Review Article

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Current state-of-the-art review of nanotechnology-based therapeutics for viral pandemics: Special attention to COVID-19

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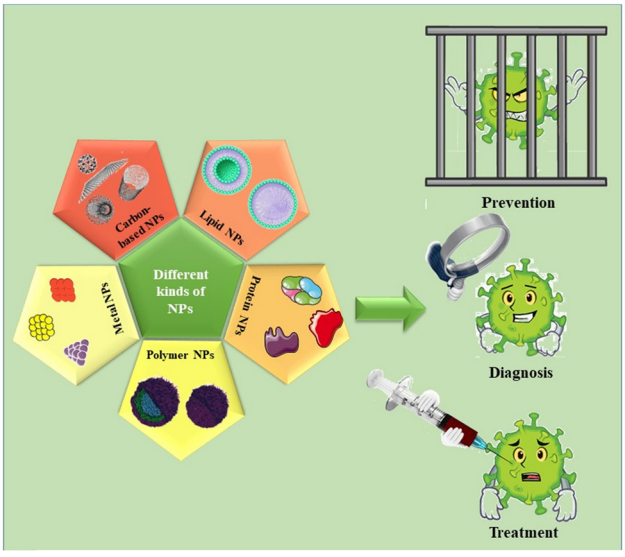
Abstract: Over the past two centuries, most pandemics have been caused by zoonotic RNA viruses with high mutation, infection, and transmission rates. Due to the importance of understanding the viruses' role in establishing the latest outbreak pandemics, we briefly discuss their etiology, symptomatology, and epidemiology and then pay close attention to the latest chronic communicable disease, SARS-CoV-2. To date, there are no generally proven effective techniques in the diagnosis, treatment, and spread strategy of viral diseases, so there is a profound need to discover efficient technologies to address these issues. Nanotechnology can be a promising approach for designing more functional and potent therapeutics against coronavirus disease 2019 (COVID-19) and other viral diseases. Moreover, this review intends to summarize examples of nanostructures that play a role in preventing, diagnosing, and treating COVID-19 and be a comprehensive and helpful review by covering notable and vital applications of nanotechnology-based strategies for improving health and environmental sanitation.

Keywords: viral pandemics, nanotechnology, prevention, diagnosis, treatment



Graphical abstract: Nanotechnology is a promising approach for preventing, diagnosing, and treating COVID-19 and related viral diseases.

Abbreviations

Alum	Aluminum hydroxide
ACE2	Angiotensin-converting enzyme II
CDs	Carbon dots
CNTs	Carbon nanotubes
CTD	Carboxy-terminal domain
CS	Chitosan
COVID-19	Coronavirus disease 2019
EWNS	Engineered water nanostructures
G	Graphene
GO	Graphene oxide
HA	Hemagglutinin
HSPG	Heparan sulfate proteoglycan
HEK	Human embryonic kidney
HIV	Human immunodeficiency virus
IPC	Infection prevention and control
IAV	Influenza A virus
IVM	Ivermectin
KGM	Konjac glucomannan

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LFIA	Lateral flow immunoassay
LNPs	Lipid NPs
Mal	Maleimide
MERS-CoV	Middle east respiratory syndrome coronavirus
MWCNTs	Multi-walled carbon nanotubes
NP	Nanoparticle
NTD	Amino-terminal domain
HTCC	*N*-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride
NA	Neuraminidase
ORFs	Open reading frames
PPE	Personal protective equipment
PF	Phenol-formaldehyde
PEG	Poly(ethylene glycol)
PEI	Poly(ethyleneimine)
PDMS	Poly(dimethylsiloxane)
PLA	Poly(lactic acid)
PLGA	Poly(lactic-*co*-glycolic)
PMMA	Poly(methylmethacrylate)
PP	Polypropylene
PS	Polystyrene
PVA	Poly(vinyl alcohol)
PVDF	Poly(vinylidene fluoride)
RBD	Receptor-binding domain
Rha(s)	Rhamnolipids
RT-PCR	Reverse transcription polymerase chain reaction
SARS	Severe acute respiratory syndrome
SARS-CoV	Severe acute respiratory syndrome coronavirus
SA	Sialic acid
ssRNA	Single-stranded RNA
SERS	Surface-enhanced Raman scattering
TMB	Tetramethylbenzidine
UV	Ultraviolet
UTR	Untranslated region

1 Introduction

A pandemic is an epidemic in which the vector contagion spreads globally. Despite technological developments, pandemics have been prevalent during the last two centuries. Except for the sixth cholera pandemic (1910–1911) that originated by a bacterium (*Vibrio cholera*), most pandemics have been caused by zoonotic RNA viruses [1]. These RNA viruses demonstrate high pandemic potential owing to the lack of a proofreader. Therefore, they show higher mutation rates than the DNA varieties and are

Table 1: Different virus pandemics that have spread globally and continue to this day (since 1918)

Pandemic	Virus	Years of activity	Country of origin	Animal vector	Global mortality rate (in millions)	Average mortality age
Spanish Flu	A/H1N1	1918–1920	Spain	Avian	50	Very young, elderly, and healthy young adults aged 20–40
Asian Flu	A/H2N2	1956–1958	China	Avian	1–2	School-age children and young adults aged 35–40
Hong Kong Flu	A/H3N2	1968–1970	Hong Kong	Avian	0.5–2	62–65
AIDS	HIV/AIDS	1981–Present	Democratic Republic of the Congo	Chimpanzee	36	Males about 50.8 years, and females about 49.7 years reported in 2013. http://www.cdc.gov/nchs/data_access/vitalstatsonline.htm.
Swine Flu	A/H1N1	2009–2010	Mexico	Pigs	0.148–0.249	37
COVID-19	SARS-CoV-2	2019–Present	China	Bats, pangolins?	5.7 through February 2022	0.02% in age of 20–49, 0.5% age of 50–69, and greater than 5.4% in age of more than 80

more adaptable to human infection and transmission. The other concerning situation is spreading through respiratory droplets, which transmit from person to person through close interactions [2]. According to Table 1, most of these pandemics are attributed to contagious respiratory illnesses induced by influenza viruses and coronaviruses, while the other is an acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) affecting the reproductive tract, the urinary tract, and the digestive tract (oral cavity, anus, and rectum). Herein, we briefly compare these three zoonotic RNA viruses epidemiologically and then focus on various strategies to prevent, diagnose, and treat the latest chronic communicable disease, which can also be applicable in other virus-induced diseases.

1.1 AIDS

The virus causing HIV belongs to the Retroviridae family with a diameter ~100 nm. Two major types of HIV are: HIV-1 (the most common and responsible for over 95% of all infections) and HIV-2 (relatively uncommon and less infectious). The spherical HIV-1 virion contains two copies of (+)ssRNA genome and replicative enzymes surrounded by a membrane containing HIV-1 envelope glycoprotein (Figure 1a). This sole antigen is a homotrimeric protein post-translationally cleaved into gp41, the transmembrane domain that constitutes the protein's fusion peptide, and gp120, a surface domain that mediates receptor binding [3]. The binding of HIV-1 envelope glycoprotein to the $CD4^+$ T cells induces conformational changes in the glycoprotein and subsequent interaction with chemokine co-receptors such as CCR5 and CXCR4 to facilitate active transport processes. Afterwards, in the presence of enzymatic machinery, RNA transforms into DNA in the host cell's cytoplasm and subsequently integrates into the cell genome. Consequently, chronic disease is a result of strong antibody responses, which can progress to AIDS [4,5].

HIV transmission mechanism: Direct contact of the infected patient's biofluids (*i.e.*, blood, breast milk, male and female sexual fluids) with the specific mucosa or bloodstream of the other person lead to HIV-1 transmission [4]. Therefore, transmission mechanisms are categorized according to three routes: sexual, parenteral, and vertical. Sexual transmission occurs with a high concentration of HIV-1 in the genital tract with a higher transmission risk for females [6]. Parenteral transmission occurs after biofluids' contact subcutaneously, intramuscularly, or intravenously [7]. Finally, vertical transmission is defined as mother-to-child-transmission, which occurs *via* three different routes, including *utero*, intrapartum, and breastfeeding [8].

HIV symptomatology: The symptoms appear as an acute infection within the first two months and chronic infection following the next six months. In the acute phase, infected people present swollen lymph nodes, fever, headache, rashes, and pains in the muscles, throat, and mouth. In the chronic phase, immunosuppression happens, and AIDS, with many life-threatening diseases, occurs in an untreated infection [4].

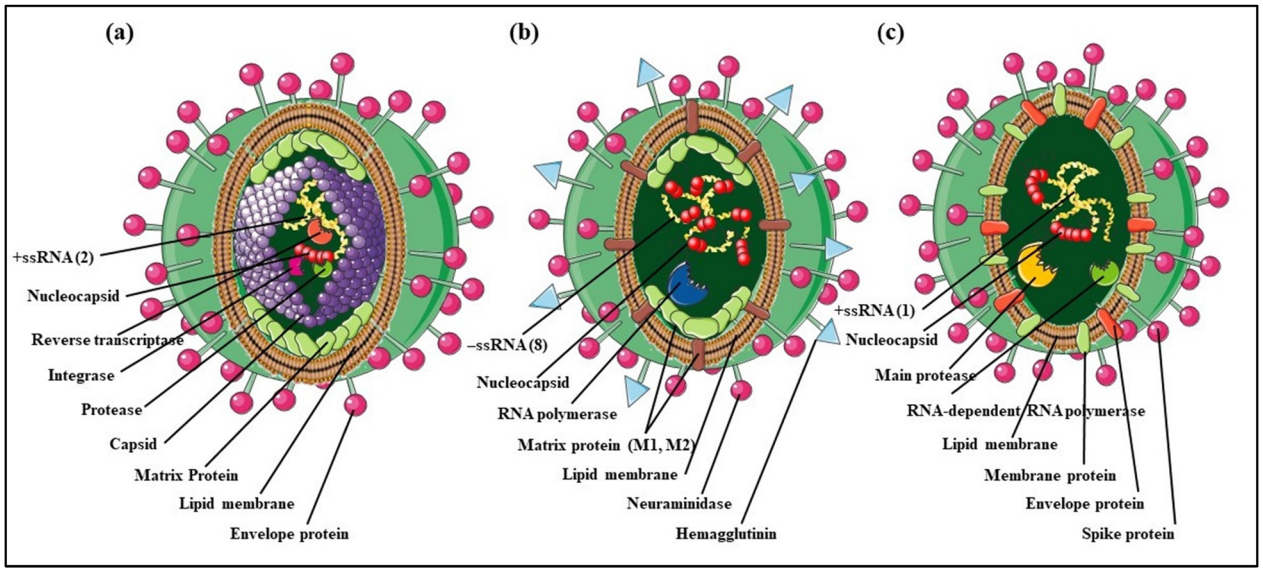

Figure 1: Schematic representation showing the structure of: (a) HIV, (b) IAVs, and (c) SARS-CoV-2.

HIV therapeutics and treatment: A *prima facie* treatment goal is to limit viral transmission by reducing the viral load in biofluids. Therapeutic vaccination is the most cost-effective, non-invasive, promising strategy for long-lasting immunity [9]. Passive antibody administration, latency reversal agents, adjuvants, and immune modulators are known to enhance vaccine potency [10]. Histone deacetylase inhibitor romidepsin [11], two major categories of Integrase Inhibitors, and single drug molecule with dual inhibitor activity against integrase and reverse transcriptase are among a suite of promising therapeutics [8].

1.2 Influenza (Flu)

Influenza viruses with A, B, C, and D subtypes belong to the Orthomyxoviridae family. They possess ~150–200 nm diameters with roughly spherical to pleomorphic and filamentous shapes. The envelope is a host-derived lipid bilayer, where the spikes are radiated outward [12]. They have seven or eight (−)ssRNA genome encoding structural and non-structural proteins. Influenza A viruses (IAVs) are the only ones with a pandemic potential (Table 1). IAVs have eight single-stranded viral RNA segments in separate viral ribonucleoprotein (RNP) complexes packaged into a single virus particle (Figure 1b). The structure of viral RNA plays an essential role in directing gene reassortment between human IAVs and animal reservoirs, which led to the emergence of pandemic subtypes [13]. There are different IVAs based on the rod-shaped spikes of hemagglutinin (HA) and mushroom-shaped spikes of neuraminidase (NA). HAs encoded by 1–16 genes and NAs encoded by 1–9 genes are involved in viral attachment and release, which happens at various pH and times during the virus life cycle [12]. Of the 144 total combinatorial possibilities, only four combinations of HAs and NAs (H1N1, H2N2, H3N2, and possibly H3N8) cause pandemics owing to partial or lacking immunity in the human genome [1].

Transmission mechanism: The most important routes of IVA transmission are *via* contact (*i.e.*, direct, indirect, and droplet), air, or a combination. Direct contact occurs *via* direct physical contact between an infected patient and a susceptible host). Indirect contact occurs by passive transfer of IVA to a susceptible host *via* contaminated hands, instruments, or other intermediate objects. Large droplets (≥5 μm diameter) generated from the respiratory tract of a colonized individual is the other way of contact transmission. Finally, airborne transmission *via* aerosols can occur over airborne particles less than 5 μm or dust particles containing IVA [14].

Symptomatology: Typical upper respiratory tract infection symptoms include fever and chills, nonproductive cough, rhinitis, muscle pain, and sore throat. In most people, these symptoms, except cough and malaise, resolve after 3–7 days, which can continue for more than 2 weeks, primarily in elder and chronic lung infected individuals. In severe disease, otitis media, respiratory, cardiac, musculoskeletal, and neurologic complications may occur [15].

Influenza therapeutics and treatment: The main treatment goal reduction of the viral load by diminishing viral replication. The treatment is initiated by prescription of NA inhibitors (oseltamivir) plus fibrates (fenofibrate). Due to virus NA mutations, Fludase (a recombinant sialidase fusion protein), Nitazoxanide (a novel thiazolide that inhibits IVA replication), and Favipiravir may cover resistant influenza strains. Corticosteroids are the other common drug, which may not be ideal for influenza viral infections [16].

1.3 Severe acute respiratory syndrome (SARS)

The life-threatening respiratory infection, SARS, is driven by an important species of the Coronaviridae family, SARS-associated coronavirus. The four genera of these coronaviruses are *alpha*, *beta*, *delta*, and *gamma* [17]. While *alpha* and *beta* originate from mammals, in particular particularly bats, *gamma* and *delta* originate from pigs and birds [18]. The enveloped (+)ssRNA viruses encode structural and non-structural proteins. Proteins of the membrane, spike, envelope, and nucleocapsid are the four main structural proteins [1]. Among the seven subtypes that infect humans, *alpha-coronaviruses* (*i.e.*, HCoV-229E and HCoV-OC43) cause asymptomatic or mildly symptomatic infections [1,18]. Whereas *beta-coronavirus* subgenuses lead to diseases with varying degrees of infectious potential, including lower respiratory tract infection through HCoV-NL63 and HCoV-HKU1, severe pneumonia through SARS-CoV, middle east respiratory syndrome coronavirus (MERS-CoV), and finally SARS-CoV-2 [1].

Table 2 describes the epidemiological characteristics of SARS infections. Infectious bronchitis virus is a *gamma-coronavirus* that produces highly contagious disease in chickens, especially in the reproductive and upper respiratory tracts [17]. However, different *delta-coronavirus* species have not caused disease in wild birds; a sickness in farmed quail in Poland and psittacine proventricular dilatation disease in green-cheeked Amazon parrot are attributed to *delta-coronavirus* [19]. Herein, we focus on

SARS-CoV-2 properties, transmission mechanisms, and symptomatologies.

1.3.1 SARS-CoV-2

This subgenus of *beta-coronavirus* shows a high sequence identity as a Bat *beta-coronavirus* [4,17]. The virion size is around 70–90 nm, whose complete genomic sequence shows a high genetic similarity with other subtypes inducing respiratory infections [4]. The genome is encapsulated by a protein-based capsid covered by a phospholipid bilayer membrane (Figure 1c). The membrane is essential for virus-cell fusion through the binding of the spike protein and cellular angiotensin-converting enzyme II (ACE2) of the target tissues (*i.e.*, lung, cardiovascular system, intestine, and kidney) [20]. After releasing the viral genome containing 6–20 open reading frames (ORFs) into the host cytoplasm, ORF1a/b is translated into two structural and 16 nonstructural proteins to assemble into replication–transcription complexes. The complexes within double-membrane vesicles synthesize sets of genomic and subgenomic RNAs that encode several structural and accessory proteins. The newly formed RNAs, nucleocapsid, and envelope proteins bud from the endoplasmic reticulum-Golgi apparatus and merge with the cell membrane to form new viral particles [4]. The viruses have demonstrated different mutations, especially on spike protein, which led to further variants with different transmission rates, reinfection risk, disease severity, and treatment [21]. This trimeric glycoprotein contains two domains of S1 and S2. The exposed S1 domain is in a more variable mode than the partially buried S2 domain. The main parts of S1 also include the receptor-binding domain (RBD), amino-terminal domain (NTD), and carboxy-terminal domain (CTD), which the RBD and the NTD show more variability than CTD [21]. The variability leads to many variants, as described in Table 3. According to the WHO, in April 2022, *delta* and *omicron* are categorized in variants of concern, and the others as variants of interest.

SARS-CoV-2 transmission mechanism: It may be transferred directly by human biofluids and indirectly by the environment (*i.e.*, waters, foods, and many surfaces) [4,37]. The primary transmission methods are through aerosols with a particle diameter of <5 μm during respiration, vocalism, or the solid residual particles after the droplet vaporization [38]. There is no report on SARS-CoV-2 infection transmission *via* food, but it should be mentioned that CoVs may survive at 4°C up to 2–4 days on fresh food [39]. According to WHO, the risk of fecal transmission seems to be low. However, feces may be a reason of hands, water, food contaminations [40], and coronavirus disease 2019 (COVID-19) transmission through fecal–oral, fecal–fomite, or fecal–aerosol [41,42].

SARS-CoV-2 symptomatology: Most cases reveal mild symptoms such as fever, cough, dyspnea, diarrhea, and abdominal pain 2–14 days after exposure. Nonetheless, most severe cases show progressive respiratory failure and even death [4].

2 Nanotechnology for prevention, diagnosis, and treatment

Infection prevention and control (IPC) relies on a thorough understanding of the factors that affect transmission [43]. To implement IPC, nanotechnology is a discipline that offers scientific and practical approaches to the prevention, diagnosis, and treatment of infectious illnesses. In the case of prevention, nano-sized vaccines mimic the virus without any replicated genome, replaceable nanoporous membrane for N95 face masks, applying self-disinfecting nanocoatings for air filters, and using nano-disinfectants in the environment are examples of nanotechnology in the prevention of virus spread [44]. Nanodiagnostics also rely on combining nanoparticles (NPs) with target molecules to produce a measurable signal for detection. In this technology, the nanoscale

Table 2: The epidemiological characteristics of SARS infections

	SARS-CoV epidemic	MERS-CoV epidemic	SARS-CoV-2 pandemic
Common symptoms	Influenza-like syndrome with dry cough, fever, malaise, body aches and pains, diarrhea	Cough, fever, breathlessness, and even gastrointestinal issues	Cough, fever, breathlessness, loss of taste or smell, potential gastrointestinal issues
Years	2002–2003	2015–present	2019–present
Potential animal reservoirs	Bats	Bats	Bats, pangolins
Intermediary hosts	Palm civets	Dromedary camels	Not identified yet
Origin	Guangdong province (China)	Jeddah (Saudi Arabia)	Wuhan (China)

Table 3: Different SARS-CoV-2 mutations and variations along with their epidemiology

Variant	Lineage	Origin	Date	Mutations	Transmissibility	Severity	Ref.
Epsilon	B.1.427 B.1.429	California	March 2020	Spike mutations: RBD, NTD, CTD, signal peptide	18.6–24% more than the wild-type strains	No evidence	[22]
Zeta	P.2 (B.1.1.28.2)	Brazil	April 2020	Spike mutations: RBD, CTD	Increase 23%	No evidence	[23]
Beta	B.1.351	South Africa	May 2020	Spike mutations: RBD, NTD deletion	50% more than the previously circulating variants	High	[24]
Alpha	B.1.1.7	UK	September 2020	Spike mutations: RBD, NTD deletions Non-spike mutations: nucleocapsid, p6:Δ106–108,	Highest with a 50–100% reproduction rate	High with 50% increased mortality	[25,26]
Delta	B.1.617.2	India	October 2020	Spike mutations: RBD, NTD, CTD, S2, proximal furin cleavage site Non-spike mutations: orf3, orf7a, orf1a/b, and Nucleocapsid gene	More than the alpha	High	[27,28]
Kappa	B.1.167.1	India	October 2020	Spike mutations: RBD, NTD, S2, proximal furin cleavage site Non-spike mutations: orf3, orf7a, orf1a/b, Nucleocapsid gene	High but less than delta	No evidence	[29]
Gamma	P.1 (B.1.1.28.1)	Brazil	November 2020	Spike mutations: RBD, Five NTD mutations	High	High	[30]
Iota	B.1.526	New York	November 2020	Spike mutations: RBD, NTD, CTD, signal peptide, Near the furin cleavage site Non-spike mutations: T85I, L438P, 9 bp deletion Δ106-108, P323L, Q88H, Q57H, P199L and M234I	High	High	[31]
Eta	B.1.525	Nigeria	December 2020	Spike mutations: RBD	Lower than Alpha variant	High	[32]
Lambda	C.37	Peru	December 2020	Spike mutations: RBD, NTD deletion	No evidence	No evidence	[33]
Theta	P.3	Philippines	January 2021	Spike mutations: RBD, NTD deletion, CTD	High	No evidence	[34]
Mu	B.1.621	Colombia	January 2021	Spike protein: RBD, NTD, CTD, S2 region	High	No evidence	[35]
Omicron	B.1.1.529	Multiple countries	November 2021	Spike mutations: RBD, NTD, CTD, fusion peptide, heptad repeat 1, proximal to the S1/S2 cleavage site, S2 protein	High	Low	[36]

procedures lead to handheld devices that are stable, highly sensitive, and marketable [44,45]. Finally, nanotechnology-based approaches can be a promising tool to enhance the potency and selectivity of physical, chemical, and biological therapies with minimized toxicity to normal cells. Targeted NPs have been designed to deliver lethal doses of therapeutics actively or passively to pathogenic cells [46]. This nanotechnology in COVID-19 mainly focuses on disrupting the cell receptor ACE2 interaction through different approaches, including recombinant ACE2, antibodies, and protease inhibitors to scavenge the virus, interfering with the spike/ACE2 interaction, and inhibit the spike protein processing, respectively [20].

2.1 Prevention

The SARS-CoV-2 virion is primarily transmitted by air spreading to the entire respiratory system of the human body. Afterwards, the virion is functionally larger due to the presence of other airway materials (*i.e.*, bacterial cells and epithelial cells) in the liquid droplets of the respiratory tract. The large droplets (>150 μm) show a low evaporation rate, which affects the aerosolized virus survival, transport, and fate. This virion is stable at RT and 4°C but inactivated under ultraviolet (UV) light and extreme pH conditions (pH > 12 and pH < 3), and heating at 65°C for 5 min [20]. Considering transmission, COVID-19 spreading should be controlled personally and environmentally. According to Figure 2, maintaining vaccination, personal protective equipment (PPE), and environmental sanitation are practical ways that lead to widespread community-level protection [47]. This section outlines the potential applications of nanotechnology for reducing infection risks to people, with a specific focus on several individual and environmental factors. Recent studies using NPs for infection prevention are shown in Table 4.

2.1.1 Vaccines

Despite a lengthy and complicated vaccination procedure in resolving the pandemic outbreak, it is highly effective. An effective vaccine is composed of antigens, adjuvants, immune enhancers, and delivery systems, which activates the immune system by generating neutralizing antibodies and T cells [48]. Many trials have been done to develop an effective vaccine that targets full-length spike protein or RBDs [49]. Currently, conventional vaccine production platforms include inactivated virus, live-attenuated, subunit-based, viral vector-based, and DNA/mRNA vaccines [47,49]. Although inactivated and live-attenuated vaccines have a rapid manufacturing process, the live-attenuated vaccine is innately immunogenic by affecting the toll-like receptors and may recover virulence. Nonetheless, inactivated vaccines are more stable and safer than live-attenuated vaccines; the antigens may be destroyed during inactivation [43,47]. Beijing-based Sinovac Biotech (NCT04383574, NCT04352608) is one of the groups that developed the inactivated vaccines [20]. Subunit vaccines are recombinant spike proteins with low immunogenicity,

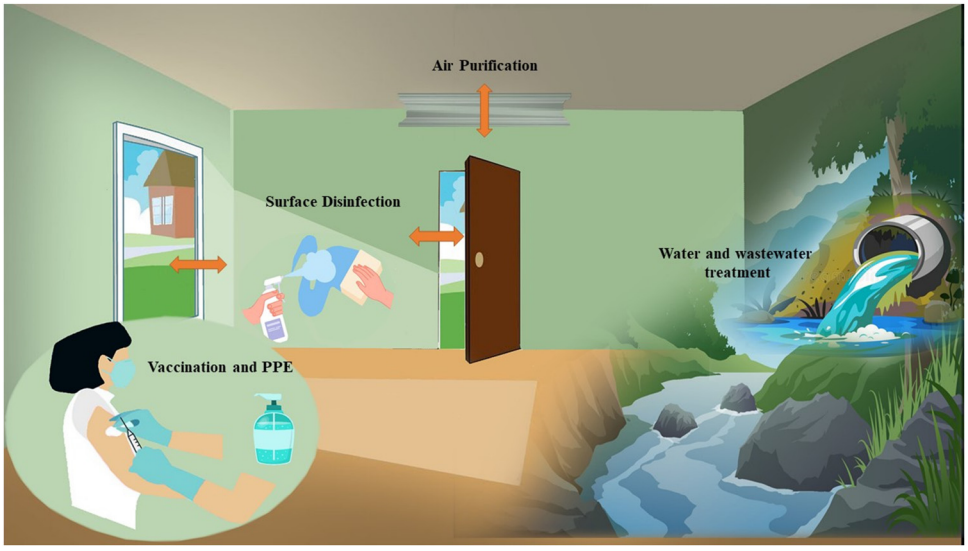

Figure 2: Schematic illustration for infection prevention against COVID-19.

Table 4: A semi-exhaustive list of selected NPs for infection prevention against COVID-19

	Organic NPs				Inorganic NPs	Inorganic/organic NPs
	LNPs	Protein NPs	Polymer NPs	Carbon-based NPs		
Vaccination	mRNA of RBD/LNPs [52], Spike protein/LNPs [53]	Spike protein/ferritin [64], RBDs/ferritin [65,67], RBD/aldolases [62,63]	DNA/PLA [84]	Recombinant peptide-modified nanodiamonds [97]	Spike protein/silica NPs [93]	mRNA-1273/PEGylated lipids [86]
PPE	nano-micelles of Rha(s) [99]	–	Synthetic polymers/oligomers [100], licorice roots extract/PVA [101]	G [102], polydopamine/GO [103]	Zn [104], Cu [105], Ag NPs [106], MOFs/Cu/Zn [107], Ag nanocluster/silica composite [108]	TiO_2 nanotubes/CS/PVA, CS/PVA, and silk/PVA [109], shellac/CuNPs [110], PVDF/PS nanofibers/Ag/Zn coated cotton [111]
Water and wastewater Treatment	–	–	CS [112]	CNTs/GO/PP [113]	Cu/TiO_2 nanofibers [114]	TiO_2/G nanohybrid materials [115]
Air purification	–	–	PMMA/PDMS/CS [116]	Laser-induced G [117], MWCNTs/PF [118]	Ag NPs [119], AgNP/SiO_2 hybrid particles [120], Ag/Al_2O_3 and Cu/Al_2O_3 [121]	nano-Ag/TiO_2/CS [122], TiO_2/crystal violet nanocomposites [123], ZnO NPs/PVA/KGM [124], nano-Ag/TiO_2/CS [122]
Surface disinfection	–	–	CS [125]	–	TiO_2 [126], AgNPs [127], silica [128]	AgNPs/cellulose [129], Cu_2O/polyurethane [130]

immunological memory, and stability but high safety and low side effects [47,49]. Adjuvants might be added to increase immunogenicity and reduce the number of vaccine cargos per dose [49]. Novavax (NCT04368988) developed a subunit vaccine containing an adjuvant named saponin-based Matrix M [20].

Viral vector-, DNA-, and RNA-based vaccines are gene delivery systems to trigger a vigorous immune response. Due to their intrinsic adjuvant activity, non-replicable viral vectors have a strong immune-stimulating effect [49]. The University of Oxford/AstraZeneca is one of the groups that developed adenoviral vector vaccines to produce the SARS-CoV-2 spike protein [20]. Another member of the genetic vaccine is the DNA vaccine. However, the synthetic DNA vaccine is thermostable and shows lower titers of antibodies than other vaccination strategies, and viral genome integration into the host DNA may lead to cancer. A DNA plasmid vaccine developed by Inovio Pharmaceuticals (INO-4800) is currently undergoing human Phase I testing (NCT04336410) [20]. The RNA vaccine contains mRNAs or siRNAs that switch off crucial target genes or synthesize vital virus proteins [20]. However, effective RNA delivery to the target is challenging because of the thermosensitivity of RNA, insertional mutagenesis risk, and anti-vector immunity [47]; they can elicit high levels of neutralizing mAbs and memory B cells and broaden the response to different variants [21].

Nanomaterials have already played key roles in vaccine delivery systems due to their stability, immunity, and delivery [20]. The relatively safe NP-based vaccines present antigens in their original forms [50] and stimulate antigen-specific immune responses even without adjuvant [51]. These nanovaccines can intrinsically or extrinsically activate the immune system because of functionalization or antigenic cargos. Biocompatible lipid, protein, polymer, carbon-based, and inorganic NPs can encapsulate antigenic cargo with high loading efficiency and improve pharmacokinetics. Major NP platforms are lipid NPs (LNPs) and protein NPs. LNPs, containing ionizable lipids, demonstrate strong potential as a gene delivery system with high loading capacity, transfection efficiency, and endosomal escaping to stabilize and protect them from degradation [43]. In two studies, LNPs were utilized for mRNA delivery of RBD [52] and full-length spike protein [53]. The current US FDA-approved mRNA-based LNP vaccines are BNT162b2 and mRNA-1273, developed by Pfizer/BioNTech and Moderna, respectively [54–56]. To improve the real-world effectiveness of the vaccine, alphaviral replicase was added to the RNA sequences and replaced the mRNA's untranslated region (UTR) with a synthetic UTR to self-amplify the RNA and increase protein

translation, respectively [49]. There are also adjuvant-encapsulated LNPs such as QS-21 included in the liposomes decorated with RBDs [57] and alum-packed on the squalene [58], which effectively activates the humoral and cellular immune system.

Protein-based NPs are constructed through self-assembling monomers, which are subsequently covalently or non-covalently bound to viral antigens [43]. These antigen-presenting NPs imitate the viral structure and elicit potent immune responses, which are helpful in reducing the immunogenicity of protein-based vaccines [59]. Popular proteins for vaccines are ferritin [60,61] and aldolase [62,63]. Recently, full-length spike protein/ferritin [64], RBDs/ferritin [65], RBD-24-mer/ferritin [66], and RBD/aldolases [62,63] were generated as a possible vaccine against the virus. Ma *et al.* conjugated RBD and/or heptad repeat to the 24-mer ferritin to induce humoral and cellular immune responses [67]. Ferritin can self-assemble into octahedral particles with three-fold axes and present multiple ordered viral antigens on the particle surface [68]. Scientists have also designed nanomer peptide vaccines using a new strategy, immunoinformatics, to map and identify epitopes in the SARS-CoV-2 protein sequences [69]. Sahoo *et al.* predicted SARS-CoV-2 nanomer epitopes for T-cell against class I and II of major histocompatibility complex, which may serve as sensitive, rapid, and cost effective vaccines [70]. Protein-based NPs can also be created with manufactured nanocomponents with adjuvant characteristics to induce immune responses [20].

Natural and synthetic polymers (Figure 3) have also been explored to prepare nanovaccines due to higher immunogenicity, biodegradability, biocompatibility, and a large surface area for targeting [71]. They are specifically developed in local and topical medications by considering their positive zeta potential to show higher immune stimulations and lower poly(ethylene glycol) (PEG) concentration to decrease the barriers [49]. These polymeric NPs, as carriers or adjuvants, can induce remarkable anti-inflammatory, antibody, and T-cell cross-reactivity responses. Chitosan (CS) [72,73], trimethyl CS/hyaluronic acid [74], β-cyclodextrin/CS [75], alginate/CS [76], dextran [77], pullulan [78], and inulin [79] are examples of natural polymers utilized in vaccine delivery systems. Chitosan NPs (CSNPs) have been extensively studied in vaccine area owing to their biodegradability, biocompatibility, lack of toxicity, and ease of shape and size processing [80]. Tailor-made polymers also offer certain advantages such as reproducibility in chemical, biological, mechanical, and interfacial properties [71]. They are mainly poly(lactic-*co*-glycolic) (PLGA) [81], poly(ϵ-caprolactone) [82], dendrimers [83], poly(lactic acid) (PLA) [84], polyanhydride [85], and PEG [86]. Among these synthetic polymers, PLGA and PLA consider major synthetic polymers for mucosal antigen delivery [87]. Biopolymers as adjuvants can be conjugated with various antigens for

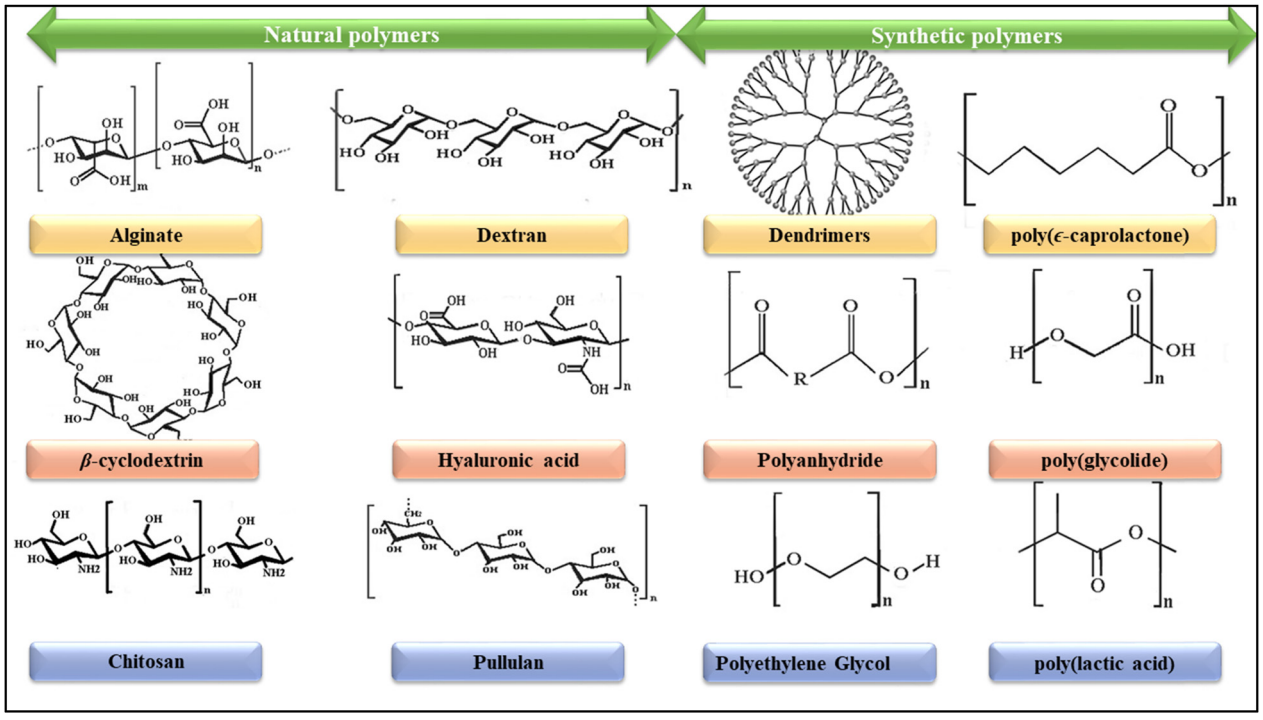

Figure 3: Few examples of natural and synthetic polymers.

intranasal delivery and trigger a strong immune response, but the proper type of polymer and the antigen affect the vaccination success [20,71].

Inorganic NPs are usually derived from non-natural materials. These intrinsically immunogenic materials show unique optical, electric, and magnetic properties making them promising vaccine design options [88]. The key categories of the inorganic NPs' library are AuNPs [89], quantum dots [90], carbon nanotubes (CNTs) [91,92], silica NPs [93], iron oxide NPs [94], graphene (G) [95,96], and nanodiamonds [97]. It is important to note that the functionalization of these inorganic NPs with a vast number of molecules, or specific motifs, is typically required for intrinsic (*i.e.*, solubility and biocompatibility) and extrinsic (*i.e.*, vaccine efficiency) capacities of the vaccines and improves human defense against random viral mutations and antigen shape changes [20,98]. Orecchioni *et al.* functionalized graphene oxide (GO) with amino groups to induce stronger cellular immunity with negligible toxicity [95]. Xu *et al.* also engineered GO–PEG–poly(ethyleneimine) (PEI) as a vaccine adjuvant for a robust stimulation of the immune system [96].

2.1.2 PPE

Proper PPEs (*i.e.*, masks, hand sanitizers, *etc.*) are critical for contagious respiratory illnesses such as influenza and COVID-19, which spread through aerosol particles or droplets. According to Asadi *et al.*, these aerosols can transmit using two possible modes: (1) droplet sprays (>5 μm) during a sneeze or a cough, which usually collect in the upper respiratory tract, and (2) inhalation of microscopic aerosol particles (<5 μm), which reaches in the deep lungs, enters the host cell and impairs multiple cellular functions [131]. Therefore, developing PPEs would significantly prevent the risk of infectious disease transmission by immobilizing the aerosols and eradicating the virus [47].

A conventional PPE mask serves as a physical barrier whose filtration efficiency only depends on the particle size and the airflow rate. They have neither been functionalized with biocides nor filtered out particles with sizes ~0.3 μm in the high airflow rate. Therefore, the newly designed masks should be dual-functional, which can increase the effectiveness of the existing masks by reducing the pore sizes under 100 nm and inducing the virucidal activity on the spot. For example, antiviral N95 masks, the most common respirators, arrest different particles through four mechanisms such as impaction (>500 nm), interception (>200 nm), diffusion (<200 nm), and electrostatic attraction, in which larger particles become surface blocking, smaller particles pass through the fibrous matrix deeply, and oppositely charged particles attract electrostatically [132]. The humid-exhaled air leads to swelling hygroscopic droplet nuclei, which influence the filter's ability to trap particles. Moreover, nanotechnology aims to synthesize superfine filters with high efficiency in improving particle capture and retention characteristics, reducing the impacts of exhaled humid air on particle redistribution, and quickly inactivating viruses upon capture [20].

There are several non-electrospinning and electrospinning techniques for nanofiber fabrication. The effectiveness of electrospinning for nanofiber production led to widespread usage in polymer nanofiber production. Over the last two decades, traditional electrospinning has developed into other derivative methods such as multi-jet electrospinning, needleless electrospinning, and bubble electrospinning [133]. These electrospun nanofibers only arrest the smallest virus-laden droplets and stop their transmission in the mask [20]. Nonetheless, nanofibers decorated with antiviral compounds such as G nanosheets, metal/metal oxide NPs, and polymer NPs can deactivate the pathogens, too. G-coated masks exhibited potent antiviral activity due to negatively charged particular nanosheet components [102]. Polypropylene (PP) filter surface spray-coated by GO and polydopamine [103], cotton/silk fabrics containing Ag/Cu NPs, and rGO [134] are examples of multifunctional electrospun nanofibers, which show an antiviral activity against pandemic SARS-CoV-2. Jeong *et al.* recently suggested a one-step nanocoating method to fabricate commercial facial masks. They synthesized a photo biocidal-triboelectric nanolayer composed of crystal violet as a photosensitizer, silica–alumina for photosensitizer immobilization, and perfluorooctyltriethoxysilane to improve wetness resistance and triboelectric effect [135].

Metal ions are characterized by oligodynamic effects to inactivate virions. Zn ions embedded polyamide 6.6 fibers [104], Cu-coated PP mask [105], CuO-impregnated masks [136], Ag NPs [106], and photocatalyst ZnO nanorods and Ag NPs loaded on poly(methyl methacrylate) [137] are the examples with antiviral activity of metal/metal oxide. FFP3 protective masks coated by Ag nanocluster/silica composite also demonstrated the virucidal effect [108]. TiO_2-coated nanofibers control and mitigate submicrometer airborne virus particles upon solar and UV radiation. These nanofibers demonstrated superior photocatalytic, photoinduced hydrophilicity, and antibacterial activity [138]. Metal–organic frameworks (MOFs) coated onto PP were also utilized as filter mask materials. Controlled release of Cu and Zn ions from ZIF-8 encapsulated Cu nanowires has proved antiviral efficiency [107].

Abbas *et al.* have also declared the antiviral activity of polymeric mixtures incorporated with inorganic compounds.

They fabricated three-layered electrospun nanofiber masks composed of TiO_2 nanotubes/CS/poly(vinyl alcohol) (PVA), CS/PVA, and silk/PVA. The outmost layer of TiO_2/CS/PVA displayed antibacterial activity *via* the double effect of TiO_2 (oligodynamic effect) and CS (acidic hydrophilic environment) [109]. Kumar *et al.* also reported a photoactive antiviral nanocomposite containing CuNPs, shellac, and a hydrophobic natural biopolymer, which conferred reusable self-cleaning surgical masks [110]. In another study, a disinfecting reusable facial mask was constructed by combining nanofibers of electrospun poly(vinylidene fluoride)/polystyrene (PS) with Ag/Zn-coated cotton [111]. The effectiveness of face masks can also be increased by combining polymers and other organic materials. For instance, synthetic polymers conjugated with oligomers developed antimicrobial activity under UV and visible light irradiation [100]. Other study utilized an electrospinning mixture of PVA and licorice roots extract containing glycyrrhizin acid and glycyrrhizin to synthesize a membrane for viral inactivation [101].

Hand sanitizer should be immediately performed before putting on and after taking off all PPE. They are utilized with soap hand washing to inactivate the virus and prevent its transmission. Few nano-based hand sanitizers mitigate transmission and control infection levels [139]. Biosurfactant with antimicrobial activities, and low dermal and irritation toxicity attracted much attention as an active ingredient for hand sanitizers [140]. Bakkar *et al.* synthesized nano-micelles of rhamnolipids (Rha(s)) as a potent bactericidal agent against both Gram negatives and positives. They proposed that hand sanitizers containing these nano-micelles' critical concentrations might be utilized against SARS-CoV-2 [99]. AgNPs represent a promising hand sanitizer ingredient if the toxicity on the skin and the environment is considered. Therefore, Fibriana *et al.* biosynthesized AgNPs from liverwort and demonstrated their antimicrobial activity in a non-alcoholic gel form hand sanitizer [141]. Although they did not evaluate the antiviral activity of the sanitizer, the virucidal activity of AgNPs has been confirmed against SARS-CoV-2 in another study [127]. Other effective disinfectants, formulated into nanocomposites and replaced with alcohol-based hand sanitizers, are herbal plant roots with low toxicity [142].

2.1.3 Water and wastewater treatment

Stools and masks are considered the main reason for polluting water and wastewater with coronavirus [143]. Enveloped viruses, including influenza viruses and coronaviruses, are too sensitive to the water environment and are often inactivated rapidly [144]. Nonetheless, shelf-life in water circumstances relies on characteristics such as pH, temperature, the concentration of suspended solids, and organic materials [143]. Rimoldi *et al.* declared that although SARS-CoV-2 RNA was present in water and raw wastewater, virus infectivity was negative [145]. In any way, the most reliable way to prevent virus transmission is the disinfection of water and wastewater. The water disinfection process includes a broad spectrum of treatment methods ranging from conventional treatment techniques (*i.e.*, chlorine in swimming pools, ultrafiltration, nanofiltration, and reverse osmosis membranes) to advanced membranes (*i.e.*, nanocomposite, distillation, bioreactor, and photocatalytic reactor) [143,144]. Herein, we focus on the most commonly used membranes based on nanotechnology with high permeability, selectivity, and antiviral activity.

Nanocomposite membranes remove charged contaminants such as bacteria and viruses from a watery component. Electrostatic interaction between the reactive functional groups of the membrane components and charged contaminants make them efficient [146]. Metal/metal oxide particles are the most used reactive compounds, affecting the membrane's permeability through hydrophilicity characteristics and antimicrobial properties due to their positive surface charge and nano-sized properties [146]. Antiviral biopolymer and its natural cross-linker were utilized in reversible coronaviral particles' adsorption in another study. Ciejka *et al.* developed novel nano/microspheres obtained by crosslinking CS with genipin, which could strongly adsorb HCoV-NL63 virus [112]. They suggested that the obtained material may be applied to purify water from pathogenic coronaviruses [112].

Membrane distillation is a thermal process that utilizes water vapor through a hydrophobic porous membrane under differential temperature, and occasionally nanotechnology for thermophilic pathogens' disinfection [147]. The primary pathogen disinfection mechanism is embedding biocidal NPs such as CNTs into the hydrophobic membrane [113] or coating the membrane with a polymer containing biocidal NPs [148]. Gupta *et al.* also reported on the biocidal activity of CNTs and GO coated onto a PP membrane, attributed to oxidation stress of GO, and diameter-dependent piercing and length-dependent wrapping of CNTs [113]. Because of the immediate inactivation of SARS-CoV-2 at high temperatures [149], this dual barrier strategy, temperature/vapor pressure, is an exemplary process for virus removal.

A photocatalytic membrane reactor is a combination of photocatalysis and membrane separation for effective

water purification. In photocatalysis reactions, semiconductor bombardment with low energy plays a crucial role in delivering excited electrons and holes for subsequent redox reactions [146]. There are different light-responsive transition metal oxides with the potential to deactivate harmful viruses [150]. TiO_2, the most effective photocatalyst, produces a significant amount of reactive oxygen species (ROS) after exposure to UV-A light to inactivate microorganisms like bacteria and viruses [151]. Zheng *et al.* showed that the Cu-TiO_2 nanofibers had a brilliant capacity to remove bacteriophage f2 and *Escherichia coli* under visible light [114]. To achieve water treatment in the presence of TiO_2, mass transfer rates should be minimized because photocatalysis happens, especially on the TiO_2 surface [115]. The other photocatalysts that attracted much attention are carbon-based materials because of no metal ion leaching in the water environment and optimal natural light-harvesting capacity [152]. These carbon-based materials such as fullerene [153], CNT [154], carbon dot (CD) [155], and graphitic carbon nitride [156] have been utilized for the inactivation of viruses. Due to the polymer membrane damage after prolonged exposure to light, ROS production, and photocatalyst agglomeration [157], developing a flexible high-performance photocatalytic membrane is an urgent challenge for water/wastewater purification.

2.1.4 Air purification

Evidence proves that the COVID-19 virus can be transmitted through air and survive in tiny aerosol droplets for a few hours [158]. Conventional disinfection strategies for removing bioaerosols are non-thermal plasma, photocatalytic oxidation (*i.e.*, UV, ozone, hydrogen peroxide), and air filters with photocatalytic activity. Electrospray ionization of active ingredient solutions, engineered water nanostructures (EWNS), is another way of inactivating airborne microorganisms through ROS production [159]. Each of these innovations could be useful in environmental chambers, but few are able to effectively combat the ongoing environmental and pathogenic disturbances in a real-world situation. Ideal air disinfection should result in effective reduction of key air pollutants, pathogens, disease transmissions, and finally, real-world clinical infections [160]. Filter media have the most significant practical potential of all strategies. They consist of myriad interwoven nanofibers utilized in mechanical ventilation systems to decrease airborne infectious disease transmission [161]. Nonetheless, these bioaerosols can multiply on these filters due to high moisture [119].

A wide range of materials, including metal/metal oxides, carbon-based nanomaterials, and biopolymers, play an important role in manufacturing efficient antiviral filters [132]. The Ag aerosol NPs generated from atomizers are efficient antimicrobial sanitizers to improve air quality passing through air filters [162]. AgNPs can improve the air quality alone or in incorporation with other supportive materials [119]. Young *et al.* utilized hybrid NPs of Ag-SiO_2 on air filtration units with a synergistic bactericidal effect on Gram negatives and positives [120]. Ag/Al_2O_3 and Cu/Al_2O_3 as supportive catalysts are useful in air-cleaning technologies because they can inactivate the SARS-CoV virus in a few minutes [121]. A multifunctional air filter composed of AgNPs-paper towel microfibers and aligned zein nanofibers also exhibited an effective antimicrobial activity [163]. The use of TiO_2 photocatalysis would also be helpful for air disinfection in ventilation and air filtration systems [20]. The other functionalized filter exhibited a potent inactivation of various bioaerosols under visible light in the presence of TiO_2–crystal violet nanocomposites. In this combination, crystal violet induces ROS production directly by itself or indirectly with the help of TiO_2 [123]. ZnO NPs were also utilized to induce photocatalytic and antibacterial activity to PVA and konjac glucomannan (KGM)-based nanofiber membranes [124].

Due to their unique physicochemical characteristics, such as high specific surface area, electrical conductivity, chemical/mechanical stability, and customizable structural properties, carbon-based nanomaterials also have antiviral activity [164]. Stanford *et al.* demonstrated a self-cleaning air filter made of laser-induced G to eliminate bacteria that can lead to illness and unfavorable biological reactions [117]. In comparison to cellulose fibers, the filter papers made of multi-walled carbon nanotubes (MWCNTs) and phenol-formaldehyde (PF) demonstrated a high specific surface area and efficient particle interception [118]. Among biopolymers, CS showed great capacity in air filter media construction. An electrospun superhydrophobic/superhydrophilic fibers composed of poly(methylmethacrylate)/polydimethylsiloxane and CS demonstrated a high bactericidal effect on *E. coli* and *Staphylococcus aureus* [116]. Wang *et al.* also showed the effective removal of viral aerosols (airborne MS2 bacteriophage) through nano-Ag/TiO_2-CS filters [122].

2.1.5 Surface disinfection

The WHO advises thoroughly sanitizing any contaminated surfaces with water, detergent, and disinfectants even if it has not been confirmed that certain surfaces can

transmit CoVs to hands [37]. There are biological (*i.e.*, probiotics or biosurfactants), chemical (*i.e.*, hydrogen peroxide or metal ions), and physical (*i.e.*, UV radiation) strategies frequently used in traditional disinfection techniques. Nanotechnology offers pathways to inactivate surface-bound and airborne viruses through spray NPs on the surfaces or develop innovative self-disinfecting surface and surface coatings [20]. These NPs are metal/metal oxide, G nanosheets, and biopolymer NPs, which can also be functionalized with antibodies against virions to improve antiviral potency [49].

Electrospray EWNS-based nano-sanitizers [159] and AgNP-loaded cellulose-based wipes [129] indicated an efficient reduction in influenza H1N1/PR/8 and MERS-CoV concentration on surfaces, respectively. The promising approach for inactivating surface-bound viruses is photodynamics, which attacks target cells *via* photosensitive agents' excitation and leads to cell death by producing ROS. Zn phthalocyanine grafted onto upconverted sodium yttrium fluoride NPs coated by PEI was used by Lim *et al.* to provide a potential method for the viral photodynamic inactivation [165]. TiO_2 photocatalysis would also be very helpful for surface disinfecting through TiO_2-doped paints after being exposed to UV light [166]. According to Khaiboullina *et al.*, UV exposure for 1 min completely eliminated coronaviruses on a TiO_2 NP-coated surface, aiding in the creation of self-disinfecting surfaces in public and healthcare facilities [126]. The glass or stainless steel coated by Cu_2O particles bound with polyurethane showed antiviral activity [130]. In contrast to stainless steel, Cu brasses or alloys containing Cu would offer efficient antibacterial surfaces for healthcare facilities [158]. CuNPs can eliminate viruses when sprayed on infected surfaces [136], but it is important to look into their antiviral effectiveness against SARS-CoV-2. AgNPs can also be modified to interact more effectively with viral proteins through surface capping agents. Through such tuning, the binding preference for viruses may be improved while the host cells' toxicity is decreased [127]. Iron oxide NPs can also be utilized for sanitizing surfaces due to lipid peroxidation, ROS production, and neutralizing surface proteins of viruses [167]. The surface plasmon resonance of the AuNPs demonstrated that these antiviral agents have mechanisms comparable to Ag and Cu [168].

In addition, fullerene and G are promising candidates for photodynamic virus inactivation and have demonstrated efficacy against a variety of viruses such as the IAV [169]. Due to the cytotoxicity of metal NPs, nanomaterials of natural herbs such as the positively charged CDs obtained from curcumin have been investigated and showed an inhibitory effect against a coronavirus model [170]. Another promising non-toxic NPs are CS-based NPs with potential antiviral activity against coronavirus. Milewska *et al.* reported the antiviral action of *N*-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC) against coronavirus HCoV-NL63 entrance [171]. Milewska *et al.* also confirmed HTCC's inhibitory effectiveness on SARS-CoV-2 and MERS-CoV coronavirus [125]. Poly(diallyldimethylammonium chloride) and poly(acrylic acid) polyelectrolyte multilayers are also utilized as antimicrobial nanocoating solutions [172]. Through an electrostatic attraction between the coronavirus's anionic spike protein and the cationic surface of these charged NPs, the microorganisms are rendered inactive [172]. In addition to the attractive effect of charged nanomaterials, the repulsive force of superhydrophobic silica nano-surfaces can also prevent the SARS-CoV-2 adhesion on surfaces [128].

2.2 Diagnosis

However, reverse transcription polymerase chain reaction (RT-PCR) is predominantly utilized in the accepted traditional method for detecting SARS-CoV-2 [20]; nanotechnology is of great interest and comparable with RT-PCR owing to specific and rapid detection of infections (*e.g.*, viral proteins and RNA) and immunities (*e.g.*, IgM/IgG) [49,173]. These NPs show two unique properties: (1) interacting with specific biomarkers and (2) transferring interacting events into measurable signals. The first step performs through surface functionalization of NPs and the second one requires unique physicochemical properties of NPs including optical, reactivity, or fluorescent properties [49,174]. Table 5 demonstrates diagnostic platforms in NPs for quick and precise SARS-CoV-2 detection.

One colorimetric detection technique is lateral flow immunoassay (LFIA) based on nanomaterials with optical properties. To detect viral proteins, most platforms are built on AuNPs and functionalized using polyclonal antibodies [173]. Anti-human IgM-functionalized AuNPs were created by Huang *et al.* to identify SARS-CoV-2 nucleoproteins colorimetrically [175]. In a different study, spike proteins were conjugated with AuNPs to detect virus-specific antibodies (IgM/IgG) [176]. Baker *et al.* utilized the immobilized glycan-AuNPs to diagnose glycan and spike protein interactions [177]. Through the use of complementary DNA sequences of the nucleocapsid protein, AuNPs can also target SARS-CoV-2 RNA [178]. Another nanomaterial introduced into LFIA constructure is SeNPs, with low toxicity and high biocompatibility. They were functionalized with

Table 5: Various SARS-CoV-2 diagnostic platforms in NPs for quick and precise detection

Technique	NPs	Components
LFIA	Inorganic NPs	Polyclonal antibodies/AuNPs [173], anti-human IgM/AuNPs [175], spike protein/AuNPs [176], glycan/AuNPs [177], nucleocapsid protein/AuNPs [178], spike protein/SiO_2 core/Ag shell/dual layers of Raman molecule [179]
	Inorganic/organic NPs	Anti-human IgG/lanthanide-doped PS NPs [180]
	Others	Nucleoprotein/selenium NPs [181], S9.6 antibodies/fluorescent NPs composed of carboxylated europium chelate [182]
Electrochemical biosensor	Carbon-based NPs	Anti-spike protein antibody/G [183]
ELISA	Polymer NPs	Anti-spike protein antibody/TMB/PLGA [184]

the SARS-CoV-2 nucleoprotein to enable the colorimetric detection of virus-specific antibodies [181]. Comparable to commercial AuNP-based LFIA, the SeNP-based LFIA displayed higher and similar sensitivity to virus-specific antibodies, IgM/IgG, respectively [49].

Fluorescent NPs conjugated with S9.6 antibodies are also nanomaterials to capture specifically the hybridized viral RNA–DNA probe on a strip. The SARS-CoV-2 genome including nucleocapsid, conserved ORF1ab and envelope proteins are targets for DNA probes [182]. In a different approach, anti-human IgG was coupled to lanthanide-doped polysterene NPs to generate a highly sensitive fluorescent signal for the detection of SARS-CoV-2-specific IgG [180]. A surface-enhanced Raman scattering (SERS)-based LFIA was reported by Liu *et al.*, which detects simultaneous anti-SARS-CoV-2 IgM/IgG with high sensitivity. They synthesized SiO_2 NPs composed of three parts: SiO_2 core, Ag shell, dual layers of Raman molecule, and spike protein with a specific target for IgM/IgG. They confirmed that SERS-LFIA demonstrated a significantly higher detection limit than commercial Au NP-based LFIA [179]. There are also peptide aptamers, Affimers, that might replace antibodies in LFIA structure. Affimers are non-antibody scaffolds that bind to target molecules. LFIA based on proprietary Biotinylated anti-SARS-CoV-2 S1 Affimer® is an ultra-sensitive technique produced against S proteins of the SARS-COV-2 [185]. They demonstrate advantages over conventional antibodies, including smaller size, more versatile, remarkable stability against pH and temperature, and equivalent affinity with higher specificity [186].

G was utilized to construct a field-effect transistor-based biosensor because of superior electrical and optical capabilities. The performance of the G-based biosensor coupled to a specific anti-spike protein antibody was determined in samples from nasopharyngeal swabs and cultivated viruses [183]. The use of G derivatives in electrochemical biosensors has attracted much attention. Singh *et al.* engineered a microfluidic chip with rGO linked to specific antibodies of the influenza virus, H1N1. This microfluidic immunosensor could capture several viral species and provide a promising platform for effective detection [187]. Khoris *et al.* conjugated anti-spike protein antibody with tetramethylbenzidine (TMB)–PLGA NPs in an improved ELISA method. The absorbance of the oxidized TMB in the presence of nanomaterial with peroxidase-like activity shows spike protein concentration [184].

2.3 Treatment

In the COVID-19 pandemic, different research activities experienced a considerable uptick in getting efficient and secure therapies. COVID-19 therapy is done initially by lopinavir (HIV medication) and remdesivir (Ebola medication) for hospitalized patients who need extra oxygen, favipiravir (influenza medication) in the clinical status of patients, and corticosteroids such as dexamethasone for critically ill patients [188]. The primary drawbacks of existing treatments are the absence of broad-spectrum antiviral drugs, the free drug molecule restrictions, and the biological barrier [20]. Therefore, there is an increased interest in developing innovative, broad-spectrum antivirals, which can combat various mutations of the spike protein and be less likely to develop resistance. The NPs are one of the most efficient ways to enhance the solubility of weakly soluble pharmaceuticals, lengthen the half-life of circulation, and achieve controlled/targeted drug release.

Because the lungs are the most critically affected organ, the medicine should target the essential host cells in the deep lung. Therefore, aerosol-based nanomaterials can be an effective carrier to penetrate the deep airways and deliver the therapeutics to the virus reservoir (*i.e.*, alveolar type II cells) and block the binding of ACE2 receptors with spike protein [20]. Intravenous injection is the other route of administration, where antiviral

medication NPs most likely optimize exposure. The challenge of non-specific interactions in systemic drug delivery might be overcome by the negative surface charge of NPs [49]. These NPs can be designed to halt viruses as therapeutics or act as a delivery vehicle for antiviral drugs. Therefore, this study focuses on NPs as intrinsic antiviral agents and therapeutic carriers (Table 6).

2.3.1 NPs as intrinsic antiviral agents

Several recent studies have described the inherent antiviral activity of NPs, including metal/metal oxides, carbon-based nanomaterials, and biopolymers, which disrupt the viral integrity, produce ROS, or generate heat to kill the viruses [49]. Inorganic NPs such as Ag [202–204], Cu [205], Au [206], and Ti [207] show intrinsic antiviral activity, which is size and dose dependent. Ag NPs' antiviral effects are mediated by various mechanisms, including the generation of ROS leading to membrane/envelope damage and toxic Ag(I) forms with a strong affinity for the thiol groups of structural and functional proteins [127]. The antiviral activity of Cu and CuO NPs is related to Cu ions' attacks on viral proteins and lipids and ROS production, too. Because of oxidation–reduction reactions, the viral disinfectant properties of CuNPs can be further enhanced when combined with bimetallic particles such as Fe [195]. NPs and nanorods of Au inactivate viruses in plasmonic photothermal treatment through intense heat emission and altering the membrane and/or surface functional groups [208], while believed to be far less harmful than Ag NPs [20]. TiO_2 inactivates SARS-CoV-2 through their photocatalytic properties under UV light by ROS production, which damages cell walls, membranes, DNA, and proteins [207]. However, viruses that are enveloped may be more protected than those that are not [209].

Carbon-based nanomaterials, such as G [192], fullerene [193], and CDs [194] are under investigation in COVID-19 treatment owing to antimicrobial activity through membrane distortion, biocompatibility, biodegradability, and tissue regeneration induction [210]. Sharp edges and negatively charged surfaces of G derivatives lead to electrostatic interaction with the positively charged virus particles [211,212]. Gholami *et al.* generated G-based heparin biomimetics through sulfating functionalized rGO sheets with biocompatible hyperbranched polyglycerol, which demonstrated antiviral activity on orthopoxvirus and herpesvirus strains [213]. Javier *et al.* also demonstrated *in vitro* antiviral activity of a multivalent disaccharide/[60] fullerene nanoballs against the Dengue and Zika viruses [193]. Finally, CD derivatives modified by an active compound (glycyrrhizic acid) demonstrated antiviral effect on

Table 6: A semi-exhaustive list of selected NPs as intrinsic antiviral agents or antiviral drug carriers

	Organic NPs			Inorganic NPs
	LNPs	Polymer NPs	Carbon-based NPs	
NPs as intrinsic antiviral agents	–	Alginate [189], sulfated glycomimetic oligomers and polymers [190], NPs decorated by HSPG or SA mimics [20], glycosylated dendritic polymers with 3′-sialyllactose- and 6′-sialyllactose [191]	G [192], multivalent disaccharide/[60] fullerene nanoballs [193]. Glycyrrhizic acid/CDs [194]	Ag NPs [127], bimetallic Fe/Cu NPs [195]
NPs as antiviral drug carriers	mRNA/β-sitosterol-doped LNPs [196], membrane NPs [197]	IVM/PLGA-*b*-PEG-Mal [198], membrane NPs of PLGA [199]	–	Chloroquine and hydroxychloroquine/Ag, Au, Ag/Au, and Pt NPs [200], polyphosphate/silica NPs [201]

porcine reproductive and respiratory syndrome virus through inhibition of proliferation, stimulation of innate immune responses, and inhibition of ROS accumulation [194].

Various polymeric compounds have antiviral activity, which comprises polymer length, hydrophilicity, and charge [20]. In nucleic acid polymers, phosphorothioated oligonucleotides were utilized to inhibit the entrance of hepatitis B and hepatitis D viruses and HBsAg release against hepatitis B virus [214]. In polysaccharides, negatively charged polymers are perhaps the most widely studied, which show a broad-spectrum antiviral effect on a variety of viruses. Alginate is an example of a negatively charged polysaccharide that shows antiviral activity due to the charge and phenolic structure [189]. Sulfated compounds with antiviral properties, including sulfated glyco-oligomers and glyco-polymers [190], Fucoidan-mimetic sulfated glycopolymers [215], PS sulfonate, PVA sulfate, polymethylene hydroquinone sulfonate, naphthalene sulfonate [214], dextran sulfate [216], heparan sulfate [190,217,218], dendritic polyglycerol sulfate [219], and carrageenan [190,220–222] are attributed to length and sulfate content. For instance, heparin sulfate blocks the non-specific cell surface adsorption by preventing membrane fusion and interaction with viral glycoproteins [190]. Moreover, NPs decorated by heparan sulfate proteoglycan (HSPG) or sialic acid (SA) mimics demonstrated *in vitro* capacity to target most known respiratory viruses through binding to the attachment ligand of viruses and block their interaction with cell membranes [20]. Polymers modified by SA derivatives also exhibited antiviral activity due to the binding of virus HA to terminal sialic acid residues on cellular glycoproteins and glycolipids. So, Günther *et al.* worked on glycosylated dendritic polymers with 3′-sialyllactose and 6′-sialyllactose and confirmed that higher valency and spacing between ligands resulted in higher antiviral activity [191].

Positively charged polymers such as CS and its derivatives can also activate innate immune responses by upregulation of cytokines and chemokines, essential for preventing viral replication. Indeed, Zheng *et al.* demonstrated that pulmonary delivery of CS could induce widespread immune responses against the H7N9 influenza virus by increasing the number of macrophages, dendritic cells, and innate lymphoid cells [223]. PEG exhibits more near-neutral ζ-potential, and mPEG is synthesized by the replacement of the CH_3 moiety to the OH group of PEG. According to Kyluik *et al.*, PEGylation of viruses with short-chain polymers can prevent infecting and invading viruses. In contrast, large chain polymers provide superior protection when grafted to host cells [224]. To permanently deactivate SARS-CoV-2, Cai *et al.* also reported a photothermal core–shell NP made of a semiconducting polymer and PEG functionalized with neutralizing antibodies [225]. The promising activity of the PEG polymer toward viruses is due to its water solubility [226], and high PEGylation of NPs may cause extended systemic circulation half-life [49]. Moreover, NPs made of antiviral polymers can affect viral infectivity by eradicating the virus effectively [20].

2.3.2 NPs as antiviral drug carriers

NPs are attractive controlled-release systems to deliver single conventional therapeutics (*i.e.*, hydrophobic/hydrophilic small molecules and macromolecules) or synergistic delivery of multiple therapeutics to the target. Apart from lowering systemic toxicity and immunogenicity in normal tissues, NPs can offer unique characteristics to the therapeutics, including solubilization, bioavailability improvement, release prolongation, protection against harsh environments, and targeting passively and/or actively [227]. Effectiveness of passive and active targeting is influenced by the physical characteristics of NPs, including charge, hydrophilicity, size, functional groups, and the conjugated moiety on the surface [228]. Targeted NPs lead to higher cellular uptake in target cells and then drug release at the site of action [227]. Several NPs were proposed as promising drug delivery systems categorized as inorganic and organic NPs. The inorganic NPs with antiviral properties are promising drug delivery systems to the target site. Chloroquine and hydroxychloroquine were loaded onto metal NPs by Morad *et al.*, who concluded that these nanostructures would be an appropriate candidate for COVID-19 treatment [200]. Silica NPs are the other inorganic NPs utilized for the delivery of polyphosphate. Polyphosphate was released gradually at the site, bound to the viral RBD electrostatically, and prevented further interaction between spike protein and host receptor [201].

LNPs, as organic NPs, can encapsulate macromolecules like mRNAs for SARS-CoV-2 suppression. For rapid ACE2 expression, which can compete with endogenous ACE2 in virus suppression, mRNA was encapsulated in β-sitosterol-doped LNPs. The mRNA can overcome limited half-life of recombinant ACE2 [196]. The antiviral potency of polymeric NPs can be enhanced by targeting and prolonging the controlled release of drugs. Targeted PLGA-*b*-PEG-maleimide (Mal) by an Fc immunoglobulin fragment was one of the polymeric NPs utilized to deliver hydrophobic ivermectin (IVM) and accumulate at the lung epithelia [198]. Nie *et al.* also noted that IAV virions bind significantly better to spiky NPs with 5–10 nm tall spikes. They predicted that cellular membrane coating and topography that matches geometry might develop nano-inhibitors for SARS-CoV-2 [229].

The other strategy for viral targeting and neutralization is coating polymer NPs with the cell membrane [199] or genetically engineered cell membranes [197,230] to mimic host cells through the critical surface receptors for viral binding. Zhang *et al.* synthesized PLGA NPs covered by either cell membrane of epitheliums or macrophages. These NPs are agnostic to current and upcoming coronaviruses since they are immune to various virus species and mutations [199]. In a different work, the genetically modified membranes were created by transiently transfecting human embryonic kidney (HEK)-293 T-hACE2 cells, after which cell membrane-based NPs were created *via* sonication and extrusion [197]. Rao *et al.* also made nano-decoys by fusing the cellular membrane of macrophages and HEK-293 T cells with a high level of hACE2. Moreover, many cytokine receptors were present on the fabricated NPs, which can efficiently bind and neutralize inflammatory cytokines like interleukin 6 and granulocyte macrophage colony-stimulating factor, as well as considerably reduce immunological dysfunction and lung damage in a mouse model of acute pneumonia [230].

3 Challenges and future perspectives of nanotechnology

Viral pandemics have introduced a global challenge to the scientific community in the past two centuries. However, many scientists believe that nanotechnology has the potential to overcome these pandemics; there are still several important challenges in high energy consumption, environmental safety, and human health that should be improved. Nanomaterial fabrication requires a lot of water and energy, and the chemicals used are often highly toxic to the environment and human health. Different factors, including the presence, concentration, and pH of organic or inorganic materials, which led to the long-term persistence of NPs in the environment, are well known as environmental pollutants [231]. Some physiochemical properties of the NPs cannot be protected by the immune and inflammatory systems and lead to immunotoxicity, inflammation, and oxidative stress, followed by severe cellular genotoxicity and fibrosis [45]. Therefore, the primary task is promoting the concept of safety by design and then performing the biocompatibility and biodegradability approaches using preclinical (*in vitro* and *in vivo*) and clinical studies for a candidate therapeutic, vaccine, medical device, or diagnostic assay [232]. Moreover, these viral pandemics require collective thought beyond ethnic frontiers and cultural diversity. To overcome such complicated challenges and achieve new and critical scientific solutions, a close collaboration among diverse researchers around the world with complementary skills is required [20]. According to this perspective, nanotechnology is an emerging technology where scientists from incredibly various backgrounds have collaborated successfully for improving complex issues in the diagnosis, detection, and treatment of viral diseases [233]. The "One Health" concept should be addressed in the future due to the interconnected health of humans, animals, and the environment.

4 Conclusions

Retroviruses have shown the potential for pandemic spread worldwide by their high contagious infections, which may lead to unexpected and very serious consequences. Although the current SARS-CoV-2 pandemic highly concerns, it is not among the most extreme threats encountered by humanity because science, technology, and innovation have enabled us to identify, control, and mitigate it. In fact, community hygiene and sanitation practices, effective vaccination, and treatment can shorten the duration of a pandemic. This work discussed nanotechnology's potential as a platform for preventing, diagnosing, and treating COVID-19 and any future pandemics. There are different types of NPs proposed as promising foundations for counteracting the current global public health threat. These nanosystems are categorized into inorganic NPs (metal/metal oxides, silica) and organic NPs (lipid, protein, polymer, and carbon based) can be intrinsically or extrinsically immunogenic. Finally, the idea of "nanotechnology" can assist scientists in designing NPs for immune regulation in vaccine development and therapy, in the creation of quick, easy, and affordable assays for the diagnosis of COVID-19 and environmental sanitization.

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