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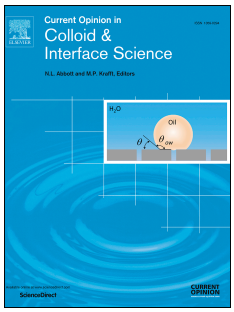

Biomolecular interactions with nanoparticles: Applications for COVID-19

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PII: S1359-0294(21)00045-5

DOI: https://doi.org/10.1016/j.cocis.2021.101461

Reference: COCIS 101461

To appear in: *Current Opinion in Colloid & Interface Science*

Received Date: 26 February 2021

Revised Date: 31 March 2021

Accepted Date: 7 April 2021

Please cite this article as: Farouq MAH, Al Qaraghuli MM, Kubiak-Ossowska K, Ferro VA, Mulheran PA, Biomolecular interactions with nanoparticles: Applications for COVID-19, *Current Opinion in Colloid & Interface Science*, https://doi.org/10.1016/j.cocis.2021.101461.

BIOMOLECULAR INTERACTIONS WITH NANOPARTICLES: APPLICATIONS FOR COVID-19

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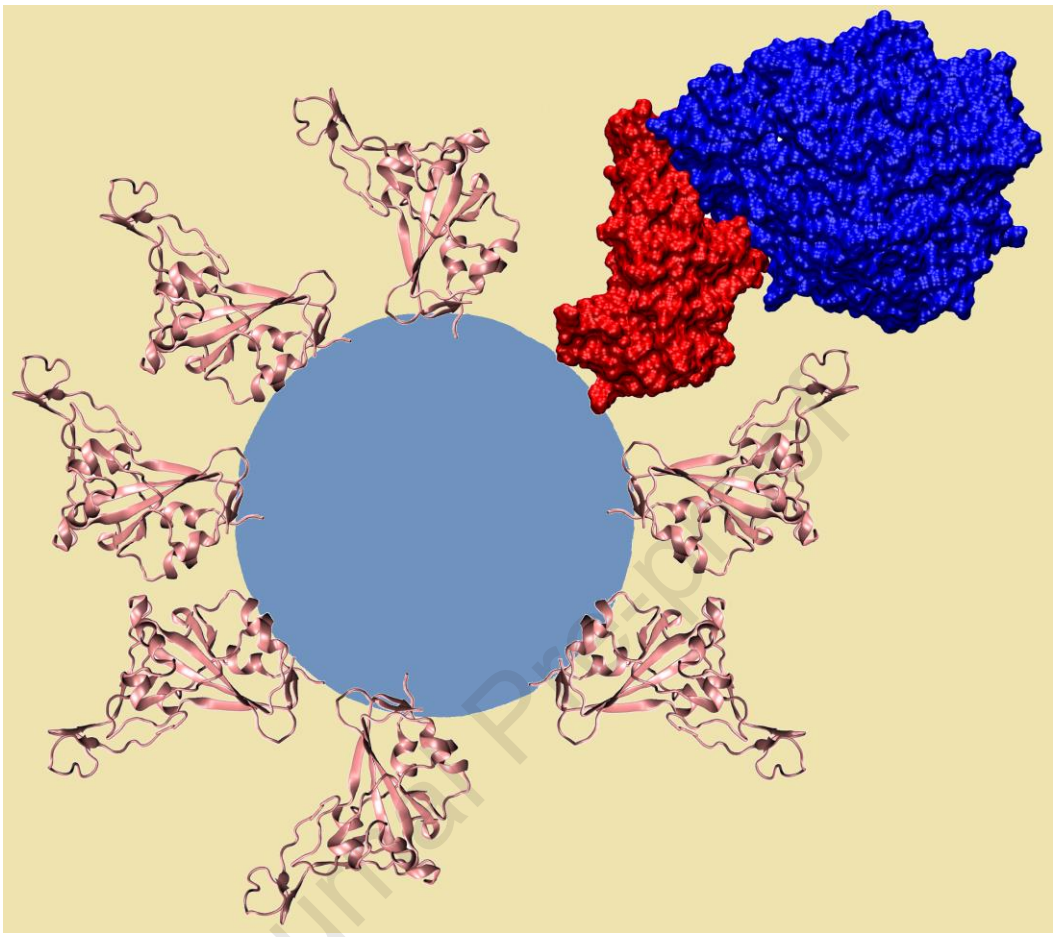
TOC Graphical Abstract



Schematic representation of the SARS-CoV-2 spike protein receptor binding domain decorating a nanoparticle. The proteins are shown as a secondary structure coloured in pink, while one of them is represented as a red surface complexed with the ACE2 receptor, which is shown in dark blue.

ABSTRACT

Nanoparticles are small particles sized 1 to 100 nm, which have a large surface to volume ratio, allowing efficient adsorption of drugs, proteins and other chemical compounds. Consequently, functionalised nanoparticles have potential diagnostic and therapeutic applications. A variety of nanoparticles have been studied, including those constructed from inorganic materials, bio-polymers, and lipids. In this review, we focus on recent work targeting the SARS-CoV-2 virus that causes COVID-19. Understanding the interactions between coronavirus-specific proteins (such as the spike protein and its host cell receptor ACE2) with different nanoparticles paves the way to the development of new therapeutics and diagnostics that are urgently needed for the fight against COVID-19, and indeed for related future viral threats that may emerge.

Keywords: nanoparticles, COVID-19, *SARS-CoV-2*, proteins, therapeutics, diagnostics

1. INTRODUCTION

Nanoparticles (NPs) are very small materials with a dimension between 1 and 100 nm. Their key physicochemical properties include a high surface area to volume ratio, solubility, surface topology/morphology and controllable aggregation, making them suitable for application in a variety of commercial and domestic sectors including electronics, catalysis, environment, imaging, energy, automotive and healthcare (1). There are various types of NPs, from inorganic materials such as gold, silica, graphene, and iron oxide, to organic materials where the main groups include liposomes, micelles, protein/peptides, and dendrimers. They are particularly useful in healthcare applications, mainly due to their high capacity for adsorbing biomolecules (2).

Pharmaceutical nanotechnology is the development of therapeutic materials and devices at a nanometre scale, and there are several advantages to exploiting NPs in drug delivery. These include, but are not limited to: (i) improvement in the solubility of certain drugs; (ii) controlled, sustained release of drugs for a long-term effect; (iii) reduction of the side effects of some drugs; (iv) targeting of specific cells; (v) administration routes; and (vi) delivery of drugs in a secure manner, so that they are protected from degradation in the body and can effectively reach the target cells intact (3). NPs can display efficient adsorption of proteins, drugs molecules, and a variety of other chemical compounds. Therefore, NPs can carry a varied cargo load (4), making them efficient not only for drug delivery, but also diagnostic and therapeutic applications.

In this review, we explore how NPs have been used to develop approaches to tackling COVID-19, focusing on the interactions between NPs and adsorption of molecules such as proteins and drugs. We start with a brief overview of NP properties and their potential anti-viral applications. We then review the SARS coronavirus (*SARS-CoV-2*) that causes COVID-19 and its proteins that are the targets for new technologies, before turning to the various types of NPs that can be used as the basis for these technologies.

Alternative approaches to treating COVID-19, for example by repurposing drugs that were previously successful against other viruses, is discussed, followed by an overview of developments in diagnostics. We finish the review with a summary and forward look as to how understanding the interactions between the different molecules and NPs could be used to rationally design new technologies to help tackle this pandemic and future coronavirus disease.

2. Nanoparticle-biomolecule interactions and applications

2.1. Physicochemical Properties

Selective and targeted delivery of modified NPs could enable specific detection and even destruction of viruses. To ensure this happens efficiently, it is important that the NPs are correctly optimised to ensure maximum efficacy and correct bioavailability, as well as negating any toxic effects, particularly those related to the formation of reactive oxygen species (ROS) (5). Furthermore, the rate of cellular uptake of the NPs depends on their physicochemical properties and the membrane characteristics at the site of interaction (6).

The key properties of NPs (**Figure 1**) make them ideal for a variety of effective systems. They can be porous or even hollow, and are often amenable to surface chemistry modification. Proteins adsorbed on NPs normally form a dynamic corona, and protein conformational changes associated with the adsorption influence the overall *in vivo* bioreactivity (7). The nature of NPs can influence the folding and unfolding properties of the protein, and by tuning the properties of the NPs, it can open new prospects in producing biologically active molecules. Thus, understanding the properties of the corona is essential (8). The interactions between NPs and a particular protein can utilise a noncovalent route, with the solvent having a critical role to facilitate the interaction (8). Consequently, it is vital to utilise a solvent *in vitro* that mediates the same interactions *in vivo* (9).

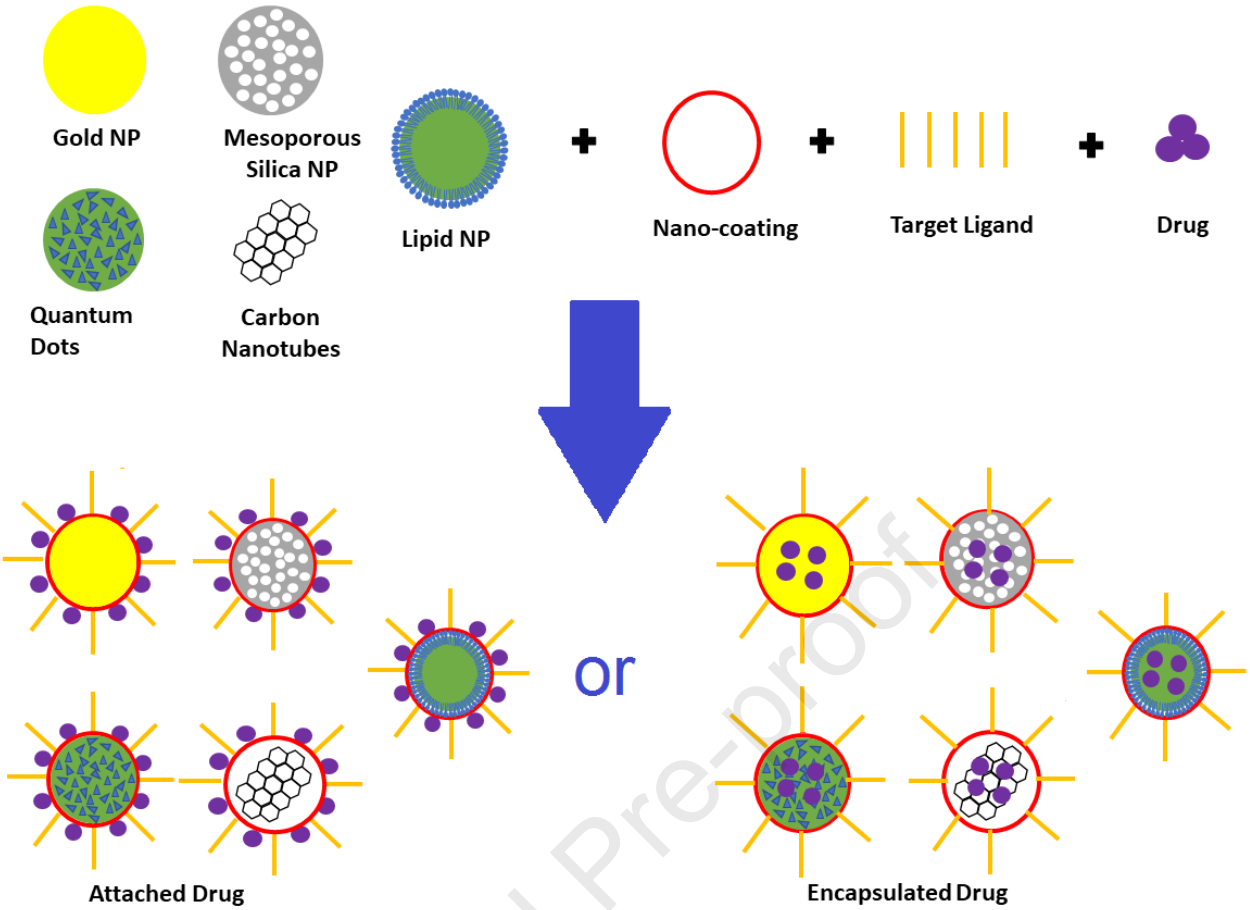


Figure 1: A schematic diagram showing drug loading options in NP targeted drug delivery.

The biodegradation of NPs also requires attention, as uniform bio-distribution kinetics and sustained drug release are key elements in the drug design process. Absorption, distribution, metabolism and excretion are pharmacokinetic features linking directly to the nature and profile of these systems, and it is therefore crucial to account for all these factors when designing a nanoparticulate therapy (10).

2.2. Anti-viral applications

Several inorganic NPs have been explored previously for their applications in drug delivery for viral infections. ***Gold*** NPs have a particular advantage in nano-vaccines as they can function as adjuvants (compounds to boost an immune response) in immunisation. For example, their use was investigated against *influenza A* virus, to combat mutations which made the virus resistant to existing anti-viral drugs (11). ***Silica*** NPs were investigated as a vaccine platform against *human immunodeficiency virus*

(HIV) (12), and ***Quantum dots,*** which have excellent sensing properties, can be used for anti-viral therapeutics as well as for detection and diagnosis (13).

Silver NPs have also been investigated for their anti-viral activity (14) (15). Anti-viral activity against *Peste des petits ruminants* virus depends on the NP interaction with virion surface, and this interaction impairs viral entry into target cells (14). These NPs may lead to better anti-viral activity when used in conjunction with bronchodilators in the lungs, and this technology could have promising applications in treating COVID-19 patients (15).

Several organic NPs have also been used in pharmaceutical applications, e.g. ***Cyclodextrin*** NPs, which are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. Garrido *et al.* (16) suggested the use of cyclodextrins against COVID-19. These NPs maybe particularly helpful due to their physical properties with polar hydroxy groups oriented specifically, allowing increased solubility and decreased toxicity of the associated drug. Furthermore, they are highly biocompatible, meaning they do not generate an immune response. ***Lipid*** NPs (LNPs), often used in novel pharmaceutical formulations, are readily integrated in medicines. This is due to their high biocompatibility, low toxicity, ability to cross membranes and seamless integration with hydrophobic/hydrophilic drugs.

NPs can be readily made with a similar size to the virus, and may interact with proteins associated with the *SARS-CoV-2* virus, disrupting viral replication and disease prognosis (17). The use of NPs against *SARS-CoV-2* has tremendous potential due to their specific properties including: i) precise targeting of cellular entry pathways; ii) targeted binding to the viral genome; iii) modulation of viral transcription; iv) triggering the production of ROS; and v) activation of signalling pathways at a mitochondrial level (18).

Tabish (18) explored the multivalent nature of nanomedicines and how this may be particularly useful in the fight against COVID-19. Multivalent NPs have several advantages over standard monovalent drugs, including a high density of binding sites

on each NP, the ability to form multivalent ligand receptor pairs, multi-fold RNA hybridisation, and the transformation of inactive NPs into multivalent conjugates (18). Multivalency may work against *SARS-CoV-2* effectively with cell entry through receptor-mediated endocytosis (19). Hassanzadeh (20) also suggested the use of multivalent NPs against COVID-19. Given the similarities in shape of synthetic NPs and *SARS-CoV-2*, they could be particularly useful for investigation with drug repurposing, enhancing properties of existing drugs and compounds against COVID-19. However, caution is required, since *SARS-CoV-2* may induce a hyperinflammatory response, driven by a dysregulated macrophage response (21). Therefore, it is important to look at the properties of any material to make sure it does not interact negatively *in vivo*.

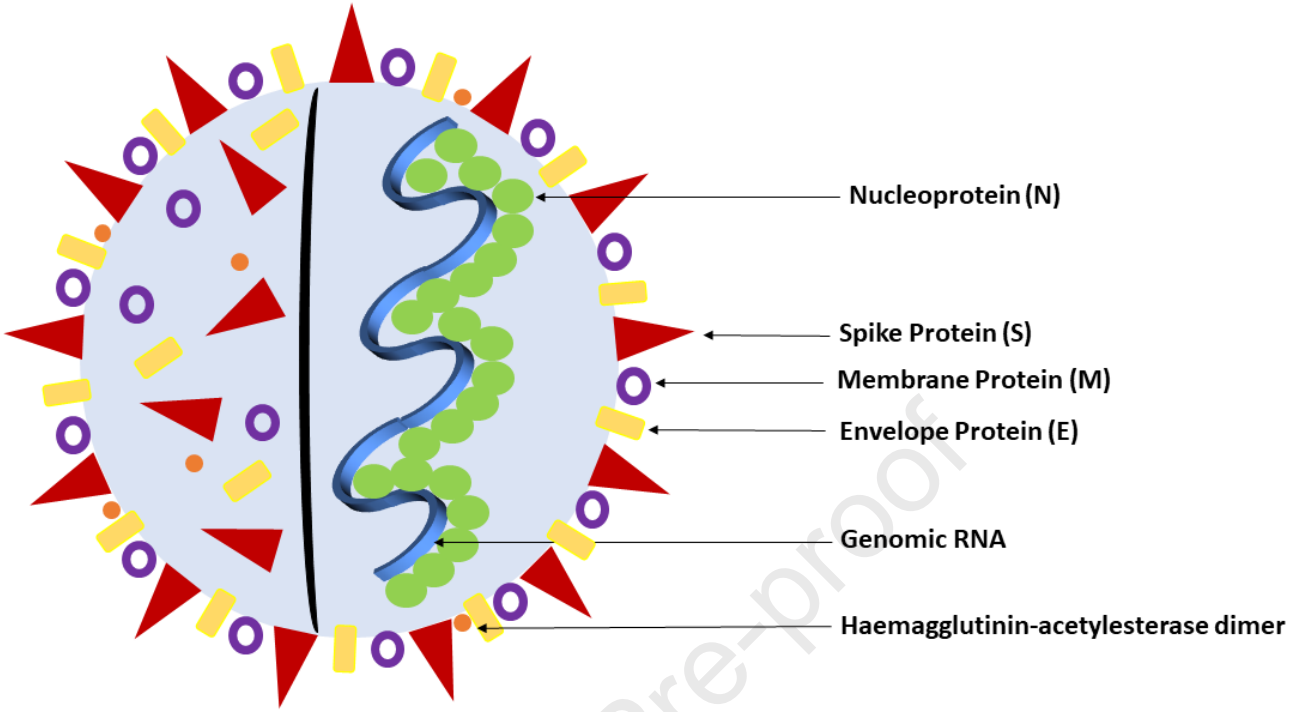
3. SARS-CoV-2

3.1. Description of the virus and its function

SARS-CoV-2 is spread predominantly from person to person, by droplets generated when an infected person coughs, sneezes or talks. Infection may also occur by touching contaminated surfaces and then the face without first washing hands, and the faecal-oral route may also be a source of transmission for the virus (22). The base symptoms include fever, cough, shortness of breath, fatigue, and loss of taste and/or smell. Depending on other factors such as infection level, age and ethnicity, the symptoms may be extended to include headache, haemoptysis, or diarrhoea. This highlights the severity of the virus, which can be fatal (23). Therefore, the development of a new treatment for this virus is a priority for researchers globally.

Analysis of the genomic sequence of *SARS-CoV-2* (24) shows there are at least six open reading frames (ORFs), which are segments of an RNA molecule that can be translated, allowing production of four main structural proteins: a Spike protein (S), Envelope protein (E), Membrane protein (M), and Nucleocapsid protein (N). There is also the viral haemagglutinin-acetylesterase (HE) glycoprotein receptor, as illustrated in **Figure 2**. The M and E proteins are involved in virus morphogenesis and assembly

(25). The N protein guards the RNA inside the M and E proteins, and the S protein is on



the outside and the focal point of infection.

Figure 2: Diagram showing the structural proteins of the *SARS-CoV-2* virus.

3.2. Potential Biomolecular Targets

The S protein is an important therapeutic and diagnostic target, as it is responsible for entry into and infiltration of the host cell. It is a homotrimer with two domains, S1 and S2 on each monomer. Analysis of these monomers shows they are highly glycosylated (26), protecting the protein from the biological environment and allowing evasion from the host immune system. The S1 subunit contains the receptor binding domain (RBD) that binds to the peptidase domain of angiotensin-converting enzyme 2 (ACE2) **(Figure 3),** a cellular receptor expressed on several cell types in human tissues, and this allows entry of *SARS-CoV-2* into the cell (27).

Upon cell entry, two ORFs, 1a and 1b, translate to two polypeptides (1a and 1ab) and this further encodes two proteases, the main protease (M^{pro}), also known as the chymotrypsin-like cysteine protease ($3CL^{pro}$), and papain-like protease (PL^{pro}) (28).

These represent significant drug targets, since inhibition of these will stop production of proteins that are critical to viral transcription and replication (29-31).

The S1 subunit allows entry of the virus into the host cell, and inhibition of this will block the protein from interacting with the ACE2 receptor (32). For example, immunoadhesins have been investigated for their interactions with the S protein through MD simulations (33). Another potential target for therapeutics development is transmembrane protease serine 2 (TMPRSS2) found on host cells (34). It cleaves (primes) the S protein into its subunits to enable cell entry, and inhibition of this process may prevent the initial entry of the virus.

High density lipoproteins (HDLs) are particles consisting of several proteins which transport all fat molecules around the body. HDL-scavenger receptor B type 1 (SR-B1) is a cell surface HDL receptor, which has been shown to facilitate ACE2-dependent entry of *SARS-CoV-2*, and further enhance uptake and increase rate of virus entry (35). Wei *et al.* (35) suggested that blockage of the cholesterol binding site on the S1 subunit or treatment with SR-B1 antagonists inhibits HDL enhanced *SARS-CoV-2* infection. Therefore, SR-B1 could also potentially be a target for therapeutic designs. Patel *et al.* have also suggested HE as a target (36) to inhibit the virus invasion mechanism.

The residues responsible for the interaction between the S protein and the ACE2 receptor have been investigated by Veeramachaneni *et al.* (37). This information is important for designing any medicine, since the residues required for interaction with the target should remain free to bind to the therapeutic molecule, to allow effective inhibition. Their analysis has identified the key residues that interact with the ACE2 receptor (see **Figure 3**).

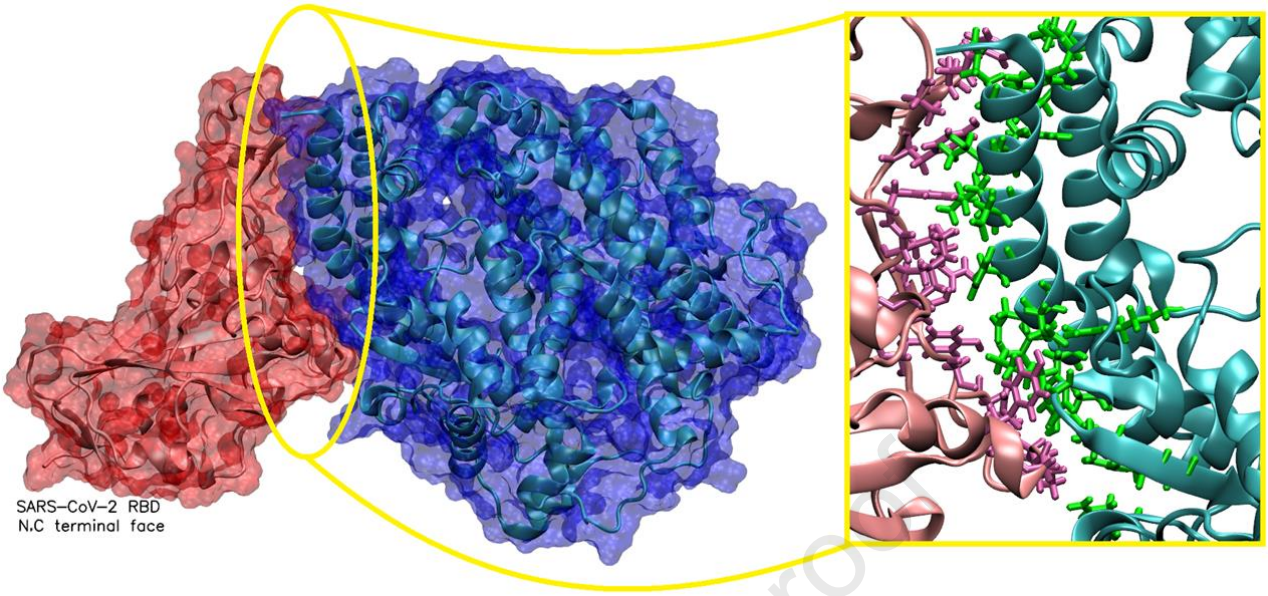


Figure 3. Interaction between the ACE2 receptor (Blue) and the S protein RBD (Red). Inset shows key interacting residues between the ACE2 receptor. The crystal structure was obtained from the Protein Databank (PDB entry 6M0J (38)). The crystal structure was viewed and analysed using VMD (Visual Molecular Dynamics 1.9.1).

4. Nanoparticle-biomolecular systems for COVID-19

4.1. Inorganic nanoparticles

The potential of NPs for the treatment of COVID-19 is promising due to their various properties. ***Iron oxide*** NPs, which have previously been investigated for their anti-viral activity, were simulated for their interaction with the RBD of the S1 subunit (39). It was found that a model Fe_3O_4 NP forms a stable complex with the protein, interacting through several hydrophobic interactions primarily with residues Leu455, Ser494 and Phe497. Therefore, these NPs, which are currently an approved treatment for anaemia, could be repurposed to treat COVID-19 (39).

Carbon nanotubes (CNTs) have a large load capacity and good bioavailability, allowing for easy interaction with biological barriers in the body (40). The electrical and thermal properties of these materials could be used to develop a CNT functionalised complex, raising the local cellular temperature using a photodynamic thermal effect and

treating COVID-19 by inhibiting viral replication (41). The binding of the S protein to biomedically relevant surfaces has been examined computationally, and it was found that the RBD of the S protein interacts with negatively charged ***silica*** surfaces so that the epitope (part of the antigen molecule, RBD in this instance, to which an antibody binds) is exposed. A model ***gold*** surface has also shown good interaction with the protein (42). The use of charged or hydrophobic surfaces in developing therapies may therefore be significant as they show good adsorption (42).

4.2. Organic nanoparticles

As researchers globally are working to develop an immediate treatment for this new virus, the development of effective vaccines is also vital. One approach for mRNA vaccines comprises mRNA (encoding a specific protein) encapsulated in organic NPs, most commonly LNPs. Once LNP conjugates reach the host cell, the cell machinery follows the encapsulated mRNA instructions and produces the target protein, which is then displayed on the cell surface and can eventually trigger an immune response (43).

The obvious target for the *SARS-CoV-2* virus is the S protein, and an example of mRNA-based vaccine has been developed by BioNTech in collaboration with Pfizer. It has been approved by the United States Food and Drug Administration (FDA), the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA), demonstrating an estimated efficacy of 95% (44) (45). Another mRNA-based vaccine was developed by Moderna, a US based biotech firm (46). Phase 3 clinical trial demonstrated that the vaccine has 94.1% efficacy in preventing COVID-19 (47). At the time of writing, this has been approved by the FDA for emergency use, and by MHRA and EMA.

Self-amplifying RNA (saRNA), is a newer type of RNA vaccine which contains a viral replication enzyme (replicase), allowing it to amplify (48). The saRNA enters the host cell, translates the replicase, making a negative copy of the mRNA. The mRNA strand is used by the replicase to synthesise more saRNA, while simultaneously binding to a sub-genomic promoter in the negative strand. This synthesises sub-genomic mRNA at a 10-

fold greater concentration than genomic RNA, encoding the viral antigen more effectively and making a more efficient vaccine.

McKay *et al.* investigated the vaccine potential of a saRNA molecule encoding the S protein, encapsulated within LNPs (49). A high concentration of *SARS-CoV-2* specific antibody titres in mice was observed. When compared to the results from a natural immune response in recovered COVID-19 human patients, the vaccine resulted in much higher antibody titres, which were able to neutralise both a pseudo and wild type *SARS-CoV-2* virus. Furthermore, there was no observation of antibody-dependent enhancement (ADE) (49), which could result in enhanced respiratory disease and acute lung injury after respiratory virus infection. This is a common concern when developing antibody dependent vaccines, which could reverse amplify the infection (50).

4.3. Administration routes

Nanoparticles can open up a variety of administration routes beyond injection. For example, liposomes can be designed for ingestion, protecting the drug from the acidic environment of the digestive tract to release it into the tissue of the gut wall (51). In addition, liposomes have been used to protect sensitive materials like mRNA encoding SARS-CoV-2 spike protein, and this technology was adapted in SARS-CoV-2 vaccines developed by Pfizer and Moderna (44-47).

For COVID-19, nasal administration would seem to be an attractive proposition. Since the virus primarily enters by breathing in particles, providing protection at the site of infection would appear beneficial. One existing flu vaccine, FluMist (https://www.flumistquadrivalent.com/) is sprayed into the patient's nose where the weakened virus induces mucosal immunity represented by IgA antibodies, as well as systemic immunity of the IgG antibodies (52). This means that the immunised patient has two layers of defence against the virus, and reduced likelihood of being able to carry and transmit the virus. Nanoparticulate systems could similarly be administered through inhalation or nasal spray, providing an attractive administration route with

potential for greater protection for the patient, and more feasible storage conditions for healthcare providers.

5. Potential new approaches

5.1. Repurposing existing drugs

Drug repurposing represents the concept of implementing an investigational drug for new uses beyond the original intention (53). Repurposing drugs for COVID-19 is an attractive approach given the need to explore all the available options to immediately reduce mortality rates. This approach allows avoidance of the financial, resource, and time implications associated with the novel drug discovery process, and researchers and pharmaceutical companies are increasingly relying on drug repurposing.

Repurposing brings several other advantages, since it can lower the risk of failure as the drug has already been evaluated for its toxicity profile. In addition, it can save additional time as many of the drugs have already undergone preclinical and safety assessments. Moreover, the drugs have already undergone trials, so they may be able to accelerate phases 1 and 2, and progress to large-scale phase 3 trials. Furthermore, drug repurposing experiments do not always need major laboratory work, and any required work can often be performed *in silico*. The identification of suitable effective drugs is an exciting prospect, and further combination with NPs may enhance their biocompatibility and physicochemical properties. Despite the aforementioned advantages, repurposing a drug must be approached with caution as some drugs can cause poly-pharmacological side effects, and intellectual property issues may arise (53).

As already discussed, the ACE2 receptor, expressed on many cell types, is key to the initial cellular entry by *SARS-CoV-2*. Therefore, Khelfaoui (54) used molecular docking combined with MD simulations to study drugs similar in structure to chloroquine and hydroxychloroquine, which are both approved medicines, aiming to block the ACE2 receptor. The studies were performed using two structures, the ACE2 receptor and *SARS-CoV-2* bound to the ACE2 receptor, and the results showed that ramipril, lisinopril, and delapril, ACE2 receptor inhibitors currently used to treat hypertension,

could bind with the ACE2 receptor better than hydroxychloroquine. Drugs that have been investigated for repurposing against key proteins associated with the *SARS-CoV-2* virus are summarised in **Table 1**. These could then be used in isolation or conjugated to NPs to enhance their properties.

Table 1: A summary of FDA approved and other anti-viral drugs that have been investigated for repurposing against key proteins involved in the replication of *SARS-CoV-2*.

Drug(s)	**Existing Use**	**SARS-CoV-2 target protein**	**Binding residues**
Paritaprevir/Simeprevir (55)	Hepatitis C virus	M^{pro}	His41/Cys145
Remdesivir (56)	Ebola Virus	RdRp	Ser759, Asp760, Asp761
Hydroxychloroquine (57) (58)	Malaria, rheumatoid arthritis, and lupus	M^{pro}	His41/Cys145
Pyronaridine (59)	Anti-malarial agent	M^{pro}	His41/Cys145
Epirubicin, Saquinavir (60) (61) (62)	Chemotherapy, HIV/AIDS	M^{pro}	His41/Cys145
Mitoxantrone, Leucovorin, Birinapant, Dynasore (63)	Chemotherapy, rectal cancer, breast cancer, perturbs endocytosis	M^{pro}	His41/Cys145, Glu166

Noscapine ligand 23B (64)	Chemotherapeutic Agent	M^{pro}	Arg40, Tyr54, Cys85, Phe181, Arg188, Glu55, Met82 and Asn84
Lopinavir-Ritonavir, Tipranavir, Raltegravir (65) (66)	HIV/AIDS, HIV, HIV/AIDS	M^{pro}	His41/Cys145
TMB607, TMC310911 (67)	HIV-1 protease inhibitor, HIV/AIDS	M^{pro}	His41/Cys145
Atazanavir, Darunavir (62)	HIV/AIDS	M^{pro}	His41/Cys145

5.2. Application of natural compounds

Natural compounds have long been studied for their application in treating disease, and have a wide range of diversity in their chemical structures. Their use with drug delivery systems and other technologies might accelerate their exploitation (68). Han (69) studied peptide inhibitors against the *SARS-CoV-2* RBD. The inhibitors were based on the protease domain of ACE2 receptor, and it was shown through MD simulation that the peptides are stable when bound to the RBD, blocking the virus from attaching to the actual ACE2 receptor expressed in human cells, thereby having the potential to stop infection. Of the 4 inhibitors studied, the work identified high stability with 3, which retained their secondary structures and therefore their fits to the RBD.

In a separate study, Chen *et al.* (70) looked at the prospect of using ***polysaccharides*** in developing treatments for COVID-19. These compounds have several advantages including low toxicity and good biocompatibility, and they are potential targets for the development of anti-viral treatments. This is because they may interfere with the viral

pathways by blocking the positive charge on the host cell surface to prevent viral entry (71). For example, ***chitosan*** NPs were investigated against the *hepatitis C* virus (72). The applications of natural compounds against COVID-19 are summarised in **Table 2**. The versatility of natural compounds may allow for easier interaction with NPs compared to pre-existing drugs.

Table 2: A summary of natural compounds that have been studied against COVID-19.

Natural Compound(s)	**Origin**	**Target**	**Key residues**
Oridonin (36)	Compound from the Naturally Occurring Plant-Based Anti-cancer Compound-Activity-Target (NPACT) Database	HE	The114, Thr159, Leu161, Ala176, Arg177, Tyr184, Phe211, Leu212, Ser213, Asn214, Leu267
Epigallocatechin gallate, epicatechin-gallate, gallocatechin-3-gallate (73)	Green tea polyphenols	M^{pro}	His41/Cys145
Peonidin 3-O-glucoside, kaempferol 3-Ob–rutinoside, 4-(3,4-dihydroxyphenyl)-7-methoxy-5-[(6-O-b-D-xylopyranosyl-b-D-glucopyranosyl)oxy]-2H-	Plant-based compounds from the Sigma-Aldrich chemical library	M^{pro}	His41/Cys145, Leu141, Asn142, Ser144, His163, Glu166

1-benzopyran-2-one, quercetin-3-D-xyloside, and quercetin 3-O-a-L-arabinopyranoside (74)			
procyanidin-a (75)	Flavonoid from plants	ACE2, M^{pro}	Ser44, Ser47, Asp350, Asp382, Tyr385, Arg393, Asn394, His401, Phe40, Phe390
Melatonin (76)	Natural hormone	M^{pro}	His41/Cys145
C1 and C2 (77)	Natural compounds from *Curcuma longa L.*	M^{pro}	His41/Cys145, Thr190, Thr25, Glu166, Thr45, Cys44, Ser46, Cys145, Pro168, Met165
Hesperidin, sesamin (78)	Natural herbal medicines	M^{pro}	His41/Cys145
Theaflavin di-gallate (66) (62)	Plant-derived natural drug	M^{pro}	His41/cys145
Azurin, peptides p18 and p28 (79)	Blue copper bacterial protein produced by *Pseudomonas aeruginosa*	S protein, M^{pro} and PL^{pro}.	N-terminal region

Human Intestinal Defensin 5 (80)	Innate defence mechanism	ACE2	Asp30 and Lys31
NPRL-334 (81)	Natural compound from the Natural Products Research Laboratories (NPRL) library	M^{pro}	His41/Cys145, His3304, Met3428, Pro3431, Gln3452, Glu3429
TCM 57025, TCM 3495, TCM 20111, TCM 31007 and TCM 5376 (30)	Traditional Chinese medicine database	N7-MTase	Asn306, Arg310, Trp385, Asn388
Luteolin (82)	Flavonoid in Honeysuckle	M^{pro}	His41/Cys145, Gln189, Leu4, Asn142, Thr26. Met49, Val3

5.3. Promising synthetic chemicals

The drug repurposing approach can also be used to analyse synthetic chemical compounds that might prove to be effective anti-virals. This can be achieved by screening a database of small molecules against viral drug targets to identify molecules with possible anti-viral activity, or by developing chemical compounds in-house. Promising synthetic chemicals which have been investigated against COVID-19 are summarised in **Table 3**.

Table 3: Summary of promising synthetic chemical compounds.

Chemical(s)	Origin	Target	Key residues
IH-009 and IH-027 (83)	Inhouse chemicals	PL^{pro}	Pro247, Pro248
Neohesperidin (84)	Selleckchem Database	TMPRSS2	Arg55, Gly97, Asn51
Ligand F2679-0163, Ligand F6355-0442, Ligand 8250 (85)	Life Chemicals Library, Asinex database	M^{pro}	Leu141, Glu166, Thr190, Gln192, Gly143, Ser144, His41/Cys145
ZINC20601870, ZINC00793735 (86)	ZINC database	M^{pro}	His41/Cys145, Hie163, Hie41, Met49, Hie164, Glu166, Met165, Thr26, Gly143, Asn142, Leu141, Gln189
α-ketoamide 13b ligand (87) (88) (89)	Inhouse molecule	M^{pro}	His41/Cys145
ZINC64606047, ZINC05296775	ZINC Database	TMPRSS2	His296, Asp345, Ser441, Asp435, Ser460, Gly462

6. Other Nanoscale Material Applications

Nano biosensor technology has a potential to enhance testing, giving rapid and accurate detection of viruses. This technology works on the premise that the biomolecule of interest selectively binds to the target conjugated to a detector, producing a sensing signal that can be digitally interpreted (90). Though limited studies have been reported so far, this technology has the potential to offer a better and

alternative approach to existing polymerase chain reaction (PCR) testing that is used to diagnose COVID-19.

A dual-functional plasmonic photothermal biosensor, combining localised surface plasmon resonance (LSPR) with a plasmonic photothermal (PPT) effect, can detect viral proteins. Qiu *et al.* (91) integrated the technologies on a two dimensional gold nano-island chip, finding that the sensitivity and reliability of the sensor was enhanced when the angle of incidence of the illuminating light was changed. This is because the plasmonic resonances of the two technologies are excited at different wavelengths, giving a real-time and label-free detection of viral sequences from *SARS-CoV-2* including: *RdRp, ORF1ab,* and *E* genes. Furthermore, the *in situ* PPT enhancement on the chip improved the specificity of genomic detection, meaning similar sequences of RdRp genes from SARS-CoV (Previous pandemic between 2002-2004) and *SARS-CoV-2* can be accurately distinguished. This dual-functional LSPR sensor represents a simple and rapid diagnostic tool, which could improve the accuracy of *SARS-CoV-2* testing in clinical diagnosis settings. In addition, it can help or even replace existing PCR tests, which often need several days to obtain results, may return false results, and need professional staff to perform the assay and interpret the results (92).

Lanthanides, a series of rare earth elements, possess unique physical and electronic features, giving rise to properties such as long luminescence lifetimes and other optical characteristics. Chen *et al.* (93) investigated lanthanide-doped NPs with a lateral flow immunoassay (LFIA) as a biosensor, to detect anti-*SARS-CoV-2* IgG antibodies in human sera. The LFIA also included mouse anti-human IgG and rabbit IgG. A nitrocellulose membrane was used as the template to mount a recombinant phosphoprotein of *SARS-CoV-2* to confine the IgG. Nineteen samples tested previously with reverse transcription PCR (RT-PCR) were then re-tested with the LFIA, which was found to detect anti-*SARS-CoV-2* IgG in ~10 minutes. Therefore, the LFIA can allow positive identification of *SARS-CoV-2* in potential cases, and be effectively used to monitor COVID-19 progression and patient responses to treatment.

Biosensor technology is generally promising, however, there are many challenges to overcome, emphasising why the technology still needs comprehensive research to develop a high-quality sensor for point-of-care diagnostics. These challenges include reproducibility, surface preparation and immobilisation conditions, incubation time and temperature, type of biological fluid used, and sample loading. Further, insufficient selectivity and specificity of many of these tests means they are currently unreliable. These factors may restrict the effective use of this technology for overall *SARS-CoV-2* detection (94).

7. Conclusions

This review has primarily focussed on the applications of NPs, and their interactions with relevant *SARS-CoV-2* proteins, as well as suggestions on how NPs maybe used to combat COVID-19. Furthermore, existing drugs that maybe repurposed against COVID-19, and natural and synthetic compounds that might be enhanced in conjunction with NPs have also been included. Little is currently known about NP-based drug delivery systems for *SARS-CoV-2*, and a thorough understanding of the pathogenesis of this novel coronavirus is required to aid development of effective agents. A collaborative global effort is required to find treatments, and the over-arching aim should be to develop anti-virals based on previous work, as not only will this save time, but is likely to work. Further enhancement of these through combination with NPs may well allow effective application of the drug.

As *SARS-CoV-2* is a recently identified virus, any attempts to tackle this should be complemented with *in silico* studies, to optimise the NP-drug interaction. Computer simulations have allowed effective interpretation of experimental data (95), e.g. the widely used carrier protein bovine serum albumin (BSA) adsorbing to a silica surface. Simulation has also previously facilitated the development of a new model NP-based vaccine using gonadotrophin releasing hormone 1 (GnRH-I) with silica NPs (96). Computer simulation is currently being used widely to aid efforts against the COVID-19 pandemic, be that in exploring the repurposing of existing drugs (58) (56) (67) (63) (66), or the development of new systems with natural compounds (79) (66) (87). In our view,

414 this approach will help design and deliver new therapies and diagnostics, not only to
415 fight COVID-19, but future viral threats that may emerge.

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Declaration of interests

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

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