Nanotechnology-Based Approach to Combat Pandemic COVID 19: A Review

Brijesh Kumar Shukla, Himanshi Tyagi, Hema Bhandari, and Seema Garg*

The emergence of a novel Corona virus (COVID 19) originated on December 19 from China. The city of Wuhan, the capital city of Hubei province, China, is responsible for an outbreak of respiratory illness known as COVID 19 and it has been rapidly spread across the world claiming millions of lives. The sudden outbreak of novel Coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or 2019-nCoV), is a big concern for their speedy mitigation using the predictable treatment and creating its approach around the world. Researchers and doctors are in search of rapid diagnosis kit, drugs, and viral-resistant personal protective equipment (PPE) to clinical diagnosis, medication, and prevent the spread of COVID 19. A rational approach with adaptability and broad viewpoint to challenge the growing pain could be overcome by the application of appropriate technology. The nanotechnology-based approach can significantly serve the purpose of the current pandemic situation of COVID 19. But same time implementation of innovative and creative nanotech approach, there is a decisive need for the full knowledge of SARS-CoV-2 pathogenesis. Moreover, to defeat COVID 19, particularly nanotech-based system with their viral inhibitory properties to increase the effective nanotech approach is essential. In this scenario, this review aims to summarize the past, present, and future of nanotech-based systems that can be used to treat COVID 19, highlighting Nano-based compounds. Lastly, the potential application of the different category of Inorganic Nanomaterials/Inorganic organic conjugate /hybrid system and their practical applicability as suitable means for inspiring against COVID 19 has also been discussed.

1. Introduction

Pneumonia-related symptoms like severe acute respiratory symptoms started in December-19 in the Hubei-province of China. Later on, it was declared New coronavirus infectious

B. K. Shukla, H. Tyagi, S. Garg
Department of Chemistry
Amity Institute of Applied Sciences
Amity University
Sector-125, Noida, Uttar Pradesh 201313, India
E-mail: sgarg2@amity.edu

H. Bhandari
Department of Chemistry
Maitreyi College
University of Delhi
Delhi 110021, India

disease -COVID 19 by WHO, caused by novel severe acute respiratory syndrome coronavirus (SARS-CoV) referred as SARS-CoV-2. SARS-CoV-2 virus worldwide infected more than 3.3 million of people and headed to more than 0.23 million of deceases, with the figures static increasing rapidly.[1]

Initial screening of infected people showed pneumonia-like symptoms and abnormal lung computed tomography (CT) image; was done with PCR (polymerase chain reaction) with known pathogen primer tested negative and later on unknown pathogen was identified by RNA genome sequencing that is distinct with previously known pathogens.[2]
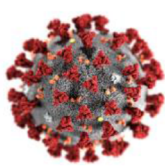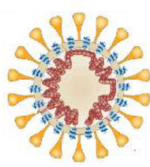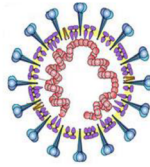
Its genetic structure exhibited that the new virus was related to severe acute respiratory syndrome (SARS) that is a viral respiratory disease of zoonotic origin that surfaced in 2002–2003 triggered by severe acute respiratory syndrome coronavirus (SARS-CoV), so it was named as SARS-CoV-2.[3–5]

The readiness of the whole genome sequence supported the researchers to develop PCR kits to diagnose patients suffering from COVID-19. Moreover, the researchers also developed several testing methods based on the serological test, lateral flow assay and loop-mediated isothermal amplification for rapid diagnosis of COVID 19.[6] But their implementation and regulatory approval by various health bodies differ by country. According to a preliminary investigation among SARS-CoV-2 infected people, about 80% show only mild flu-like signs such as fever and cough and mild pneumonia and acute respiratory failure.[7] Earlier epidemiological revisions have evidenced that is the number of situations for widespread of the virus, i.e., the infection sources, transmission path, and exposure[3] and similar for COVID 19 too.[8]

Sequence homology study of the viral genome disclosed that the CoV identified in this study is distinct from any of the known human CoVs, including severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).[2–4] The most closely related known viruses are two bats like SARS-CoV. Formally, the recognized genome in 2005 in Zhoushan, Zhejiang, China, which is geologically distant from Wuhan.[9] In a study, Ren et al.[10] confirmed genome

Epidemiological Comparison of Respiratory Viral Infections

Disease	Flu	COVID 19	SARS	MARS
Disease Causing Pathogen	Influenza Virus	SARS-CoV-2	SARS-CoV	MERS-CoV
Ro Basic Reproductive Rate	1.3	2.0-2.5	3	0.3-0.8
CFR Case Fatality Rate	0.05-0.1%	3-4%	9.6-11%	34.4%
Incubation time	1-4 days	4-14 days	2-7 days	6 days
Hospitalization rate	2%	20%	Most cases	Most cases
Community attack rate	10-20%	30-40%	10-60%	4-13%
Annual Infected (Global)	~1billion	~1.45 billion (till 24-April-2021)	8098(in 2003)	420
Annual Deaths (US)	10,000-61,000	~3.08 Million (till 24-April-2021)	8(in 2003) None since 2003	2(in 2014) None since 2014

WHO coronavirus (COVID-19) dashboard as on 24 April-2021

Figure 1. Epidemiological Comparison of Respiratory Viral Infections.

sequence by Sanger sequencing method and identified a novel strain of SARS-CoV, while the portion of 50-ORF1ab–S–E–M–N–30 genome structure was similar to well-recognized bat SARS-CoV,[10] researcher across world investigating relationship the novel coronavirus genome sequence with SARS and MERS to determine if any of the medications established against SARS and MERS can work against this novel SARS-CoV-2. Based on a comparative study, few probable drug targets of SARS-CoV-2 have been acknowledged. Among several, human angiotensin-converting enzyme 2 (hACE2),[11] papain-like protease (PL pro),[12] 3C-like protease (3CL pro),[13] RNA-dependent RNA polymerase (RdRp),[14] helicase,[15] and N7 methyltransferase[16] are some of primary receptor targets. While, biaryl-based dipeptidyl peptidase (DDP4),[17] SARS-CoV receptor-binding domain (RBD),[18] cathepsin L,[19] trans-membrane serine proteinase 2 (TMPRSS2),[20] nsp7–nsp8 as replication and transcription complex,[21] ADP-ribose-100-phosphatase,[22] nsp8 –primase,[14] nsp14 exoribonuclease,[23] nsp15 endoribonuclease,[24] and ER-GIC and Golgi region[25] are several specific target for development of target-oriented drugs against coronavirus and other target site that already used for approved antiviral drugs also illustrated (Figure 4) . In parallel with diagnostic test progresses, scientists are exploring numerous drug combinations to facilitate supportive treatment to the COVID-19 infected persons.

Additional several wide-ranging medications like chloroquine, arbidol, remdesivir, and favipiravir in combination with other drugs such as azithromycin gave some promising results in pre-liminary trials in china.[26] However, the major restriction of these drugs due to broad-spectrum activity and lack of specific target receptor lead to the probability of host cell toxicity.[27,28]

The principal element of the present review article comprises pathogenesis of 2019-n-CoV infection. Detail overview of nanomaterial-based research finding of therapeutic value against other viruses, and future scope for potential applicability of nanotech approach in concern with COVID 19 diagnosis, treatment, and prevention (**Figure 1**).

1.1. Virus Structure and Genome Sequence

Coronaviruses (CoVs) is an enveloped single positive-sense RNA genome, having ~80-120 nm size and originates from the family of Coronaviridae. It has been further subdivided to α-coronavirus (α-CoV), β-coronavirus (β-CoV), δ-coronavirus (δ-CoV), and γ – coronavirus (γ-CoV).[29–31]

The organization of coronavirus genome is composed of four structural proteins, Spike (S1, S2), envelope (E), membrane (M), and nucleocapsid (N), with accessory genes spread within the essential genes (**Figure 2**).[29,30]

The genetic makeup of SARS-CoV-2 is revealed by several researchers and finds SARS-CoV-2 closely related Bat Sars like-CoVs. These close relations further indicated that the novel CoVs are of bat origin, whereas some sequences of the novel CoV showed several distinct features[10,32–35] (**Figure 3**).
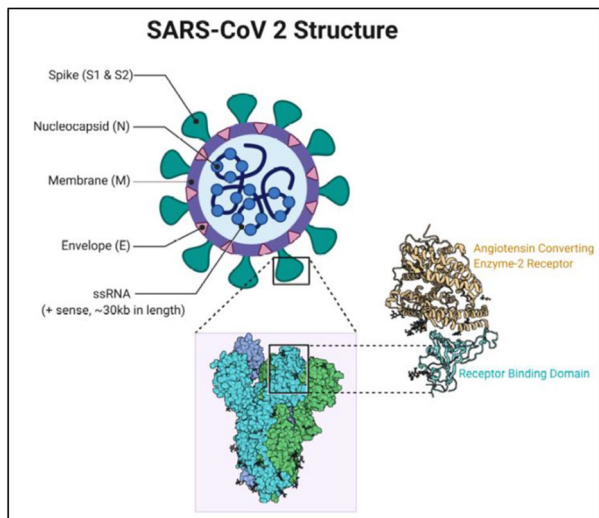
Figure 2. Coronavirus Structure and Protein Visualization (created using biorender software).

1.2. Pathogenesis and Target Site for Antiviral Drugs

In initial finding with clinical diagnosis, the infected people from COVID 19 have appeared pneumonia-related symptoms by computed tomography (CT scan) along with mild fever, dry cough and runny nose,[36] and are related to sign of SARS and MERS (Middle Eastern Respiratory Syndrome) outbreak.[37] Later on, asymptomatic people have also been detected positive with SARS-CoV-2 in RT-PCR (reverse transcription polymerase chain reaction) test.[1] As of now, biological mechanism of COVID-19 can be compared with the related mechanisms of SARS-CoV and MERS-CoV, which provide useful information on the biological mechanism of 2019-SARs-CoV infection and that could be helpful to understand COVID-19 biological information about genome entry and replication cycle.

Coronavirus S glycoprotein has been stated as substantial information on virus entry and replication into the cytoplasm of host cell.[38,39] The binding of the spike glycoprotein S with host cell occurs with the different receptor, for example, SARs-CoV[40] and SARs-CoV-2[41,42] with human angiotensin-converting enzyme-2 (hACE-2), SARs-CoV with C-type lectins L-SIGN,[43] and MERs-CoV with dipeptidyl peptidase-4 or adenosine deaminase complexing protein-2 or CD-26.[44] Ambiguity for the viral genome entry of SARs-CoV into the cytoplasm arises when Belouzard et al.[45] identified that a sequential proteolytic cleavage at two distinct sites mediated the membrane fusion whereas Simmons et al. firstly reported characterization of Coronavirus glycoprotein S mediated entry of lentiviral-based vector.[42,46]

Millet et al. findings suggested that spike S protein of MERS-CoV might be activated by furin mediated, by two-step cleavage mechanism at the distinct site for viral fusion.[47] Moreover, Spike S protein fusion and SARS-CoV entry mediated through clathrin-dependent and independent endocytosis also reported.[48,49]

Replication cycle will start after viral genome enters the host cell cytoplasm, the RNA genome translated to a different type of proteins, after which the RNA viral genome begins to replicate and formed Genomic and sub-genomic RNA (+) with help of viral polymerase.[30] The newly formed structural proteins spike (S), envelop (E), and membrane (M) are injected into the membrane of the Golgi or ER, and the nucleo-capsid is formed by the amalgamation of genomic RNA and nucleocapsid proteins. Then, genome enters into the Golgi vesicle, i.e., ERGIC. After that, the vesicles comprising the virus units fuse with the host cell membrane for exocytosis of the viral genome.[39,50] The detail proposed mechanism of replication cycle and exocytosis of the viral genome is well represented (**Figure 4**) by Clercq et al., that will help to design different target based nano compounds.

The paper illustrates a dozen different viral approved drugs which have the potential to target viral replication endocytosis and exocytosis to combat viral infection.

As of now, there is no approved medication, so that WHO and other worldwide public health groups have largely focused
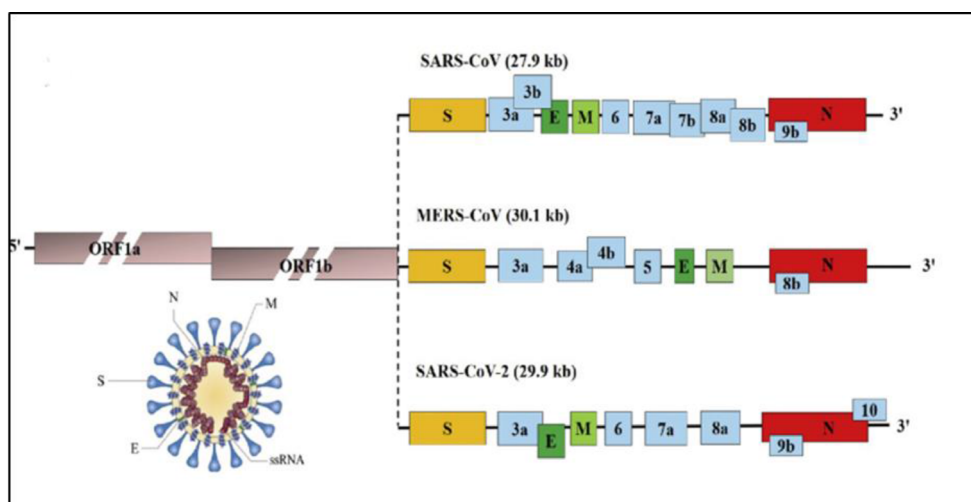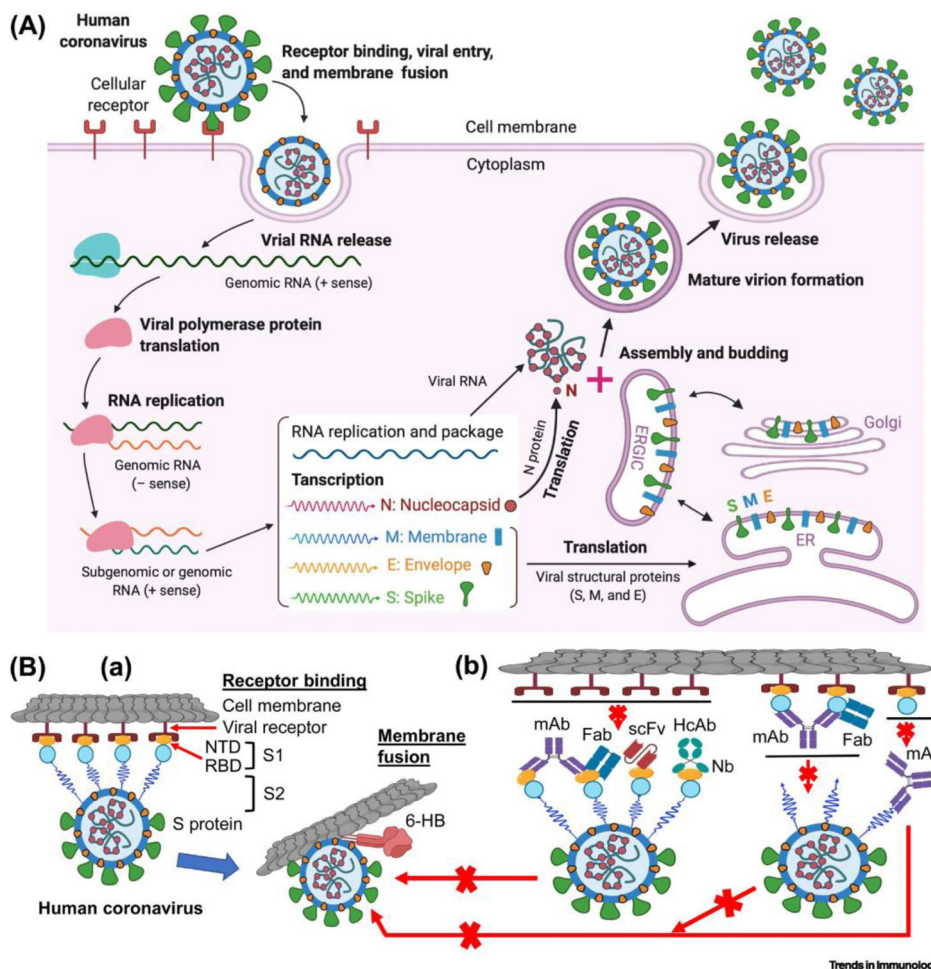

Figure 3. Genome organization of SARS-CoV-2. Coronavirus Comparative analysis diagram; spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins, as well as several accessory proteins. Reproduced with permission.[35] Copyright 2020, Elsevier.

Figure 4. Schematic illustration of viral replication cycle and mechanisms of drug actions at different sites. Reproduced with permission.[56] Copyright 2020, Elsevier.

on preventing transmission, infection control procedures, and screening of travelers.[51] Whereas Lupia et al. summarize clinical finding of the novel SARS-CoV-2 infection and its symptomatic medication provided to patients in China.[52]

The pandemic of novel SARS-CoV-2 and their diversity are mounting at the distressing rate as its magnitude among the 212 countries worldwide and recorded more than 1.45 billion infections and lead more than 3.079 million deaths till 24 April 2021. Case of infection and death is more than any other outbreak such as Flu, SARS and MERS (Figure 1).

The sudden outburst of Coronavirus (SARS-CoV-2) and speed of their transmission across the world have elevated thoughtful concern regarding their immediate prevention strategy using traditional medication and diagnostic process. Consequently, there is an instant need to develop novel treatment strategies based on specific ligands or receptors binding drugs that can be enhanced by Nanotechnological approach.[53]

However several broad-spectrum antiviral drugs have been developed and found poor bioavailability at the target site to render their use.[54] Despite this, Nano-based approach can be utilized to enhance their efficacy and target delivery at the site with sustained release.[55]

(A) Life cycle of highly pathogenic human CoVs. These CoVs enter host cells by first binding to their respective cellular receptors [angiotensin-converting enzyme 2 (ACE2) for severe acute respiratory syndrome (SARS)-CoV-2 or SARS-CoV and dipeptidyl peptidase 4 (DPP4) for Middle East respiratory syndrome (MERS)-CoV] on the membranes of host cells expressing ACE2 (e.g., pneumocytes, enterocytes) or DPP4 (e.g., liver or lung cells including Huh-7, MRC-5, and Calu-3) via the surface spike (S) protein, which mediates virus–cell membrane fusion and viral entry. Viral genomic RNA is released and translated into viral polymerase proteins. The negative (−)-sense genomic RNA is synthesized and used as a template to form subgenomic or genomic positive (+)-sense RNA. Viral RNA and nucleocapsid (N) structural protein are replicated, transcribed, or synthesized in the cytoplasm, whereas other viral structural proteins, including S, membrane (M), and envelope (E), are transcribed then translated in the endoplasmic reticulum (ER) and transported to the Golgi. The viral RNA–N complex and S, M, and E proteins are further assembled in the ER–Golgi intermediate compartment (ERGIC) to form a mature virion, then released from host cells. (B) Potential targets of nAbs against SARS-CoV-2 and other pathogenic humanCoVs. (a) Human CoV

Table 1. Inorganic Nanomaterials for Inhibitory action.

Nanoparticles	Virus	Details mechanism of activity	References
Silver (Ag)			
AgNP synthesized using Cinnamomum cassia	Avian influenza A virus, subtype H7N3	NPs interactions with the viral genome (RNA or DNA), cellular factors, or pathways of host cells block viral replication pathway	[79]
Argemone maxicana mediated AgNPs	Peste des petits ruminants (PPR) virus a prototype morbillivirus	SNPs impair the PPRV replication at the level of virus entry into the target cells and thus has a potential as an antiviral therapeutic agent	[77]
AgNPs	HSV-2	Sulfadryl group of glycoprotein membrane strongly interact with Ag-NPs. This interaction prevents internalization of the virus by inhibiting the interaction between the glycoprotein and a receptor.	[76]
GT-AgNPs and C-AgNPs	S. cerevisiaeds RNA viruses	Interaction with viral genome and inhibition of viral replication	[65]
PHBV18 /AgNP fiber	Influenza A and Feline calicivirus	No viral infection observed in 24 h exposure to the fiber	[70]
Electrochemical Synthesized AgNPs	Poliovirus type-1	AgNPs were non-toxic to cell cultures up to 100 ppm and toxic to non-enveloped viruses. The antiviral activity was found at 3.13 ppm for 30 min of incubation with poliovirus	[74]
Titanium (Ti) Nanoparticles			
TiO2 NPs	MS2	Interaction with viral surface proteins	[79]
TiO2~DNA Nano composites	H1N1, H5N1, and H3N2	Targeted binding to conservative regions in the viral genome and inhibition of viral reproduction	[82]
TiO2 particle	MS2, ΦX174, PR772	Interaction with viral capsid/surface proteins	[83]
Gold Nanoparticle			
AuNPs	DENV	Inhibiting viral replication and infectious virion release	[84]
Au NPs	Foot- and- mouth diseases	Arrests viral replication along with transcription	[85]
Iron (Fe)			
Magnetic NPs Aptamers	HCV	Magnetic Nps Aptamers specifically binding to the E1E2 glycoprotein of HCV and efficient removal of viral particle	[86]
Silica (Si) based NPs			
Glycosaminoglycan Mesoporous SiNPs Conjugate	HSV-1, 2	Inhibition of viral attachment to the host cell	[87]
Alkoxysilane Mesoporous SiNPs Conjugate	GFP lentiviral vector harboring a vesicular stomatitis virus G glycoprotein, GFP lentivirus harboring an HIV-gp120 derived envelope	Attachment with the viral envelope protein	[88]
SWCNT	GCRV	Affects viral transcription	[89]
Graphene			
Cationic polymer PDDA, nonionic PVP-Graphene oxide (GO) conjugate	Pseudo rabies Virus, porcine epidemic diarrhea virus	Negatively charged GO interacts with viruses prior to viral entry resulting in virus damage due to its single-layer structure and sharp edge	[90]
β-cyclodextrin (CD) functionalized-GO-Curcumin based NPs	Respiratory syncytial virus (RSV)	The NP mimics heparin sulfate on the host cell surface and inhibits viral attachment	[91]
Hybrid Nano-material			
Silver nanorods conjugated with sodium 2 mercapto ethane sulfonate (Ag-MES)	HIV, HSV-1	Inhibition of viral replication	[92]
Oseltamivir modified AgNPs (Ag@OTV)	H1N1	Inhibits the activity of Neuraminidase (NA) and Hemagglutinin (HA) prevents viral attachment, inhibit the accumulation of reactive oxygen species (ROS) by virus, activates AKT and p53 phosphorylation	[93]
Titanium dioxide nanoparticles and polylysine (PL)- containing oligonucleotides (TiO2·PL-DNA) Nano composite	H1N1, H5N1, H3N2	Targeted binding to conservative regions in the viral genome and inhibition of viral reproduction	[94]
GO sheets with silver particles (GO-Ag)	Feline coronavirus (FCoV)	Association with viral lipid tails leading to aggregation with attachment of AgNPs with –SH group of protein and rupture of the envelop	[95]

(Continued)

Table 1. (Continued).

Nanoparticles	Virus	Details mechanism of activity	References
SiRNA-modiated Polyethylenimine (PEI) encapsulated AgNPs (Ag@PEI@siRNA)	Enterovirus 71 (EV71)	Block EV71 from infecting host cells and prevent DNA fragmentation, chromatin condensation and activation of caspase-3	[96]
OTV decoration of SeNPs (Se@OTV)	H1N1	Neuraminidase (NA) and Hemagglutinin (HA) prevents viral attachment, inhibit the accumulation of reactive oxygen species (ROS) by virus, activates AKT and p53 phosphorylation	[97]
Mannosylated Niosomal system (AuNPs and Efavirenz (EFV)	HIV-1	Viral inhibition	[98]
AuNPs and AgNPs	H1N1, H3N2, H5N1	Efficient delivery and viral inhibition	[99]
Surface decoration of selenium NPs by Amantadine (AM) (Se@AM)	H1N1	Induces apoptosis, inhibits generation of ROS, and activates phosphorylation and AKT pathway	[100]

receptor binding and membrane fusion process. The CoV first binds a viral receptor (ACE2 or DPP4) through the receptor-binding domain (RBD) in the S protein, followed by fusion of the virus with cell membranes via the formation of a six-helix bundle (6-HB) fusion core. NTD, N-terminal domain. (b) Potential targets of nAbs on the S protein of human CoVs. Monoclonal antibody (mAb), antigen-binding fragment (Fab), single-chain variable region fragment (scFv), or single-domain antibody [nanobody (Nb) or VHH derived from camelid heavy chain antibody (HcAb)] binds to the RBD, S1 subunit (non-RBD, including NTD), or S2 of the viral S protein, blocking binding between the RBD and the respective receptor (for RBD-targeting nAbs), interfering with the conformational change of S (for S1-targeting nAbs), or hindering S2-mediated membrane fusion (for S2-targeting nAbs), leading to the inhibition of infection with pathogenic human CoVs in the host [Reprinted with permission from ref. 56].

2. Nanotech-based Antiviral Therapy

Antiviral drugs development against deadly viruses such as SARS-CoV-2 are under an initial stage and will take time to get clinical finding. Moreover, Nanomaterials based approach against various viruses is well documented. Antiviral activity of Nanomaterials (NMs) depends on their morphology and type. Accordingly, to distinct the activity of NMs a wide-ranging outline, various types and forms of NMs/Nanotech system are essential. Nanotech based antiviral agents have a great range from common inorganic Nanomaterials (iNMs) to metal-organic framework (MOF) and Homogeneous to heterogeneous (Hybrid) Nano conjugate. Hybrid Nano conjugate is uniform inorganic Nanomaterials (INPs), composite of organic-inorganic, inorganic-inorganic, and organic-organic nano conjugate such as Core–shell-type lipid–polymer hybrid nanoparticles (CSLPHNs) fabricated based on specific or target-oriented condition or delivery at target receptor.[57]

2.1. Inorganic Nanomaterials

The Inorganic Nanomaterials (INMs) having intrinsic properties such as light-emitting, varied morphology (nanoparticles, nanotubes, nanowires, Nanoflowers, nanocubes), and intrinsic physicochemical properties have strengthened the significance of INMs in the biomedical field such as biosensors,[58] cells and biomolecules marker,[59] and tumors diagnosis and therapy.[60] Along with these claims, INMs are highly biocompatible and engineerable surface offers an innovative plethora to improve advance therapeutic and diagnostic kit for rapid and specific detection and effective medication for emerging diseases.[61] The intrinsic property of these NMs are used to synthesize trastuzumab -Bi2S3@mPS nano-platform, which shows cancer-targeted Imaging for diagnostic and photothermal/chemotherapy.[62] Based on applications of inorganic Nanomaterials in the field of biomedical, most common metal nanoparticle are gold, silver, magnetic and nanocarries of bismuth, silicon dioxide, titanium dioxide and carbon, etc.

2.2. Silver and Silver Nanocomposite NPs

Silver nanoparticles are well studied and explored from several years due to their remarkable, stimulating and encouraging distinctive feature for numerous biomedical arenas.[63] Moreover, their synthetic methods, mode of mechanism and the various bio-based applications[64] are well summarized. Silver nanoparticles were used in the field of virology to treat the viral infection and detection as well as used as antiviral agents in textile to prevent the infection.[65] However silver nanoparticles were well explored as antiviral agents against the several viruses and few of them are HIV,[66,67] RSV,[68] Influenza A/H1N1 virus,[69,70] MPV[71] or hepatitis B virus,[72] Transmissible gastroenteritis virus (TGEV)[73] poliovirus type-1[74] HSV and human parainfluenza viruses(subtype HPIV-3),[75] herpes simplex virus,[76] ruminants virus,[77] norovirus surrogates,[78] Avian influenza A (H7N3),[79] chicken diseases (IBDV),[80] and Saccharomyces cerevisiae double-stranded RNA viruses.[65]

The mechanism of silver nanoparticle is based on the, inhibiting protein binding with host receptor to stop viral entry into the host cell or virucidal activity and viral to viral infection and it has been summarized in **Table 1**. Galdiero et al. presented various key steps in replication cycle (**Figure 5**), indicating various sites, which helped to design antiviral drugs.[81]
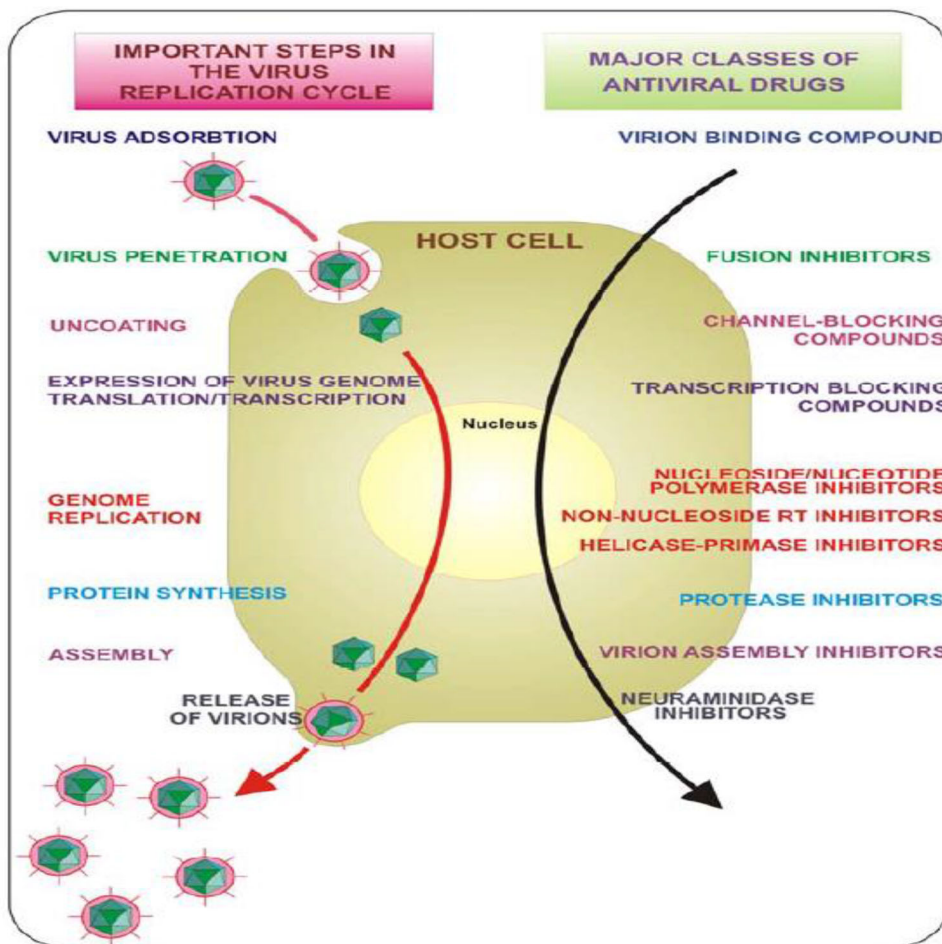
Figure 5. Key Steps in the virus replication cycle that provide antiviral targets. Reproduced with permission.[81] Copyright 2020, MDPI.

2.3. Gold and Gold Nanocomposite NPs

Gold nanoparticles have remarkable applications in the arena of biomedical payable to their versatile and engineered feature.[101] Several researchers summarize their biomedical applications such as diagnosis,[102] bioimaging,[102,103] therapeutic delivery,[104] biosensors,[103,104] and minimally invasive surgeries and point-of-care diagnostics.[105] However Gold nanoparticles were restricted for direct use as antiviral medication except few biologically suitable polymer conjugate, which were effective against human immunodeficiency virus Type-1, Influenza A/H1N1 virus, Influenza A/H3N2 virus, Influenza A /H5N1, DENV, BVDV, and animal FMDB.[106,85,107] The virucidal mechanism of AuNPs is unclear but speculated mechanism of action, maybe by blocking gp120 attachment with CD4, which ends in inhibited viral entry.[106,108] Gold nanoparticles inhibit FMDV during replication after entering in the cytoplasm, specifically during RNA genome transcription in host cell.[85] However, Kim et al. illustrated (**Figure 6**) mechanism of porous gold nanoparticles; nanoparticles interact with surface protein and inactivate the viral cell.[108] Nano based formulation of gold nanoparticle in amalgamation form is used for catalytic activities, photothermal Nano therapy, bio-sensing, bio-imaging.[109] There intrinsic engineered feature

has also been utilized, which was based on their size-dependent surface.[110] For instance, charged AuNPs have detection ability for Influenza A/H1N1 virus and Influenza A/H3N2 virus, by peroxidase simulating enzymatic response test. Similarly, there are further illustrations where conjugated gold NPs has proven activity against viral infections (Table 1).[107]

2.4. Iron Oxide Nanoparticles (IONPs)

The application of Iron Oxide Nanoparticles as therapeutic is restricted due to several challenges.[111] However, the magnetite (Fe3O4) or maghemite (Fe2O3, γ-Fe2O3) are the most used Iron Oxide in Nano particulate system.[112] IONs with functional building block were explored for bioimaging, biological fluids cleansing, tissue restoration, diagnostic, hyperthermia, and drug delivery. Currently, the direct use of IONPs has been evaluated against Bacteriophages, Zika virus, HCV, and H5N2.[86,113–115]

2.5. Titanium Nanoparticles (TiNPs)

Titanium dioxide (TiO_2) NPs have tremendous applications in the various segment, e.g., catalytic, medical, and engineering
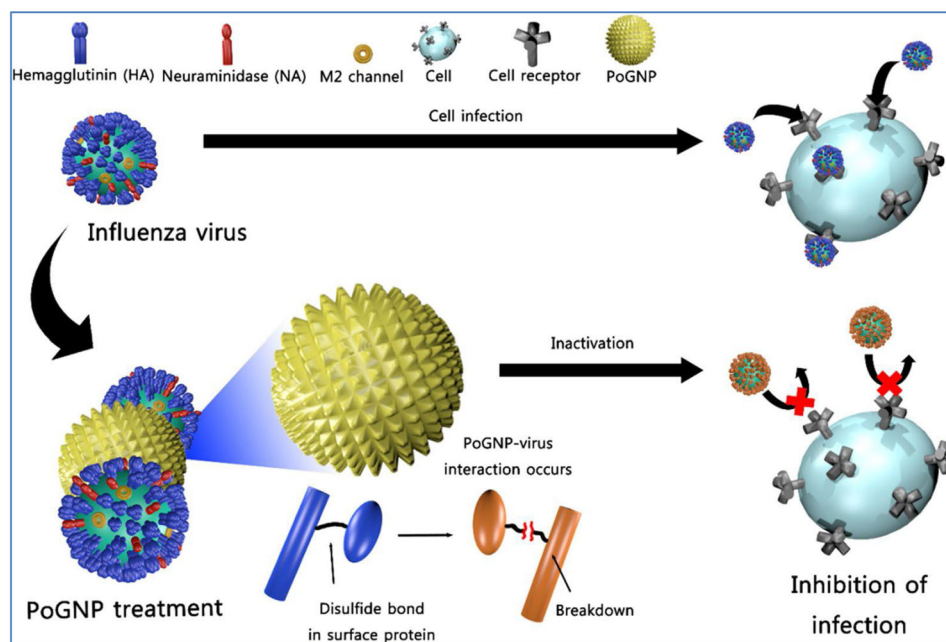
Figure 6. Illustration of inhibition of Influenza A Virus treated with porous gold nanoparticle. It binds with viral surface proteins and breaks their disulfide bonds and inactivated the viruses that have lower infectivity to cells. Reproduced with permission.[108] Copyright 2020, BMC.

to environmental. These properties are due to high solubility, photocatalytic and anticorrosive properties of TiO_2.[116] The ample amount of research study related to biomedical applications of titanium oxide based functional hybrid materials has been reported.[117,118] TiNPs function hybrid materials applications are not only limited towards few sectors of the biomedical fields but explored in many arenas comprising Photo-therapy[119] for cancer, Drug delivery structure,[120,121] Bio-imaging,[122] Biosensors.[123]

Although their reach in the biomedical sector is phenomenal but still have an excellent opportunity in current research for antiviral application. Limited studies of Titanium-based Nanoparticles to influenza-virus (H3N2) and bacteriophages like MS2, PRD1 have been reported and few studies[124–126] were reported for poor evaluation of existing toxicity of TiNPs.[127]

2.6. Silica Nanocarriers (SiNCs)

Exceptional physical characteristics of SiNCs like tunable-diameter, pore-size, biocompatibility and easily fabricable, etc., are well valued for exploration everywhere in the world for their use in biomedical applications.[128–130] The Silica Nanoparticle have been explored against various viruses like HPV, PCV, HBV, Herpes simplex viruses type-1,type-2, and human immunodeficiency virus. The manner of viral inhibition is either facilitated by vaccination of the model organism against disease or by obstructing the entry of viral genome.[88,131] Viral-genomic protein-based luminous recognition and DNA or RNA probe-target interaction are the main foremost procedures of virus-related diagnosis. Despite the progress, the emerging demand for unique rapid diagnosis method and antiviral-medication can only be upgraded by strategic research and investigation.

2.7. Other Inorganic Nanoparticles

Including above explain inorganic nanomaterial several other nanoparticles or their functional nano-conjugate systems such as Selenium NPs, Copper NPs, Zinc oxide NPs, and hydroxyapatite have also been summarized[132] for biomedical applications. However, their antiviral activities were not much detected despite their broad-spectrum utilization and has large scope to develop nano-based system against antiviral medication.

2.8. Possible Nano-based Approach for COVID 19 Diagnosis

Identification of COVID 19 infection is principally supported and based on travel profile of people of infected countries, direct contact of the infected person, clinical appearances, and a few supporting examinations, like super molecule (nucleic-acid) recognition, Computed Tomography Scan, immunological techniques of IgM-IgG, enzyme linked-immunosorbent-assay (ELISA), and culture study of the blood sample. Nucleic-acid detection technology such as real-time reverse transcription PCR (RT-PCR) and genome sequencing.[133,134] High-throughput sequencing method is accurate and specific but high cost and complicated equipment dependency. But RTqPCR is that the commonest, current, and uncomplicated methods for identifying pathological viruses in breathing excretions, blood, and saliva,[135–137] but have highly time-consuming. However, some result varied but repeated sample gives positive result[138] and having 50–79% sensitivity, betting on the procedure and collected clinical specimens number.[139] Thus, it's needed to develop other sensitive and specific simple methods for COVID 19 that may help to fast screening and isolation for treatment. Now research dynamic has been changed and shifted towards the additional trend in the

Table 2. Inorganic Nanomaterials for Diagnostic Application.

Nanoparticles	Virus	Details mechanism	References
Gold NPs			
Au NPs	Virus (FMDV)Influenza virus A (H1N1, H3N2)	With transcription Peroxidase-mimic enzymatic reaction for viral detection	[107]
DNAzyme AuNPs (DDZ-AuNPs)	Dengue virus (DENV)	DDZ activation mediated salt induced aggregation of AuNP give signal for viral detection	[143]
Antibody (immuno-AuNP)	H3N2	Nanodot deposition on the periphery of viral surface give signal of viral detection	[144]
Monoclonal anti-hemagglutinin antibody (mAb) AuNPs hybrid	H3N2	Viral surface deposition of NP- mAb for Colorimetric immunosensor viral detection	[145]
Charge-neutral peptide nucleic acids (PNA)Unmodified AuNPs	Bovine Viral Diarrhea virus (BVDV)	BVDV-RNA based PNA induced aggregation of the AuNPs and Colorimetric based viral detection assay	[146]
Silica (Si) based NPs			
Bioconjugate of streptavidin to carboxylic functionalised SiO2:Eu nanoparticles	HIV (HIV-1 p24 antigen	Binding to HIV-1 p24 antigen and used fluorescence based sandwich immunoassay detection of virus	[147]
Hybrid Nano-material			
Silica (SiO2) coated magnetic Fe3O4 NPs	Hepatitis B virus (HBV), Epstein–Barr virus (EBV	Higher sensitivity in PCR based viral detection	[148]
Gold/Copper Sulfide Core/ Shell NPs	Human Norovirus Virus-Like Particles	Capsid protein degradation and capsid damage gives signal for Viral detection	[140]
Antibody conjugated AuNPs-carbon nanotubes (CNTs) hybrid	H3N2	Peroxidase-like activity of the nanohybrid	[141]
Chiral AuNPs-quantum dot Nano composites	Avian influenza A (H4N6) virus, fowl adenovirus and coronavirus	Chiral plasmon–exciton systems	[149]
Hybrid Nano-material			
Anti-NoV antibody Graphene-AuNPs nanohybrid	Norovirus-like particles	Peroxidase-like activity and give Colorimetric immunoassays for viral detection	[150]
Glycan-functionalized AuNPs (gAuNPs)	Various type of influenza viruses	Aggregation of gAuNP probes on the viral surface and signal for viral detection	[151]
Antibody conjugated Silica-shelled magnetic (Fe3O4) Nano beads (MagNBs) and AuNPs	H1N1, H3N2	MagNB mediated target separation and signal amplification by the pe roxide-like activity of AuNZ sand give Ultra-sensitive colorimetric assay	[152]
Gold/iron-oxide nanoparticle-CNT hybrid nanomaterial	H1N1, norovirus	DNA hybridization gives High sensitivity and selectivity detection of viral DNA	[153]

rapid clinical diagnosis of viral infection. Broglie et al. developed core/shell Au/CuS NPs, having virucidal activity against human Norovirus by inactivating capsid protein.[140] Similar approach can be utilized for COVID 19 to develop a nano-hybrid system for rapid point care diagnostic and viral inhibition.

Ahmad et al.[141] developed specific antibody-conjugated Au CNT nanohybrids for influenza A virus (H3N2) and have peroxidase-like mechanism give colorimetric viral detection assay. Zagorovsky et al. developed gold nanoparticles DNAzymes conjugate for point care detections of various targets by simple and sensitive colorimetric assay[142] and mechanism of action is also illustrated.

Similarly, to tackle the pandemic situation of COVID 19, it is a need to develop cost-efficient rapid diagnostic kit to identify the maximum infected person and isolate them for supportive medication or attention to control SARS-CoV-2.

Likewise, there are varieties of Nano-based methods (**Table 2**) are summarized for diagnosis of viral infection. Anticipating on presenting views, the chances to develop a unique Nano based diagnosis method for identifying COVID 19 can be accomplished.

2.9. Possible Nano-based Approach for COVID 19 Inhibition

If detection of SARS-CoV-2 can be promising, then inhibition/elimination/prevention of viral infection through a nanotech-based approach is possible through generous research. As Inorganic Nanoparticle has a broad range of antiviral activity could be used for coating materials, panting materials, fiber materials for mask manufacture and clothing material for PPE clothing to control infection spread in hotspot area and hospitals.
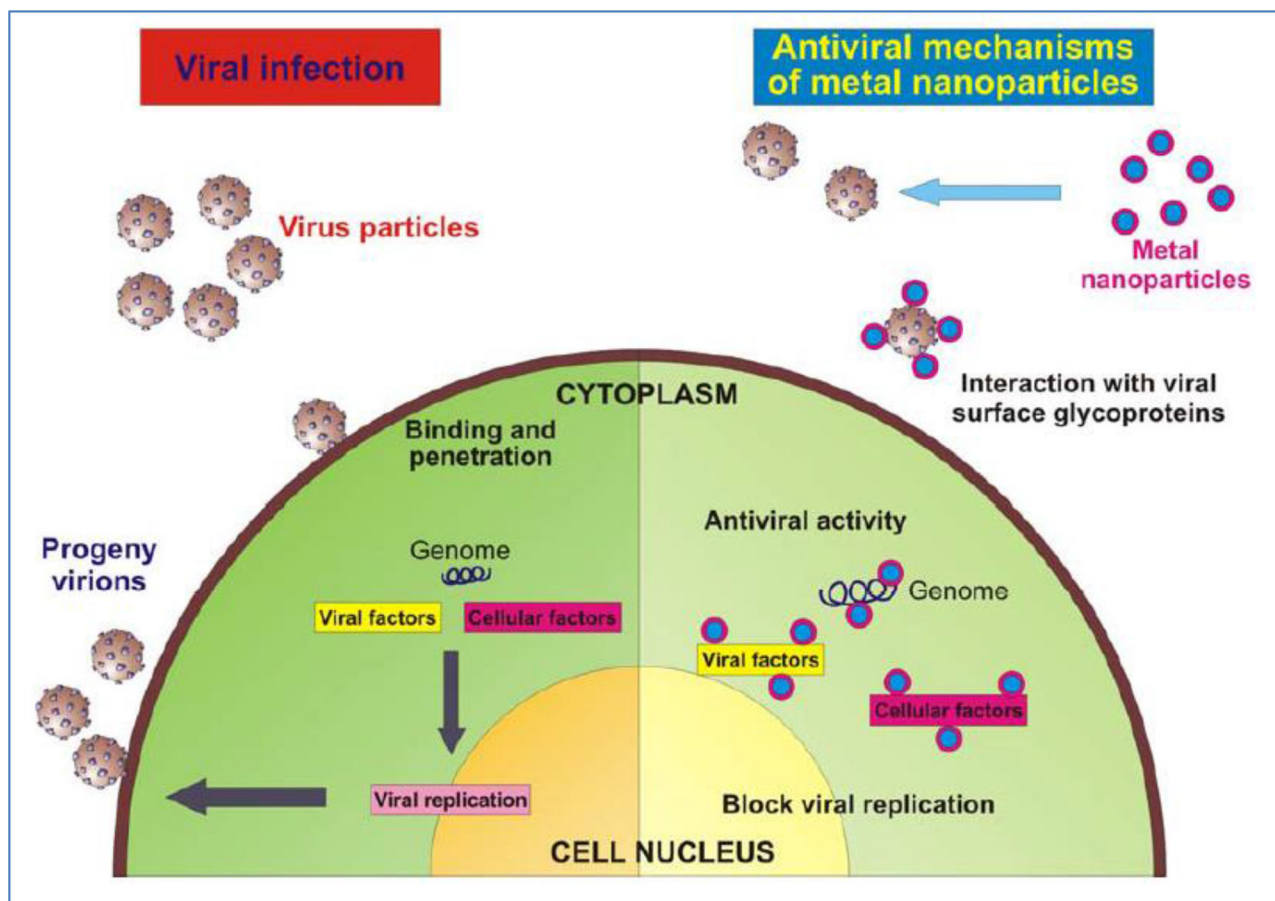
Figure 7. Schematic illustration of viral infection and antiviral mechanism metal nanoparticle. Reproduced with permission.[81] Copyright 2020, MDPI.
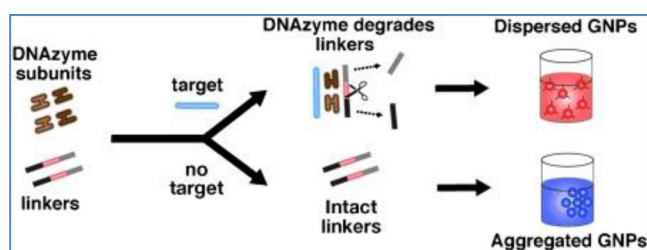

Figure 8. Schematic illustration of mechanism of action: Au-DNAzymes conjugate give a simple and sensitive colorimetric assay for various genetic targets; a) in presence of target protein DNAzyme degrades linkers and give dispersed AuNPs with red colour, b) In absence of target protein linkers is intact and give aggregated AuNPs with blue colour. Reproduced with permission.[142] Copyright 2020, BMC.

Parallel, need to develop specific target-oriented antiviral drugs candidates based on nanotechnological approach utilizing available references.

In the study, Vijay Kumar et al. found that AuNPs act as an inhibitor or anti-HIV and proposed mechanisms is the deactivation of surface protein by gold nanoparticles result in inhibitory effect against HIV in a test tube.[106] Likewise, nanoparticles with the ability to interrelate with SARS-CoV-2 external glycoproteins likes could encourage being hopeful agents as viral receptor blocker. Moreover, several other targets also give the direction for viral inhibition such as regulation of reactive-oxygen-species level to activate protein kinase (Akt) and P53 phosphorylation could even be an approach for blocking the entry of viral genome. Li et al. presented the same approach against HIN1 virus using fabricated SeNPs-Oseltamvir conjugate[97]

The researcher can use a similar approach and make suitable drugs conjugate NPs for in-vitro investigation in case of SARS-COV-2. Also improving the viral activity by improving drug delivery using single-walled carbon nanotubes (SWCNTs) – ribavirin conjugate by Zhu et al[89] and Lavina.et al projected TiO2.PL-DNA nano conjugate could be used highly effective and target-site specific (target binding on the conservative region of Viral RNA) inhibition of influenza A[94] and Torrecilla et al. shown the capability of solid lipid-shRNA Nanocomposite, non-viral-SLN based vector to silence an HCV replication,[154] etc. all opinion within the similar way. The latest research for Nanomaterials application in the field of virology as, antiviral and diagnostic agent portfolio well summarizes (Table 1 and 2) with working mechanism and therapeutic outcome. Moreover, Rout et al.[155] proposed a Nano-based system for combat NIPAH virus and mentioned several approaches for virology.

Researchers from across the world are working tirelessly to search out rapid diagnostic kit, antiviral medication, and vaccine to combat the pandemic COVID 19 through various approaches
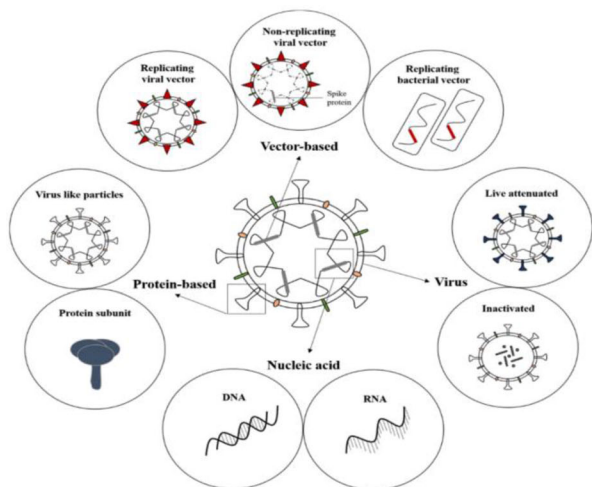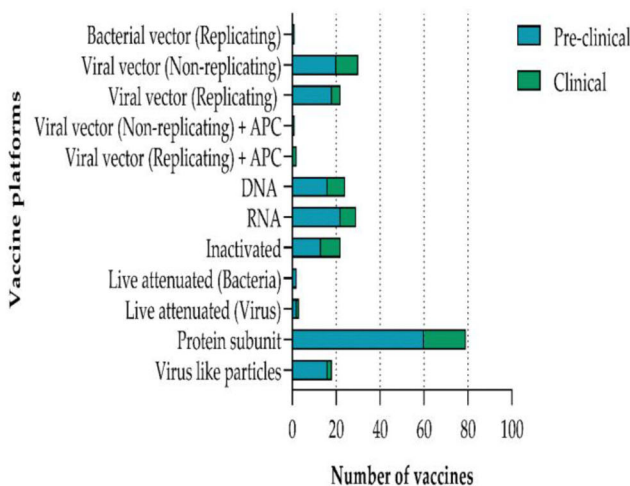
Figure 9. A- SARS-CoV-2 vaccine types. SARS-CoV-2 vaccines currently in pre-clinical and clinical evaluation make use of various platforms B: Platforms in use for COVID-19 candidate vaccine development in pre-clinical (blue) and clinical (green) trials [APC: antigen presenting cell; DNA: deoxyribonucleic acid; RNA: ribonucleic acid. Reproduced with permission.[157] Copyright 2021, MDPI.

within the nanotechnology that may help for research activity. As of now limited target based nanoparticles have developed for antiviral medication, despite several targets have identified and target specific antiviral drugs developed and approved for viral infections medications.[156] This review paper gives them quick knowledge about recent approaches within the area of nanotechnology that may help for fast research activity to develop target-based nanoparticles.

Though the efficacy of NPs as a medication against COVID 19 is part of evaluation, still it can be roughly predicted that these studies are a straightforward illustration that nanoparticles hold huge prospective as a medication for COVID 19 described in **Figure 7**.

In order to overcome the COVID-19 pandemic by controlling transmission, deep worldwide work has been done and going on also to develop a successful vaccine against SARS-CoV-2. Since the worldwide impact of COVID-19 in second wave is more dangerous compared to first one, the development and testing of a new vaccine are being expedited (**Figure 9**)[157] and here nanotechnology-based approach have vital role for developing safe and effective vaccine (**Figure 8**).

3. Conclusion

Nanotechnology engineering creates enormous numbers of materials for diagnostics and therapy. Nanotechnology grasps a noteworthy prospect for virus-mediated disease prevention, diagnostics, and their therapy. Though it is promising that above mentioned nanotech methodologies are the subsequent suitable approach to tackle COVID 19 as NPs. These are well established broad-spectrum antiviral activity, which will help to form antiviral drugs. Moreover, these potential materials can also be utilized in personal protective equipment, coating material, sanitizing material by doping appropriate amount NPs into based materials. It has been proved that nanomaterials can be a hands-on approach to control and inhibit viral infections, which are very difficult to handle with current available conservative medication. However, it is promising that nanotech methodologies are the subsequent appropriate approach to pander to COVID 19. But parallel, it is also required to complete understanding of COVID19 pathogenesis; otherwise, it is very difficult to develop specific receptor/ligand-based nanoparticles. Accordingly, this assessment affords momentary details about COVID 19 pathogenesis; somewhere it might be informal to prepare a unique target specific antiviral nanoparticle to combat pandemic COVID 19. A short brief of various types of nanoparticles such as metal, metal oxide, organic, hybrid and organic-inorganic composite conjugate based studies presented in this review that is possible diagnostic and therapeutic value against viral infections would be helpful in quick assessment for their suitability for COVID 19 diagnostics and therapeutics.

Lastly, the summaries of foremost nanotech-based approaches for viral inhibition and diagnosis, which have been previously studied is exemplified in tabular presentation, that could be support to research finding for antiviral agents and mitigate the current situation of COVID 19.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Keywords

2019-nCoV, antiviral agents, coronavirus, COVID 19, nanoparticles, nanotechnology, SARS-CoV, therapeutics and diagnosis

[1] W. H. Organisation, *World Health Organization: Coronavirus Disease (COVID-19) Pandemic.* 14 APRIL, **2020**; Available from: https://www.who.int/emergencies/diseases/novelcoronavirus-2019

[2] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K. S. M. Leung, E. H. Y. Lau, J. Y. Wong, X. Xing, N. Xiang, Y. Wu, C. Li, Q.i Chen, D. Li, T. Liu, J. Zhao, M. Liu, W. Tu, C. Chen, L. Jin, R. Yang, Q.i Wang, S. Zhou, R. Wang, H. Liu, Y. Luo, Y. Liu, G.e Shao, H. Li, Z. Tao, Y. Yang, Z. Deng, B. Liu, Z. Ma, Y. Zhang, G. Shi, T. T. Y. Lam, J. T. Wu, G. F. Gao, B. J. Cowling, B.o Yang, G. M. Leung, Z. Feng, *N. Engl. J. Med.* **2020**, *382*, 1199.

[3] Y. Ruan, C. L. Wei, A.i E.e Ling, V. B. Vega, H. Thoreau, S.u Y. Se Thoe, J.-M. Chia, P. Ng, K. P. Chiu, L. Lim, T. Zhang, K. P. Chan, L. O. Lin Ean, M. L. Ng, S. Y. Leo, L. F.p Ng, E.e C. Ren, L. W. Stanton, P. M. Long, E. T. Liu, *Lancet* **2003**, *361*, 1779.

[4] W. M.-C. R. Group, *PLoS Curr* **2013**, Nov 12 [cited 5; 2013/11/26:].

[5] S. Tong, C. Conrardy, S. Ruone, I. V. Kuzmin, X. Guo, Y. Tao, M. Niezgoda, L. Haynes, B. Agwanda, R. F. Breiman, L. J. Anderson, C. E. Rupprecht, *Emerg. Infect. Dis.* **2009**, *15*, 482.

[6] B. Udugama, P. Kadhiresan, H. N. Kozlowski, A. Malekjahani, M. Osborne, V. Y. C. Li, H. Chen, S. Mubareka, J. B. Gubbay, W. C. W. Chan, *ACS Nano* **2020**, 3822.

[7] D.i Wu, T. Wu, Q. Liu, Z. Yang, *Int. J. Infect. Dis.* **2020**, 44.

[8] C. Sohrabi, Z. Alsafi, N. O'neill, M. Khan, A. Kerwan, A. Al-Jabir, C. Iosifidis, R. Agha, *Int J Surg* **2020**, *76*, 71.

[9] A. Wong, X. Li, S. Lau, P. Woo, *Viruses* **2019**, *11*, 174.

[10] L.i-L.i Ren, Y.e-M. Wang, Z.-Q. Wu, Z.i-C. Xiang, L.i Guo, T. Xu, Y.-Z. Jiang, Y. Xiong, Y.-J. Li, X.-W. Li, H. Li, G.-H. Fan, X.-Y. Gu, Y. Xiao, H. Gao, J.-Y. Xu, F. Yang, X.-M. Wang, C. Wu, L. Chen, Y.i-W. Liu, B.o Liu, J. Yang, X.-R. Wang, J. Dong, L.i Li, C.-L. Huang, J.-P. Zhao, Y.i Hu, Z.-S. Cheng, L.-L. Liu, Z.-H. Qian, C. Qin, Q.i Jin, B. Cao, J.-W. Wang, *Chin. Med. J. (Engl.)* **2020**, 1015.

[11] R. Yan, Y. Zhang, Y. Li, L.u Xia, Y. Guo, Q. Zhou, *Science* **2020**, *367*, 1444.

[12] K. Ratia, K. S. Saikatendu, B. D. Santarsiero, N. Barretto, S. C. Baker, R. C. Stevens, A. D. Mesecar, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 5717.

[13] K. Anand, *Science* **2003**, *300*, 1763.

[14] I. Imbert, J.-C. Guillemot, J.-M. Bourhis, C. Bussetta, B. Coutard, M.-P. Egloff, F. Ferron, A. E. Gorbalenya, B. Canard, *EMBO J.* **2006**, *25*, 4933.

[15] A. Bernini, O. Spiga, V. Venditti, F. Prischi, L. Bracci, J. Huang, J. A. Tanner, N. Niccolai, *Biochem. Biophys. Res. Commun.* **2006**, *343*, 1101.

[16] E. Decroly, C. Debarnot, F. Ferron, M. Bouvet, B. Coutard, I. Imbert, L. Gluais, N. Papageorgiou, A. Sharff, G. Bricogne, M. Ortiz-Lombardia, J. Lescar, B. Canard, *PLoS Pathog.* **2011**, *7*, e1002059.

[17] L. Qiao, C. A. Baumann, C. S. Crysler, N. S. Ninan, M. C. Abad, J. C. Spurlino, R. L. Desjarlais, J. Kervinen, M. P. Neeper, S. S. Bayoumy, R. Williams, I. C. Deckman, M. Dasgupta, R. L. Reed, N. D. Huebert, B. E. Tomczuk, K. J. Moriarty, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 123.

[18] F. Li, *Science* **2005**, *309*, 1864.

[19] G. Simmons, D. N. Gosalia, A. J. Rennekamp, J. D. Reeves, S. L. Diamond, P. Bates, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 11876.

[20] D. Meyer, F. Sielaff, M. Hammami, E. Böttcher-Friebertshäuser, W. Garten, T. Steinmetzer, *Biochem. J.* **2013**, *452*, 331.

[21] Y. Zhai, F. Sun, X. Li, H. Pang, X. Xu, M. Bartlam, Z. Rao, *Nat. Struct. Mol. Biol.* **2005**, *12*, 980.

[22] H. Malet, K. Dalle, N. Brémond, F. Tocque, S. Blangy, V. Campanacci, B. Coutard, S. Grisel, J. Lichière, V. Lantez, C. Cambillau, B. Canard, M.-P. Egloff, *Acta Crystallogr. Sect. F Struct. Biol. Cryst. Commun.* **2006**, *62*, 405.

[23] P. Chen, M. Jiang, T. Hu, Q. Liu, X. S. Chen, D. Guo, *J. Biochem. Mol. Biol.* **2007**, *40*, 649.

[24] S. Ricagno, M.-P. Egloff, R. Ulferts, B. Coutard, D. Nurizzo, V. Campanacci, C. Cambillau, J. Ziebuhr, B. Canard, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 11892.

[25] S. Stertz, M. Reichelt, M. Spiegel, T. Kuri, L. Martínez-Sobrido, A. García-Sastre, F. Weber, G. Kochs, *Virology* **2007**, *361*, 304.

[26] L. Dong, S. Hu, J. Gao, *Drug Discov Ther* **2020**, *14*, 58.

[27] Y. Furuta, T. Komeno, T. Nakamura, *Proc Jpn Acad Ser B Phys Biol Sci* **2017**, *93*, 449.

[28] M. L. Agostini, E. L. Andres, A. C. Sims, R. L. Graham, T. P. Sheahan, X. Lu, E. C. Smith, J. B. Case, J. Y. Feng, R. Jordan, A. S. Ray, T. Cihlar, D. Siegel, R. L. Mackman, M. O. Clarke, R. S. Baric, M. R. Denison, *mBio* **2018**, *9*.

[29] P. C. Y. Woo, S. K. P. Lau, Y.i Huang, K.-Y. Yuen, *Exp. Biol. Med. (Maywood)* **2009**, *234*, 1117.

[30] S. Perlman, J. Netland, *Nat. Rev. Microbiol.* **2009**, *7*, 439.

[31] J. F.-W. Chan, K. K.-W. To, H. Tse, D.-Y. Jin, K.-Y. Yuen, *Trends Microbiol.* **2013**, *21*, 544.

[32] X.-Y.i Ge, J.-L.u Li, X.-L. Yang, A. A. Chmura, G. Zhu, J. H. Epstein, J. K. Mazet, B. Hu, W. Zhang, C. Peng, Y.u-J.i Zhang, C.-M. Luo, B. Tan, N. Wang, Y. Zhu, G. Crameri, S.-Y.i Zhang, L.-F.a Wang, P. Daszak, Z.-L.i Shi, *Nature* **2013**, *503*, 535.

[33] C. Wu, Y. Liu, Y. Yang, P. Zhang, W.u Zhong, Y. Wang, Q. Wang, Y. Xu, M. Li, X. Li, M. Zheng, L. Chen, H. Li, *Acta Pharm. Sin. B* **2020**, 766.

[34] H. Zhang, J. M. Penninger, Y. Li, N. Zhong, A. S. Slutsky, *Intensive Care Med.* **2020**, *46*, 586.

[35] X. Li, M. Geng, Y. Peng, L. Meng, S. Lu, *J Pharm Anal* **2020**, *10*, 102.

[36] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y.i Hu, L.i Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L.i Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q.i Jin, J. Wang, B. Cao, *Lancet* **2020**, *395*, 497.

[37] J. S. M. Peiris, Y. Guan, K. Y. Yuen, *Nat. Med.* **2004**, *10*, S88.

[38] S. Bertram, I. Glowacka, M. A. Muller, H. Lavender, K. Gnirss, I. Nehlmeier, D. Niemeyer, Y. He, G. Simmons, C. Drosten, E. J. Soilleux, O. Jahn, I. Steffen, S. Pohlmann, *J. Virol.* **2011**, *85*, 13363.

[39] E. De Wit, N. Van Doremalen, D. Falzarano, V. J. Munster, *Nat. Rev. Microbiol.* **2016**, *14*, 523.

[40] W. Li, M. J. Moore, N. Vasilieva, J. Sui, S. K. Wong, M. A. Berne, M. Somasundaran, J. L. Sullivan, K. Luzuriaga, T. C. Greenough, H. Choe, M. Farzan, *Nature* **2003**, *426*, 450.

[41] F. Wu, S.u Zhao, B. Yu, Y.-M. Chen, W. Wang, Z.-G. Song, Y.i Hu, Z.-W.u Tao, J.-H. Tian, Y.-Y. Pei, M.-L.i Yuan, Y.u-L. Zhang, F.a-H. Dai, Y.i Liu, Q.i-M. Wang, J.-J. Zheng, L. Xu, E. C. Holmes, Y.-Z. Zhang, *Nature* **2020**, *579*, 265.

[42] R. Lu, X. Zhao, J. Li, P. Niu, B.o Yang, H. Wu, W. Wang, H. Song, B. Huang, N.a Zhu, Y. Bi, X. Ma, F. Zhan, L. Wang, T. Hu, H. Zhou, Z. Hu, W. Zhou, L.i Zhao, J. Chen, Y. Meng, J.i Wang, Y. Lin, J. Yuan, Z. Xie, J. Ma, W. J. Liu, D. Wang, W. Xu, E. C. Holmes, G. F. Gao, G. Wu, W. Chen, W. Shi, W. Tan, *Lancet* **2020**, *395*, 565.

[43] S. A. Jeffers, S. M. Tusell, L. Gillim-Ross, E. M. Hemmila, J. E. Achenbach, G. J. Babcock, W. D. Thomas, L. B. Thackray, M. D. Young, R. J. Mason, D. M. Ambrosino, D. E. Wentworth, J. C. Demartini, K. V. Holmes, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 15748.

[44] V. S. Raj, H. Mou, S. L. Smits, D. H. W. Dekkers, M. A. Müller, R. Dijkman, D. Muth, J. A. A. Demmers, A. Zaki, R. A. M. Fouchier, V. Thiel, C. Drosten, P. J. M. Rottier, A. D. M. E. Osterhaus, B. J. Bosch, B. L. Haagmans, *Nature* **2013**, *495*, 251.

[45] S. Belouzard, V. C. Chu, G. R. Whittaker, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 5871.

[46] G. Simmons, J. D. Reeves, A. J. Rennekamp, S. M. Amberg, A. J. Piefer, P. Bates, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 4240.

[47] J. K. Millet, G. R. Whittaker, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 15214.

[48] H. Wang, P. Yang, K. Liu, F. Guo, Y. Zhang, G. Zhang, C. Jiang, *Cell Res.* **2008**, *18*, 290.

[49] K. Kuba, Y. Imai, T. Ohto-Nakanishi, J. M. Penninger, *Pharmacol. Ther.* **2010**, *128*, 119.

[50] M. A. Shereen, S. Khan, A. Kazmi, N. Bashir, R. Siddique, *J. Adv. Res.* **2020**, *24*, 91.

[51] A. Zumla, D. S. Hui, E. I. Azhar, Z. A. Memish, M. Maeurer, *Lancet* **2020**, *395*, e35.

[52] T. Lupia, S. Scabini, S. Mornese Pinna, G. Di Perri, F. G. De Rosa, S. Corcione, *J Glob Antimicrob Resist* **2020**, *21*, 22.

[53] L. Singh, H. G. Kruger, G. E. M. Maguire, T. Govender, R. Parboosing, *Ther Adv Infect Dis* **2017**, *4*, 105.

[54] H. Hassan, S. K. Adam, F. Othman, A. F. Shamsuddin, R. Basir, *J. Nanomater.* **2016**, *2016*, 1.

[55] J. K. Patra, G. Das, L. F. Fraceto, E. V. R. Campos, M. D. P. Rodriguez-Torres, L. S. Acosta-Torres, L. A. Diaz-Torres, R. Grillo, M. K. Swamy, S. Sharma, S. Habtemariam, H.-S. Shin, *J Nanobiotechnology* **2018**, *16*, 71.

[56] S. Jiang, C. Hillyer, L. Du, *Trends Immunol.* **2020**, *41*, 355.

[57] B. Mandal, H. Bhattacharjee, N. Mittal, H. Sah, P. Balabathula, L. A. Thoma, G. C. Wood, *Nanomedicine* **2013**, *9*, 474.

[58] J.-M. Nam, *Science* **2003**, *301*, 1884.

[59] Z. Zhang, J. Wang, C. Chen, *Adv. Mater.* **2013**, *25*, 3869.

[60] Y.u-F. Li, C. Chen, *Small* **2011**, *7*, 2965.

[61] M. Jiao, P. Zhang, J. Meng, Y. Li, C. Liu, X. Luo, M. Gao, *Biomater. Sci.* **2018**, *6*, 726.

[62] L. Li, Y. Lu, C. Jiang, Y. Zhu, X. Yang, X. Hu, Z. Lin, Y. Zhang, M. Peng, H. Xia, C. Mao, *Adv. Funct. Mater.* **2018**, *28*, 1704623.

[63] A.-C. Burdușel, O. Gherasim, A. M. Grumezescu, L. Mogoantă, A. Ficai, E. Andronescu, *Nanomaterials* **2018**, *8*, 681.

[64] R. Shanmuganathan, I. Karuppusamy, M. Saravanan, H. Muthukumar, K. Ponnuchamy, V. S. Ramkumar, A. Pugazhendhi, *Curr. Pharm. Des.* **2019**, *25*, 2650.

[65] A. Rónavári, D. Kovács, N. Igaz, C. Vágvölgyi, I. Boros, Z. Kónya, I. Pfeiffer, M. Kiricsi, *Int J Nanomedicine* **2017**, *12*, 871.

[66] J. Elechiguerra, J. L. Burt, J. R. Morones, A. Camacho-Bragado, X. Gao, H. H. Lara, M. Yacaman, *J Nanobiotechnology* **2005**, *3*, 6.

[67] H. H. Lara, N. V. Ayala-Nuñez, L. Ixtepan-Turrent, C. Rodriguez-Padilla, *J. Nanobiotechnol.* **2010**, *8*, 1.

[68] L. Sun, A. Singh, K. Vig, S. R. Pillai, S. R. Singh, *J. Biomed. Nanotechnol.* **2008**, *4*, 149.

[69] D.-X.i Xiang, Q. Chen, L. Pang, C.-L. Zheng, *J. Virol. Methods* **2011**, *178*, 137.

[70] S. Seino, Y. Imoto, T. Kosaka, T. Nishida, T. Nakagawa, T. A. Yamamoto, *MRS Advances* **2016**, *1*, 705.

[71] J. V. Rogers, C. V. Parkinson, Y. W. Choi, J. L. Speshock, S. M. Hussain, *Nanoscale Res. Lett.* **2008**, *3*, 129.

[72] L. Lu, R. W. Sun, R. Chen, C. K. Hui, C. M. Ho, J. M. Luk, G. K. Lau, C. M. Che, *Antivir. Ther.* **2008**, *13*, 253.

[73] X. Lv, P. Wang, R.u Bai, Y. Cong, S. Suo, X. Ren, C. Chen, *Biomaterials* **2014**, *35*, 4195.

[74] T. Q. Huy, N. T. Hien Thanh, N. T. Thuy, P. V. Chung, P. N. Hung, A.-T. Le, N. T. Hong Hanh, *J. Virol. Methods* **2017**, *241*, 52.

[75] S. Gaikwad, A. Ingle, A. Gade, M. Rai, A. Falanga, N. Incoronato, L. Russo, S. Galdiero, M. Galdiero, *Int J Nanomedicine* **2013**, *8*, 4303.

[76] R. L. Hu, S. R. Li, F. J. Kong, R. J. Hou, X. L. Guan, F. Guo, *Genet. Mol. Res.* **2014**, *13*, 7022.

[77] N. Khandelwal, G. Kaur, K. K. Chaubey, P. Singh, S. Sharma, A. Tiwari, S. V. Singh, N. Kumar, *Virus Res.* **2014**, *190*, 1.

[78] J. L. Castro-Mayorga, W. Randazzo, M. J. Fabra, J. M. Lagaron, R. Aznar, G. Sánchez, *LWT – Food Science and Technology* **2017**, *79*, 503.

[79] M. Fatima, N.-U.s-S. S. Zaidi, D. Amraiz, F. Afzal, *J. Microbiol. Biotechnol.* **2016**, *26*, 151.

[80] P. Rosa, E. Rahaju, *KnE Life Sciences* **2017**, *3*.

[81] S. Galdiero, A. Falanga, M. Vitiello, M. Cantisani, V. Marra, M. Galdiero, *Molecules* **2011**, *16*, 8894.

[82] A. Levina, M. Repkova, V. Zarytova, N. Mazurkova, *TiO2~DNA nanocomposites as efficient site-specific antiviral agents against influenza A virus in cell culture.* 2015 IEEE 15th International Conference on Nanotechnology **2015**. 1509–1512.

[83] D. B. Misstear, L. W. Gill, *J. Photochem. Photobiol. B* **2012**, *107*, 1.

[84] A. M. Paul, Y. Shi, D. Acharya, J. R. Douglas, A. Cooley, J. F. Anderson, F. Huang, F. Bai, *J. Gen. Virol.* **2014**, *95*, 1712.

[85] S. Rafiei, S. E. Rezatofighi, M. R. Ardakani, S. Rastegarzadeh, *IEEE Trans. Nanobioscience* **2016**, *15*, 34.

[86] N. Delaviz, P. Gill, A. Ajami, M. Aarabi, *RSC Adv.* **2015**, *5*, 79433.

[87] E. C. Lee, N. Davis-Poynter, C. T. H. Nguyen, A. A. Peters, G. R. Monteith, E. Strounina, A. Popat, B. P. Ross, *Nanoscale* **2016**, *8*, 16192.

[88] J. M. De Souza E Silva, T. D. M. Hanchuk, M. I. Santos, J. Kobarg, M. C. Bajgelman, M. B. Cardoso, *ACS Appl. Mater. Interfaces* **2016**, *8*, 16564.

[89] B. Zhu, G.-L.u Liu, F. Ling, G.-X. Wang, *Antiviral Res.* **2015**, *118*, 29.

[90] S. Ye, K. Shao, Z. Li, N. Guo, Y. Zuo, Q. Li, Z. Lu, L.u Chen, Q. He, H. Han, *ACS Appl. Mater. Interfaces* **2015**, *7*, 21571.

[91] X. X.i Yang, C. M. Li, Y. F. Li, J. Wang, C. Z. Huang, *Nanoscale* **2017**, *9*, 16086.

[92] M. Etemadzade, A. Ghamarypour, R. Zabihollahi, G. Shabbak, M. Shirazi, H. Sahebjamee, A. Z. Vaziri, A. Assadi, M. S. Ardestani, S. A. S. Shandiz, M. R. Aghasadeghi, *Asia Pac. J. Trop. Dis.* **2016**, *6*, 854.

[93] Y. Li, Z. Lin, M. Zhao, T. Xu, C. Wang, L. Hua, H. Wang, H. Xia, B. Zhu, *ACS Appl. Mater. Interfaces* **2016**, *8*, 24385.

[94] A. S. Levina, M. N. Repkova, E. V. Bessudnova, E. I. Filippova, N. A. Mazurkova, V. F. Zarytova, *Beilstein J. Nanotechnol.* **2016**, *7*, 1166.

[95] Y.i-N. Chen, Y.i-H. Hsueh, C.-T.e Hsieh, D.-Y. Tzou, P.-L. Chang, *Int J Environ Res Public Health* **2016**, *13*, 430.

[96] Y. Li, Z. Lin, T. Xu, C. Wang, M. Zhao, M. Xiao, H. Wang, N. Deng, B. Zhu, *RSC Adv.* **2017**, *7*, 1453.

[97] Y. Li, Z. Lin, M. Guo, Y.u Xia, M. Zhao, C. Wang, T. Xu, T. Chen, B. Zhu, *Int J Nanomedicine* **2017**, *12*, 5733.

[98] T. Malik, G. Chauhan, G. Rath, R. N. Kesarkar, A. S. Chowdhary, A. K. Goyal, *Artif Cells Nanomed Biotechnol* **2018**, *46*, 79.

[99] Z. K. Alghrair, D. G. Fernig, B. Ebrahimi, *Beilstein J. Nanotechnol.* **2019**, *10*, 1038.

[100] Y. Li, Z. Lin, M. Guo, M. Zhao, Y.u Xia, C. Wang, T. Xu, B. Zhu, *Int J Nanomedicine* **2018**, *13*, 2005.

[101] I. Venditti, *Bioengineering (Basel)* **2019**, *6*.

[102] K. Kalimuthu, B. S. Cha, S. Kim, K.i S. Park, *Microchem. J.* **2020**, *152*, 104296.

[103] A. Irshad, M. Zahid, T. Husnain, A. Q. Rao, N. Sarwar, I. Hussain, *Appl. Nanosci.* **2019**, *10*, 2453.

[104] N. Elahi, M. Kamali, M. H. Baghersad, *Talanta* **2018**, *184*, 537.

[105] H.-H.o Jeong, E. Choi, E. Ellis, T.-C. Lee, *J. Mater. Chem. B* **2019**, *7*, 3480.

[106] S. Vijayakumar, S. Ganesan, *Curr. HIV Res.* **2012**, *10*, 643.

[107] S. R. Ahmed, J. Kim, T. Suzuki, J. Lee, E. Y. Park, *Biotechnol. Bioeng.* **2016**, *113*, 2298.

[108] J. Kim, M. Yeom, T. Lee, H.-O. Kim, W. Na, A. Kang, J.-W. Lim, G. Park, C. Park, D. Song, S. Haam, *J. Nanobiotechnol.* **2020**, *18*, 54.

[109] V. P. Zharov, K. E. Mercer, E. N. Galitovskaya, M. S. Smeltzer, *Biophys. J.* **2006**, *90*, 619.

[110] P. Suchomel, L. Kvitek, R. Prucek, A. Panacek, A. Halder, S. Vajda, R. Zboril, *Sci. Rep.* **2018**, *8*, 4589.

[111] N. Tran, T. J. Webster, *J. Mater. Chem.* **2010**, *20*, 8760.

[112] E. Tombácz, R. Turcu, V. Socoliuc, L. Vékás, *Biochem. Biophys. Res. Commun.* **2015**, *468*, 442.

[113] T.-C. Chou, W. Hsu, C.-H.o Wang, Y.u-J.u Chen, J.-M. Fang, *J Nanobiotechnology* **2011**, *9*, 52.

[114] J.-A. Park, S.-B. Kim, C.-G.u Lee, S.-H. Lee, J.-W. Choi, *J Environ Sci Health A Tox Hazard Subst Environ Eng* **2014**, *49*, 1116.

[115] T. Shelby, T. Banerjee, I. Zegar, S. Santra, *Sci. Rep.* **2017**, *7*, 7377.

[116] H. Shi, R. Magaye, V. Castranova, J. Zhao, *Part. Fibre Toxicol.* **2013**, *10*, 15.

[117] Z.i Fei Yin, L. Wu, H. Gui Yang, Y. Hua Su, *Phys. Chem. Chem. Phys.* **2013**, *15*, 4844.

[118] D. Ziental, B. Czarczynska-Goslinska, D. T. Mlynarczyk, A. Glowacka-Sobotta, B. Stanisz, T. Goslinski, L. Sobotta, *Nanomaterials* **2020**, *10*, 387.

[119] G. Lan, K. Ni, S. S. Veroneau, X. Feng, G. T. Nash, T. Luo, Z. Xu, W. Lin, *J. Am. Chem. Soc.* **2019**, *141*, 4204.

[120] N. Salahuddin, M. Abdelwahab, M. Gaber, S. Elneanaey, *Mater. Sci. Eng., C* **2020**, *108*, 110337.

[121] L. Li, C. Xie, X. Xiao, *J. Drug Delivery Sci. Technol.* **2020**, *56*, 101537.

[122] D. Flak, L. Yate, G. Nowaczyk, S. Jurga, *Mater Sci Eng C Mater Biol Appl* **2017**, *78*, 1072.

[123] M. Wang, H. Yin, Y. Zhou, C. Sui, Y. Wang, X. Meng, G. I. N. Waterhouse, S. Ai, *Biosens. Bioelectron.* **2019**, *128*, 137.

[124] D. Gerrity, H. Ryu, J. Crittenden, M. Abbaszadegan, *J Environ Sci Health A Tox Hazard Subst Environ Eng* **2008**, *43*, 1261.

[125] N. A. Mazurkova, Y.u. E. Spitsyna, N. V. Shikina, Z. R. Ismagilov, S. N. Zagrebel'nyi, E. I. Ryabchikova, *Nanotechnol. Russ.* **2010**, *5*, 417.

[126] V. I. Syngouna, C. V. Chrysikopoulos, *J. Colloid Interface Sci.* **2017**, *497*, 117.

[127] H. C. Winkler, T. Notter, U. Meyer, H. Naegeli, *J Nanobiotechnology* **2018**, *16*, 51.

[128] J. Liu, T. Liu, J. Pan, S. Liu, G. Q. (M.) Lu, *Annu. Rev. Chem. Biomol. Eng.* **2018**, *9*, 389.

[129] S. Bayir, A. Barras, R. Boukherroub, L. Szunerits, L. Raehm, S. Richeter, J.-O. Durand, *Photochem. Photobiol. Sci.* **2018**, *17*, 1651.

[130] R. Sun, W. Wang, Y. Wen, X. Zhang, *Nanomaterials* **2015**, *5*, 2019.

[131] H.-C. Guo, X.-M. Feng, S.-Q.i Sun, Y.-Q. Wei, D.e-H. Sun, X.-T. Liu, Z.-X. Liu, J.-X. Luo, H. Yin, *Virol J* **2012**, *9*, 108.

[132] M. Stevanović, et al., in *Materials for Biomedical Engineering*, V. Grumezescu, and A.M. Grumezescu, Eds. **2019**, Elsevier, Amsterdam. pp. 1–46.

[133] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, H.-R. Si, Y. Zhu, B. Li, C.-L. Huang, H.-D. Chen, J. Chen, Y. Luo, H. Guo, R.-D.i Jiang, M.-Q. Liu, Y. Chen, X.u-R. Shen, X.i Wang, X.-S. Zheng, K. Zhao, Q.-J. Chen, F. Deng, L.-L. Liu, B. Yan, F.a-X. Zhan, Y.-Y.i Wang, G.-F.u Xiao, Z.-L.i Shi, *Nature* **2020**, *579*, 270.

[134] D. K. W. Chu, Y. Pan, S. M. S. Cheng, K. P. Y. Hui, P. Krishnan, Y. Liu, D. Y. M. Ng, C. K. C. Wan, P. Yang, Q. Wang, M. Peiris, L. L. M. Poon, *Clin. Chem.* **2020**, *66*, 549.

[135] V. M. Corman, O. Landt, M. Kaiser, R. Molenkamp, A. Meijer, D. K.w Chu, T. Bleicker, S. Brünink, J. Schneider, M. L. Schmidt, D. G. Mulders, B. L. Haagmans, B. Van Der Veer, S. Van Den Brink, L. Wijsman, G. Goderski, J.-L. Romette, J. Ellis, M. Zambon, M. Peiris, H. Goossens, C. Reusken, M. P.g Koopmans, C. Drosten, *Euro Surveill.* **2020**, *25*.

[136] K. K.-.W. To, O. T.-.Y. Tsang, C. C.-.Y. Yip, K.-H. Chan, T.-C. Wu, J. M.-.C. Chan, W.-S. Leung, T. S.-.H. Chik, C. Y.-.C. Choi, D. H. Kandamby, D. C. Lung, A. R. Tam, R. W.-.S. Poon, A. Y.-.F. Fung, I. F.-.N. Hung, V. C.-.C. Cheng, J. F.-.W. Chan, K.-Y. Yuen, *Clin. Infect. Dis.* **2020**, 841.

[137] P. C. Y. Woo, S. K. P. Lau, B. H. L. Wong, H.-W. Tsoi, A. M. Y. Fung, R. Y. T. Kao, K.-H. Chan, J. S. M. Peiris, K.-Y. Yuen, *J. Clin. Microbiol.* **2005**, *43*, 3054.

[138] X. Xie, et al., *Radiology* **2020**, *296*, 200343.

[139] W. C. Yam, K. H. Chan, L. L. M. Poon, Y. Guan, K. Y. Yuen, W. H. Seto, J. S. M. Peiris, *J. Clin. Microbiol.* **2003**, *41*, 4521.

[140] J. J. Broglie, B. Alston, C. Yang, L. Ma, A. F. Adcock, W. Chen, L. Yang, *PLoS One* **2015**, *10*, e0141050.

[141] S. R. Ahmed, J. Kim, T. Suzuki, J. Lee, E. Y. Park, *Biosens. Bioelectron.* **2016**, *85*, 503.

[142] K. Zagorovsky, W. C. W. Chan, *Angew. Chem., Int. Ed.* **2013**, *52*, 3168.

[143] J. R. Carter, V. Balaraman, C. A. Kucharski, T. S. Fraser, M. J. Fraser, *Virol J* **2013**, *10*, 201.

[144] S. C. B. Gopinath, K. Awazu, M. Fujimaki, K. Shimizu, T. Shima, *PLoS One* **2013**, *8*, e69121.

[145] Y. Liu, L. Zhang, W. Wei, H. Zhao, Z. Zhou, Y. Zhang, S. Liu, *Analyst* **2015**, *140*, 3989.

[146] M. Askaravi, S. E. Rezatofighi, S. Rastegarzadeh, M. R. Seifi Abad Shapouri, *AMB Express* **2017**, *7*, 137.

[147] L. A. A. Chunduri, A. Kurdekar, M. K. Haleyurgirisetty, E. P. Bulagonda, V. Kamisetti, I. K. Hewlett, *Sci. Rep.* **2017**, *7*, 7149.

[148] D. V. Quy, N. M. Hieu, P. T. Tra, N. H. Nam, N. H. Hai, N. T. Son, P. T. Nghia, N. T. Van Anh, T. T. Hong, N. H. Luong, *J. Nanomater.* **2013**, *2013*.

[149] S. R. Ahmed, É. Nagy, S. Neethirajan, *RSC Adv.* **2017**, *7*, 40849.

[150] S. R. Ahmed, K. Takemeura, T.-C. Li, N. Kitamoto, T. Tanaka, T. Suzuki, E. Y. Park, *Biosens. Bioelectron.* **2017**, *87*, 558.

[151] L. Zheng, J. Wei, X. Lv, Y. Bi, P. Wu, Z. Zhang, P. Wang, R. Liu, J. Jiang, H. Cong, J. Liang, W. Chen, H. Cao, W. Liu, G. F. Gao, Y. Du, X. Jiang, X. Li, *Biosens. Bioelectron.* **2017**, *91*, 46.

[152] S. Oh, J. Kim, V. T. Tran, D. K. Lee, S. R. Ahmed, J. C. Hong, J. Lee, E. Y. Park, J. Lee, *ACS Appl. Mater. Interfaces* **2018**, *10*, 12534.

[153] J. Lee, M. Morita, K. Takemura, E. Y. Park, *Biosens. Bioelectron.* **2018**, *102*, 425.

[154] J. Torrecilla, A. Del Pozo-Rodríguez, M. Ÿ. Solinís, P. S. Apaolaza, B. Berzal-Herranz, C. Romero-López, A. Berzal-Herranz, A. Rodríguez-Gascón, *Colloids Surf. B Biointerfaces* **2016**, *146*, 808.

[155] R. G. Kerry, S. Malik, Y. T. Redda, S. Sahoo, J. K. Patra, S. Majhi, *Nanomedicine* **2019**, *18*, 196.

[156] E. De Clercq, G. Li, *Clin. Microbiol. Rev.* **2016**, *29*, 695.

[157] J. Mellet, M. S. Pepper, *Vaccines* **2021**, *9*, 39.