A review paper on nanotheranostic insight into combatting impediments of the COVID-19 pandemic

Submitted by:

Tabassum Binte Jamal

Student ID: 16236007

A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of
Bachelor of Science in Biotechnology

Department of Mathematics and Natural Sciences
BRAC University
February,2020.

Declaration

It is hereby declared that

1.The thesis submitted is my original work while completing the degree at BRAC University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material that has been accepted or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all the main sources of help.

Student's Full Name & Signature:

Tabassum Binte Jamal
Student ID: 16236007

Approval

The thesis/project titled "A review paper on nanotheranostic insight into combatting impediments of the COVID-19 pandemic" submitted by

1. Tabassum Binte Jamal (16236007)

of Fall, 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Science in Biotechnology on [11 May 2021].

Examining Committee:

(Member)

_____

Fahim Kabir Monjurul Haque, PhD
Assistant Professor, Department of Mathematics and Natural Sciences
BRAC University

Program Coordinator and Supervisor :
(Member)

_____

Iftekhar Bin Naser, PhD
Assistant Professor, Department of Mathematics and Natural Sciences
BRAC University

Departmental Head:
(Chairman)

_____

A F M Yusuf Haider, PhD
Professor and Chairperson, Department of Mathematics and Natural Sciences
BRAC University

Dedication:

I dedicate this thesis to my late grandmother.

Acknowledgement

First and foremost, praises and thanks to the Almighty, for His showers of blessings throughout my research work to complete the research successfully.

I would like to express my deep and sincere gratitude to my research supervisor, Dr. Iftekhar Bin Naser, Professor, Department of Mathematics and Natural Sciences, BRAC University for his constant guidance, faith and help throughout my thesis project.

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Tabassum Binte Jamal

ID: 16236007

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Abstract

The COVID-19 pandemic is an ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its emersion in Wuhan,China in 2019, the virus has affected every corner of the world except Antarctica.The world has witnessed a tragic milestone of more than three million deaths and every family out there is going through an intolerable burden of loss of their loved ones.SARS-CoV-2 possess an egregious ability to escape anti-viral measures that imposes a massive threat to global health as well as socioeconomic state of the world.Such circumstances demand for a therapeutic accomplishment that acts multifunctionally and holds target specificity and lower toxic properties.This review represents a panoply of solutions in nanotheranostic point of view. Nanotheranostics is deemed a potential approach for annihilating different viral infections. Besides nanotechnology has much to offer in the field of developing nanomaterials like sanitizers,lab cots,diagnostic tools,nanocarriers as therapeutics and nano-vaccines.Finally some comments have been made on the inconvenience and drawbacks that require addressing.

Introduction

The entire planet is on contingent funk for a pandemic outbreak caused by a novel coronavirus officially termed as acute respiratory syndrome coronavirus 2 (SARS- CoV-2)**(Wu et al., 2020).** Pneumonia cases of strange aetiology were first detected in Wuhan, China, on December 31st, 2019 and due to the severity of the situation on January 30th,2020 WHO declared this as a Public Health Emergency of International Concern naming as Coronavirus disease-19 (COVID-19**) (Events as They Happen, 2020).** The world has been in viral outbreaks before causing by Ebola, Influenza A (H1N1), Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Zika. All of these diseases brought about momentous impact on public health and disrupted world economy.**(Boopathi et al., 2020).** But none was as vigorous as the novel coronavirus infecting 105 million individuals and killing about 2.3 million people worldwide as of February 06th,2021.(2) Covid-19 is considered to be the greatest humanitarian crisis of the twenty-first century being as contagious as it can be.People get infected with the virus particles if they come in contact with previously infected individuals for example,generated by coughing, sneezing, or talking **(Prather et al., 2020).** This can happen by direct contact or by imperceptible fomites. (fnano) Direct transmission occurs via saliva, respiratory secretions, or droplets expelled by infected persons.Fomite transmission happens if anyone contacts or touches a contaminated object or surface **(Yee et al., 2020, Sharma et al., 2020).**

On the basis of the severity of a disease and scheme of transmission,congenial methods are required to minimize the affect of the infectious disease **(Events as They Happen, 2020).** It is worth mentioning that the high transmissibility of COVID-19 is due to its elevated viral loads in the upper respiratory tract and the reason of many individuals remaing asymptomatic,and transmitting the virus **(Bai et al., 2020).** COVID-19 has already shown its potential for tremendous consequences at all levels and its current impact on global health is evident.What is more, the worldwide impact on the economy,employees, and companies might entail deep economic and negatory social impacts as ulterior consequences **(Elcano Royal Institute, 2020).** The number of infected patients is continuously rising yet there are no officially approved drugs

for this deadly virus.Treatment strategies are mainly focused on symptomatic relief and respiratory support is provided to severy ill patients **(Zumla et al., 2020).** Therapeutic response against this novel virus somewhat comprises the development of several clinical trials to define treatments for instance,treatments with chloroquine, antivirals (e.g. Remdesivir and interferon),and convalescent plasma **(Dong et al., 2020,Cortegiani et al., 2020,Salvi & Patankar, 2020).** On the other hand,viral mutations and the uprising of new viral strain slowly made the efficacy of conventional anti-viral treatments fade away **(Strasfeld & Chou, 2010)**. Another effective way to bid a farewell to viral diseases is the development of vaccines as it train our bodies to fight against infections.Scientists have been working twenty four a day to develop a feasible vaccine to save the world from the curse of COVId-19 since the arrival of the virus.Atlast,at the end of the 2020 three of the vaccines got officially approved to use against COVID-19 breaking all the previous records times to first in human trials.All these were made possible by the blessing of 'nanotechnology' as well as recombinant DNA technology.

Nanotechnology can be difined as the creation and application of structures,devices,or systems that hold novel properties where at least one dimension is less than 100 nanometres.It is that branch of science that assigns the use of nanoscale particles to obtain desirable outcomes in the fields of Engineering, Medicine, Agriculture, or Pharmaceuticals **(Jackson et al., 2017).** Hence this review provides information with the role of nanotechnology in helping the fight against SARS-CoV-2 that comprises of **(a)** design of personal protective equipment (PPE) and development of effective antiviral disinfectants and surface coatings to ensure safety of the healthcare workers and prevent viral spreads **(b)** design of exceptionally specific and sensitive nano-based biosensors to detect infection and immunological response with high efficiency **(c)** evolution of new therapeutics with tissue specificity,aggravated activity with decreased toxicity and finally, **(d)** development of a nano-vaccines to facilitate humoral and cellular immune responses.

Background Check

SARS-CoV-2 is an enveloped virus belonging to the Coronaviridae family in the Nidovirales order.Based on the genomic structure,the family is organized into four genera;α-CoV,β-CoV,γ-

CoV,and δ-CoV.Coronaviruses are minute in size (65–125 nm in diameter) and contain a single-stranded RNAgenome as a nucleic material, size ranging from 26 to 32kbs in length **(Pal et al., 2020).** When viewed under a transmission electron microscope (TEM) they show a crwon-shaped protein spikes on their surface,hence came the name 'coronavirus' **(Chauhan et al., 2020).** These viruses were thought to be animal viruses ,but to their utter surprise people witnessed a severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV, 2002 in Guangdong, China **(Zhong et al., 2003).** Not only that, another pathogenic coronavirus, known as Middle East respiratory syndrome (MERS-CoV) caused an endemic in Middle Eastern countries only a decade later **(Wang et al., 2013).** And now the world is under a pandemic because of this novel coronavirus SARS-CoV-2 that killed more than eighteen hundred and infected over seventy thousand individuals within the first fifty days of its outbreak **(Pal et al., 2020).** This mighty coronavirus belongs to the β-CoV genera of Coronaviridae family and shares 80% similarity to the SARS-CoV and 96% to the BatCoV RaTG13 **(Zhou et al., 2020).**

Genomic sequence of SARS-CoV-2 reveals that around two-thirds of the RNA is composed of replicase ORF1a/1b,encoding 16 non-structural proteins and translating two polyproteins, followed by approximately 13 downstream ORFs.The essential structural proteins encoded by the rest of the viral genome are spike (S), envelope (E), membrane (M) and nucleocapsid (N) **(Cui et al., 2018,Lu et al., 2020,F. Wu et al., 2020).** The functions and activities of these proteins represent how SARS-CoV-2 infects host cells.For instance,**(i)** the envelope-anchored glycoprotein S is a trimeric class I fusion protein that promotes virus entry into the host cell by attaching to human angiotensin converting enzyme 2 (ACE2) receptor, an integral membrane protein responsible for cleaving angiotensin I and II on the plasma membrane of human epithelial cells;**(ii)** shape, size, and assembly of the virus is largely defined by the umpteen M protein that occupies three trnansmembrane domains;**(iii)** the smallest E protein is abundantly expressed inside the infected cell playing vital roles in pathogenesis,replication,assembly and,budding of the virus;**(iv)** Localized in the endoplasmic reticulum-Golgi region,the N protein mainly binds to the (+) ssRNA and creates a helical nucleocapsid to assist viral replication inside the host cell **(Masters, 2006,D. X. Liu et al., 2014).**

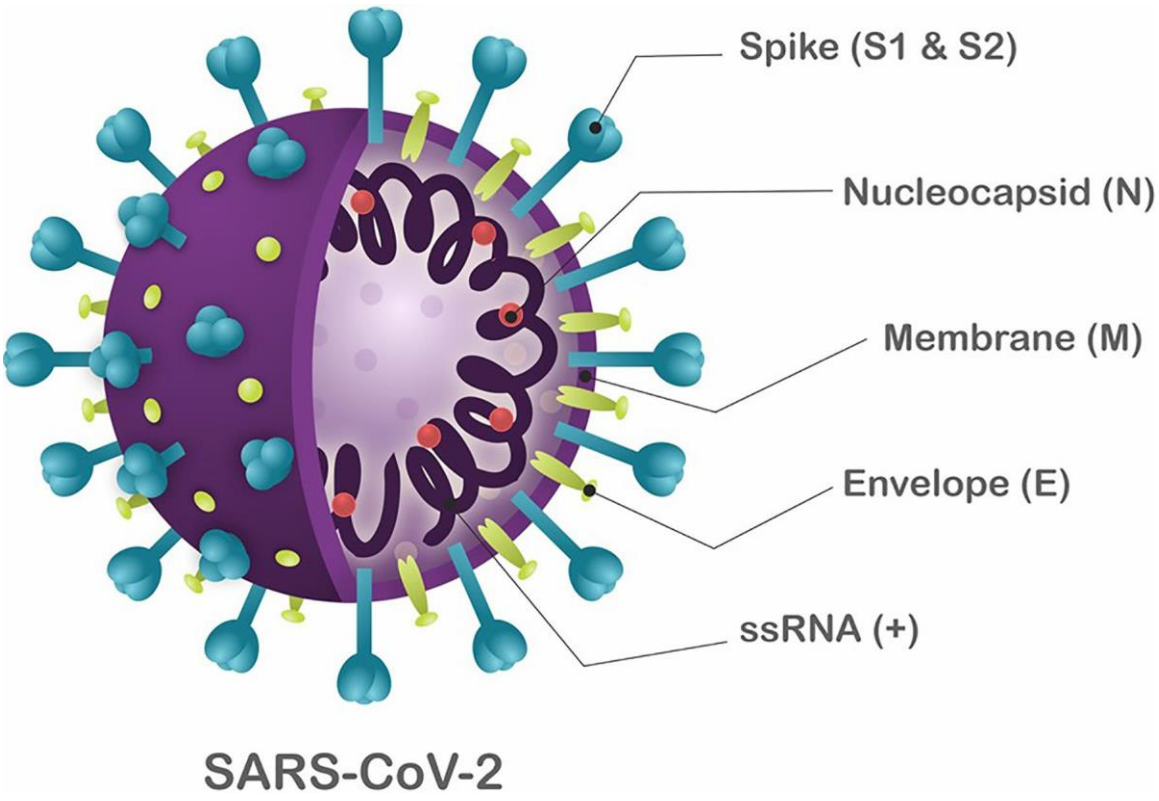

Figure 3: Schematic representation of the SARS-CoV-2 structure.

Pathogenecity of human SARS-CoV-2

What makes SARS-CoV-2 S protein virulent?

The ~1200 aa long S-protein of SARS-CoV-2 belongs to class-I viral fusion proteins that ultimately ends up binding to the cell receptors,contributing tissue tropism and pathogenesis **(Coutard et al., 2020, p. 104742).** Ergo, S protein is the most crucial one among other proteins of SARS-CoV-2.The trimetric S-protein contains number of conserved domains and motifs..The two main domains of S protein includes the N terminal S1 doamin responsible for binding to the angiotensin-converting enzyme 2 (ACE2) cell surface receptor and a membrane anchored C-terminal S2 domain that helps the virus to get inside the host cell **(Coutard et al., 2020, p. 104742,Shi et al., 2020, p. 345).** The S1 domain has a subdomain named Receptor Binding Domain (RBD) which in actual recognizes the ACE-2 binding site. The RBD surface of S1 domain shows 14 aa in the S1 of SARS-CoV.Now to prove their hypothesis that ACE-2 is also

the receptor for the novel corona virus,scientists proved that 8 of that 14 aa are strictly conserved in 2019-nCoV **(Coutard al., 2020, p. 104742).** The S2-protein includes the fusion peptide (FP), a second proteolytic site (S2′), followed by an internal fusion peptide (IFP) and a transmembrane domain (TM) which precedes two heptad-repeat domains **(Shi et al., 2020, p. 345).**

The S protein holds two cleavage site; arginines R667 and R797. The R667 site is at the division between S1and S2 and the final S2 polypeptide is resulted by cleaving at the R797 **(Shi et al.,2020, p. 345).** It is to be mentioned that the S protein must likely be cleaved at both S1/S2 and S2′ cleavage sites for virus infusion since both FP and IFP participate in the viral entry process.An affluent number of cellular proteases can cleave the S peptide at these two sites, including cathepsin L,trypsin,elastase,serine transmembrane proteases (TMPRSSs) and factor Xa.Although protease(s) involved in a key event to the final activation of the S-protein which is cleavage at S2′ have not yet been conclusively identified **(Coutard al., 2020, p. 104742,Shi et al., 2020, p. 345).**

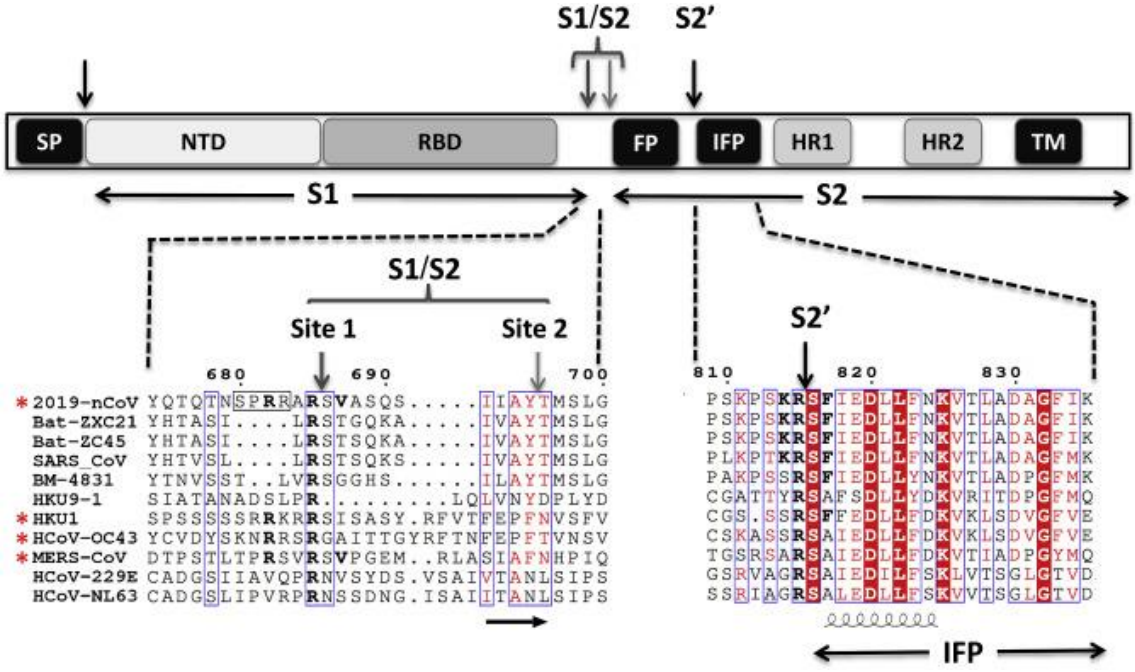

Figure 02. Schematic representation of the human 2019-nCoV S-protein with a focus on the putative maturation sites. The domains were previously characterized inSARS-CoV and MERS-CoV: Signal peptide (SP), N-terminal domain (NTD), receptor-binding domain (RBD), fusion

peptide (FP), internal fusion peptide (IFP), heptadrepeat 1/2 (HR1/2), and the transmembrane domain (TM). The SP, S1↓S2 and S2′ cleavage sites are indicated by arrows.Insertion of furin like cleavage site is surrounded by a black frame. Red asterisks indicate the presence of a canonical furin-like cleavage motif at the S1/S2 site (Source : Coutard, B., Valle, C., de Lamballerie, X., Canard, B., Seidah, N. G., & Decroly, E. (2020b). The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Research, 176, 104742. https://doi.org/10.1016/j.antiviral.2020.104742).

Binding affinity Of SARS-CoV-2 S protein

Although being the inner joint neighbors of SARS or SARS-like coronaviruses, including the human-infecting ones ,the novel corona virus posses an unusual amount of differences from that of SARS-CoV **(Xu et al., 2020, p. 458).** To draw a line between them, the structural model of the SARS- CoV-2 S-protein was constructed by Swiss-model using the crystal structure of SARS coronavirusS-protei based on computer-guided homology modeling method **(Xu et al., 2020, p. 458).** Toppingly the similarity of the amino acid sequence between SARS-CoV-2 S and SARS-CoV S proteins is significantly limited; only76.47%.The similarity is even quite low within the S1 domains(64%) of the S proteins of the clade coronaviruses where it shows comparatively greater similarity within the S2 domains (up to 90%).The N-terminal region is overall less conserved (51%) within the S1 domain, while the C-terminal RBD subdomain has relatively high conservation (74%).As such,allowing interactions with the same cell surface receptor ACE2 **(Shi et al., 2020, p. 355).**

However computational modelling was carried out to find out binding free energies between S proteins and host ACE-2 receptors of these two corona viruses. Results show that SARS-CoV exhibits –78.6 kcal mol–1 binding free energy between S-protein and human ACE-2 ,on the contrary SARS-CoV-2 exhibits –50.6 kcal mol–1. Due to the breakage of hydrogen bond interactions for replacing Arg426 with Asn426 in the SARS- CoV-2 S-protein,the binding free energy augmented upto28 kcal mol–1 **(Xu et al., 2020, p. 458).** Assummately these changes within a critical motif in S peptide might have lead to ahigher binding affinity to host ACE-2.

Besides binding of quantities as low as 15 nmol/L of the S1 domain of SARS-CoV-2 could be detected at the ACE2 using optical biosensing via surface plasmon resonanance **(Wrapp et al.,**

2020, p. 1261). These results proves that the S protein of SARSCoV-2 possess a 10–20 fold distinguished affinity for this receptor than does that of SARS-CoV.

Role of furin like cleavage site in distinguishing 2019-nCoV from CoV of the same clade:

After the release of the genome sequence of SARS-CoV-2,several group of researchers came to notice a distinctive four amino acid insert at the S1/S2 juntion of the S protein of the virus.This insert; (underlined, SPRRAR ↓S) ; one of the prominent feature of 2019-nCoV ; has been identified as a potential cleavage site for the protease furin **(Jaimes et al., 2020)**. Conersely the S protein of SARS-CoV remains largely uncleaved after biosynthesis,possibly due to the lack of a favourable furin-like cleavage site (SLL**R**ST) **(Coutard et al., 2020a, p. 104742).** The insertion sequence is so unique that it has not been found in any other known coronaviruses, not even RaTG12 coronavirus from the bat (**Zhou P et al., 2020**). Probably this is why SARS-CoV-2 is a highly transmissible coronavirus; may be 3- and 10-fold higher than those of SARS-CoV and MERS, respectively **(Jiang et al., 2020, p. 275).** Moreover, the high expression of furin in human lungs may be the reason why SARS-CoV-2 has vigorously spread throughout the population in comparison to SARS-CoV and MERS **(Voto et al., 2020).**

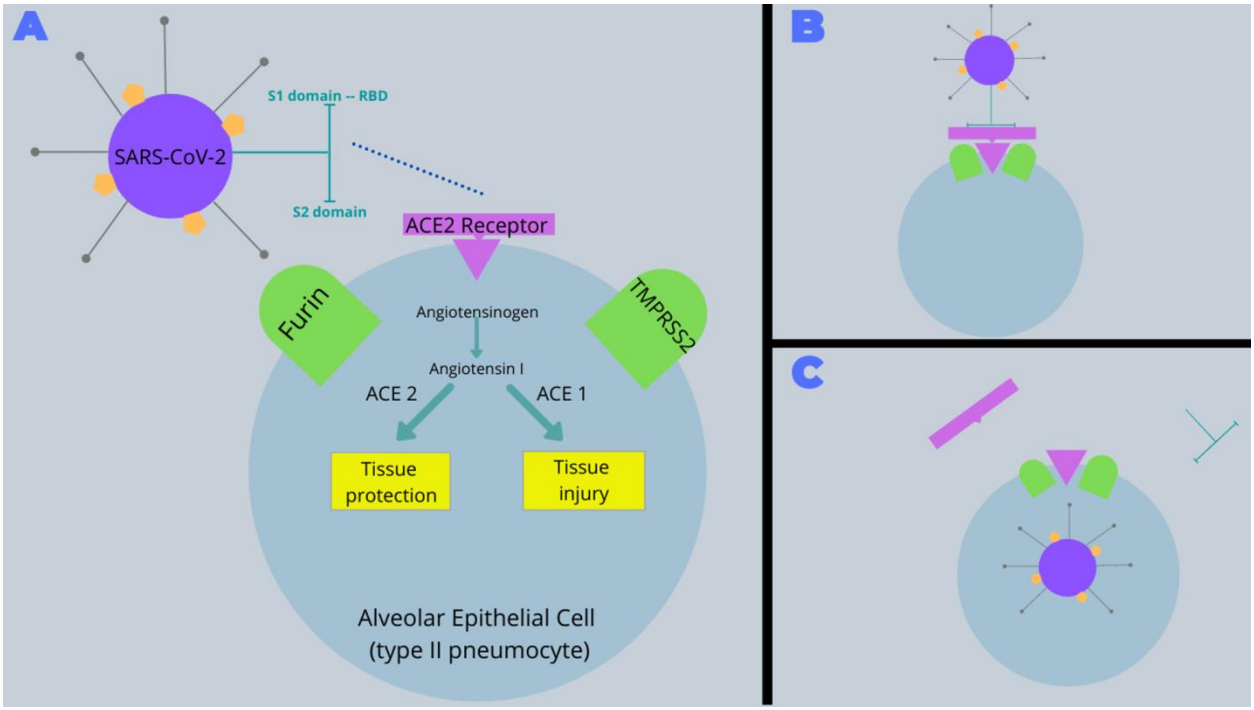

Figure 03: Pathogenesis of SARS-CoV-2.(A)SARS-CoV-2 utilizes a spike (S) protein on its

surface in order to bind to ACE2 receptors on the surface of human alveolar epithelial cells. The S protein is divided into two domains, S1 and S2, which are responsible for receptor binding and cell membrane fusion, respectively. The S1 domain contains the RBD, which has thespecific ACE2 receptor affinity. (B) Human secretory proteases, such as TMPRSS2 and furin, localize to virally-target cells. (C) These proteases enhance viral entry into host cells through the proteolysis of both the S1, S2, and ACE2 proteins (S1/S2 priming and ACE2 down-regulation).

ACE2, angiotensin-converting enzyme 2; RBD, receptor-binding domain; TMPRSS2, transmembrane protease/serine subfamily member 2 (source: Voto, C., Berkner, P., & Brenner, C. (2020).Overview of the Pathogenesis and Treatment of SARS-CoV-2 for Clinicians:A Comprehensive Literature Review. Cureus, 0. https://doi.org/10.7759/cureus.10357).

Other than furin there are some other proteases,for example trypsin, PC1, and the type II transmembrane serine protease (TTSP) matriptase,and cathepsins B that cleave SARS-CoV-2 much more readily than SARS-CoV. The only protease that showed mor efficacy on SARS-CoV compared with SARS-CoV-2 was cathepsin L **(Jaimes et al., 2020).**

Cytokine Upheaval

Our immune response safeguards our body from exposing to any kind of viral or bacterial infection.Among varieties of role that our immune system play,releasing of cytokines are of great importance. A rapid and well-coordinated innate immune reaction is the first line of defense against viral infection **(Ye et al., 2020,p.608).** The fruitful result to get red of any viral attack is mediated when an antiviral CD4+ T helper (Th) cell accompanied by CD8+ cytotoxic T lymphocytes are activated and a B cell-response leading to the production of specific antibodies. However,if human organisms fail to develop an adequate immune reaction,virus persistents and carries out dysregulated amplification of innate immune mechanisims,which can cause ‘hyperinflammatory known as cytokine upheavel/storm **(Pelaia et al., 2020).** The vast majority of patients that died for the coronavirus disease 2019 (COVID-19) showed abnormally higher concentration of pro-inflammatory cytokines which eventually caused them Acute respiratory distress syndrome (ARDS) and multiple-organ failure.

Studies showed that ARDS was the leading cause of death in patients infected with SARS-CoV or MERS-CoV **(Ye et al., 2020,p.608).** It is now known that several proinflammatory cytokines

such as IL-6, IL-8, IL-1 β, granulocyte- macrophage colony-stimulating factor (Gm-CSF) activated CD14+ CD16+ monocytes(migrating from blood to lung,thus becoming dendritic cells or alveolar macrophages),reactive oxygen species and chemokines such as CCL2, CCL-5, IFN γ-induced protein 10 (IP-10), and CCL3) all contribute to the occurrence of this 'hallmark' immune-mediated clinical consequence.In severe cases COVID-9 patients tends to develop abnormal types of CD4+ and CD8+ T lymphocytes, characterized by a high co-expression of surface markers as PD-1 (programmed cell death protein-1) and Tim-3 (T-cell immunoglobulin and mucin domain containing-3),which may be the reason behind rapid T cell deterioration during viral infections **(Pelaia et al., 2020, p.175346662093350,Ye et al., 2020,p.608).**

The cytokine storm is also suspected to lead to apoptosis of epithelial cells and endothelial cells,vascular leakage,shock,acute kidney injury, acute cardiac injury, liver dysfunction, coagulopathy, infection,thrombotic disease eventually death **(Tang et al., 2020, p. 1708,Voto et al., 2020).** Moreover,the comorbidities (respiratory, cardiovascular, metabolic, oncologic,etc.) involved, the senescence of the immune system plays a role in the worst outcomes observed in the elderly **(Pelaia et al., 2020, p.175346662093350).**

Pediatric Challenges

A former study on pediatric patients reveals that children with COVID-19 show less comorbid complications than adults. As of February 8, 2020, of the 2135 pediatric patients included in the study of the children in china, only 1 child died and most cases were mild, with much fewer being severe and critical cases (5.8%) than in adult patients (18.5%) **(Y. Dong et al., 2020).** The study also shows that children of all ages are susceptible to COVID-19 and the disease prognosis is not dependent on gender at all.Why infants and adolescences show inferior severity than adults is confusing.One of that reason can be smoking.Smoking increases ACE2 expression;thus enhances coronavirus entry into pulmonary epithelial cells. Indisputably smoking is more prevalent among adults than among children,children become less susceptible to COVID-19 **(Chang et al., 2020, p. 983).** Another reason is that children often get exposed to RSV (respiratory syncytial virus) in winter and may have higher levels of antibody against virus than adults.Moreover children do not generally develop underlying diseases like diabetes mellitus,chronic obstructive pulmonary disease or cardiovascular diseases like adults. These are the diseases that make the patients more vulnerable to the virus and worsen their clinical

condition.However, the definite pathogenesis is still puzzling **(Y. Dong et al., 2020,Chang et al., 2020, p. 983).**

Surprisingly,a post-infectious complication of SARS-CoV-2 is being reported, known as multisystem inflammatory syndrome in children (MIS-C).Syndromes for this disease represents fever, prominent gastrointestinal upset, rash, conjunctivitis, and neurological findings which shows similarity with another pediatric disease called KAWASAKI. Kawasaki disease is an acute and usually self-limiting vasculitis of the medium calibre vessels, which almost exclusively affects children.However the connection between SARS-CoV-2 and MIS-C has not been proven yet. But areas heavily affected by the pandemic showing an increased incidence of Kawasaki like disease speculated to have an epidemiological link **(Verdoni et al., 2020, p. 1773, Voto et al., 2020).**

Human immune system evasion process

SARS-CoV and MERS-CoV follow several mechanisms to avoid immune responses to subsist in host cells.When a pathogen infects host cell,pathogen-associated molecular patterns (PAMPs) are recognized by pattern recognition receptors(PRRs),one of fundamental function of host immune cells. However, SARS-CoV and MERS-CoV induces the production of double-membrane vesicles which lack PRRs,thus replicates in these vesicles, and subsequently avoids host detection of their dsRNA **(Snijder et al., 2006, p. 5937)**. Li et al reviewed a paper on molecular immune pathogenesis of corona viruses and found the IFN-I pathway is inhibited in infected mice whereas IFN-I(IFN-a and IFN-b) has a immense protective effect on SARS-CoV and MERS-CoV infection.(immune patho of cov) Antigen presentation can also be altered by the attack of corona viruses for instance,gene expression related to antigen presentation is down-regulated after MERS-CoV invades host cell **(Menachery et al., 2018).** Moreover, MERS-CoV accessory Protein 4a fuctions as a Type I Interferon antagonist at the level of MDA5 (melanoma differentiation-associated protein) activation through direct interaction with double-stranded RNA **(Niemeyer et al., 2013, p. 12492).** Following the information available on SARS-CoV-2 cognate viruses (SARS-CoV and MERS-CoV),it can be understood how this novel virus escapes host's immune response as data on SARS-CoV-2 remain limited **(Lu et al., 2020, p. 567).** Hence destruction of host immune evasion is obligatory in the development of COVID-19 therapeutics and vaccines.

Entry and Replication

A typical interspecies transmission and successful viral infection profoundly depends on virus binding to host cell surface receptors. Coronavirus spike proteins are capable of recognising carbohydrates and protein receptors found at the host cell surface **(Millet et al., 2020).** Zhou et al found that SARS CoV-2 utilizes hACE2 for cell entry like SARS-CoV and MERS-CoV.(8)**.**The entry process is mediated by the envelope embedded surface-located spike (S) glycoprotein.As previously discussed,virus S1 is divided into an N-terminal domain (NTD) and a C-terminal domain (CTD), both of which can function as a receptor-binding entity (RBD) **(Q. Wang et al., 2020).** In addition, entry requires S protein priming by cellular proteases, which entails S protein cleavage at the S1/S2 and the S2' site and allows fusion of viral and cellular membranes, a process driven by the S2 subunit **(Hoffmann et al., 2020).** The priming process is carried out by two cellular proteases;TMPRSS2 and Furin. Furin cleavage at the S1/S2 site may lead to conformational changes in the viral S protein that exposes the RBD and/or the S2 domain. TMPRSS2 is reported to cleave the SARS-CoV-2 S protein to enable the fusion of the viral capsid with the host cell to permit viral entry **(Hoffmann et al., 2020,Millet et al., 2020).**

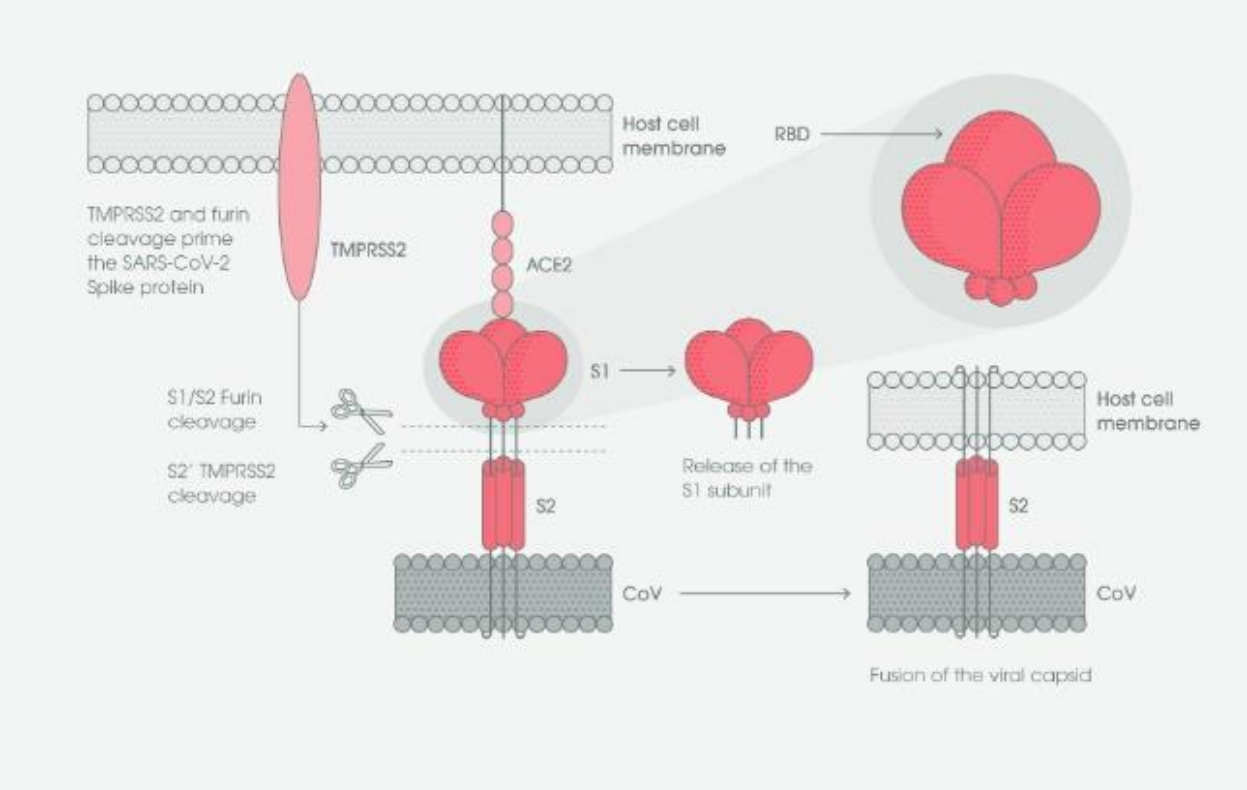

Figure 4: Schematic diagram of SARS-CoV-2 entry into host cell.

Research evidence suggests concerning SARS-CoV-2 that virus can also bind to cell surface molecules to gain cell entry other that hACE-2. Neuropathological analysis of human COVID-19 autopsies showed that neuropilin proteins that are expressed in neurons, provides an entry system for the virus into the nervous system **(Cantuti-Castelvetri et al., 2020).** The cleaved form of the SARS-CoV-2 S protein binds to both Neuropilin-1 and Neuropilin-2 to mediate host cell entry **(Cantuti-Castelvetri et al., 2020,Daly et al., 2020).** An earlier study suggested that the SARS-CoV-2 S protein is also able to bind to CD147 on the cell surface,thus enters the cell **(K. Wang et al., 2020).** Why diabetes is a factor for poor prognosis in cases of COVID-19 can be explained based on this fact that higher blood sugar facilitates CD147 expression **(Bao et al., 2010).** Moreover a structural modeling study indicated that SARS-CoV-2 can bind to sialic acid glycoproteins and gangliosides on the cell surface. Sialic acid is known to be expressed highly on the surface of all of the cell types targeted by SARS-CoV-2 including neuronal cells **(Roe, 2020).**

Following release of the viral genome in the host cytosol,a large polyprotein is translated from the positive-strand genomic RNA that undergoes a proteolytic processing to generate an RNA-dependent RNA polymerase.A full-length, antisense negative-strand template is generated by the action of this polymerase. Subgenomic mRNAs are then synthesized supposedly from subgenomic negative-strand templates. The hallmark of coronavirus transcription is the production of these subgenomic mRNAs that contain sequences corresponding to both ends of the genome.Viral structural proteins (S, E, and M) are translated from the subgenomic mRNAs,inserted into the endoplasmic reticulum and move to the endoplasmic reticulum-Golgi intermediate compartment(ERGIC). Packaging of genomic RNA is executed by collective copies of the nucleocapsid (N protein) into helical structures (riboncleoprotein complexes) in the cytoplasm and interact with hydrophobic M proteins (envelope protein) in the ERGIC that serve to direct assembly of the virion.Virion-containing vesicles budded from the membranes of the ERGIC are then transported via the constitutive exocytic pathway out of the cell **(V'kovski et al., 2020,M.N. Iqbal et al., 2020).**

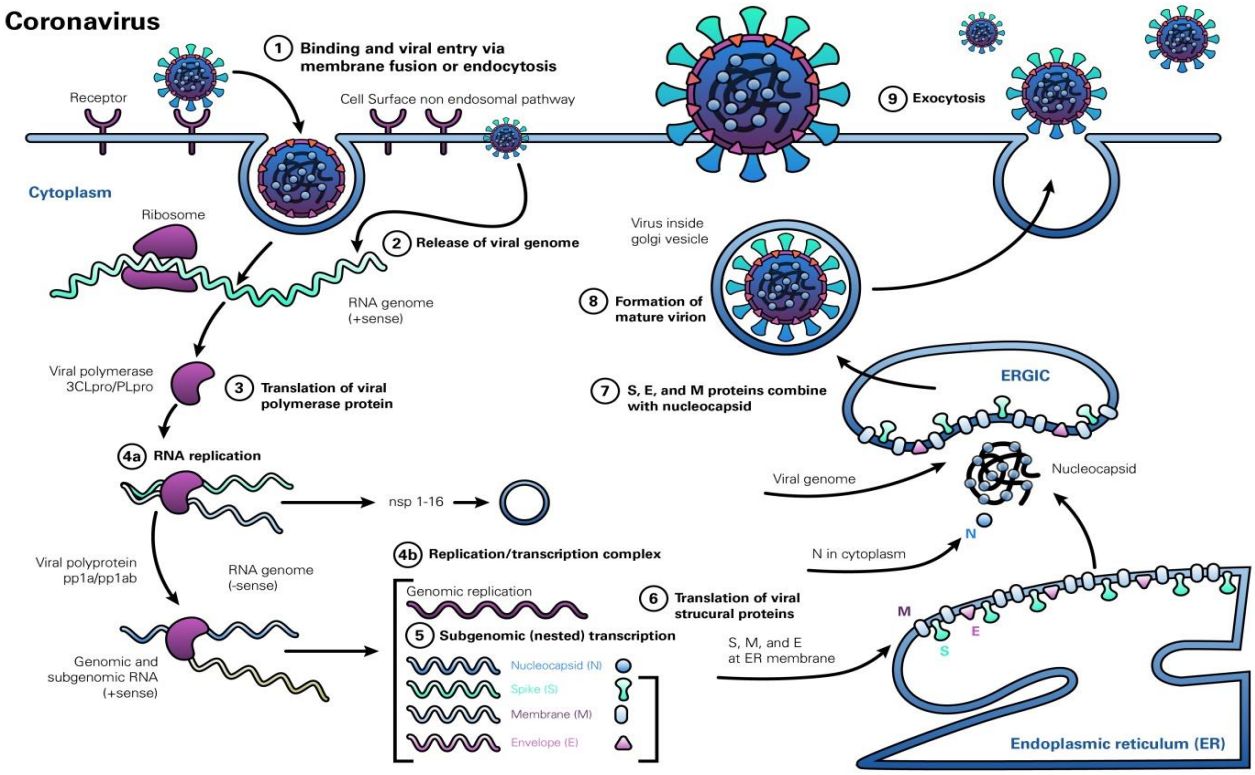

Figure 5: Diagram of SARS-CoV-2 replication.

Application of nanotechnology to fight battle against COVID-19

Preventive strategies for COVID-19 using nanotechnology:

Development of disinfectants and sanitizers:

Current advancement in nanotechnology exhibits a novel platform for the development of potential and efficacious disinfectant agents.A whole lot of nanoparticles are being used worldwide for their promising antiviral and antimicrobial activity. Dyshlyuk et al conducted a study on nanoparticles of zinc oxide and titanium dioxide as disinfectants.Result of this study demonstrated zinc oxide nanoparticle as a promising agent of antimicrobial substance **(Dyshlyuk et al., 2020).** Another metal object,silver nanoparticles comprise strong antibacterial, antifungal and antiviral potential to boost the host immunity by attacking pathogens (**Rai et al., 2014).** An Italian biotechnology company, The Nanotech Surface has used a special disinfectant developed based on titanium dioxide and silver ions for cleaning Milan's buildings during the period of COVID-19. As per the company manager, the antibacterial substance leaves the surfaces self strelizing for upto two years. Surfaces coated with nanomaterials such as silver, zinc oxide, and copper NPs oxidize and release ions with antimicrobial properties.These nanoparticles covering surfaces are also referred to as self-disinfecting and are potential candidates for the prevention of the spread of COVID-19.In addition to antiseptics UV light-activated nanophotosensitizers are also being used by many companies out there..One such example is mineral nanocrystal-based coating produced by NanoTouch.This nanoseptic yields a strong oxidation reaction in presence of light and kills pathogen keeping the surface (like door handles, elevator buttons,cell-phone) clean and safe **(Murphy et al., 2020, p. 999).**

Graphene is an another photoactivated particle that generates heat to disinfect clothes and filters **(Palmieri & Papi, 2020, p. 100883).** Graphene sheets and carbon nanotubes (CNT) share the characteristics of attaching viral membrane by forming hydrogen bonds and electrostatic forces.Based on this, air purifier devices can be developed to entrap infectious agents and killinf them by shrinkage in carbon-based fibers **(Brady-Estévez et al., 2008,Rashid & Ralph, 2017, p.99).** Besides,Yang et al performed a literature review on how some new elements such as silicone,glass,alumina ceramics and cellulose substrates have been superficially modified with

nanostructures to set up polyfunctional devices to remove contaminants from air **(Cardoso et al., 2020, p. 588915).**

Nanomaterial enabled PPE :

According the United States Centers for Disease Control and Prevention (CDC), transmission of SARS-CoV-2 occurs via respiratory droplets of infected persons from face to face contact primarily and, to a smaller extent, via contaminated surfaces **(Wiersinga et al., 2020, p. 782).** Hence comes the need of wearing protective clothes,wearing face masks;covering mouth and nose profoundly and, respirators. The blessing of nanotechnology can be utilized in the modification of personal protection equipment (PPEs) and in the development of more proficient face masks solving the current complications such as unavailability and appropriateness of PPE products,facemasks not fitting properly or unsuitable for restricting viral particles **(Conlon et al.,2014,Lustenberger et al.,2016).** One of the well_known respirator to fudge SARS-CoV-2 is N95 face mask with a efficiency rate 85 (pore size of around 300 nm) **(Bar-On et al., 2020).** A flexible nanoporous silicon based replaceable membrane can be used to get a N95 mask that is not only reusuable but also holds enhanced filtration efficiency **(El-Atab et al., 2020).** Recently a research team at the Korea Advanced Institute of Science and Technology (KAIST) declared on the development of a new nano-filtered face masks containing nanofibres that can be washed more than 20 times, without causing deformation in the nanomembrane structure **(Ullah et al.,2020).** In addition,application of nanoengineering provides new features to facemasks and lab aprons like wrinkle-freeness,static-elimination,stain-repellency,electrical conductivity even without affecting the material's breathability or flexibility.**(Yetisen et al., 2016)**

Another insight of nanotechnology into the field of textiles is producing hydrophobic PPE that prevents absorption of airborne droplets during sneezing.These hydrophobic lab aprons are made upon nanowhiskers consist of billions of hydrocarbons; 3-fold smaller than a cotton fibre **(Yetisen et al., 2016).** Other attractive nanomaterials for filters, face masks, and protective clothing, are copper iodide NPs and AgNPs. Zhong et al. developed a super hydrophobic d graphene oxide face mask that sterilizes on its own upon exposure to sunlight and recycling of these mask benefits the environment by desalinating seawater **(Zhong et al., 2020).** As Balagna et al (2020) reported,a crucial virucidal effect was observed on facial masks coated with compositing silver nanocluster/silica.This coating lessened SARS-CoV-2 titre almost to zero and

can be accumulated on particularly every kind of filtering media and even on metallic, ceramic, polymeric and glassy surfaces **(Balagna et al., 2020, p. 100006).** Last but not the least,researchers are trying to develop biodegradable PPE materials by exerting functionalized cellulose fibers and other biopolymers that holds promising antimicrobial activity to bring about a solution for the conventional plastic disposal complications **(Ma et al., 2018).**

Nanotechnology in the detection and diagnosis of COVID-19:

The recent development in detecting variations in human genome sequences have found an indispensable role in understading how genetic factors contribute to the development of disease and consequently new ways have been established to treat genetic-related conditions at early stages **(Wei et al., 2010).** Among the discovered types of genetic alternation diseases, sequence-specific mismatch dominates,although it is extremely hard to detect especially in case of single-nucleotide polymorphism (SNP) **(Yang & Rothman).** Therefore, better detection policies with operational simplicity are required for the containment of COVID-19. Nanotechnology being an efficient and thrifty tool is taking the root against SARS-CoV-2 by improving interactions between the sensor and the analyte, increasing detection limit and decreasing detection time **(Talebian et al., 2020).**

Nucleic acid tests based on polymerase chain reaction (PCR) is the current reference method to detect the presence of viral genome in samples.Nonethless, there remains a risk of false-positive or -negative results with PCR based detection. Qiu et al (2020) invented a dual-functional plasmonic biosensor combining the plasmonic photothermal (PPT) effect and localized surface plasmon resonance (LSPR) to provide an alternative solution for COVID-19 diagnosis.There device is integrated on a chip by two-dimensional gold nanoislands functionalized with complementary DNA receptors which is able to exhibit higher sensitivity toward the selected SARS-CoV-2 sequences and detect it precisely in a multigene mixture **(Qiu et al., 2020).** Besides,Protein-based tests (serology) are excellently accepted method in large-scale testing for the detection of viruses;based on the presence of specific viral antigens or corresponding antibody responses of the immune system.A research team has recently developed a colorimetric assay based on gold nanoparticles (AuNPs) modified with antisense oligonucleotides specific for two of theN-gene regions of SARS-CoV-2.This device allows detection of target viral RNA with a naked-eye in almost 10 min **(Moitra et al., 2020).** Additionally a diverse range of

nanomaterials for instance, metallic nanoparticles, polymeric nanoparticles, silica nanoparticles, carbon nanotubes, and quantum dots, are already used for virus detection (**Draz & Shafiee, 2018, Halfpenny & Wright, 2010).** Before using ,these nanomaterials are modified with biomolecules derived from the virus, for example DNA, RNA, antibody, antigen (hemagglutinin antigen H1N1), peptide or pentabody (avian influenza virus–pVHH3B) **(Campos et al., 2020).**

In addition to diagnosis of COVID-19,several biosensor molecules have been reported to date.Biosensors are devices that combine a sensitive biological recognition component and a physical transducer;transforming their result into a measurable readout in the form of electrical, thermal, or optical signals to detect analytes within solutions and bodily fluids.Nanotechnology are also an integral part of developing biosensors in search for new solutions to the current global pandemic.Table 01 provides an overview of the sensors developed for the detection of SARS-CoV-2,and other related corona viruses.

Table 01. Biosensors reported in the literature for the detection of close-related COVID19 viruses (SARS-CoV-1 and MERS-CoV) (Source: Palestino, G., García-Silva, I., González-Ortega, O., & Rosales-Mendoza, S. (2020). Can nanotechnology help in the fight against COVID-19? Expert Review of Anti-Infective Therapy, 18(9), 849–864. https://doi.org/10.1080/14787210.2020.1776115).

Table:01 . Biosensors reported in the literature for the detection of close-related COVID19 viruses

Biosensor description	**Target virus (MERS/SARS)**	**Probe**	**Detection approach**	**Main findings**

SPR chip with immobilized specific oligonucleotides of nine common respiratory virus	SARS-CoV-1	Oligonucleotide (DNA)	Refractive index signal enhanced by biotinstreptavidin interaction in labeled primers	Simultaneous identification of SARS-CoV-1 (2 nM), influenza A and B (5 nM, 1 nM), H1N1 (3 nM), PIV-1 (1 nM), PIV-2 (2.5 nM), PIV-3 (3.5 nM), RSV (3 nM), Adenovirus (0.5 nM)
Photo crystals (PCs)-based biosensor Chip	SARS-CoV-1	Surface envelope protein	Refractive index signal	Photonic crystal biosensor efficiently and effectively detected protein–protein, DNA–DNA and protein-metal interaction
Carbon nanotube field-effect transistor (FET)-based biosenso	SARS-CoV-1	Engineered antibody mimic protein (AMP	Conductance	Lower nanotube density offers higher sensitivity. Efficient detection of SARS nucleocapsid protein with a detection limit of 5 nM
Arch-shaped multi-target sensor: immobilized isothermal amplification enzyme and oligonucleotide primers onto a silicon microring resonator	MERS-CoV	Oligonucleotide (DNA > 50 bp)	Resonance wavelength	The detection limit was 10-fold more sensitive than that of real time reverse transcription-PCR. MERS-CoV was rapidly (20 min) detected in 20 clinical specimens

DhITACT-TR system	MERS-CoV	Oligonucleotide (ssDNA)	Fluorescence and naked eye	10 nt long target RNA strand was required for stable hybridization.
RCA microfluidic device: RCA process occurs at the surface of microbeads packed in microchannels leading to DNA hydrogel formation	MERS-CoV	Oligonucleotide (ssDNA)	Naked eye	Multiple detection of pathogens was achieved in 15 min with a limit of detection of 0.1 pM.
ESPS microfibers: multiplex antibody immunoassay test platform incorporating electrospun polystyrene	MERS-CoV	His-MERS-NP antigen protein	Fluorescence (FITCconjugated antiMERS-CoV NP Antibodies)	Detection limit resulted < 100 µg/mL for MERS-NP antigen alone and of 200 µg/mL when performing multiplex microfiber platform
Competitive electrochemical immunosensor based on an array of carbon electrodes (DEP) modified with gold nanoparticles	MERS-CoV	S1 protein	Square wave voltammetry	The immunosensor was effectively applied to spiked nasal samples and the low detection limit was of 1 pg/mL

S.aureus nanobioparticles	MERS -CoV	MER-CoV nucleoprotein	Agglutination test	The agglutination was caused by the reaction among IgG-MERS NP anti-bodies, protein A on the surface of one S. aureus nanobioparticle and the MERS NP-CBD bound with another particle
Dual-functional plasmonic biosensor combining PPT effect and LSPR sensing	SARS-CoV-2	Oligonucleotide (DNA)	Plasmonic resonance wavelength	The LSPR biosensor showed high sensitivity toward selected SARS-CoV-2 sequences with a LOD of 0.22 pM. Precise and effective detection of the specific target in a multigene mixture
FET-based biosensor (COVID-19 FET)	SARS-CoV-2	Specific antibody against SARS-CoV -2 S protein	Electrical response	The COVID-19 FET biosensor detected SARSCoV-2 in medium culture with a LOD of 1.6 × 101 PFU/mL and in nasopharyngeal swab samples from COVID-19 patients with a LOD of 2.42 copies/mL

Practice of nanomedicines to treat COVID-19

A.Nanoparticle selection to overcome conventional drug delivery limitations: The role of nanoparticle-based drug delivery system in overcoming obstacles affiliated with conventional drug therapies is unprecedented and therefore aroused extraordinary interest in the treatment of viral infections.According to Singh at el (2017) recent advances in nanomedicine such as ability to encapsulate or incorporate drugs with surface modification, targeted drug delivery (intracellularly or to specific cell populations), biocompatibility, and the ability to achieve slow and sustained drug release offer superior therapeutic potential, compared to conventional approaches.**(Singh et al., 2017)** Till date no specifically validated therapeutic is available for the treatment of COVID-19. Several drugs have been approved by Food and Drug Administration (FDA) as capable candidates to treat COVID-19 based on their effectiveness against other medical conditions, and against earlier strains of CoVs (such as SARS-CoV and MERS-CoV) **(Abd El-Aziz & Stockand, 2020, p. 104327,Nile et al., 2020)** However, these drugs often create side effects, due to their accumulation in off-target organs and most of them are poorly water-soluble, which reduces their successful use.**(Tabish & Hamblin, 2020, p. 100962)** Not only that,some of them are only effective when administrated in high concentrations that cause toxicity to host cells.**(X. Wang et al., 2020)** To improve the efficacy of antiviral treatment ,promising strategies to limit the toxicity as well as deliver drugs into targeted organs need to be established**. (Lembo et al., 2017)** Many studies showed that nanoparticles(NP) are able to improve the pharmacokinetics parameters of encapsulated antivtiviral drugs and create a better therapeutic efficacy with reduced side effects by decreasing drug concentration required for biological activity.**(Abo-zeid et al., 2018,McNeil, 2016, p. 1)** Moreover the physicochemical properties of nanocarriers enable the delivery of antiviral agents to their target specific sites **(Lembo et al., 2017)** and decrease the speed of the development of resistance through encapsulation. **(Campos et al., 2020)** This target specificity squeezes collateral damage to normal cells and tissue. The interplay between optical features and sizes of NPs cannot be tuned in the same way with other drug delivery approaches. **(Juliano, 2013)**

B.As a carrier of mRNA based therapeutics: Several biopharmaceutical companies are trying to develop a potential therapeutic candidate, mRNA-encoded neutralizing anti-SARS-CoV-2 monoclonal antibodies (MAbs) delivering directly to the mucosa of the respiratory tract and into

the lungs via nebulizers with NP aerosols for the treatment of SARS-CoV-2.Some companies followed the similar approach but the administration is done via intravenous infusion.But to get into the target cells,mRNA requires a carrier which will enable it to bypass the cell membrane. This is why,researchers have designed a delivery system that consists of lipid nanoparticles (LNP) that encapsulate the mRNAs coding for the MAbs.**(Sahin et al., 2014)** Additioally,the LNPs enhance their mucosal and cellular uptake and improve their biocompatibility. (adhm) Another mRNA-based potential therapeutic approach against coronaviruses is the use of small interfering RNA (siRNA).The function of siRNA is to significantly silence the expression of the desired gene against many diseases.**(Sohrab et al., 2021)** As coronaviruses are positive-sense single-stranded RNA (ssRNA) viruses, RNA interference could be a forcible approach to control the virus by silencing the viral mRNA at particular stages of infection.LNPs are proven delivery systems for siRNAs as they protect siRNAs from enzymatic degradation by RNAases,elevates their bioavailability, and deliver to target sites.**(Wan et al., 2013)**

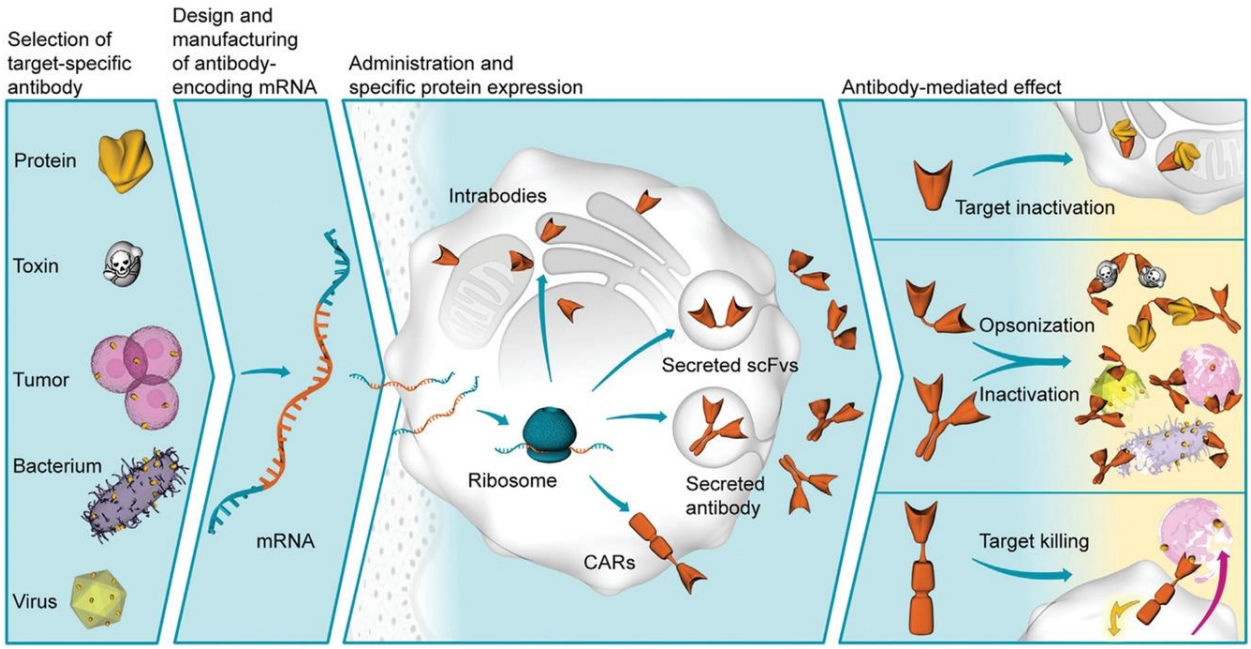

Figure 6: Schematic Illustration of mRNA-Based Antibody Treatment

In the first step, effective antibodies have to be raised or selected for the target of interest. The respective amino acid sequence can then be encoded in an mRNA designed to produce high

amounts of protein. Upon in vivo administration, typically using specific formulations for delivery and mRNA protection against degradation, transfected cells produce the encoded protein, which is not limited as to antibody format or localization. Depending on its mode of action, the mRNA-encoded protein finally triggers the desired therapeutic effect.(Source: Schlake, T., Thran, M., Fiedler, K., Heidenreich, R., Petsch, B., & Fotin-Mleczek, M. (2019b). mRNA: A Novel Avenue to Antibody Therapy? Molecular Therapy, 27(4), 773–784. https://doi.org/10.1016/j.ymthe.2019.03.002)

C.To alleviate cytokine storm: Dynamic upregulation of cytokine production in patients severy ill with SARS-CoV-2 has been demonstrated in clinical intervensions.As previously discussed, cytokine storm causes multiple-organ failure leading to deterioration of health and lastly, death. **(Ye et al., 2020b)** Leuschner et al (2011) in his studies ,shows usage of nanotechnology to mitigate cytokine storm produced in disease infected people. A chemokine receptor CCR2 is responsible for localization of inflammatory monocytes to injured tissue.Silencing of CCR2 messenger RNA in monocytes will avoids its accumulation in inflammatory sites.This is done by small interfering RNA (siRNA) encapsulated in lipidic nanoparticles.By this, control less recruitment of monocytes in injured sites was unraveled,with a promising result acquired in mice. **(Leuschner et al., 2011)**

Evidence collected over the past two decades points to cabalistic cohesion between inflammation and oxidative stress, both processes contributing to thrive one another,thereby establishing a protocol for the antioxidant management of acute inflammatory diseases was necessary**.(Biswas, 2016,Lugrin et al., 2014)** Dormont et al (2020) in his studies reported on development of multidrug nanoparticles for demolishing uncontrolled inflammation as well as oxidative stress in cells. Squalene, a natural lipid is conjugated to adenosine (Ad), an endogenous immunomodulator is produced to reduce pro-inflammatory cytokines and increase the levels of IL-10(interleukins function as immunotherapy).Further encapsulation of an antioxidant, α-tocopherol resulted in high drug loading, biocompatible, multidrug nanoparticles.These SQ-based NPs could be a milestone brainchild in the field of CVID-19 therapeutics as it holds significant potential for the antioxidant management of acute inflammatory diseases as well as paves a way for improved use of Ad as a proresolving pharmaceutical agent. **(Dormont et al., 2020)**

D.Role of Curcumin: Curcumin sets one fine example within the wide range of natural compounds that has potentiality to be used as a control of viral infections, including COVID-19.Recently Loutfy et al investigated the role of curcumin chitosan (CuCs) nanocomposite against hepatitis C virus genotype 4a.Their prepared nanocomposite demonstrated a powerful multitarget antiviral agent against HCV-4a that are able to inhibit 100% of viral entry and replication, and this proved competence on molecular and protein levels. **(Loutfy et al., 2020**) The antiviral activity of nanoparticles containing curcumin was because of disturbances in the fluidity of the virion membrane, but no changes in virion integrity were observed(how can nanotech) Also, curcumin exhibited antiviral activity against several viral infections, including hepatitis, influenza, Zikavirus, chikungunya virus and some sexually transmitted viruses. **(Campos et al., 2020)**

E.Development of a nanogel: Entry process of viruses into host cells is complex and initially begins with attachment to heparan sulfate (HS) proteoglycans on the cell surface.This is why blockage of initial interactions of viruses with cellular receptors has been a great deal of interest in antiviral research.The development of a nanogel which can seize the viable virus particles efficiently blocking their infection is hence an promising findings.Nanogels were seen to capture the viruses that tried to invade host cells through HS moieties with great robustness.**(Dey et al., 2018)** As SARS-CoV-2 follows a similar mechanism to infect host cell, this nanomaterial can play a potential role in the fight against the caused disease

F.As acarrier of combination drug therapeutics: The evaluation of drug combination process is an arresting solution to the unabated effects of COVID-19 pandemic; offering handful advantages like lesser dosages of the individual drugs,saves time,multiple therapeutic targets and, reduced drug resistance.**(Rayner et al., 2020)** Such combinations of drugs to treat COVID-19 are registered in the WHO landscape information. (Table-02) (source: Chauhan, G., Madou, M. J., Kalra, S., Chopra, V., Ghosh, D., & Martinez-Chapa, S. O. (2020). Nanotechnology for COVID-19: Therapeutics and Vaccine Research. ACS Nano, 14(7), 7760–7782. https://doi.org/10.1021/acsnano.0c04006)

Nanoparticles can work as an intrinsic carrier of combined drugs promising the complete potential of combination therapies.Shibata et al (2013) proposed the utilization of combined antiretroviral nanoparticles (cART NPs) as a classic treatment approach for the inhibition of

HIV-1 replication.A biodegradable polymer poly-dl-lactide-co-glycolic acid; PLGA was developed containing efavirenz (EFV),lopinavir and ritonavir by high pressure homogenization method.This method proficiently inhibited HIV-1 infection and transduction.**(Shibata et al., 2013)** This is one example on how nanotechnology can be used to facilitate combination drug therapies that are currently on trial.

Table 02. Combination Drug Treatments Proposed for COVID-19

Combination Description	Candidates	Status
protease inhibitors	ritonavir + lopinavir	under trial of COVID-19
non-nucleoside reverse transcriptase inhibitor + nucleotide reverse transcriptase inhibitor	emtricitabine + tenofovir	under trial of COVID-19
nucleoside inhibitor + protease inhibitor	ribavirin + ritonavir/lopinavir	clinical study of SARS NCT00578825
antiretroviral protease inhibitor + cobicistat (to improve bioavailability and t1/2)	darunavir + cobicistat	under trial of COVID-19
antiviral + type I interferons - signaling proteins made and released by host cells during viral infections	IFN (α, β, IFNα2a or rIFN-α2b or IFN-β1a) + ribavirin	clinical study of SARS, MERS
interferons - signaling proteins made and released by host cells during viral infections + antiviral + steroid hormones	IFN + ribavirin + steroids	clinical study of SARS
protease inhibitor + proteins	lopinavir + ritonavir + IFN +	clinical study of MERS

made and released by host cells + antiviral	ribavirin	
type I interferons - signaling proteins made and released by host cells during viral infections + immunosuppressant	IFN-β1a + mycophenolate mofetil	clinical study of MERS
protease inhibitors + proteins made and released by host cells	lopinavir + ritonavir + IFNβ1b	clinical study of MERS
synthetically developed recombinant type-I interferon + steroid hormones	IFN alfacon-1 + corticosteroids	clinical study of MERS

G.Carbon-dots in antiviral therapy: The possibility of carbon nano-dots to combat COVID-19 is enormous. Carbon dots are photoluminescent carbon nanoparticles;smaller than 10 nm in dimension that can be surfaced modified according to their function. **(Kotta et al., 2020)** On account of their cell membrane permeability, biocompatibility and,low cytotoxicity they are gaining eminent attention especially in the field of therapeutics.**(Lim et al., 2015)** Ting et al (2018) reported to develop an uniform method applying curcumin cationic carbon dots' (CCM-CDs) antiviral properties on coronaviruses.It was found that CCM-CDs was able to alter the structure of surface protein of the viruses,hence resisting viral entry.Not only that, the research suggested that it has the potential to inhibit the synthesis of negative-strand RNA of the virus,exocytosis of the virus,even more suppress viral replication by stimulating the production of interferon-stimulating genes (ISGs) and proinflammatory cytokines.**(Ting et al., 2018**) In a completely different experiment Loczechin et al.(2019) used carbon quantum dots (CQDs) combining with boric acid for the treatment of human coronavirus HCoV-229E infection.These resulted in the inhibition of the viral entry as well as viral replication.**(Łoczechin et al., 2019)** Besides,carbon dots are largely practised in biomedicine other than therapy like biosensing, bioimaging, photocatalysing and,electrocatalysing.**(Lim et al., 2015)** These properties along with

lesser toxicity make carbon dots a superior nanoparticulate to develop therapeutic delivery systems for COVID-19.

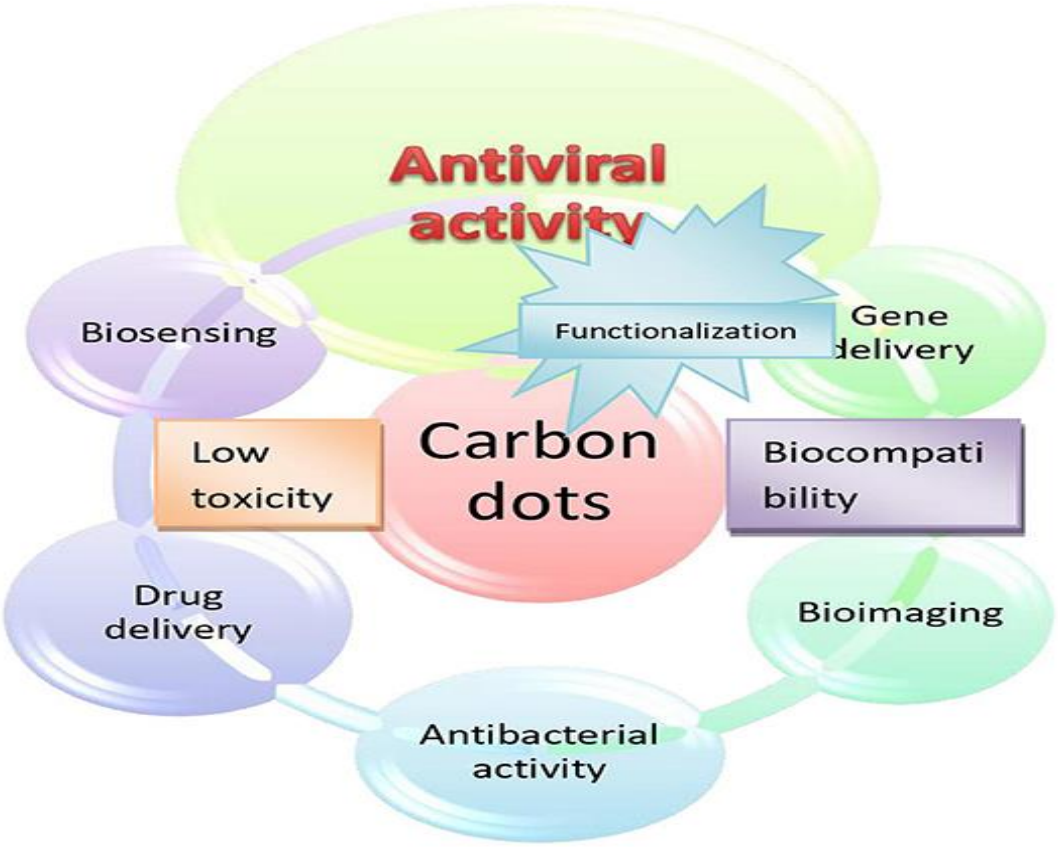

Figure 7: Various properties of carbon dots.

H.Anti-viral potential of metallic nanoparticles: The multifunctionality and unique physicochemical features have made metallic NPs as promosing therapeutic agents.**(Barabadi et al.,2019)** For instance, gold NPs (AuNPs) and magnetic NPs (MNPs) are mostly used nanoparticles owing to their eminent properties and features.**(Ibrahim Fouad,2021)** Idiosyncratic magnetic features have made MNPs to be utilized as contrast agents or as carrier of drugs in the field of cancer therapeutics.**(A. Singh & Sahoo, 2014)** Gold nanoparticulates are used as effective suppressors of Herpes simplex virus type 1while capping with mercaptoethanesulfonate (Au-MES NPs). **(Baram-Pinto et al., 2010)** Silver nanoparticles are

also a potential source of anti-viral therapeutics owing to their multi-target and multi-direction properties. **(Ibrahim Fouad,2021)** Graphene has exhibited an exceptional viral inhibition ability against heparan sulfate receptors, due to its potent binding with viruses through electrostatic interactions and redox reactions.**(Ziem et al., 2017)** The link between metallic NPs and SARS-CoV-2 is yet to explore.Ergo, a collaborative platform is needed to boost up clinical implementation of nanotheranostics to fight the battle against COVID-19. Table 03 shows anti-viral potential of some metallic NPs for viral inhibition and detection. (source: Ibrahim Fouad, G. (2021). A proposed insight into the anti-viral potential of metallic nanoparticles against novel coronavirus disease-19 (COVID-19). Bulletin of the National Research Centre, 45(1), 36. https://doi.org/10.1186/s42269-021-00487-0)

Table 03: Anti-viral potential of metallic NPs for viral inhibition and detection

Chemical composition and size (nm) of NPs	Characterization method	Virus	Application and function
Gold NPs (AuNPs) (15 nm)	Data not shown	Hepatitis C virus (HCV)	Gold (Au) NP probes (GNP) for ultrasensitive detection of HCV core antigen (HCVcAg)
Gold NPs (AuNPs) (30 nm) and Fe3O4 NPs (15–20 nm)	SEM,TEM	Hepatitis B virus (HBV) surface antigen	Immunosensor for surface antigen detection based on Hemin/G-quadruplex horseradish peroxidase-mimicking DNAzyme-signal amplification
Gold NPs (AuNPs) (15 ± 4 nm	Data not shown	Hepatitis B virus (HBV) surface antigen	DNA/AuNPs sensor: a sandwich assay and surface-enhanced Raman scattering (SERS) sensor for ultrasensitive detection of viral DNA

Gold NPs (AuNPs) (2 nm and 14 nm)	TEM	Influenza virus A (H1N1)	Multivalent Sialic-Acid-Functionalized AuNPs: anti-viral activity
Gold NPs (AuNPs) (35 nm)	Filter-based multimode microplate reader, TEM	Influenza virus A (H1N1)	A modified enzyme-linked immunosorbent assay (ELISA) with nanomaterials: anti-viral activity
Gold NPs (AuNPs) (2–50 nm	SEM	Hepatitis C virus	For direct detection of unamplified viral RNA in clinical specimens
Gold NPs (AuNPs) (19 nm)	TEM, DLS	Middle East respiratory syndrome coronavirus (MERS-CoV)	Detection method of MERS-CoV with a potential detection limit of 1 pmol/μL
Gold NPs (AuNPs) (40 and 100 nm)	DLS and TEM	Severe acute respiratory syndrome coronavirus (SARS-CoV)	AuNPs -adjuvanted S protein: to induce immune response (IgG)
Gold NPs (AuNPs) (5–20 nm)	XRD, SEM, AFM	Adenoviruses	AuNPs encapsulated in a SiO2 shell: Anti-viral activity
Gold NPs (AuNPs) (12 nm)	TEM, UV–Vis spectrophotometry, DLS	Influenza A virus	AuNPs—matrix 2 protein (M2e) conjugate coformulated with CpG: to induce immune response
Gold NPs (AuNPs) (18 nm)	CLSM	Influenza virus	AuNPs-based vaccination to enhance adaptive immunity

Gold NPs (AuNPs)	UV–Vis spectroscopy, TEM	Bovine viral diarrhea virus (BVDV)	Peptide nucleic acids (PNA)-AuNPs colorimetric detection assay of viral RNA
Gold NPs (AuNPs) (13 nm)	TEM, DLS	Influenza A virus	A colorimetric immunosensor based on AuNPs modified with monoclonal anti-hemagglutinin antibody (mAb)
Gold NPs (AuNPs) (10, 20, and 40 nm)	SEM	Influenza A virus	Immuno-AuNPs conjugates: for detection
Gold NPs (AuNPs) (12.92 nm)	UV–Vis spectroscopy, DLS	Dengue virus	Cationic AuNPs–siRNA complexes: in vitro anti-viral activity
Silver NPs (AgNPs) (30–50 nm)	Data not shown	Human immunodeficiency virus 1 (HIV-1)	Therapeutic (anti-viral) action at an early stage and at post-entry stages
Silver NPs (AgNPs) (13, 33 and 46 nm)	TEM, SEM	Herpesviruses (HSV-2) infectivity	Tnnic acid modified AgNPs: Size-related in vitro and in vivo anti-viral activity
Silver NPs (AgNPs) (33 nm)	TEM	Herpes simplex virus (HSV) type 1 and 2	Tannic Acid/ AgNPs-Based Mucoadhesive Hydrogel: anti-viral activity
Silver NPs (AgNPs) (5- 25 nm)	High-resolution transmission and field-emission scanning electron microscopes	Non-Enveloped (feline coronavirus (FCoV)) and Enveloped (bursal disease virus (IBDV)) Viruses	Graphene–Silver Nanocomposites: anti-viral activity

Silver NPs (AgNPs) (10 nm)	TEM	Influenza virus A (H1N1)	Anti-viral activity
Silver NPs (AgNPs) (3.5, 6.5, and 12.9 nm)	SEM and TEM	Influenza virus A (H1N1)	AgNPs/chitosan (Ch) composites: anti-viral activity
Silver NPs (AgNPs) (7–20 nm)	UV–Vis spectrophotometry, Nanoparticle tracking and analysis, TEM	Herpes simplex virus and human parainfluenza virus type 3	Smaller-sized AgNPs: anti-viral activity through decreasing viral replication
Silver NPs (AgNPs) (4–9 nm)	UV–Vis spectrometry, TEM, EDX- FE-SEM	Poliovirus and non-enveloped viruses	Electrochemical –synthesized AgNPs: anti-viral activity
Silver NPs (AgNPs) (11.4 nm)	TEM	Adenovirus type 3 (Ad3)	In vitro anti-viral activity
Silica NPs (SiNPs) (200 nm)	TEM, SEM	Porcine circovirus type 2 (PCV2)	Hollow mesoporous silica nanoparticles (HMSNs): to act as a protein delivery system or vaccine carriers
Silica NPs (SiNPs) (50–70 nm)	FESEM, FTIR, TGA	Human immunodeficiency virus (HIV)	Silica NPs-based Immunoassay (SNIA): for detection using time resolved fluorescence- enhanced sensitivity
Silica NPs(SiNPs) (150–200 nm)	DLS, TEM	Herpes simplex virus (HSV) infections	Glycosaminoglycans (GAG) mimetic functionalised solid and mesoporous SiNPs (MSNs and SSNs): acting as viral binding/entry

			inhibitors
Iron oxide NPs (IONPs) (10–15 nm)	HR-TEM, DLS-zeta, XRD, FTIR	Pandemic influenza strain A/H1N1/Eastern India/66/PR8-H1N1	Inhibition of virus growth
Iron oxide magnetic NPs (MNPs) (90 ± 30 nm)	TEM, XRD	Influenza A virus	An assay combining efficient magnetic separation and MALDI-TOF MS: For detection
Iron oxide NPs (IONPs) (103 ± 2 nm)	Malvern's zetasizer-ZS90	Zika Virus	Magnetic relaxation-sensitive nanoparticles (MRNPs): Magnetic Nanosensors for detection
Zinc oxide NPs (ZnONPs) (20–50 nm)	ICP-MS, XRD, TEM, FE-SEM	Influenza virus A (H1N1)	Anti-viral activity
Zinc oxide (ZnO)-nanostructures (diamters:200 nm to 1 µm; arm lengths:5 µm to 30 µm)	SEM	Herpes simplex virus type-2 (HSV-2)	ZnO tetrapod micro-nanostructures synthesized by flame transport approach: anti-viral activity
Graphene oxide(GO) (127.7 nm)	UV–vis spectroscopy Raman spectroscopy	Respiratory syncytial virus (RSV)	Curcumin functionalized GO: anti-viral activity
Titanium dioxide (TiO2) (4–10 nm)	EM	Influenza Virus	Anti-viral activity

Ceria NPs (6 nm)	TEM	Influenza virus	Nano-ceria aqueous sol containing no stabilizer: to enhance immune response
Selenium NPs (SeNPs) Se@ZNV: 82 nm	TEM, EDX, FTIR, XPS	Influenza virus A (H1N1)	Zanamivir modified SeNPs (Se@ZNV): anti-viral activity

Nanotechnology being a mode of delivery for CRISPR/CAS9

Clustered regularly interspaced short palindromic repeats-associated protein (CRISPR/Cas9) system is a revolutionary tool for editing gene with high precision and potential,used in gene therapy.CRISPR/CAS9 gene editing has been an exclusive alternative to be explored in the search for containment of SARS-CoV-2. Researcherrs have developed a master plan where Cas13d RNA endonuclease along with guide RNA have been used to inhibit and degrade SARS-CoV-2 viral genome. **(Abbott et al., 2020)** Several recent studies have focused on how CRISPR based gene editing tool can inhibit viral insertion and replication inside host cells and gained promising results], making this approach to be further explored for application against COVID-19. **(Nguyen et al., 2020, Tanaka et al.,2020)**

CRISPR/CAS9 are needed to insert into the cells and are inserted generally as a form of plasmids,mRNA or ribonucleotide proteins.The most common delivery system of CRISPR/CAS9 includes viral vectors,but it induces insertional mutagenesis,immunologic responses and have lesser cloning capacity. Since physical delivery methods are not supposed to carried out in vitro, chemical delivery methods require extensive optimization to improve their efficiency in vivo and, naked DNA delivery is not an option, the nontoxic, non-viral delivery of CRISPR/Cas9 components are in urgent need.**(Rohiwal et al., 2020,Yip, 2020)** Nanotechnology can play an indispensable role in contributing with new delivery alternatives for the exploitation of CRISPR-based systems.**(Givens et al., 2018)** For instance, a delivery vehicle based on gold nanoparticles attached to DNA and functionalized with cationic endosomal disruptive polymers

are able to deliver Cas9 ribonucleoprotein with high efficiency in vitro.**(Deng et al., 2019)** Another very effective CRISPR/Cas9 genome editing in vitro and in vivo is usage of bioreducible lipid/Cas9 messenger RNA (mRNA) nanoparticle.These technique edits genomic information inside the cell as fast as 24h post mRNA delivery. **(Lee et al., 2017)** Rohiwal et al proposed a in vitro delivery system using polyethylenimine (PEI) magnetic nanoparticles (MNPs) though further studies are needed to check whether this can be used in in vivo conditions.**(Rohiwal et al., 2020)**

Nanotechnology Perspective for COVID-19 Vaccine

Nanotechnology has much to offer to the fight against COVID-19 since it holds advantages of nano-sized range, high antigen loading,increased immunogenicity, controlled antigen presentation,more retention in lymph nodes and promote patient compliance by a lower frequency of dosing. Nanovaccine induces both cell-mediated and antibody-mediated immunity rendering long-lasting immunogenic memory and can alleviate the need of booster doses required by conventional vaccines.**(Bhardwaj et al.,2020)**

On the vaccine front, Moderna,in collaboration with Vaccine Research Center at the U.S.National Institutes of Health, has developed the mRNA-1273 vaccine which is a lipid nanoparticle–encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of 2(SARS-CoV-2). **(Baden et al., 2021)** The WHO Strategic Advisory Group of Experts (SAGE) on Immunization has already issued Interim recommendations for use of the Moderna vaccine against COVID-19 in people aged 18 years and older**.(The Moderna COVID-19 (MRNA-1273) Vaccine: What You Need to Know, 2021)**

Another wonderful frontline vaccine against the deadly SARS-CoV-2; designed by Pfizer and sponsored by BioNTech is BNT162b2.This is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. Polack at el (2020) published a study in the New England Journal of Medicine, that shows vaccine efficacy between the first and second doses was 52% (95% credible interval 29.5% to 68.4%), with 39 cases of covid-19 in the vaccine group and 82 cases in the placebo group.Right after the second dose vaccine efficacy rose to 95% (90.3% to 97.6%),

with eight covid-19 cases reported in the vaccine group and 162 cases in the placebo group.The vaccine has already been approved by FDA (the Food and Drug Administration) to be rolled out to healthcare workers and people over 80.**(Polack et al., 2020, Mahase, 2020)**

A vaccine candidate formulating the full-length S protein of SARS-CoV-2 combined with saponin-based Matrix-M™ adjuvant has been developed by Novavax and is currently in Phase 3 clinical trials (NCT04368988).It has been demonstrated that the Matrix-M™ adjuvant stimulates the entry of APCs (Antigen presenting cells) into the injection site, which enhances the antigen presentation in local lymph nodes, increasing the immunological response.**(Magnusson et al., 2018, "CEPI Commits $384 Million to Novavax's COVID-19 Vaccine," 2020)** The company said that this Novavax vaccine appeared to be 86% effective against a new variant of the virus first reported in Britain and 60 per cent effective against the variant circulating in South Africa, The efficacy against the original strain of virus that causes COVID-19 is thought to be around 95.6 per cent. (1)

Furthermore,liposome-based vaccines targeting coronaviruses might be another potential candidate to develop vaccines against SARS-CoV-2.Kohyama at el (2009) attempted to identify HLA-A*0201-restricted CTL (cytotoxic T lymphocytes) epitopes derived from a non-structural polyprotein;pp1a of SARS-CoV and got an efficient CTL-based vaccine candidate against SARS.**(Kohyama et al., 2009)** A similar approach targetting N protein peptides of SARS-CoV led to the successful induction of CTLs responses in mice. (90)Moreover,liposome-based complexes have also been implemented for immunization aiming to generate monoclonal antibodies against MERS-CoV.(91)It is to be mentioned that one of the prominent vaccines under development against SARS-CoV-2 is based on liposomes that contain an mRNA encoding for the prefusion stabilized spike protein 2019-nCoV (mRNA-1273**)** Table 3 summarizes diverse platforms and nanotechnology approaches for COVID-19 vaccines currently under investigation.(Source :Ruiz-Hitzky, E., Darder, M., Wicklein, B., Ruiz-Garcia, C., Martín-Sampedro, R., del Real, G., & Aranda, P. (2020). Nanotechnology Responses to COVID-19. Advanced Healthcare Materials, 9(19), 2000979. https://doi.org/10.1002/adhm.202000979)

Table-3.Nanotechnology approaches for COVID-19 vaccines currently under investigation.

Vaccine platform	Nanotechnology	Advantages
RNA	LNP-encapsulated mRNA or self-amplifying RNA encoding SARS-CoV-2 glycoproteins, the receptor binding domain or encoding VLP	Protection RNA from RNases; adjuvant effect; induction of potent T helper response and high number of germinal center B cells; production of high affinity neutralizing antibodies; induction of local innate immunity
Subunit vaccines (CoV-2 recombinant proteins, peptides	Full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M; saponine-based adjuvant, cholesterol and phospholipid particle	Stimulates strong and long-term humoral and cellular neutralizing immune responses to SARS-CoV-2 S-protein, reduces the antigen dose
	Capsid VLP display of SARS-CoV-2	Generates dense antigen display and elicits strong neutralizing antibody responses, high safety and efficacy
	Peptide antigens formulated in LNP	Allows a specific, robust, and sustained humoral immune response to non-overlapping neutralizing epitopes of the spike-protein; high safety profile
	Recombinant-protein, nanoparticles (based on spike-protein and other epitopes)	Induces strong neutralizing antibodies
	Adjuvanted microsphere peptide	Induces a strong immune response; generates neutralizing antibodies
	ADDomerTM multiepitope display (VLP); self-assembling protein-based nanoparticles encapsulating multiple peptide antigens	Trigger B cell receptor clustering and cross-presentation inducing a strong immune response

CONCLUSION

COVID-19 is the most awe-inspiring humanitarian disease the world has witnessed in the past few decades.The outbreak of SARS-CoV-2 from a seafood market of China highlights the mystic virus repository in wild animals and their ability to spill over into human populations once and again.The pandemic has already reached the pinnacle and it is high time we considered the blessings of nanotechnology to fight this mighty battle against COVID-19.

In this review,focus has been given on how nanoparticles play crucial roles in PPE things such as masks,disinfectants,lab coats and how it may assist the diagnosis,therapeutics and vaccine development against the novel coronavirus respectively.There lies a possibility to get new antibody-including and monoclonal counteracting agents as the information about SARS-CoV-2 is progressing promptly.

Although it is to keep in mind that nanotechnology application has some bottlenecks like what might take place when these nanotheranostics would finally be administered to an animal model or what would be the doses for viral inhibihition, the lack of standardized protocols for physicochemical and biological characterization of nanomaterials and many others.However it can be said undoubtedly that with more R&D and broad understanding of SARS-CoV-2,nanotechnology will revolutionize the battle against COVID-19,not to mention other posterior viral diseases.

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