production. Live vaccines best mimic natural infection and produce the strongest T and B cell responses. Preparation of live vaccines takes a long time and poses a safety risk.[79]

Inactivated vaccines are relatively safe. The presence of inactivated vaccines such as the currently used flu vaccine and the fact that these vaccines are produced with a similar technology are among the advantages.[80] In order for the immune response to be sustained, it needs booster doses. One of the most important difficulties in vaccine production is the necessity of generating a large number of live viruses and inactivating them without losing their immunogenic properties. During inactivation, the antigenic region necessary to elicit the immune response can also be destroyed. The storage conditions are at refrigerator temperature due to the traditional inactivated vaccine, and this is a great advantage in terms of transport.[81]

Nanotechnology has played an important role in the success of the SARS-CoV-2 vaccines that are currently used.[82,83] The first vaccines approved by the FDA and EMA for emergency use, due to their immense success (~90−95% efficacy) achieved after the phase 3 clinical trials, were mRNA-based vaccines produced by nucleic acid engineering encoding the equivalent variation of the S protein (Moderna) or the receptor binding domain of this protein (Pfizer/BioNTech).[84,85] However, such a high success can only be achieved with nanocarriers that protect the mRNA units from ribonuclease and provide high levels of expression required for immunogenic efficiency by translation of sufficient mRNA unit to the target site. Both Pfizer/BioNTech and Moderna pursue the approach of encapsulating mRNAs in lipid nanoparticles (LPNs) to protect them from the extracellular environment and deliver them intracellularly. LPNs provide better stability of the transported structure compared to bilayer liposomes. The structure also aids in better cellular penetration.[82] These LNPs contain around 100 mRNA molecules per nanoparticle, and their sizes vary between 70 and 100 nm in diameter.[86,87] The main functional part is the ionizable lipid layer (ALC-0315 and SM-102 for Pfizer/BioNTech and Moderna, respectively), which is neutral at physiological pH and positively charged at low pH. The pH-induced change of the surface charge facilitates RNA complexion, reduces possible toxic effects, and provides an mRNA payload from LNP to the targeted region. The other helper lipids of 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC) and cholesterol encapsulate and pack the mRNAs into LPNs. The PEGylated lipids provide a hydrophilic steric layer that prevents nonspecific bindings and promotes circulation and degradation time.[82] Collaboration with biochemistry and nanoscience, formulations obtained as a result of decades of research, and experience in cell mechanics have formed the basis for the creation of nanoenabled new-generation vaccines by encapsulating mRNA, DNA, and protein segments with NLPs in a purposeful manner, as in these vaccines. Another example of nanoenabled vaccines with ongoing III phase clinical trial is Novavax. It contains prefusion self-assembled recombinant nanoparticles of the full-length S protein. The encrusted spike is administered with an adjuvant named Matrix-M, which is a complex of 40 nm honeycomb-like nanoparticles derived from saponin mixed with cholesterol and phospholipids.[88] As a result of the development of traditional protein-based approaches with nanoengineering, it has been reported that this spike and adjuvant complex has presented thermostable properties with high efficacy up to 89% against different SARS-CoV-2 variants.[89] Another successful approach in which nanomaterials play a direct role utilizes adenoviruses as nanocarriers. Nonenveloped icosahedral structures of adenoviruses with a diameter of ~100 nm allow surface and structural engineering at the nanoscale, providing a suitable platform for the development of redesigned versatile and capable functional vectors.[90] There are currently several approved vaccines in circulation based on adenovirus nanoparticle with different designs used against SARS-CoV-2 (University of Oxford/AstraZeneca, Janssen Pharmaceutical/Johnson & Johnson, and Gamaleya Research Institute/Sputnik-V). These adenoviral nanoparticles are genetically modified to carry corresponding DNA encoding sequences of SARS-CoV-2 S protein or the receptor binding domain.

5. TREATMENT STRATEGIES FOR COVID-19

One of the most important stages in the fight against COVID-19 is the application of the appropriate treatment method after the diagnosis of infected people.[91,92] To date, the administration of broad-spectrum antiviral drugs is the treatment adopted for COVID-19. Alternative approaches to antiviral drugs for the treatment of COVID-19 have also been explored. For example, the isolation of antiviral antibodies produced in healed patients from blood plasma was used.[6] Several studies have reported the effectiveness of nanomaterial-based therapy with the emergence of antimicrobial-resistant pathogenic bacteria and new viruses.[93−96]

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Nanotechnology is useful for many applications such as the synthesis and use of nanomaterials and the emergence of innovations that can be applied in various aspects, including medical aspects.[97−99] Nanomedicine, a special branch of nanoscience, is a treatment platform using particles designed in the nanoscale size range to offer active pharmaceutical ingredients (APIs) that aim to increase compliance with the targeted treatment of diseases. Nanoparticles can increase the efficacy and safety in treatment with specific drug targeting and controlled drug release rates.[100] The use of nanomaterials is known as facilitators of treatment methods against COVID-19. Some studies have reported that antiviral drugs significantly increase their effectiveness when given with certain nanocarriers. Metal and magnetic nanoparticles are among the various nanoparticles used for coronavirus detection.[101,102] The purpose of using nanoparticles in combating SARS-CoV-2 may include mechanisms that affect the virus from its entry into the host cell to its inactivation. Blocking viral surface proteins can inactivate viruses; therefore, targeted nanoparticles specific for virus-expressed proteins can reduce viral internalization.[16,102,103]

Metal NPs, showing significant potential against many viral diseases, can prevent viral entry into cells, inhibit DNA replication in viruses, and deactivate viruses. NPs bind to the viral capsule or the protein to which it is attached and disrupt the interaction with the host cell. The size, shape, and surface load of the NPs are important in the effectiveness of the treatment. At the same time, concentration-related safety precautions should be taken, considering the rate of toxic effect of host cells on living cells. Studies have shown the effects of NPs composed of titanium (Ti), silver (Ag), gold (Au), and zinc (Zn) against various viruses such as HIV, influenza virus, herpes simplex virus, monkey pox virus, and zika.[104,105]

Gold NPs can bind with the envelope glycoprotein in the HIV virus and prevent DNA replication in the virus. Gold NPs show antiviral effects against subtypes of influenza virus. Colorimetric methods can be used to detect SARS-CoV. In this method, the difference between the electrostatic properties of DNA in single- and double-stranded structures is utilized.[106]

Silver NPs have antiviral properties against many viruses such as gold NPs (hepatitis B virus, herpes simplex virus, monkey pox virus, and respiratory syncytial virus). Silver NPs can interact with cell receptors and prevent the virus from entering the host cell. Silver NPs can even kill viruses and prevent them from multiplying.[107]

Organic NPs have been used to deliver targeted antiviral efficacy and effectively dispense the drug by administering antivirals such as zidovudine, acyclovir, and dapivirin. The main limitation of antivirals is that they do not have a specific targeting, which causes cytotoxicity of the host cell that can be handled by organic nanoparticles. By using the versatile properties of NPs, by focusing on the virus and providing disease-specific drug distribution, organic NPs can also be transformed into important agents in combating viruses. In summary, nanoparticles can play an important role in the overall set of changes that occur in the organism at the origin of COVID-19 disease and during its development.

Rothan et al. reported that Auranofin, an FDA-approved gold drug, inhibited SARS-CoV-2 replication in human cells at a low micromolar concentration. The study claimed it could be a useful drug to limit SARS-CoV-2 infection and associated lung injury.[108]

te Velthuis et al. reported that they can efficiently disrupt the replication of various RNA viruses by increasing the intracellular Zn^{2+} concentration with zinc-ionophores such as pyrithione (PT).[109]

Fujimori et al. investigated the antiviral activity of 160 nm copper iodide (CuI) nanoparticles against the swine flu virus, pandemic H1N1, by titration. They found that the virus titer in titration decreased due to incubation with CuI nanoparticles in a dose-dependent manner.[110]

Rai et al. investigated the antibacterial and antiviral effects of metallic NPs in their literature review. As a result of their research, Rai et al. reported that metallic nanoparticles with or without surface modification can be used as an effective antiviral agent, but the antiviral activity of metal nanoparticles has not been discovered to a large extent.[111]

Kim et al. used gold-functionalized specific thiolated probes that can form disulfide bonds with complementary RNA from the target for MERS-CoV detection. Gold nanoparticles modified with thiol on the surface are functionalized with probes that hybridize with the target and prevent a color change. They stated that this application can be easily applied to other infectious diseases such as COVID-19.[112]

Seo et al. developed graphene-based nano-biosensors to detect SARS-CoV-2 in clinical samples. They used samples such as antigenic protein and nasopharyngeal swabs from COVID-19 patients to determine the accuracy of the sensor produced using graphene nanosheets embedded with a specific antibody against the S protein of SARS-CoV-2. With this method, they were successful in detecting the S protein of SARS-CoV-2. According to Seo et al., this method does not require any pretreatment of the samples and is very sensitive.[59]

Chen et al. developed a lanthanide-doped polystyrene nanoparticle-based system. With this system they developed, they detected anti-SARV-CoV-2 IgG in the serum of COVID-19 patients. With this system based on the principle of lateral flow immunoassay (LFIA), the recombinant nucleocapsid phosphoprotein of the coronavirus was immobilized on the membrane to bind with the target IgG. Chen et al. reported that IgG antibodies coated on NPs serve as a fluorescent reporter.[113] For an in-depth discussion of existing nanotechnology developments and their potential usage in COVID-19 therapeutics, readers are referred to recent review articles.[114,115]

6. USE OF NANOMATERIALS IN ANTIMICROBIAL TEXTILES AND FABRICS FOR PROTECTION AGAINST COVID-19

In the fight against COVID-19 during the pandemic period, to protect health professionals and the general public from the COVID-19 virus and to minimize the transmission of the virus, the production, development and use of wearable personal protective equipment including facial masks and full-body suits, filters with increased performance and antiviral properties, and other pioneering technologies based on nanoparticles, nanofibers, and nanomaterials have gained importance. On the other side, the current personal protective equipment (PPE) does not have any antibacterial and antiviral properties. PPE cannot inactivate the virus as it provides a passive protection effect.[116,117] Therefore, significant studies have been conducted to enhance PPE with antiviral and antibacterial properties that can prevent virus transmission by killing and reducing the binding of the virus to the surface. These products with antiviral and antibacterial properties are designed through

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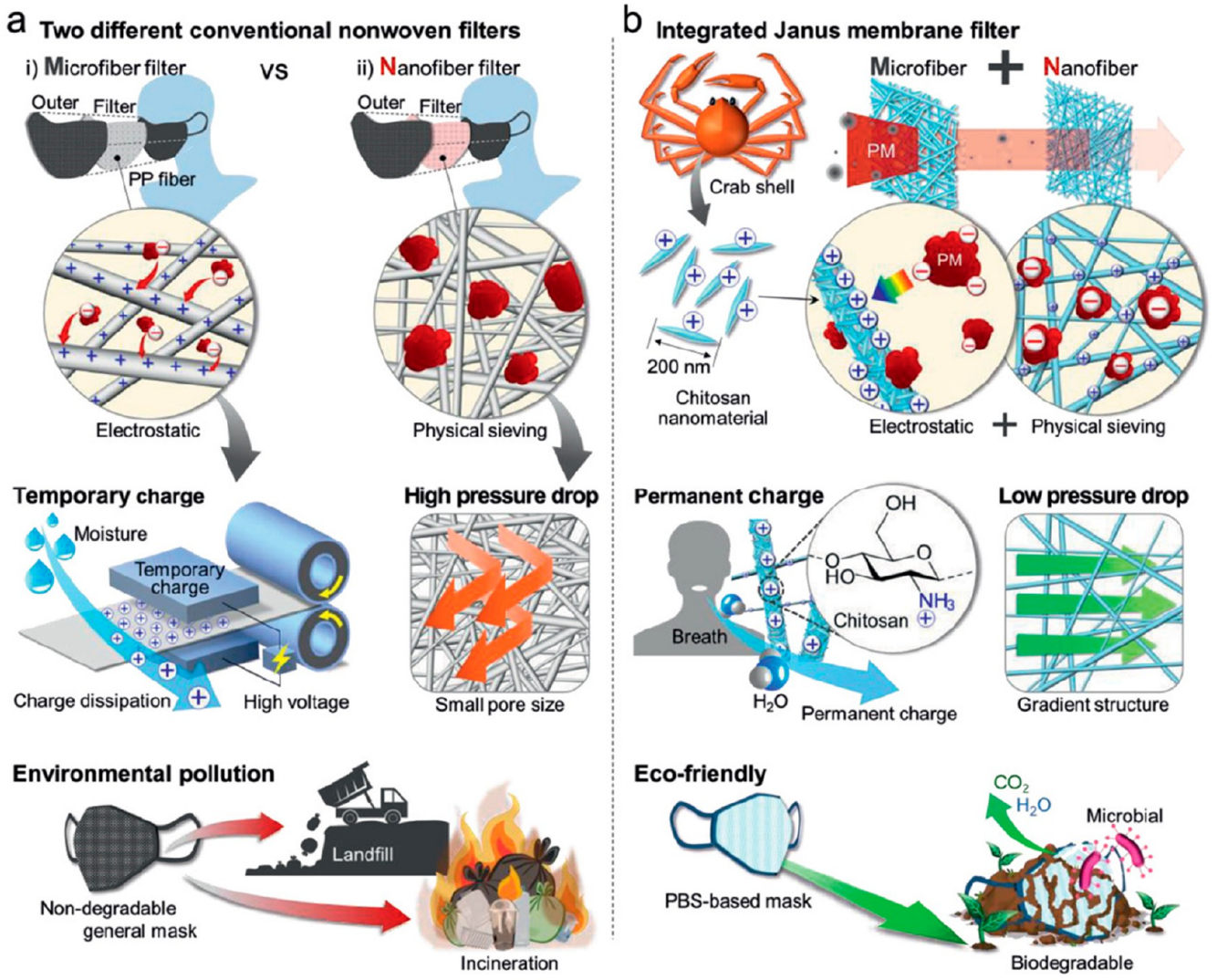

Figure 10. Filtration mechanisms for particulate matter (PM), characteristics in use, and environmental impact of conventional and developed mask filters. (a) Two different representative PM capturing mechanisms of conventional nonwoven filters and their consequential shortcomings: temporary charge of a microfiber-based electrostatic filter, the high pressure drop of a nanofiber-based physical filter, and environmental pollution (as the masks are disposable). (b) Outstanding characteristics of the developed chitosan-coated PBS nanofiber/microfiber integrated Janus membrane filter: permanently preserved ionic charges, low pressure drop facilitates comfortable breathing by the user, and biodegradability.[128] Reprinted with permission from ref 128. Copyright 2021, John Wiley and Sons.

coatings or nanofiber surfaces with protective and preventive properties developed by using nanomaterials comprising a variety of metal, metal oxide particles (such as silver, copper, titanium and zinc), and 2D materials (graphene, MoS) on a textile surface. Nanofibers and nanoparticles are incorporated into personal protective products, providing antiviral, high breathability, and filtration efficiency thanks to the high surface area of nanofibers and the virus removal and killing properties of nanoparticles. So far, there have been a few studies reported on the production, development, and use of personal protective equipment during the COVID-19 outbreak.

In this section, studies on applications such as masks and filters developed by using nanomaterials on personal protective-preventive equipment made after the COVID-19 epidemic or during the production phase of these equipment are compiled. In particular, the prevention of surface interactions of SARS-CoV-2 can be achieved with nanomaterials. Nanomaterials such as metallic nanoparticles, polymer nanofibers, graphene and MoS, and photoactive inorganic and organic materials have attracted a lot of attention in recent years. Most of these studies are about posing a barrier against the transmission of virus and bacteria. Protective masks have been produced with functional materials by spray coating, electrospinning, sputtering, laser-induced on-site synthesis, immersion, and many other similar methods.

One of the most important factors in the transformation of the SARS-CoV-2 and similar respiratory viruses into such a widespread epidemic is the fact that this virus has a high infiltration ability and can be carried by airborne aerosols.[118] This situation directly affects the current ventilation, heating, and air conditioning systems. Although current technology systems are able to prevent the air transmission of these diseases due to filters used in these systems that reduce the circulation of particulate matters (PM) and microorganisms in the air, they are predisposed to microbial colonization, and therefore they are contaminated. Kim et al.[119] developed an ecofriendly two-layered (poly(vinyl alcohol) (PVA) nanofiber/polypropylene (PP) nonwoven fabric) air filter fabricated by

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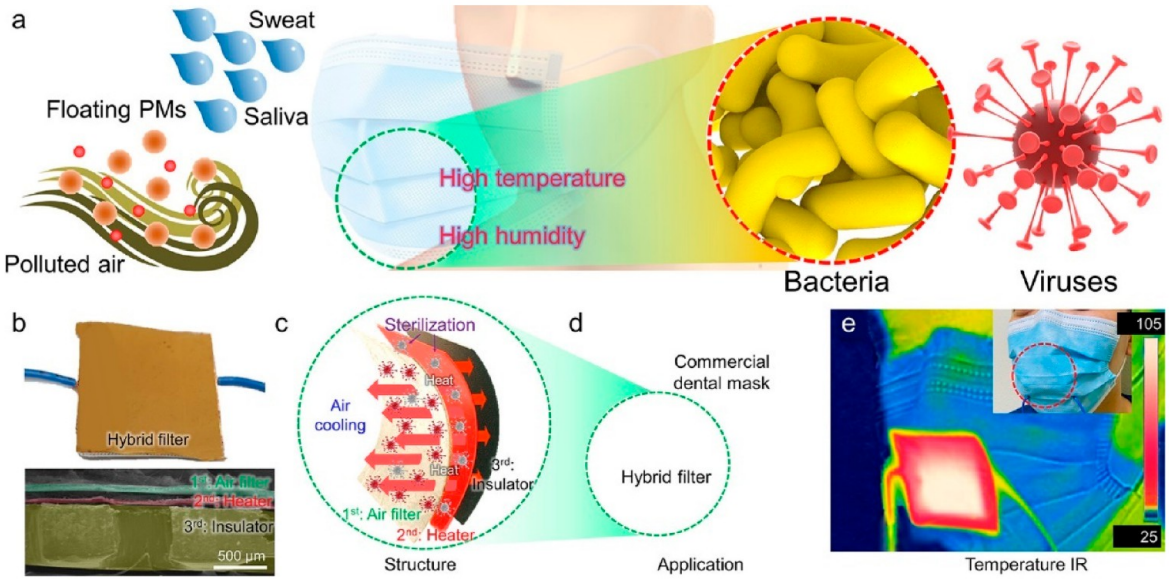

Figure 11. (a) Schematic of the existing face mask that is not only exposed to PMs in air but also to bacteria and viruses from the saliva and sweat of humans. (b) Photograph and a cross-sectional SEM image of the hybrid air filter. Illustrations of (c) the multilayered structure of a hybrid air filter composed of air filtration, heating, and thermal insulation layers, and (d) the hybrid air filter that is installed inside a commercial face mask. (e) Infrared image of the face mask equipped with the hybrid air filter, where the voltage of 3 V was applied to the thermal heating layer. The inset photograph is a real snapshot.[132] Reprinted with permission from ref 132. Copyright 2021, American Chemical Society.

electrospinning. The filtration efficiency of the optimized PVA NF-based filter was reported as comparable to commercial air filters, such as dust masks, cabin filters, and HEPA filters. In addition, contaminated PVA NFs can be easily removed from PP nonwoven filters by soaking them in water. It is of great importance to develop efficient and functional filtering materials that not only capture virus and bacteria-rich aerosols but also neutralize these microorganisms by functionalizing these filters, thus providing a safe indoor air environment and protection for humans. In this context, Balagna et al.[120] prepared antiviral filters by coating nanostructured composites of silver nanoclusters/silica directly on conventional glass, metal, and cotton filter fibers by an RF cosputtering method. The antiviral and filtering properties of these coated fiber-based structures were compared with their uncoated forms. As a result, it was stated that the properties of fiber porosity were maintained after coating, so the filtration performance was not affected. On the other hand, when their antibacterial activities against respiratory syncytial virus (RSV), the influenza A virus (FluVA), and the human rhinovirus (HRV) were characterized, it was stated that silver nanoclusters/silica composite coatings showed great virucidal activity against RSC (more than one order of magnitude virus titer reduction between coated and uncoated metal fibers) and FluVA (about two orders of magnitude virus titer reduction independently of the material of filters used). The same group also evaluated the virucidal activity of silver nanocluster/silica composite coated on disposable FFP3 face masks against SARS-CoV-2.[121] It has been reported that this coating strategy is able to completely reduce the titer of SARS-CoV-2.

Current advances in nanotechnology can offer viable strategies to minimize the risk of transmission of infectious agents from potentially contaminated protective equipment such as face masks. Most conventional protective masks used for protection against PM and microorganisms carried by aerosols consist of layers of wet resist spun-bond and melt-blown nonwoven fibers. The filtration performance of face masks is determined by the characteristics of fibrous structures (thickness of layers, fiber charge, fiber density, fiber diameter) and the characteristics of PM on air (particle size, shape, surface charge, etc).[122,123] In standard tests determined by National Institute for Occupational Safety and Health (NIOSH), the maximum filtration efficiency of these masks were tested against the aerosol particles (NaCl) with a size of 0.3 μm. As an example, the filtration performance of N95 masks are evaluated as 95%. Since size of the virus is around 100 nm, the size of airborne virus carriers may not exceed 0.3 μm depending on external factors. Konda et al.[124] tested filtration efficiencies of common fabrics including cotton, silk, chiffon, flannel, various synthetics, and their combinations. It is reported that efficiencies of hybrid materials such as cotton/chiffon, cotton/silk, and cotton flannels against PM below and above 300 nm were higher than 95% with a pressure drop of only 3 Pa. The use of nanofibers, instead of conventional microfibers, can increase both filtration performance and air permeability in face masks, especially against nanoaerosols that allow the penetration of nanosized viruses such as influenza and COVID-19. In a study,[125] PP melt-blown masks and PVDF nanofiber masks were compared for their filtration performance after cleaning treatments. It has been reported that the melt-blown filter exhibited around two times better permeability than the NF filter, but while the filtration performance of the reused melt-blown filter after cleaning treatment is observed to decrease by around 60%, the NF filter preserved almost all of its filtration performance with 98% even with multiple reuses.

An effective strategy to increase filtration efficiency without compromising air permeability is the use of electrospun nanofibers treated with electrets. As examples in the studies of reported by Leung et al.,[126,127] multilayer electrospinned nanofibers were produced. The fabricated PVDF face mask fibers were positively charged with quasi-permanent dipoles by a corona discharge treatment. The performance of electrostatically charged PVDF nanofilters was investigated using

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monodispersed NaCl aerosols of 50, 100, and 300 nm simulating microorganisms, and the filtration efficiency was found to be 92%, 94%, and 98%, respectively. Moreover, when compared with conventional N95 masks, this protection level is reported to achieve 10 times more air permeability.

Another strategy to develop filtration efficiency and breathability is use of complementary properties of micro- and nanofibers functionalized with various active agents. Choi et al.[128] developed biodegradable, moisture resistant, highly breathable, and high performance fibrous masks by electrospinning of poly(butylene succinate)(PBS)-based microfiber and nanofiber Janus mats coated with chitosan nanowhiskers (CsWs). As shown in Figure 10, the integrated Janus-like fibrous mats with CsWs nets show both electrostatic and physical sieving mechanisms, which are the filtering mechanisms of conventional nano- and microfilters, and they eliminate negative effects such as the decrease in efficiency due to moisture observed in microfibers or the high pressure drop due to high packing density observed in nanofibers. As a comparison, the researchers evaluated the dry and wet filtration performance of a Janus-like mat and a commercial N95 mask and found that the optimized filter is as efficient as the N95 with a filtration performance of 98% against 2.5 μm PM and a lower pressure drop (59 Pa) than the N95. Also, while the filtration efficiency of N95 was critically affected by the introduction of moisture, the optimized filters demonstrated great filtration efficiency of over 95% (against 1 μm PM) even after 45 wet−dry cycles. Furthermore, they reported that, unlike commercial disposable face masks, the optimized filters can be completely biodegraded within 1 month.

One of the important problems experienced globally in the period with the COVID-19 pandemic is environmental pollution caused by the fact that the majority of medical masks are disposable. Studies on self-sterilizing, self-cleaning, active virucidal PPE equipment have accelerated with the advent of the pandemic, especially in the last two years, thanks to the advantages of nanomaterials and nanotechnology, and significant developments and even commercial products have been revealed.[3,129,130] One strategy to fabricate self-sterilizing, reusable masks is the use of functional materials that enable in situ joule or photoactive heating since most of the bacteria and viruses can be incapacitated under high temperature. In the case of thermal inactivation conditions of COVID-19, 65 °C for 5 min are sufficient.[131] Kim et al.,[132] as shown in Figure 11, fabricated a fiber-based reusable filter by superimposing layers with different functional properties, such as air filtration (electrospun PAN nanofiber mat), joule heating (Cu-plated microfiber mat), and heat insulation (PTFE mesh), on each other. It has been reported that the multilayered filters can capture PM particles (less than 1 μm) with over 95% efficiency, the Cu-plated PAN nanofiber layer by joule heating can increase the surface temperature to ∼100 °C at a low applied voltage, and the insulation layer can prevent heat transmission to the inner layer human skin. They reported that the heat produced from the Cu-plated fiber mat completely inactivates *Escherichia coli*, so reusable filters augmented with heating microfibers can be used for antiviral and antibacterial sterilization. In a study by Kumar et al.,[133] reusability, filtration efficiency, and photothermal methods that induced in situ disinfection properties of polycotton fabrics modified with 2D MoS_2 nanosheets were evaluated. Nanosheet-modified fabric was reported to filter around 96% of 100 nm particles. It has also been stated that MoS_2 can increase the surface temperature of nanosheet-modified fabrics to ∼77 °C due to its sunlight-induced photothermal properties; therefore, it exhibits self-disinfection within 3 min of irradiation, and it is reusable and microbicidal even after 60 washing cycles.

Similarly, Zhong et al.[134] developed masks consisting of graphene layers that can be directly transferred with a dual mode laser-induced transferring technique on disposable surgical masks that can be produced in a roll-to-roll production-line-compatible way. The fabricated graphene-coated mask was reported to have self-cleaning ability due to the highly hydrophobic (water contact angle of 141°) nature of laser-modified graphene that enables incoming respiration droplets to be repelled. Furthermore, it has been stated that the surface temperature of the functional mask can reach up to 80 °C due to the sunlight-induced photothermal activity of the produced graphene layers, so these masks have a very high use potential with their self-disinfection and reusability properties against viruses and bacteria. In another study, the same group (Zhoung et al.) used the laser-induced transfer method for the direct production of plasmonic silver nanoparticles on N95 masks, thus achieving excellent hydrophobic and photothermal performances, synergistically better protection, as well as silver ion release in respiratory droplets against bacteria and the SARS-CoV-2 virus.[135]

In addition to the passive protection of face masks and other PPE equipment, one of the most effective strategies used to actively in situ destroy viral activity is modification with nanoparticles (especially with metal, metal oxide species) that can inactivate viruses through oxidation by metal and metal oxide species into equipment.[136] In one study,[137] copper oxide microparticles were impregnated on the outer layers of N95 and surgical masks. The antiviral performance of masks against SARS-CoV-2 were reported as a 3 log reduction of virus titers within 1 min of contact. Kumar et al.[138] reported a simple strategy for synthesis of copper-ZIF8 (zeolitic imidazolate framework 8) core−shell nanowires (Cu@ZIF-8 NWs). These NWs were applied to medical masks by dip coating. The results indicated that fabricated masks demonstrate good biocompatibility and antibacterial and as well as antiviral activity against SARS-CoV-2 (with a 55% inhibition of the virus replication after 48 h). Bataglioli et al.[139] performed viral inhibition and cytotoxicity assays of alginate-copper hybrid coatings on disposable PP masks. Results showed that hybrid coatings of alginate-copper presented around a 7 log inhibition against SARS-CoV-2, which represents 99.99% efficiency with a low toxicity of L299 cells. In another study, Trimiliosi et al.[140] used silver colloidal solutions stabilized with organic polymers that were applied on polycotton fabrics (Polycotton AgNP-OP) by using an easy pad-dry-cure method. The results exposed that polycotton AgNP-OP has excellent virucidal activity against SARS-CoV-2 (99.99% in 5 min) as well as high microbial activity against several other pathogens (*S. aureus*, *E. coli*, and *Candida albicans*). Nanofibrous mats introduced with antimicrobial natural compounds can be also used for PPE applications. Tian et al.[141] synthesized a novel polymer of polystyrene grafted by 5,5-dimethylhydantoin and trimethylamine (PSDT). PSDT integrated with covalently bound N-halamine combined with ammonia salt (PSDT/PU NNMs) was electrospun to fabricate nanofibrous membranes. It is reported that the resulting membranes exhibited a Voronoi-like nanonet structure with decent bacteria filtering efficiency (96.7%) and air permeability (pressure drop of 95.4 Pa). Beside filtration performance, bioprotection performance of

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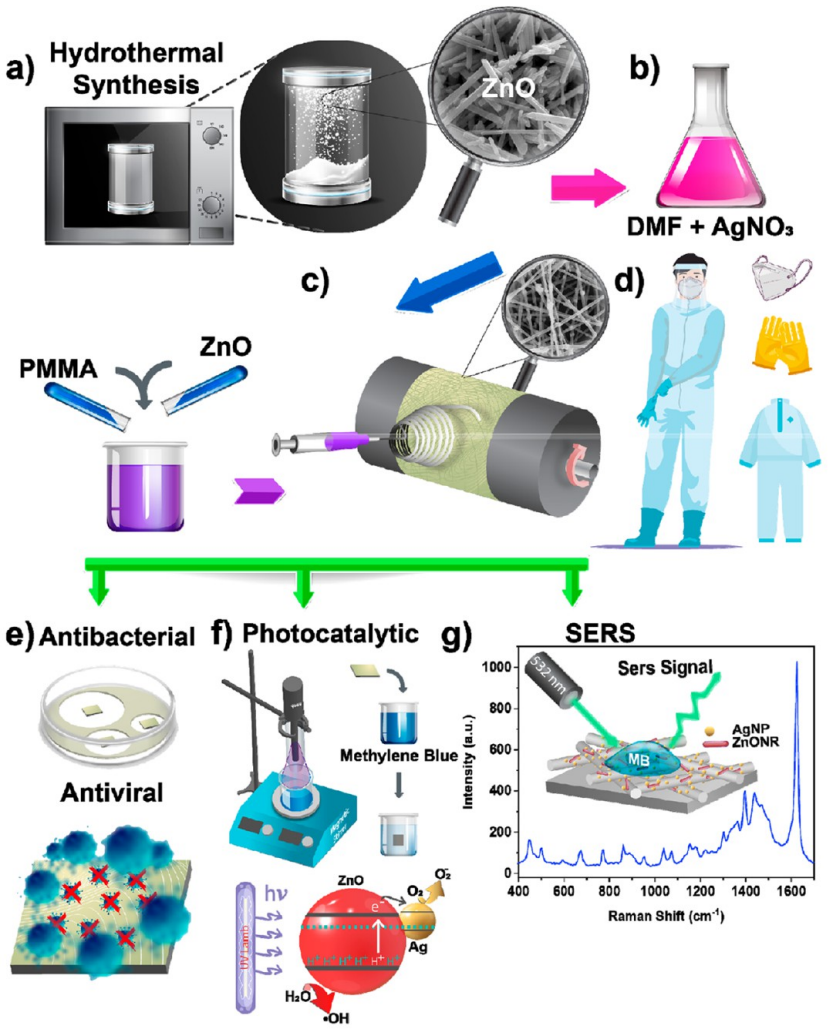

Figure 12. Fabrication steps of PMMA/ZnO-Ag NFs (a–d) (a) synthesis of ZnO nanorods by the hydrothermal method and SEM image of ZnO nanorods, (b) preparation of the electrospinning solution by mixing PMMA and ZnO nanorods with a solution of Ag NPs synthesized by in situ reduction of $AgNO_3$ in the presence of DMF, (c) fabrication of PMMA/ZnO-Ag NFs on a mat by electrospinning and integration of NF mats to use protective clothes, (d) schematic illustration of protective clothing containing PMMA/ZnO-Ag NF mats, and (e–g) multifunctional properties of the fabricated of PMMA/ZnO-Ag NF mats.[147] Reprinted with permission ref 147. Copyright 2021, American Chemical Society.

PSDT/PU NNMs was characterized as 6 log (>99.9999%) and 5 log (>99.999%) reduction against bacteria (*E. coli* and *S. aureus*) and viruses (*Escherichia coli* phages), respectively, in a contact time of 2 min. Zhang et al.[142] developed daylight-induced antibacterial and antiviral nanofibrous membranes of polyacrylonitrile (PAN) and hydrophilic poly(vinyl alcohol-co-ethylene) (PVA-co-PE) polymers blended with vitamin K derivatives, which can generate daylight and UV light-induced radical oxygen species. It has been reported that the resulting photoactive membranes can inhibit bacteria (*E. coli* and *L. innocua*) and viruses (bacteriophage T7) at a level of >99.9% under short-term (less than 90 min) sunlight and UV-A/B exposure and that these membranes can also maintain their microbial activity even after microbial contact was repeated five times, thus demonstrating excellent reusability and potential use as self-sterilizing PPEs. As shown in cell studies, the species containing zinc as a nanomaterial and the combination of these species with different functional materials come to the fore in the fight against COVID-19. It has been demonstrated that Zn^{2+} effectively inhibits activity of enveloped positive-strand RNA (RNA+) nidoviruses, which include major human and livestock coronaviruses such SARS-CoV-2 and also COVID-19.[109,143−145] Gopal et al.[146] used polyamide 6.6 fibers (PA66) embedded with zinc ions during polymerization, and they the tested microbial activity of the obtained fabric. Results showed that these PA66 fibers modified with Zn ions were able to absorb SARS-CoV-2 and influenza A viruses and reduce on-site the titer of these viruses by around 2 logs. In addition, these fabrics were able to retain their zinc content, so they maintained their microbicidal properties even after 50 washings.

Karagoz et al.[147] investigated the potential of using multifunctional electrospun poly(methyl methacrylate) (PMMA) nanofibers decorated with hydrothermally synthesized ZnO nanorods and in situ synthesized Ag NPs (PMMA/ZnO−Ag NFs) in protective mats. The PMMA/ZnO-Ag NFs showed high performance with multifunctionalities as shown in Figure 12: antibacterial agents for killing of Gram-negative and Gram-positive bacteria, antiviral agents for inhibition of coronavirus (3.75 and 4.75 log reduction in 1 and 24 h, respectively) and influenza viruses (reduction of 1.5 and 4 log reduction in 1 and 24 h, respectively), and photocatalysts for

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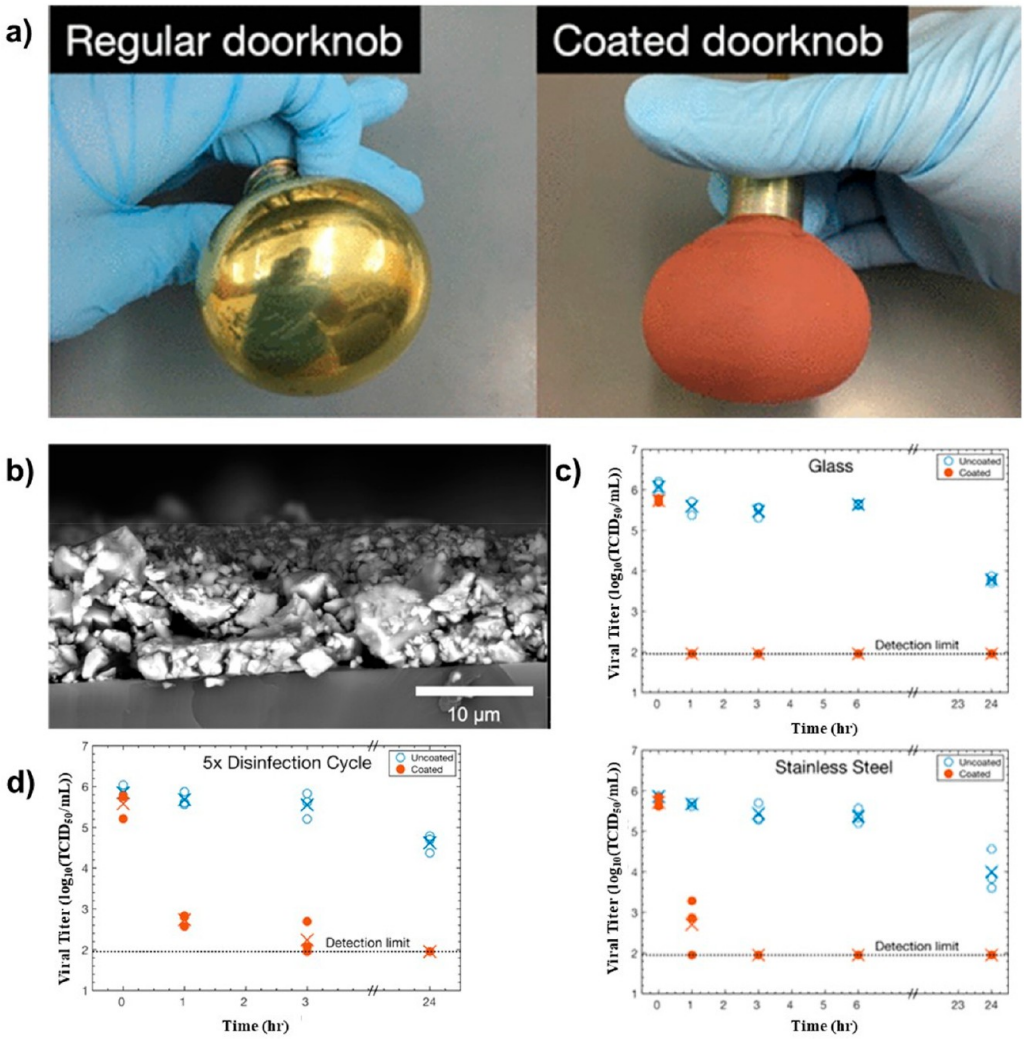

Figure 13. Touchable surfaces coated with copper oxide (Cu_2O) particles bonded with polyurethane and data of characterization (a–d). (a) Door handle coated with copper oxide (Cu_2O) particles bonded with polyurethane. (b) SEM image of Cu_2O/polyurethane film as a cross-section. (c) The graphs showing exposure times of Cu_2O/polyurethane-coated and uncoated surfaces to SARS-CoV-2 virus. (d) The graph showing the viable times of SARS-CoV-2 on glass coated with Cu_2O/PU purged five times with SARS-CoV-2 and 70% ethanol.[155] Reprinted with permission ref 155. Copyright 2020, American Chemical Society.

degradation of organic dye and air pollutants, enabling a self-cleaning protective mat, and reusable surface-enhanced Raman scattering substrates for quantitative analysis of trace pollutants on the nanofibers.

7. NANOMATERIAL-BASED COATINGS FOR THE FIGHT AGAINST COVID-19

One pathway for the spread of SARS-CoV-2 is through common-use surfaces. To prevent this spreading pathway, the surfaces can be coated with materials that inactivate the virus. It is recommended to use sodium hypochlorite, hydrogen peroxide, alcohol, and soap-based disinfectants for cleaning these surfaces. Cleaning with 0.5% hydrogen peroxide, 0.1% sodium hypochlorite, and 62–71% ethanol solutions have been determined to be effective on coronavirus.[148] In addition, there are many examples of fiber surfaces in most applications with coatings, as well as examples that have been applied to many surfaces such as glass, steel, and wood. In performing modifications and current structure designs of antiviral coating samples developed against COVID-19, priority was given to nanomaterials with antimicrobial properties and known antiviral effects against different viruses. Different mechanisms of action of nanomaterials in consideration of Au and Ag nanoparticles with antimicrobial properties of nanoparticles, Cu antiviral effects, daylight or under UV light self-cleaning properties of TiO_2 and ZnO nanoparticles have been used.[137,149−152] Among these new types of nanomaterials are examples made with polymeric materials. Self-cleaning surfaces have been obtained thanks to the super-hydrophobic property added to the modification and design of nanomaterials.[153]

The most important nanoparticles for coating on surfaces are Cu-based ones. Among the main reasons for this are Cu and CuO nanoparticles have properties such as cheapness and excellent antibacterial/antiviral effects.[2] The antiviral coatings can control the speed at which the coronavirus spreads. It has been noted that the coronavirus can remain for several days on plastic and stainless steel surfaces that make up many items.[154] But on copper surfaces, this period is estimated to be 4–8 h. Because the antibacterial/antiviral activity of "Cu" ions, they damage pathogens on the surface, causing pathogens to

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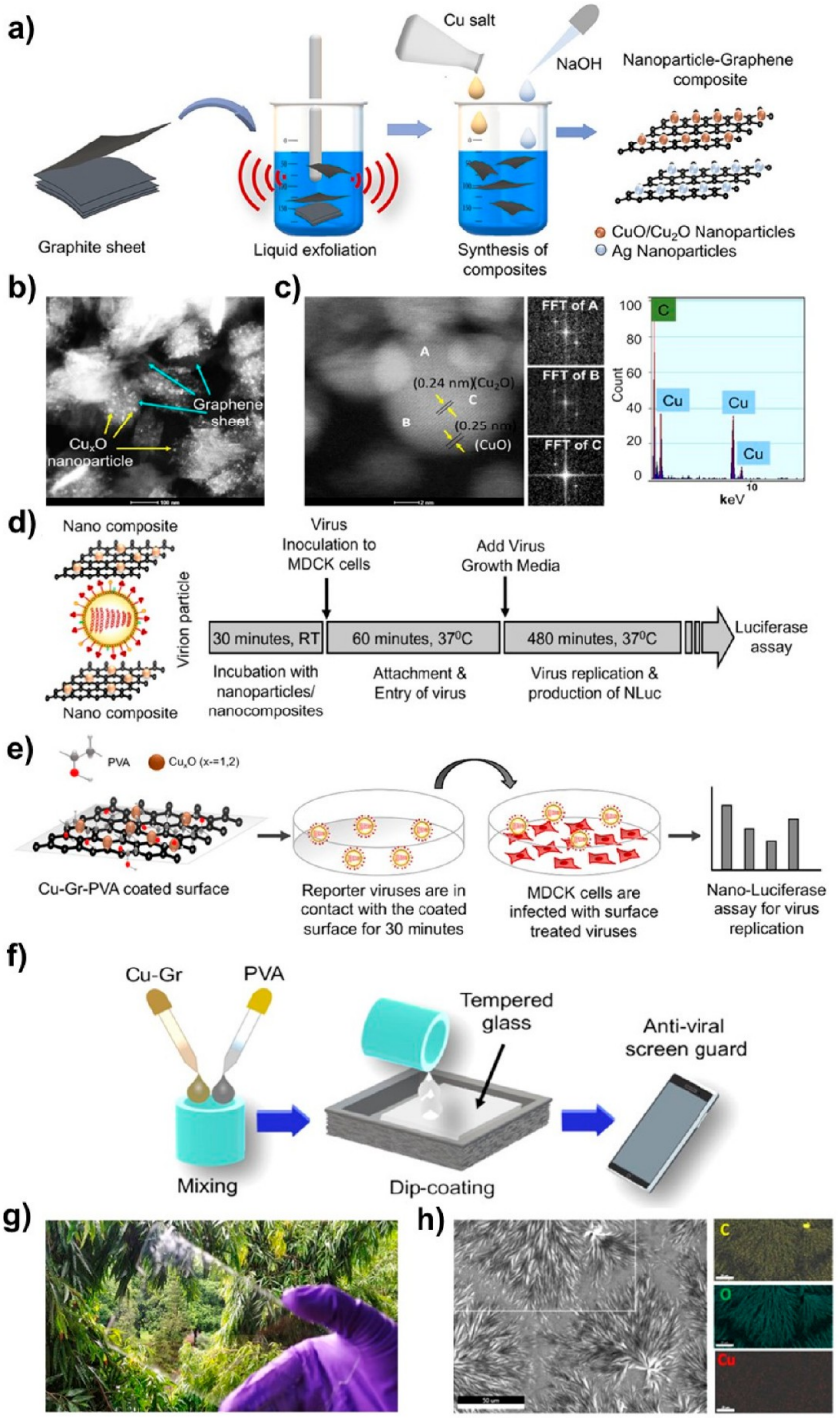

Figure 14. Synthesis, characterization, and screening of Cu-Gr nanocomposite for antiviral activity. (a) The scheme of synthesis of Cu-Gr nanocomposites. (b) Bright-field TEM image Cu-Gr sample. (c) High-resolution TEM (HRTEM) image of Cu_xO nanoparticles and Fast Fourier transform (FFT) patterns of CuO and Cu_2O. (d) The scheme of the "Nano-Luc reporter assay". (e) Nanoluciferase influenza A virus was exposed to solutions containing Cu−Gr nanocomposites, and virus replication was monitored. (f) The process of transparent antiviral coating of the mobile phone screen. (g) The transparent phone glass covered with dip coating. (h) The SEM image and mapping of Cu-Gr nanocomposite material.[152] Reprinted with permission ref 152. Copyright 2021, American Chemical Society.

become ineffective. For this reason, Cu and CuOs are usually used in coatings of large and solid surfaces that are touched. Because coronavirus can stay close to a week on solid surfaces, porous Cu_2O/polyurethane film coatings were made by Behzadinasab et al. for use in reducing this process. These coatings are applicable to all surfaces that can be touched. After treatment of Cu_2O/polyurethane-coated surfaces with corona-virus, it was found that there was 99% reduction in glass and steel surfaces within 1 h. In addition, it has been reported that the coating responds highly positively to many endurance tests.[155]

In another effort, transparent copper coatings were obtained. The coating used graphene-impregnated-copper(II) oxide and copper(I) oxide. The structure, prepared by dispersion of CuO

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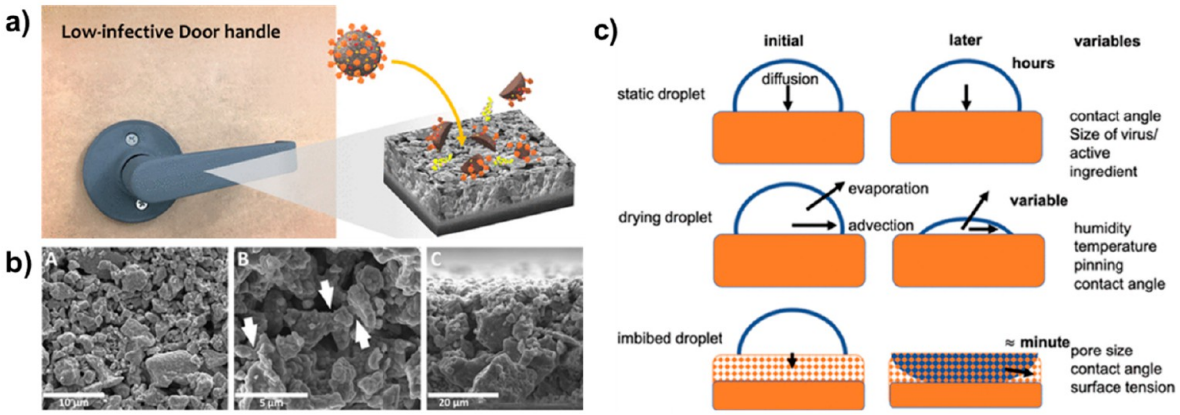

Figure 15. Low infection door handle CuO coating process. (a) CuO coated door handle. (b) The SEM image of CuO nanocomposite. (c) The diagram of the different states that make contact between the virus and the active surface.[149] Reprinted with permission from ref 149. Copyright 2021, American Chemical Society.

and Cu_2O nanoparticles on graphene layers, was noted to neutralize the virus by copper oxides following their interaction with double-layer peptide membranes. The material was made transparent by combining with polymer and applied as a coating to mobile phone glasses. As a result of optical measurements, the transparency of the material was confirmed, and COVID-19 was presented as an antiviral coating that prevents it. The authors proposed that surfaces such as door handles, medical materials, and masks can be covered transparently with this material.[152]

The most important reason for developing surface coatings is that there is a risk of transmission from touched surfaces. Another CuO-based coating has been developed to minimize the risk of transmission and reduce infection caused by the coronavirus. After heat treatment of Cu_2O coating, hydrophilic CuO coating was formed, and as a result of this coating, it neutralized coronavirus by 99.8% in 30 min and 99.9% in 60 min. The coating retains its hydrophilic property for 5 months and also does not deteriorate when treated with bleach and ethanol. The application of the coating has been tested using metal door handles.[149]

TiO_2 coatings are alternatives to copper-coated surfaces. In general, the inactivation of the coronavirus is carried out with TiO_2-mediated photocatalytic reactions. A study conducted in 2021 showed that the efficiency of virus decreased by 99.9% on surfaces such as glass that were treated for 20−120 min. It has been confirmed by various analyses that the protein structure of the virus is damaged by the TiO_2-based disinfectant.[150] In another study, TiO_2 coatings were made on ceramic tiles, which are widely used in environments such as hospitals where the virus is observed a lot. Thanks to the semiconductor TiO_2 coatings, which are activated by light energy in indoor lighting systems, coating surfaces gain the ability to clean themselves easily. In this case, microorganisms can be effectively disrupted by a photocatalytic mechanism. After the surfaces of ceramic tiles were coated, it was found that no virus remained after 2 h of visible light exposure.[151]

8. CHALLENGES AND FUTURE PERSPECTIVES

The COVID-19 pandemic has strongly catalyzed the development of innovative solutions based on nanostructures for the prevention, diagnosis, and treatment of SARS-CoV-2. The translation of nanostructures from the laboratory to practical applications has been slow due to challenges associated with disrupting conventional technologies. The immediate need for solutions to the challenges faced by society in the pandemic has highlighted the importance of nanostructures. The broad utilization of mRNA-based vaccines is perhaps the best example of such developments. Nanostructures have played key roles in the success of such vaccines. The COVID-19 has been a strong driving force for clinical trials and has substantially accelerated authorization procedures. These vaccines have been the stepping stone for the practical utilization of nanomaterials in medicine. This fact motivates researchers and industrial entrepreneurs for exploration of new forms of drugs and vaccines for healthcare applications. mRNA vaccines, for example, appear to be accelerating vaccine development for cancer and other diseases.

There are several important challenges, which strongly encourage future studies in a broad range of different contexts. In the case of mRNA vaccines, for example, thermostability is an important issue. To avoid degradation of mRNA encapsulated inside the NLPs, the mRNA vaccines have to be stored and transported at ultralow temperatures (−80 °C to −60 °C for Pfizer/BioNTech, − 25 °C to −15 °C for Moderna). Also allergic symptoms have been reported in a small proportion of people vaccinated against PEGylated substances used in the architecture of NLPs.[156] Although approaches such as the use of precisely designed adenoviruses as nanocarriers as in the Oxford/Astra Zeneca vaccine or the self-assembled protein segments within nanoparticles as in the Novavax vaccine allow thermostable systems that can be used at room temperature, these approaches have not yet been as successful as mRNA vaccines. For these reasons, it is essential to pursue studies on nanotechnology-enabled vaccines and to design nanocarriers, adjuvants, and active agents with advanced multifunctional properties including stimuli-responsivity, high biocompatibility, thermostability, and controllable biodegradation. Plant viruses and bacteriophages, which act as stable nanocontainers that protect their genome loads under various environmental conditions, have emerged as an important nanotechnology platform, not only because of the high stability they promise against environmental effects but also because they are suitable for different vaccination approaches, especially orally. As an example, a plant virus Cowpea mosaic virus can be administered from the gastrointestinal system as it can show excellent stability at high and low pH and temperatures up to 60 °C.[157] It is also necessary to focus on

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promising manufacturing concepts made in the past for the cost-effectiveness and scale-up of these vaccines/therapeutics. In this context, molecular farming of protein subunits and antibodies via plant-based systems acting as bioreactors appears to be a promising strategy.[158,159] Although the plant molecular farming approach is a new technology, it has proven to be cost-effective and highly efficient when used for manufacturing antibodies for treating patients via the Zmapp drug in the 2014 Ebola epidemic.[158−160] The most important features that distinguish plant-based molecular farming strategies from other production platforms, such as expression through mammalian, bacteria, yeast, insect cells, are that they are scalable and inexpensive, and possess low risk of human pathogen contamination, and need a relatively unsophisticated infrastructure.[161,162]

Current SARS-CoV-2 vaccines are administered by conventional intramuscular or intradermal injection, which require trained professionals for safe injection. This fact challenges vaccination campaigns and their distribution in underdeveloped countries. With the emergence of more effective nanomaterials or innovative delivery approaches, developing one-shot, slow-releasing vaccines/therapeutics is crucial. Microneedle-based patches show great promise in overcoming these limitations. Compared to other delivery methods, these patches have advantages such as low doses, reduced biohazard waste, and self-administration intradermally without pain. In addition, they can be equipped with features such as the ability to encapsulate fragile structures such as DNA, mRNA, protein subunits, and the ability to release these agents over time and then self-degrade thanks to site-specific-adjusted biodegradation.[77,163−165]

One of the biggest crises experienced by the healthcare system along with the pandemic is the difficulties in treating patients with acute respiratory distress syndrome due to deficient oxygen levels with conventional drugs and oxygen therapies, and the inadequacies in mechanical ventilation systems required for patients with severe acute hypoxemic respiratory failure. According to the WHO report, approximately 15% of COVID-19 patients develop a severe illness that requires oxygen therapy, and 5% become seriously ill, requiring intensive care treatment, and most of them need mechanical ventilation.[166] In this respect, nanobubbles (NBs), spherical stable gas-containing vesicles suspended in an aqueous solution, are an excellent nanocarrier platform for medical aid and efficient site-specific delivery of gas molecules and drugs.[167] The nanobubbles have unique features such as nanoscopic sizes, high surface-to-volume ratio, high internal pressure, long-term stability, surface charge properties, and are not agglomerated or deflated before reaching the target area. With their biocompatibility and noninvasive nature, nanobubbles are very promising nanomedicine platforms for COVID-19 treatment and next-generation biomedical applications.[168]

Diagnosis plays a crucial role in ending this pandemic to isolate confirmed cases as early as possible and prevent its spread, especially at this time of emergence of new SARS-CoV-2 variants. Conventional detection and diagnostic kits of viruses such as ELISA and PCR are costly, time-consuming, lack analytical sensitivity, and are labor-intensive and require specialized laboratory equipment and expertise. Nanomaterial-based biosensors can potentially initiate high-efficiency surface interactions between the analyte and the sensor, which can provide fast, accurate, and reliable detection of the virus. Moreover, nanotechnology approaches allow miniaturization of devices so that there is no need for special facilities and qualified personnel, all while improving sensitivity and efficiency. Field-effect transistors fabricated by using semiconductor nanostructures of 2D nanomaterials, nanotubes, and nanowires have been used for enhanced and versatile detection. Despite the intense studies and remarkable developments accelerated by the pandemic on behalf of nanoenabled biosensors, the challenges in scaling up and low-cost production, commercialization, limited deployment to clinical trials, and increasing their effectiveness still need to be overcome. Such applications, where detection and sequencing can be brought together on the same platform, especially against pathogens that undergo rapid mutations such as SARS-CoV-2, reduce false negative rates caused by variants that escape conventional diagnostic approaches and thus effectively allow epidemic data collection and therefore effectively use drug and vaccination application strategies exhibiting vital importance. Particularly, observations on variants that recently emerged beta and the newest one, omicron, show they are insensitive to inactivated vaccines, and PCR tests indicated that sequencing technologies have to be developed for increasing the number of sequenced samples to obtain critical epidemiological data. In the light of current developments, it seems that more advanced and feasible nanosensors and nanotheranostic devices and tools will emerge in the future, and these obstacles will be overcome. The remarkable contributions of these nanotechnology-based exemplary innovative technologies and tools on diagnostic and sequencing applications can already be seen. For example, nanoneedle technology is one of these innovative approaches that allows detection of viruses at a single virus resolution. In one of the most recent studies, it has been reported that an ACE2-modified SERS sensor containing plasmonic gold nanoneedles fabricated by conventional thin film deposition provided 109-fold electromagnetic enhancement so that detection can be utilized in as short as 5 min even at very low SARS-CoV-2 concentrations. It has been emphasized also that subsequent signal processing with machine-learning-enabled rapid detection of yet-unknown coronaviruses variants.[169] Companies such as NanoMosaic are also emerging, which are interested in commercialization initiatives for this technology, which enables many potential applications such as label-free, real-time disease monitoring, early and sensitive detection, and biomarker discovery, with nanoneedle-integrated CMOS chips.[170]

Nanopore technology is another nanostructure-based technology that will show itself at the forefront of future state-of-art approaches with its development in recent years, which allows for precise detection of subunits as well as pathogen sequencing of DNA and RNA strands in an effective and versatile way.[171,172] Briefly, nanopores fabricated from self-assembled protein or peptide nanosegments, solid-state (SiN) thin films, or 2D nanomaterials (graphene, MoS_2) are used as electrochemical detection platform.[172−175] Real time detection and sequencing of nucleotides can be acquired by reading the base-by-base electrical signals while passing nucleotides through these nanopores driven by the electrical field. Nanopore-based sequencing systems, especially Oxford Nanopore Technologies which is the industrial pioneer of this technology, have been successfully applied to the SARS-CoV-2 strains at the early stage of the pandemic.[175−177] The rapid and real-time detection and sequencing ability of mutagenized virus variants are one of the major advantages of this technique,

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providing critical data for further epidemiological analysis. During the pandemic, nanopore sequencing platforms combined with machine learning and artificial intelligence have proven to be more suitable than clinical diagnostic systems in terms of virus genome and viral target identification.[176] Apart from these examples, there will doubtless be more efficient, market-viable nanomaterial-based diagnosis platforms equipped with key attributes from an ideal biosensor[2,178] by advancements of nanofabrication and nanomaterial synthesis techniques.

During the pandemic, protective barriers, especially face masks, made important contributions, although not enough, considering their effectiveness in slowing down the aerosol transmission rate of SARS-CoV-2. Since at no time in history has such a large amount of protective equipment been needed, our unpreparedness for this has revealed the main concerns. First, we realized that the filtration efficiencies of commonly used PPEs were not designed for virus transmission. The second is that existing disposable masks made from nonrenewable synthetic polymers cause the production of environmentally harmful and non-biodegradable microplastics. The development of cost-effective large-area manufacturing methods and materials through materials science and nanotechnology for face masks that exhibit high filtration efficiency, antimicrobial activity, self-sterilizability, reusability, and/or biodegradability can address these concerns. As a matter of fact, preliminary studies that yielded successful results for nanotextiles with both high filtration efficiency and active or inactive antimicrobial functions met these requirements and became a roadmap for new-generation face masks in the fight against SARS-CoV-2. It has been shown that nanofibers produced from functional nanomaterials exhibiting various properties such as photothermal, photocatalytic, self-sterilizing, and electrothermal activity have great importance in PPE applications. Our foremost conclusion from these studies is that the electrospinning technique, and therefore electrospun nanofibers, is the most prominent way for the introduction of new-generation active masks, other protective textiles, and even ventilation filters into our daily lives. Multineedle or needleless electrospinning techniques are low cost and suitable for large-area production, making them easy to integrate into existing industrial systems.[179,180] Liquid repellent surfaces with additional functionalities such as bactericidal and SERS activity appear to be promising not only for preventing the spread of diseases but also for their sensing.[181] Apart from the aforementioned issues, we believe that it is necessary to focus on the synthesis of environmentally friendly nanomaterials that do not produce hazards, and studies on the production of plant-derived materials should increase.[182]

Overall nanostructures enable efficient vaccines, medicines, diagnostic tools, and protective equipment in fighting against pathogens. However, common concerns about some of the bottlenecks arising from the current state of nanomaterials and nanotechnology need to be addressed. As most of the studies still assess their biocompatibility using in vitro approaches, there is a need for daily life integration and clinical translation of nanotechnology. Therefore, closer collaboration between regulatory agencies and scientists is essential to establish standard regulations for fabrication of nanomaterials, their use, and toxicological assessments. Sustainability and its effects on the environment should be investigated on a long-term basis. Large-scale production capacity is another hurdle to overcome for the commercialization of nanotechnology-based tools, equipment, and devices. We are hopeful that these hurdles can be overcome and many advances will be made in the diagnosis, treatment, therapy, and prevention of potential pathogens using nanotechnology-based strategies. In addition, we think that it is essential to raise public awareness about nanotechnology and nanomaterials in order not to give rise to extreme views such as antivaccination and technophobia.

9. CONCLUSIONS

Academia and industry around the world are working on studies from basic research to advanced technology to eliminate or mitigate the pandemic conditions posed by the COVID-19 health crisis. As in other fields, approaches and technologies using nanomaterials are promising in the fight against COVID-19. Scientific studies and commercial products for the diagnosis, treatment, and prevention of the COVID-19 virus or COVID-19-based health problems using nanomaterials, along with the structure, cell incorporation, infection routes, replication mechanism, and dangers SARS-CoV-2 are emphasized. It is obvious that there is a need for studies that carefully examine every stage, from computer simulation studies to the interaction mechanisms of this virus with nanomaterials.

Important information and solutions will be obtained from examining and elucidating the interaction mechanisms between different solids and SARS-CoV-2. It would be recommended to expand research on this topic to ascertain the persistence of SARS-CoV-2 virus on common smooth and rough surfaces, to try to improve the current knowledge on this matter to avoid the spread of viruses and to clarify some discrepancies found in different recently published studies. Even though very rapid progress has been made in the diagnosis and treatment of COVID-19, which is much more complex and aggressive than typical seasonal flu infections, the effect of promising drugs such as chloroquine and hydroxychloroquine, which were used at the beginning of the pandemic, has still not been clarified.

Although the common treatment method for patients with COVID-19 symptoms is the use of some antiviral drugs, the main goal is to develop new drugs that can be used specifically for SARS-CoV-2. It is possible that nanomaterials used in the controlled release of drugs used in the treatment of many diseases, especially cancer, will also be used in the treatment of SARS-CoV-2. With targeted nanocarrier drugs, more people will be able to regain their health, and it is expected that deaths will decrease.

The same situation that applies to drug studies is also similar for vaccine studies. The development of vaccines based on nanoarchitectures is also an important task of scientists working in nanotechnology. Vaccines based on spike protein nanoparticles or used virus-like particles that mimic the nanovesicles have been developed to combat MERS-CoV. Similar nanotechnological approaches can be used to develop vaccines against COVID-19.

Currently, the most common use of nanotechnology in the fight against COVID-19 is detection technology. The need for fast, inexpensive, and sensitive detection methods comes into prominence day by day. For example, test kits using biological fluids such as blood or mucus and saliva are critical in providing rapid identification of asymptomatic patients, as well as identifying people with mild symptoms and isolating the virus before it infects more people. In addition to the currently used test kits, it is expected that faster, cheaper, and more

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sensitive test kits that can be tested by each person will be developed using nanomaterials.

In summary, nanotechnology is a powerful multidisciplinary field that offers a variety of strategies and approaches that can effectively contribute to the execution of worldwide research projects in the fight against the coronavirus disease that has affected the whole world.

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Notes

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ABBREVIATIONS

NP, nanoparticle
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2
COVID-19, coronavirus disease 2019
MERS-CoV, Middle East respiratory syndrome coronavirus
α, alpha
β, beta
γ, gamma
δ, delta
2019-nCov, 2019 new type of coronavirus
S, spike
M, membrane
E, envelope
N, nucleocapsid
RNP, ribonucleoprotein
ACE2, angiotensin converting enzyme 2
S-NTD, S1 subunit N-terminal domain
S-CTN, S1 subunit C-terminal domain
RTC, replication-transcription complex
CD4+ and CD8+, T cells
NK, natural killer
TNF-α, tumor necrosis factor α
IL-1β, interleukin 1β
IL-6, interleukin 6
IL-8, interleukin 8
MIP-1α, macrophage inflammatory protein-1 alpha
IP-10, interferon gamma-induced protein-10
G-CSF, granulocyte colony-stimulating factor
MCP-1, monocyte chemoattractant protein-1
LSPR, localized surface plasmon resonance
LFIAs, lateral flow immunoassays
MK201027, recombinant receptor binding domain of S protein
acpcPNA, ryrrolidinyl peptide nucleic acid
RNaseH, ribonuclease
ASO-capped AuNPs, thiol-modified antisense oligonucleotides capped gold nanoparticles
PIT, photochemical immobilization technique
PCR, polymerase chain reaction
FET, field-effect transistor
S protein, spike glycoprotein
QDs, quantum dot
FLISA, fluorescent-linked immunosorbent assay
ELISA, enzyme-linked immunosorbent assay
LFA, lateral flow assay
FDA, U.S. Food and Drug Administration
EMA, European Medicines Agency
LPNs, lipid nanoparticles
DSPC, 1,2-distearoyl-*sn*-glycero-3-phosphocholine
APIs, active pharmaceutical ingredients
Ti, titanium
Ag, silver
Au, gold
Zn, zinc
HIV, human immunodeficiency virus

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PT, pyrithione
H1N1, influenza A
CuI, copper iodide
PPE, personal protective equipment
PM, particulate matter
PVA, poly(vinyl alcohol)
PP, polypropylene
RSV, respiratory syncytial virus
HRV, human rhinovirus
NIOSH, National Institute for Occupational Safety and Health
PVDF, polyvinylidene fluoride
NF, nanofiber
PBS, poly(butylene succinate)
CsWs, chitosan nanowhiskers
PTFE, polytetrafluoroethylene
copper-ZIF8, zeolitic imidazolate framework 8
Cu@ZIF-8 NWs, core−shell nanowires
PSDT, trimethylamine
PSDT/PU NNMs, N-halamine combined with ammonia salt
PAN, polyacrylonitrile
PVA-co-PE, poly(vinyl alcohol-co-ethylene)
PA66, polyamide 6.6 fibers
PMMA/ZnO-Ag NFs, poly(methyl methacrylate) (PMMA) nanofibers decorated with hydrothermally synthesized ZnO nanorods and in situ synthesized Ag NPs
Cu_2O, copper oxide
TEM, transmission electron microscopy
FFT, fast Fourier transform
HRTEM, high-resolution transmission electron microscopy
IgG, immunoglobulin G
IgM, immunoglobulin M

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