



# SARS-CoV-2 and its new variants: a comprehensive review on nanotechnological application insights into potential approaches

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## Abstract

SARS-CoV-2 (COVID-19) spreads and develops quickly worldwide as a new global crisis which has left deep socio-economic damage and massive human mortality. This virus accounts for the ongoing outbreak and forces an urgent need to improve antiviral therapeutics and targeted diagnosing tools. Researchers have been working to find a new drug to combat the virus since the outbreak started in late 2019, but there are currently no successful drugs to control the SARS-CoV-2, which makes the situation riskier. Very recently, new variant of SARS-CoV-2 is identified in many countries which make the situation very critical. No successful treatment has yet been shown although enormous international commitment to combat this pandemic and the start of different clinical trials. Nanomedicine has outstanding potential to solve several specific health issues, like viruses, which are regarded a significant medical issue. In this review, we presented an up-to-date drug design strategy against SARS-CoV-2, including the development of novel drugs and repurposed product potentials were useful, and successful drugs discovery is a constant requirement. The use of nanomaterials in treatment against SARS-CoV-2 and their use as carriers for the transport of the most frequently used antiviral therapeutics are discussed systematically here. We also addressed the possibilities of practical applications of nanoparticles to give the status of COVID-19 antiviral systems.

**Keywords** COVID-19 · Coronavirus · SARS-CoV-2 · Nanomaterials · Antiviral

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## Introduction

A rising number of cases of novel coronaviruses recognized as severe acute respiratory coronavirus-2 syndrome known as SARS-CoV-2 have been causing serious human infections with viral pneumonia (COVID-19) since December 2019 (Huang et al. 2019; Zhou et al. 2020a). In fall 2019, many of the enigmatic pneumonia patients of unknown etiology have been recorded in Wuhan, Hubei, a province of China which has received worldwide attention (Zhu et al. 2019). Unlike, previous coronavirus outbreaks like the severe acute respiratory syndrome coronavirus (SARS-CoV) from China and the Middle East Respiratory Syndrome coronavirus (MERS CoV) from Saudi Arabia (Wit et al. 2016), SARS-CoV-2 has a high infectious rate. By the time of this writing, COVID-19 has infected almost all inhabited areas of the world and seriously impacted on more than 123 million of people and 2,727,837 who have died (WHO, report) (as on 25th March, 2021) with a worrisome feature of major global rises in the number of cases every day. Therefore, the World Health Organization has formally declared COVID-19 a pandemic.

Although several nations and international research groups are working on COVID-19 vaccine development, no specific antiviral therapies, monoclonal antibodies (mAbs) or vaccines have been available to date. However, this is not a fast process; scientists estimate the period to be, some few more months. Treatments focus mainly on symptomatic and respiratory assistance according to protocols issued in each country by health authority, where several countries follow the World Health Organization (WHO) protocol (Guan et al. 2019; Guo et al. 2019).

Nanotechnology has received much interest and application over more than two decades to particles with dimension(s) falling within the range of the nanometer ( $10^{-9}$  or 1 billionth of a meter) due to their unique properties (Parboosing et al. 2012). Because of their physical and chemical characteristics and the adaptable nanotechnological accomplishments of the past, it is clear that nanoscience is gradually accelerating its worldwide perspective in the present and will be in the centuries ahead (Aiswarya et al. 2019; Kerry et al. 2019). Furthermore, nanomaterials may play protective feature, prevent the encapsulated drug or anti-infection agent from degradation due to the shielding properties of these nano-sized materials (Wang et al. 2018). These nanoparticles can be biomimetic in nature, and the adjustable surface charge makes them attractive tools for viral treatment, resulting in endogenous antiviral properties (Bowman et al. 2008; Sanvicens and Marco 2008; Caron et al. 2010; Petros and Desimone 2010; Gagliardi 2017) against various viruses including Herpes Simplex Virus (HSV), human immunodeficiency virus (HIV), hepatitis B virus (HBV), (Galdiero et al. 2011). Silver sulfadiazine is officially classified as an essential anti-infective topical medication by the World Health Organization (WHO 2015). The potential of metal nanoparticles for early detection, diagnosis, and treatment of disease was explored in medicine, but their biological properties remained mostly unexplored (Bhattacharya and Mukherjee 2008). Silver nanoparticles (SNPs) are one of the most successful symbols of noble nanoparticles but have also had strong antimicrobial activity, so particular attention has been paid to the production of various products to fight infectious diseases (Abou El-Nour et al. 2010; Marambio-Jones and Hoek 2010; Lara et al. 2011). Some silver nanoparticles applications have earned US Food and Drug Administration clearance (Dunn and Edwards-Jones 2004). Metallic NPs, such as gold NPs (AuNPs) capped by properly engineered antisense oligonucleotides, have recently been introduced to detect the SARS-CoV-2, such as in the naked-eye virus screening approach (Moitra et al. 2020). Novel nano-vaccine metastasis tools, as well as effective nano drugs for treating SARS-CoV-2 infections, are being developed as delivery vehicles for SARS-CoV-2 therapeutics. Dexamethasone, a nanotechnology based therapeutic drug against SARS-CoV-2 was developed using an

anti-edema and anti-fibrotic mechanism as an effective drug delivery system (Lammers et al. 2020). Different nanoparticulate delivery systems against viral infections are discussed here, in addition to their use as carriers for delivering in the widely used antiviral therapies.

## Coronavirus origin and its virology

Coronaviruses have developed several times over the past 1000 years (Forni et al. 2017). These viruses are enveloped with a positive-sense single-stranded RNA genome (26–32 kb) (Su et al. 2016). The initial discovery of diseases in animals proceeded by the diagnosis of infectious bronchitis virus (IBV) from chickens in 1937 (Beaudette and Hudson 1937) and murine hepatitis viruses (MHV) from mice in 1949 (Cheever et al. 1949). Later on, numerous other coronavirus strains were reported in several animals like cats, calves, sparrows, dogs, bats, turkeys and rabbits (Lai et al. 2007). Human coronaviruses first emerged from respiratory tract infections in the 1960s (Kahn and McIntosh 2005). Coronavirus virions have large peplomers (spike projections from the virus envelop) under the electron microscope which making it look like a crown, hence the title corona, meaning in Latin 'crown' or 'halo' and the diameter of the virus is variable from 60 to 140 nm (Wang et al. 2006; Ge et al. 2013; Chen et al. 2016).

Classification according to International Committee of Taxonomy of Viruses (ICTV) (2018), 4 coronavirus genera ( $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ) have been described in the *Coronaviridae* family. *Gammacoronaviruses* and *Deltacoronaviruses* can infect mammals and birds but have never caused any disease in humans (Woo et al. 2012; Cui et al. 2019). In contrast to this, the genera *Alphacoronaviruses* and *Betacoronaviruses* are capable of causing gastrointestinal illness in animals and respiratory disease in humans especially *Human coronavirus NL63*, *Human coronavirus 229E*, *Betacoronavirus 1*, *Human coronavirus HKU1*, Severe Acute Respiratory Syndrome-related coronavirus (SARS-CoV), Middle East Respiratory Syndrome-related coronavirus (MERS-CoV) can able to infect humans (Helmy et al. 2020). Based on the genomic analysis the recently identified SARS-CoV-2 belongs to the *Betacoronavirus* lineage B, having the RNA genome of about 30 kb, which has 74–99% identity than that of pangolin coronavirus (*Munisjavonica*) and horseshoe bat (*Rhinolophussinicus*), respectively (Zhou et al. 2020a; Zhu et al. 2019; Woo et al. 2012; Cui et al. 2019).

Evolutionary study of COVID-19 showed that it is most similar to SARS-like coronaviruses and was called SARS-CoV-2 for the similarity (Alanagreh et al. 2020). Coronaviruses are zoonotic pathogens, and bats have been documented as the rich source (Chen et al. 2020a; Yang et al. 2011) and can be transmitted by direct contact to humans

through intermediate host animals. The human race has seen three coronavirus outbreaks with high rates of morbidity in the last two decades. The world was stunned by the first pandemic of this century in 2003, with the emergence of SARS-CoV in Guangdong, China that resulted in 744 deaths in 29 countries and more than 8000 patients in 29 countries corresponding to a 9.6% fatality rate (Wang et al. 2006; Alnagreh et al. 2020). The outbreak was linked explicitly to market civet cats and was considered a SARS-CoV intermediate host, with the bats as the natural host (Hu et al. 2017; Guan et al. 2003).

Years later, on 23 September 2012, the WHO declared MERS-CoV, a new coronavirus, was discovered, which appears to have a higher mortality rate (> 35%) from the Middle East in with more than 80% of Saudi Arabia cases recorded. A detailed study of the evolutionary relationships showed that MERS-CoV was transmitted from dromedary camels as an intermediate host to humans that may originate from bats (Zaki et al. 2012; Wang et al. 2015; Dudas and Rambaut 2016). SARS-CoV-2 is believed to have originated on the seafood market in Wuhan, China (Huang et al. 2019). Recent researches have indicated that SARS-CoV-2 is a modified bat-derived coronavirus (Zhou et al. 2020a; Zhang et al. 2019) resulting from zoonotic transmission to humans (Lu et al. 2019; Xu et al. 2020). A coronavirus detected in the Malayan pangolin was found to be 99% similar to SARS-CoV-2 (Nadeem et al. 2020). Infected pangolins exhibit similar pathological signs to those suffering from COVID-19, and the antibodies circulating in their blood can react with the SARS-CoV-2 spike protein. Latest researches point out that SARS-CoV-2 may derive from Pangolin-CoV recombination with bat-CoV-RaTG13-like virus where pangolin is considered as one of the possible intermediate hosts between bat and human (Ge et al. 2013; Lu et al. 2019; Xu et al. 2020). Investigations are underway to identify possibilities of snakes, minks, and tortoises as intermediate hosts (Li et al. 2020a; Xiao et al. 2020). The majority of the scientific study believes that SARS-CoV-2 was transmitted to humans on the seafood market which originated from bats through the intermediate animal host (Lu et al. 2019). However, a conclusive response to which animals function as intermediate hosts is yet to be found.

Andersen et al. (2020) analyzed the spike protein amino acids from SARS-CoV and SARS-CoV-2 revealed that they differ in the hypothesis that the theory of laboratory origin of SARS-CoV-2 by manipulating SARS-like viruses. According to the literature, urbanization, more and more frequent combining of different animals, may have facilitated the emergence and re-emergence of some of these viruses in densely populated regions. In contrast, coronaviruses are known to have high rates of mutation and recombination that may allow them to cross barriers to species and adapt to a new host (Liu et al. 2020). Further studies are therefore

needed to confirm intermediate hosts of coronaviruses for zoonotic transmission control and to prevent future outbreaks of such viral infections (Lau and Chan 2015).

## New variants of SARS-CoV-2

Viruses keep evolving by mutation and a new form emerges in itself, and is not a serious concern. Many new mutants would not selectively favor the virus. However, certain mutations or mutation blends may have a selective benefit for the virus, such as increased transmissibility resulting in an increase in receptor binding, or the capacity of the host immune response to modify antibodies-recognized surface structures. Prior studies into the D614G variant showed that while the 614G variant offered a select gain, there was no observable influence on the severity or result of the infection due to increased cellular infectivity (Li et al. 2020b).

In mid-December 2020, the world watched with interest and growing concern as scientists in the United Kingdom characterized the newly discovered coronavirus variant ('VUI – 202012/01' (in December 2020 first variant to be investigated)) as being more communicable than existing circulating viruses. By 21 December 2020, 1108 cases with this variant were detected, mainly in the South and East of England and recently also in Australia, United States, Denmark, India, Iceland, Italy and the Netherlands (WHO). The mutations found in this new form have to do with the receptor binding site as well as other surface structures that may change the virus' antigenic properties. Initial report reveals that the variant can spread easier among individuals and this variant having mutation in 'spike' protein. Alterations of this spike protein will make the virus more contagious and also more easily spread through people. According to WHO report, the variant have mutations resulting in 14 amino acid modifications and 3 deletions (deletion 144, deletion 69–70, D614G, N501Y, A570D, P681H, S982A, T716I, D1118H). Any one of these mutations can impact human transmissibility of the virus. One mutation (N 501Y) found is that an amino acid varies within the receptor binding domain (RBD) of the six main residues. Another biologically significant mutation, P681H, was detected in the RBD. Finally, deletion at 69/70 was found that impact the efficiency of some diagnostic PCR tests that use an S gene target (<https://www.who.int/csr/don/21-december-2020-sars-cov2-variant-united-kingdom/en/>).

## Pathogenesis of SARS-CoV-2

COVID-19 patients display multiple clinical signs and symptoms, such as fever, running nose, sore throat, non-productive cough, myalgia, dyspnea, fatigue, loss of smell and taste, normal or decreased leukocyte counts, and viral

conjunctivitis which are evidence of SARS-CoV and MERS-CoV infections (Huang et al. 2019; Lu et al. 2019; Volz et al. 2020; Chan et al. 2019). However, the complete and systematic clinical expression for COVID-19 has not been clear to date. The related SARS-CoV and MERS-CoV mechanisms can still provide us with a significant amount of knowledge on pathogenesis of infection with SARS-CoV-2 to promote our identification of COVID-19. Patients with moderate signs and symptoms have been reported to improve their health after one week, at the same time, the patients with significant respiratory symptoms leading to acute respiratory distress syndrome (ARDS) (Xia et al. 2020). Epidemiological studies indicate the time of incubation for COVID-19 was estimated to be between 1 and 14 days, while the serial period was estimated at 4–8 days. It requires around 3–7 days for the epidemic to double the infections (Adhikari et al. 2020).

COVID-19 showed higher rates of pandemic and transmission risk compared with SARS-CoV as it was found that the sufficient reproductive number (R) of COVID-19 (2.9) was more than the ones mentioned earlier sufficient reproductive number (R) of SARS-CoV (1.77) (Park et al. 2020). Four structural proteins in the coronavirus family include the large homogeneous 'spike surface glycoprotein' (S), matrix protein (M), a small envelope protein (E), and nucleocapsid protein (N). The Spike protein in coronaviruses has been reported as a significant determinant for receptor binding and interacting with the host cells and responsible for the infection (Wrapp et al. 2020). The life cycle of the virus with the host consists of five phases: attachment, penetration (reach the host cells by endocytosis or membrane fusion), biosynthesis (viral RNA enters the nucleus for replication and mRNA is used to generate viral proteins), maturation (making of new viral particles) and release. After entering the target cell's cytoplasm and being a positive-sense RNA genome, the viral genome translates into two polyproteins 1a, b (pp1a, pp1b) and form a replication-transcription complex (RTC) that pertains to genome transcription and replication (Lau and Chan 2015). The newly synthesized glycoproteins are then incorporated into the endoplasmic reticulum or Golgi membrane, and the nucleocapsid is developed by merging of genomic RNA with the nucleocapsid protein. Viral particles then germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC), and the vesicles containing the virus particles merge into the plasma membrane for virus release (Adhikari et al. 2020).

## Immune reaction to SARS-CoV-2

As reported earlier by several scientist groups from China, angiotensin-converting enzyme 2 (ACE2) is the primary receptor for both SARS-CoV2 and SARS-CoV (Zhou et al.

2020a; Li et al. 2003). Since ACE2 expresses itself strongly in the alveolar space of epithelial cells on the apical side of the lung, this virus will probably enter and kill them (Hemming et al. 2004; Jia et al. 2005). A recent report indicated that the binding efficiency between SARS-CoV-2 and ACE2 glycoprotein is 10–20 folds higher than that of SARS-CoV, which could clarify SARS-CoV-2's highly infectious capability (Guo et al. 2019; Letko et al. 2020). ACE2 is widely expressed in the nasal mucosa, lung, bronchus, heart, esophagus, stomach, kidney, ileum, and bladder, all of which are vulnerable for SARS-CoV-2 (Zou et al. 2020). Clinicians have also recently suggested that SARS-CoV-2 be potentially pathogenic to testicular tissues, which implies fertility concerns in young patients (Letko et al. 2020).

Once the virus got entry into the cell, the SARS-CoV antigen presentation depends primarily on the MHC I molecules, to the antigen presentation cells (APC), which is a central part of antiviral immunity of the body but also contributes to its presentation by MHC II (Liu et al. 2010). Afterwards, antigen presentation stimulates body's humoral and cellular immunity, mediated by virus-specific B and T cells.

## Acute respiratory distress syndrome (ARDS) and cytokine storm

ARDS is a cytokine storm, which threatens life, a joint immunopathological event for SARS-CoV, MERS-CoV, and SARS-CoV-2 infections. The main mechanism of ARDS is to prevent adequate oxygen from entering the lungs and circulation, leading to death by most respiratory disorders and acute lung injury (Thompson et al. 2017). Individuals experience extreme respiratory failure involving mechanical ventilation in fatal human infections with SARS-CoV, MERS-CoV and SARS-CoV-2, and the histopathology findings also support ARDS (Xu et al. 2020; Ng et al. 2014). Rapid viral replication can cause massive death and vascular leakage of the epithelial and endothelial cells, triggering the release of pro-inflammatory cytokines (TNF- $\alpha$ , TGF- $\beta$ , IFN- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-12, IL-18 etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) in large amount by immune effector cells in SARS-CoV and MERS-CoV infections (Huang et al. 2019; Cameron et al. 2008; Williams and Chambers 2014; Min et al. 2016; Channappanavar and Perlman 2017). SARS-CoV-2 commandeers the same entry receptor, ACE2, indicates the probability of the targeted and infected cell population as SARS-CoV for infection (Gu et al. 2005; Jin et al. 2020). For SARS-CoV and SARS-CoV-2, few patients have chronic inflammation, ARDS, and even sudden death, especially those who produce early neutralizing antibodies, though most patients overcome inflammatory response and clear the virus (Jin et al. 2020; Fu et al. 2020).

## Diagnostic tests for COVID-19

Laboratory diagnosis is a priority for the management and control of COVID-19 outbreaks. Respiratory samples have the highest yield, but other specimens, such as blood and stools, may also be used (Wang et al. 2020; WHO 2020). Molecular techniques are more appropriate for accurate diagnosis as they can target particular pathogens and classify them. Nucleic acid detection technology used to detect COVID-19 is a real-time quantitative polymerase chain reaction (RT-qPCR) and high-throughput sequencing. RT-qPCR is still widely used because of high-throughput sequencing is equipment dependency and high cost. Researchers have added more than 1000 sequences on the Global Initiative on Sharing All Influenza Data (GISAID) and GeneBank, which helps scientists to establish a RT-qPCR diagnostic assay (Chudhary et al. 2019). Primers are designed with a two-target system, where the first detects various coronaviruses, like SARS-CoV-2, and the second one is specific for the SARS-CoV-2. Though RT-qPCR is very specific, and its false-negative rate leads clinicians to propose computed tomography (CT scan) as a necessary auxiliary diagnostic method. Both RT-PCR and CT scans have their drawbacks. The significant problems in RT-PCR are a shortage of kits and lack in the identification of the early stage of infection or asymptomatic patient. In contrast, CT scans are expensive and require technical expertise. The problems, as mentioned earlier, should be rectified by adopting more tests that are sensitive. Moreover apart from rtPCR and CT scan diagnosis, antibodies such as IgM and IgG were also detected where it will take at least 10 to 15 days after onset of symptoms to develop these antibodies by the patient (Zhao et al. 2020). Another study indicated that, it may take up to 22 days to produce antibodies after onset of symptoms (Guo et al. 2020). However, further research is necessary to investigate the pathogenesis and design an efficient diagnoses method to overcome the false-negative results.

### Possible nano-based method for diagnosing viruses

Colorimetric bioassays based on nanotechnology are comfortable and desirable for their usability; visual performance and no need for sophisticated Biosensor instruments design (Pan et al. 2010,2014). Over the last two decades, gold nanoparticles (AuNPs) have gained tremendous interest in colorimetric-based biosensing applications. They have been used for detecting a wide range of biological and chemical targets, such as small molecules, metal

ions, proteins and nucleic acids, where particles change color in response to nanosized particle reactivity to external conditions (Saha et al. 2012; Curry et al. 2014; Misra et al. 2018; Peng et al. 2018; Li et al. 2018).

In 2017, Teengam et al. (2017) developed a multiplex colorimetric paper-based analytical tool using AgNPs as a colorimetric reagent for viral infection-related DNA detection such as MERS-CoV. They reached a detection limit of 1.53 nM under optimum conditions. In 2019, Layqah and Eissa (2019) identified an electrochemical immunosensor using a range of carbon electrodes modified with AuNPs that allowed human coronavirus (HCoV) and MERS-CoV proteins to be detected in spiked nasal samples. They observed a strong linear relationship between the sensor response and the concentration of viruses where linear ranges of 0.01–10.000 ngml<sup>-1</sup> and 0.001–100 ng/mL were obtained for HCoV, and MERS-CoV, respectively.

### Point-of-care testing (PoCT)

Transferring diagnostic tests for COVID-19 from laboratory environments to the point of treatment is theoretically revolutionary in the pace and quantity of tests that may be done. PoC testing is described as testing conducted at home or at a location where the patient is treated using a kit or strip. The biosensor, which is used to conduct a biochemical assay to identify the pathogen, is the most important part of PoC research (Vashist 2020). Colorimetric biosensors are desirable POCTs because they allow the analyte to be detected through simple colour changes that are noticeable to the eye without assistance. One such PoC method that is under development for the diagnosis of COVID-19 is the lateral flow assay (LFA) for SARS-CoV-2 detection (Xiang et al. 2020). The nanoparticles-connected LFA makes the device more stable and sensitive. An LFA has demonstrated 81, 100, and 86% clinical sensitivity, specificity, and accuracy for IgG and 57, 100, and 69% for immunoglobulin M (IgM), respectively. The test identifies IgM and IgG with 82% sensitivity (Teengam et al. 2017). Anti-SARS-CoV-2 antibodies could be detected using these LFA in healthy blood donors and health-care staff. From COVID-19 positive patients, Villarreal et al. (2021) recorded an 87% positivity rate for both IgM and IgG antibodies.

In another study, Huang et al. (2020a) achieved a rapid diagnosis and on-site detection of the IgM antibody against the SARS-CoV-2 virus using colloidal gold nanoparticle-based lateral-flow (AuNP-LF) assay. The SARS-CoV-2 nucleoprotein (SARS-CoV-2 NP) was coated to a sample capture analytical membrane to prepare AuNP-LF strips, and the antihuman IgM was combined with AuNPs to form the detector reporter. AuNP-LF test output was evaluated by analyzing serum samples of COVID-19 patients and healthy humans. AuNP-LF's sensitivity and specificity proved 100

and 93.3%, respectively, and the results were obtained within 15 min, which requires only 10–20  $\mu\text{L}$  serum for each test.

### Colorimetric assay

The simple, quick and precise "naked-eye" colorimetric SARS-CoV-2 identification test is a matter of urgency at this time. Moitra et al. (2020) developed a gold nanoparticulated (AuNPs) colorimetric assay, capped with appropriately designed thiol-modified antisense oligonucleotides (ASOs) specific to SARS-CoV-2's N-gene (nucleocapsid phosphoprotein), used for the detection of positive COVID-19 cases from isolated RNA samples within 10 min. The thiol-modified ASO-capped AuNPs agglomerate targets the SARS-CoV-2 RNA sequence and demonstrate a change in its plasmon resonance on the surface. Furthermore, the virus RNA material leads to a visually detectable precipitate from the solution mediated by the new agglomeration between the AuNPs. The unique designs of the diagnostic test SARS-CoV-2 can selectively detect SARS-CoV-2 presence in a biospecimen by the naked eye without requiring any complex instrument (Fig. 1) (Zhu et al. 2020).

### Separation based on magnetic nanoparticle

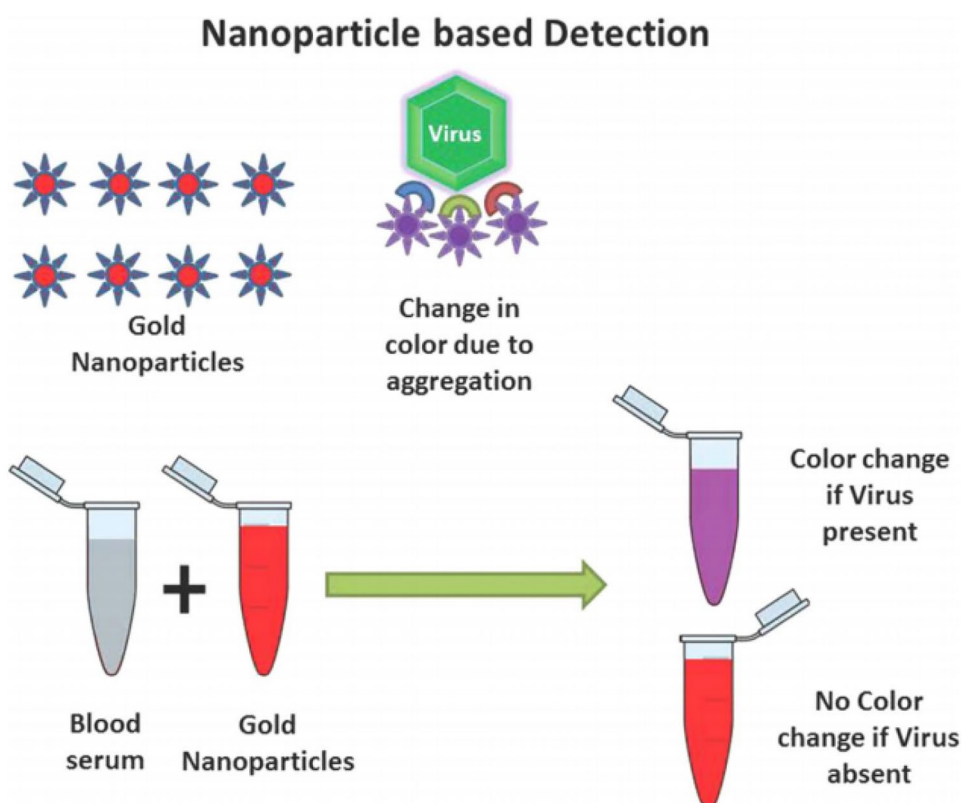
The very first step in the molecular diagnosis of SARS-CoV-2 is nuclear acid extraction from a clinical specimen

which takes a lot of work and time. Magnetic carboxyl polymer-coated nanoparticles (pcMNPs) have been developed to simplify extraction to detect SARS-CoV-2 RNA sensitively (Zhao et al. 2020) which may also incorporated in RT-PCR protocol. The advantages of pcMNPs over a traditional column based extraction process include strong viral RNA binding efficiency that results tenfold increase in sensitivity. This approach can also be used for the design of PoC devices.

### Biomolecules-based detection

A biosensor includes components of biorecognition, are referred as biomolecules that are used to target based on the assay type. Antibodies are the commonly used biomolecules in ELISA and the other biomolecules are nucleic acids and enzymes. For specific diagnosis of SARS-CoV-2 nucleic acid, a double functional plasmonic biosensor was designed. This biosensor is a two-way platform that combines the plasmonic photothermal (PPT) and with localized surface plasmon resonance sensing transduction. The system consists of a complex two-dimensional gold nano-islands (AuNIs) chip where a RdRp, ORF1ab, or E gene cDNA receptor has been immobilised by gold-thiol attachment linkage. The output of this biosensor has yet to be tested in clinical samples (Qiu et al. 2020). Teengam et al. suggested an alternative paper-based colorimetric assay technique based on pyrrolidinyl

**Fig. 1** Nanoparticle-based virus colorimetric detection. This figure shows the process by which the virus allows nanoparticles to be aggregated, leading to a change in color from red to purple (Zhu et al. 2020)



peptide nucleic acid-induced NP aggregation for the detection of SARS-CoV-2 DNA (Teengam et al. 2017). These nucleic acid probes showed significant selectivity for the DNA targets. Seo et al. reported a novel antibody-based biosensor for detecting SARS-CoV-2 spike proteins. The antibody of SARS-CoV-2 was coated on field-effect transistor (FET) graphene sheets employing nasopharyngeal swab specimens from clinical patients as antigens. The virus was also observed in the growth media with an identification value of  $1.6 \times 10^1$  pfu/mL using this sensor. The COVID-19 FET detector can distinguish among infected and safe individuals with a detection limit of  $2.42 \times 10^2$  copies/mL (Seo et al. 2020).

## Current potential treatment

No drug synthesized or in use for SARS-CoV-2 infection (unfortunately), up to now; the latter leads to a lethal and acute inflammatory response and pulmonary injury. To establish an effective COVID-19 treatment using nanoparticles, one must understand the nanoparticles' versatile mode of viral inhibition mechanism. SARS-CoV-2 also uses a 'lock and key' mechanism similar to SARS-CoV and MERS-CoV, in which the angiotensin converting enzyme II (ACE2) acts as a 'key' for entering specialized cells keeping its "lock", which is mostly present in lungs, heart, intestine cells, arteries, and kidneys (Yang et al. 2019). After the virus has reached the cell, they replicate and invade other cells of the host cell and organelles, on that basis, the treatment that stops the virus from entering the cell may be beneficial (Itani et al. 2020). SARS-CoV-2 Mpro protease is one of the most promising candidates for antivirals in the design and production of SARS products. Ton et al. (2020) created a groundbreaking forum for profound learning called deep docking (DD) and performed docking tests of 1.3 billion compounds in the library of ZINC15, and listed the top 1000 ligand capacity for SARS-CoV-2 Mpro protein. These systems are made available for subsequent studies in cell culture and animal pattern experiments by the scientific community. This research is very important as it is very easy to obtain docking results from in-silico experiments and allows a structural simulated virtual screening of billions of compounds to be purchased in a limited period of time. But in the other side, contradictory evidence suggests that SARS-CoV-2 Mpro is not appropriate since the protein target has already been mentioned (Bzowka et al. 2020). Qamar et al. (2020) performed a successful SARS-CoV2 multi-epitope vaccine (MEV) by the use of seven proteins (B cell, IFN- $\beta$  and T-cell). Docking experiments have shown a solid and clear affinity between MEV and TLR8 and TLR3, while optimization of codon and in-silico cloning has enhanced the output of the *E. coli* K-12 system. For the production of

vaccines, potential experimental validations in this direction will yield useful outcomes.

## Usage of supportive drugs

As there is no scientifically proven active antiviral agent against SARS-CoV-2, a variety of drugs are licensed for use in clinical trials such as Chloroquine phosphate, Darunavir, Favipiravir, etc., (most commonly used antiviral drugs are listed in Table 1). Moreover, these drugs are not specific against SARS-CoV-2 but have general antiviral activity, which can interfere with viral entry or block receptors of the virus. Coronaviruses are usually not responsive to existing antiviral drugs, and in the case of coronavirus infections, combinations of various treatments were also used for treatment (Zylka-Menhorn 2020). Such successful combinations for the treatment of COVID-19 are lopinavir/ritonavir plus arbidol (Huang et al. 2015) and lopinavir with ritonavir (Han et al. 2020; Lim et al. 2020). Another study suggests that ribavirin could be a potent drug inhibiting coronaviruses replication if combined with interferon- $\beta$  (Al-Tawfiq et al. 2014; Arabi et al. 2020). Very recently, a combination of remdesivir and chloroquine gained more attention because of its effectiveness in halting SARS-CoV-2 replication process (Alanagreh et al. 2020). Some of the therapies mentioned above are not unique to COVID-19 and are supportive treatments, including cardiovascular/hemodynamic or respiratory therapies that assist patients with the virus. However, these drugs can reduce symptoms and risks but should not kill the virus effectively.

## Antibody and plasma therapy

Convalescent plasma therapy contains the acellular components of blood from the COVID 19 recovered patients that contains SARS-CoV-2 antibodies. This passive immunization (PI) has also been reported for short-term fortification against infectious agents in which the coronavirus-specific human monoclonal antibody (mAb) (CR3022) can bind powerfully to the SARS-CoV-2 receptor-binding domain (RBD) (Tian et al. 2019). When the human body is infected with viruses, it produces antibodies to fend off the virus. Such antibodies can be obtained as convalescent plasma in a healed patient's blood and transferred to a newly infected patient's blood where they can neutralize the pathogen, and improve the patient's immunity. Patients with pandemic influenza A(H1N1) 2009 virus infection who received convalescent plasma had lower respiratory tract viral load, serum cytokine response, and mortality in previous studies (Hung et al. 2011). In another report, SARS patients who received convalescent plasma had a higher percentage of hospital discharge at day 22 from the initial infection than those who did not receive convalescent plasma (Cheng et al.

**Table 1** Common antiviral drugs/treatments in current use against SARS-CoV-2 based on the literature Helmy et al. (Chen et al. 2016) and Alanagreh et al. (Woo et al. 2012)

Drugs	Therapy strategy categories	Mechanisms of therapy	Antiviral activity against COVID-19-related viruses	Status
Chloroquine phosphate/ hydroxy-chloroquine	Anti-malaria anti-viral anti-inflammatory	Increasing host cell lysosomes pH, immunomodulator, interferes with the glycosylation of cellular receptors of SARS-CoV-2	Exhibited a promising antiviral effect against SARS-CoV-2 in vitro; Improved COVID-19-pneumonia patients and shortened the course of the disease	FDA approved to be used in an emergency situation, implemented in many treatment protocols
Griffithsin	An alga-derived lectin against HIV	Broad-spectrum antiviral activity against HIV, SARS and MERS	Viral entry inhibition by attachment to the virus surface glycoproteins such as HIV gp120 and SARS-CoV-2 S protein	Investigational antiviral, clinical trials are in progress
Remdesivir	Antiviral drug (Nucleosideanalogue)	A monophosphoramidate of adenosine prodrug that incorporates into nascent viral RNA chains causing pre-mature termination	Used against a wide range of RNA viruses such as Filoviridae, Paramyxoviridae, Pneumoviridae, and Coronaviridae; used successfully in COVID-19 treatment in the United States and showed no adverse events	Investigational antiviral, clinical trials are in progress
lopinavir/ritonavir	HIV protease inhibitor	Could act by inhibiting SARS-CoV-2 protease for proteins cleavage, interfering with virus replication	Provided good results against SARS-CoV decreased the viral load significantly and provided good results in COVID-19 patients	FDA approved
Baricitinib	Rheumatoid arthritis (RA) drug, AP2-associated protein kinase 1 (AAK1) Inhibitor	Interfering with viral entry by inhibiting one of the endocytosis regulators	By its affinity for AP2-associated protein AAK1, reducing SARS-CoV-2 endocytosis	FDA approved
Darunavir and Cobicistat	HIV protease inhibitor	Could act by inhibiting SARS-CoV-2 protease for proteins cleavage, interfering with virus replication	Used for the treatment of MERS-CoV in experimental animals; Used for the treatment of HIV-1 patients	FDA approved
Favipiravir	Nucleoside analog	Inhibits viral RNA polymerase and mRNA capping	Demonstrated an inhibitory effect on all influenza subtypes including neuraminidase- and M2 inhibitor-resistant strains; Showed inhibitory effects against Arenaviruses, Bunyaviruses, and Filoviruses	Investigational
CamostatMesylate	Transmembrane protease, serine 2 (TMPRSS2) inhibitor	Interfering with viral entry	Cellular entry of SARS-CoV-2 can be blocked	Japan approved
Ivermectin	Anti-parasite and antiviral	Inhibits SARS-CoV-2 replication in vitro	Inhibits the in vitro replication of SARS-CoV-2 on Vero-hSLAM cells with 5000-fold reduction in viral RNA in 48 h	FDA approved



Table 1 (continued)

Drugs	Therapy strategy categories	Mechanisms of therapy	Antiviral activity against COVID-19-related viruses	Status
Oseltamivir	Anti-viral	Neuraminidase inhibitor	Anti-influenza drug; Combination of nitazoxanide and oseltamivir is more effective in the treatment of ferrets infected with influenza virus compared to oseltamivir monotherapy	Investigational
Cepharanthine, Selamectin, and mefloquine hydrochloride	Anti-viral Anti-inflammatory activities	Significantly reduced cytopathic effects of SARS-CoV-2, and decrease the viral load	Cepharanthine and mefloquine are likely to affect host cell pathways while selamectin may be a particular inhibitor for SARS-CoV-2	Investigational

2005). These results suggest that the use of convalescent plasma transfusion can be candidate therapy for the prevention and treatment of COVID-19 patients, particularly in life-threatening situations.

### Current vaccines

Scientific research on vaccine development strategies against SARS-CoV-2 is growing and research-tested in animals and humans, such as inactivated virus, live attenuated virus, recombinant protein, subunit vaccines and nucleic acid vaccines (Chen et al. 2020b) are in their preliminary stage. Out of more than 200 candidate vaccines, few of them completed clinical trials and are administered to humans as successful SARS-CoV-2 vaccines to prevent viral shedding and transmission, thereby helping to control coronavirus outbreaks. There are numerous studies underway, especially in the US, India, China, Russia and the UK. Pfizer and BioNTech have developed mRNA-based vaccine (BNT162b2), where it got authorization in several countries for public use. By coding a mutated version of full-spike protein of the virus, BNT162b2 produces an immune response to SARS-CoV-2. Another important mRNA-based vaccine (mRNA-1273) was developed by Moderna, is also ready for human. Russian company ‘Gamaleya Research Institute’ developed Sputnik V, a non-replicating viral vector vaccine in partnership with Health Ministry of the Russian Federation. Vaccine developed by Oxford University and AstraZeneca named ChAdOx1 nCoV-19 (chimpanzee adenovirus-vectored vaccine expressing the SARS-CoV-2 spike protein) (NCT04324606) has demonstrated an appropriate safety profile and a homologous improvement in antibody responses (Folegatti et al. 2020). A randomized, double-blind, placebo-controlled, was designed to determine the immunogenicity and safety of Ad5-CoV, which codes for a full-length SARS-CoV-2 spike protein (NCT04341389).

### Possible effects and efficacy of vaccine on VUI –20212/01 new variant

The new variant has no phenotypic information and no data are available about the ability of antibodies developed by the emerging vaccines to neutralize this variant. As already described, the latest virus strain reveals multiple mutations on the spike protein, as well as in the receptor binding site. The latest vaccines candidates are mostly based on the spike protein sequence. Therefore the modifications in spike protein of the circulating SARS-CoV-2 strains must be observed for assessing potential antigenic changes. The antigenic description of the new variant is underway and the findings are expected in the upcoming days. Monitoring of field efficacy of COVID-19 vaccines in use would be significant,

if possible having variant-virus-specific estimates. Monitoring of primary vaccine problems using variant-virus-specific effects can also help to understand whether there is an influence on vaccine efficacy. It must be noted that T-cell immunity plays an important role in the defense against and evacuation of COVID-19 viral diseases. While T-cell immunity is evaluated both after infections with SARS-CoV-2 and after vaccination, it is still unclear what function it could play in defense correlations.

## Traditional herbal medicines

Researchers are focusing on complementary and alternative medicinal systems (CAM's) due to the lack of specific treatments or vaccines against SARS-CoV-2. Several compounds of medicinal plants have gained significant attention for their efficacy in various therapies for viral diseases where the bio-active compounds have no or limited side effects (Tian et al. 2019). CAM's are currently part of the medicinal system in various countries such as India, China, South Korea, Singapore etc., (Qamar et al. 2019). Indian traditional medicine method includes the convergence of Ayurveda, Yoga, Unani, Siddha, and Homeopathy under one umbrella called AYUSH. Ayurveda and Homeopathy employ natural drugs of plant, animal and mineral origin for treatment and are accepted worldwide (Prajapati 2020). Rastogi et al. (2020) proposed Ayurvedic intervention with graded response depending on the stage of infection and disease proximity among individuals within a population. Though there is no proven effective medicine against the SARS-CoV-2 pathogen, their proposal may give remedies and subsequent treatment choices. Girija and Sivan (2020) tested Ayurvedic medicine such as Sudarsana Churna, Talisadi Churna and Dhanwantara Gutika against a positive COVID-19 patient. They found the medication to halt the progression of the disease to a more severe state.

Traditional Chinese and South Korean medicine also comprises of herbal medicines close to Ayurveda, which appear to have some effect in the promotion of COVID-19 prevention and treatment therapies (Ang et al. 2020) and also used in the past during SARS-CoV and H1N1 influenza epidemic outbreaks (Chen et al. 2011; Xiaoyan et al. 2018). A total of 28 traditional medicine guidelines are provided out of this 26 were Chinese government-issued, and two were by Korean medicine-professional associations (Yang et al. 2020). In China, more than 85% of COVID-19 patients had received the Traditional Chinese Medicine form of treatments (Ma et al. 2020). These traditional medicines may be capable of targeting ACE2, and these demonstrate some promises to avoid SARS-CoV-2 infection (Girija and Sivan 2020; Zhou et al. 2020b) and also manifest possible immunosuppressive effects by reducing TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8,

IL-10 and other cytokines levels (Rastogi et al. 2020; Wang et al. 2008; Chang et al. 2015; Liu et al. 2019).

## Nanotechnology against viral infections

Viruses have high mutation rates that make vaccination a difficult job because they can quickly develop resistance to existing drugs, and new viruses often emerge. There is a growing need for new medicines to be found, as well as enhancing the current drug formulations. In view of the lack of effective specific vaccine or treatment strategies against SARS-CoV-2, the development of a new method of treatment is required. Nanoparticles provide specific physical properties associated with delivery of the drugs and their usage as carriers for the transportation of most widely used antiviral therapies. Nanoparticle's antiviral properties are mainly due to particle size that facilitating the delivery of drugs, large surface area by volume ratio to accommodate large drug payloads, and the particle's adjustable surface charge with the possibility of encapsulation (Parboosing et al. 2012; Caron et al. 2010; Petros and Desimone 2010; Kumar et al. 2012). As a result of the chemical interactions on the virus surface, between the molecules-functionalities and the molecules-receptors, the particular nanoparticle exhibit the antiviral properties. Several nanomedicines are under investigation to establish possible nanotherapeutics for their antiviral activities. In the past, MERS or SARS have substantially lower infection rates than COVID-19, but treatment and vaccine candidates have not been thoroughly researched and developed. The initial research results on these viruses, on the other hand, provided a foundation for overcoming the current pandemic situation. Kato et al. (2019) developed nano-sized virus-like particles (VLPs) using recombinant S, membrane, and envelope proteins that found in MERS-CoV and SARS-CoV, and confirmed that the immunogenicity of the tested animal model was increased. In animal studies, these nano-sized VLPs have been shown to effectively defeat viruses by increasing the immune response.

## Specific antiviral nanoparticles (Nanovaccinology)

Staroverov et al. (2011) analyzed the protective immune response in immunized mice and rabbits by administrating gold nanoparticles linked to a type of coronavirus known as transmissible swine gastroenteritis virus (TGEV). The authors stated that immunization with the antigen-colloidal gold complex increased T cell propagation by tenfold compared to free antigen response, resulting in enhanced expression of respiratory macrophage performance and increased protective immunity to TGEV. The research revealed that the gold nanoparticles conjugated to a virus could be suggested

as a possible vaccine candidate for viruses. The antiviral effects of silver nanoparticles against herpes simplex virus type 1 (Baram-Pinto et al. 2009), HIV-1 (Sun et al. 2005), respiratory syncytial virus (Sun et al. 2008), hepatitis B virus (Lu et al. 2008), and monkeypox virus (Rogers et al. 2008) have been reported.

Schmitt et al. (2020) reported that the respiratory syncytial virus (RSV) was removed with RSV fusion protein-like nanoparticles (FVLP) in mice animal model. Natural killer cells activated IFN- $\gamma$ (+), and T-cells are induced by the use of FLVP against infection stage, RSV in the lung and bronchiolar airways. Still, they do not form harmful lung plasmacytoid dendritic cells (DCs) and effector T-cells. Gold nanorods also successfully inhibit RSV by 56% in BALB/c mice through upgraded antiviral genes due to the NOD-like signaling pathways and RIG-I-like receptor. In another study by Gaikwad et al. (2013), the siRNA loaded lipid-based nanocarrier, ALN-RSV01, battles the “N” nucleocapsid gene, a core RSV viral protein. This was the first RNAi-based therapy approved for clinical trials and has now entered Phase II, showing very safe and effective antiviral effects.

The earlier report of Hendricks et al. (2013) has interestingly noted that the ‘Nanotraps’ is a heat-stimulating hydrogel that successfully traps live viral cells, RNA, and proteins, and it can also be used to treat infectious disorders including influenza virus. Hendricks et al. (2013) also successfully used liposomes to transport a synthetically derived receptor (glycan sialylneolacto-N-tetraose c (LSTc) sialoside) by dose-dependent fashion to bind and capture the influenza A virus. The antiviral ability of copper iodide nanoparticles has been extensively studied against the influenza A strain because of its impact on viral proteins such as hemagglutinin and neuraminidase, resulting in virus degradation and inactivation via the formation of reactive oxygen species (ROS) (Fujimori et al. 2009). Liu and Chen (2016) presented an insightful viewpoint on the use of nanotechnology in synthesizing HIV/AIDS vaccines. Their review highlights the potential of various nanomaterials and nano-architectures for use as vector or adjuvant HIV vaccines due to excellent potential to enhance conventional HIV vaccine delivery, permeability, stability, solubility and pharmacokinetics. In 2019, Cao and Woodrow (2019) analyzed the nanotechnology strategies used to remove HIV reservoirs and the nanocapsules of gene delivery and therapies used in cancer with the potential for HIV treatment.

Yadavalli et al. (2019) studied the ability of particles with highly porous activated carbon (HPAC) as a model for limiting the entry of HSV-1 and HSV-2 into target cells. The surface-active charcoal which could have antiviral effects via a virion sequestration method, and the HPAC compound showed a reduction of 40 to 60% HSV-1 and HSV-2 entry for concentrations as low as 1 mg/mL. The adsorbed or

encapsulated acyclovir (ACV) molecules inside the HPAC pores showed a sustained drug release that works synergistically to achieve an enhanced therapeutic effect. In vivo studies of ocular (HSV-1) and genital (HSV-2) infection using a murine model, ACV loaded HPAC works by trapping the virus and releasing the encapsulated drug, preventing inflammation and penetration of the immune cells into the targeted tissue. The potent antiviral activity was allocated to the charged surface of its pores, which can interact with the surface of the cell, stimulating an active ion exchange (Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>+</sup>, Cl<sup>-</sup>, and OH<sup>-</sup>), when ACV has been acquired sustained or gradually released.

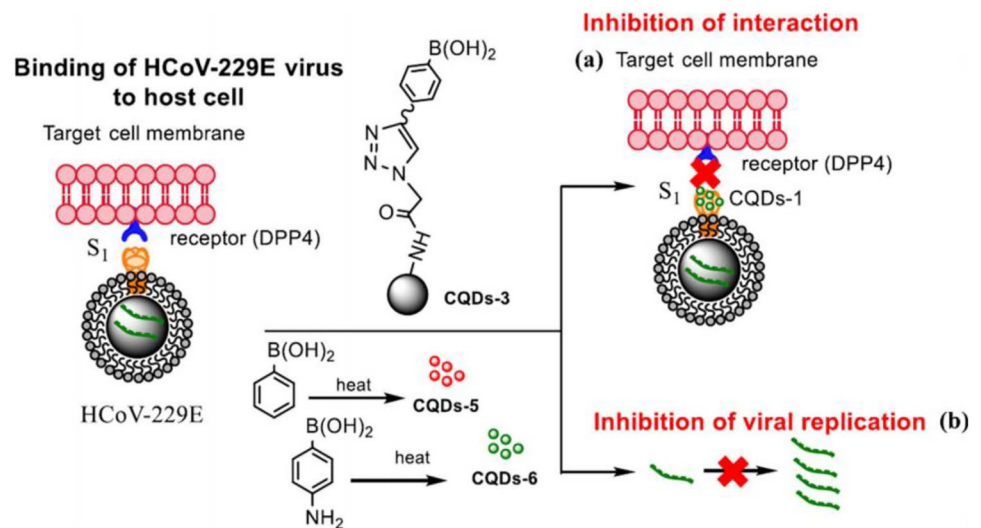
Jung et al. (2018) tried to develop an immunogenic MERS-CoV vaccine using a heterologous prime-boost strategy concerning a recombinant adenovirus serotype 5, which encodes the spike gene of MERS-CoV (Ad5/MERS) and spike protein nanoparticles. The mice groups (female BALB/c mice), which are three times immunized with the prime-boost vaccination, show that the homologous spike protein NPs effectively induced higher antibody titers relative to the Ad5/MERS group alone. However, they suggest that the heterologous one-stage Ad5/MERS prime and two-stage spike protein NPs boosting appeared to be more successful for longer-lasting immunogenicity and an appropriate Th1/Th2 response balance than the homologous prime-boosting scheme using either Ad5/MERS or spike protein nanoparticles alone. Another research revealed that HPIV-3 replication was inhibited, likely because of a blocking role of the cell-virus that leverages AgNPs. The findings of this study show that inhibitory activity depends on both the size of the NPs and the zeta potential (Lee et al. 2015).

Many nano-based solutions are designed to specifically bind the virus particles so that they do not approach the host cell. For example, carbon quantum dots interact with human coronavirus (HCoV-229E strain) S protein to prevent the viral protein interaction with the host cells which will reduce the viral replication (Fig. 2). As boronic acid was used in the carbon quantum dots, they had even greater antiviral activity (Łoczechin et al. 2019).

### New developments of SARS-CoV-2 nanotherapy

Many newly existing therapists for COVID-19 use nano-based techniques. SARS-coV-2 virus-like particles are being developed by iBio and Beijing CC-Pharming using iBio’s Quick Pharma method (ibioinc; visit related links). The virus-like particulate matter (VLPs) is purified from plants and screened as candidates for vaccines. NanoViricides, Inc. has developed SARS-CoV-2 virus particulate nanoviricides (nanomicelle bonded with ligands) that can bind and engrave. Moderna has created an mRNA encapsulating lipid nanoparticle vaccine in which mRNA codes spike protein of SARS-CoV-2 (Moderna, Inc., visit

**Fig. 2** Carbon quantum dots prevent the interaction of human corona viruses with their receptor(s) (a) and inhibit the replication of virus genome (b) (Łoczechin et al. 2019)



related links). This vaccine based on nanoparticles has already been clinically validated and ready for public.

### Examples of biocompatible systems

Nanomedicine is one of the promising platforms for virus detection and neutralization. Several experimental reports of antiviral action of nanoparticles against different viruses like influenza virus H3N2 and H1N1 (Mazurkova et al. 2010; Lysenko et al. 2013), herpes simplex virus (Lysenko et al. 2013; Hu et al. 2014), hepatitis B virus (Lu et al. 2008), HIV-1 (Elechiguerra et al. 2005; Lara et al. 2010), dengue virus type-2 (Sucipto et al. 2017), Foot and Mouth disease virus (Rafiei et al. 2016), vesicular stomatitis virus (Lokshyn et al. 2014). Nanoparticles of silver (Hu et al. 2014), gold (Sucipto et al. 2017; Rafiei et al. 2016), silicon Dioxide (Botequim et al. 2012), copper (Sucipto et al. 2017), titaniumdioxide (Mazurkova et al. 2010), ceriumdioxide (Lokshyn et al. 2014) are the few of the evaluated delivery system for their suppressive properties of viruses. Elechiguerra et al. (2005) and Rafieiet al. (2016) demonstrated the adsorption of nanoparticles on the surface of the virus, which leads to local surface transformations, such as glycoprotein agglutination, thus preventing virus penetration into the cell.

Chemistry, architecture of each nanosystem and its unique properties determine the mechanisms of nanomaterial mediated drug delivery. Many forms of nanoparticles have been suggested as promising for viruses and are divided into three broad categories based on their composition, such as inorganic, organic, and virus-like or self-assembling protein nanoparticles.

### Organic nanoparticles

Organic nanoparticles are nanomaterials based on carbon, which are usually characterized by high biocompatibility and increased drug load ability. Organic nanoparticles are the most extensively studied method of drug delivery nanoparticles, and the most widely accepted method for human therapeutic use (Zazo et al. 2016). The use of organic nanoparticles over inorganic nanoparticles is highly recognized in the biomedical sector due to various safety concerns and may prove beneficial in efficiently carrying or supplying the drug load (Mitragotri and Stayton 2014; McClements and Xiao 2017).

**Lipid-based nanoparticles, liposomes and niosomes** Nanoparticles made from lipids have proven their potential in advanced medicine as an extremely efficient biocompatible platform for therapeutics. Anomalous bio-absorbable and biocompatible properties of lipid-based NPs have created interesting opportunities for these nanosystems (Joshy et al. 2017). To check drug release parameters for hemocompatibility and non-toxic viral inhibition in cell lines VK2/E6E7 challenged with human papillomavirus (HPV), Gao et al. (2018) developed a nanostructured nanolipid carrier loaded with podophyllotoxin (POD). Both the types of lipid-based NPs that are solid-lipid NPs and nanostructured lipid nanocarriers have been reported as vehicles for successful antiviral delivery against certain viruses, such as HIV, Hepatitis C virus, and HPV. Still, their therapy efficiency against SARS-CoV-2 has yet to be assessed. Using solid-lipid nanoparticles has additional benefits include increased toxicity compared to synthetic polymer nanoparticles, with better drug release profiles (Patel and Patravale 2011; Xie et al. 2014).

Argenta et al. (2014) studied lipid nanoemulsions encapsulating coumestrol as Topical Treatment for herpes simplex virus. They formulated the bioactive compound coumestrol, trapped in a hydroxyethylcellulose gel by fluid or rigid phospholipid nanoemulsions (dioleoylphosphocholine, DOPC, and distearoylphosphocholine, DSPC, respectively). Coumestrol formulation using DOPC-based nanoemulsions showed an improved antiviral activity against HSV-1 and HSV-2, which might be considered for advanced therapy studies.

Among the numerous possible applications of lipid-based NP formulations, liposomes composed of phospholipid bilayers containing an aqueous nucleus have been thoroughly researched in vaccine studies because of their ability to function as immunologic adjuvants (Perrie et al. 2008; Kumar et al. 2016). Liposomes provide various benefits, including relatively non-toxic, successful conjugated agent encapsulation and easy alteration to improve further their mucosal and cellular uptake and biodegradable properties (Khan et al. 2020). Like any other form of nanoparticles, surface charge plays a vital role in affecting liposome pharmacokinetic properties. In particular, liposomes were used as carriers for the topical application of acyclovir and the treatment of ocular CMV infections and as carriers for the oral administration of interferon- $\alpha$  (Milovanovic et al. 2017). Another type of vesicle, noisome, is similar to a liposome but formed from nonionic surfactant instead of lipid noisome.

**Polymer nanoparticles** As an attractive delivery mechanism, polymeric nanoparticles in colloidal solids have been documented, and their progress in successful antiviral treatment has been going on for over a decade. They can be synthesized by adding many monomers that are approved by the World Health Organization (WHO) and the Food and Drug Administration (FDA) (Uskokovic and Stevanovic 2009). Their small size can promote them for use in medicine and pharmaceuticals by its capillary penetration and absorption by cells leading to increased concentrations at the target sites (Ochekpe et al. 2009). Nanocapsules (are hollow spheres, where the drug is confined) or nanospheres (are matrix structures where the drug is distributed physically or equally) are the two primary forms of polymeric nanoparticles. Chitosan polymer nanoparticles have drawn particular interest in internal administration because of their superior in vivo biocompatibility and biodegradability profiles, and their ability to open strong links between epithelial cells (Sonaje et al. 2012; Zhao et al. 2014). Joshy et al. (2017) conducted a study against HIV using amine-functionalized polymer gelatin NPs loaded with zidovudine. Studies were also conducted on hemolysis and aggregation and found that drug-conjugated NPs displayed promising biocompatibility and antiviral activity.

**Dendrimer nanoparticles** A dendrimer is a well-organized hyperbranched, symmetrical molecule, also an outstanding medium for genes, peptide or drugs (natural/synthetic) delivery inside the biological system at the desired site (Xu et al. 2018). Antiviral activity of dendrimer combined with therapeutic agents avoided host infection by inhibiting viral entry into the cells, activation of CD8<sup>+</sup> T cell against viruses like influenza virus, ebola virus, zika virus, HSV-1, 2 have already been reported and have become an effective tool for the treatment of HIV viral infections (Chahal et al. 2017; Asgary et al. 2018). Nandy et al. (2015) documented the development of dendrimeric nanoparticles with anionic naphthalene disulphonate surfaces based on Poly-L-lysine (PLL), which may prevent the entry of HIV viruses by binding to the viral envelope protein gp120 and preventing the formation of a complex CD4-gp120.

**Nanomicelles** Nanomicelles are the supramolecular assembly of a surfactant molecule size ranging from 10 to 100 nm (Letchford and Burt 2007), having powerful and most attractive nanotechnological properties including effective drug encapsulation, biocompatibility, colloidal stability and prolonged circulation (Talelli et al. 2015). Micelles also exhibit dissociation, thus allowing a longer drug retention period, and therefore a higher accumulation of the medication at the target site (Mahajan et al. 2012). Naseri et al. (2017) developed a nanoformulation using a bioactive compound encapsulated with nanomycelle and reported better bioavailability and adequate antiviral activity.

### Inorganic nanoparticles

Metal nanoparticles can be categorized under inorganic nanoparticles, which are smaller than organic nanoparticles, ranging in size from 1 to 100 nm, while their loading efficacy is far greater (Mahajan et al. 2012). Two major regions namely a *core* containing the inorganic portion (such as gold, quantum dots, silica, or iron oxide) and a *shell* region consisting organic polymers, providing an adequate substratum for the conjugation of biomacromolecules or shielding the core area against unnecessary physicochemical interactions (Swierczewska et al. 2011; Giner-Casares et al. 2016). This concept of multiple interactions with the targeted molecule at a particular site further leads to the use of these NPs in actively targeted imaging for diagnostics, hyperthermia therapy and medication (Li et al. 2018).

**Gold nanoparticles** Gold nanoparticles have shown particular interest in the production of vaccines because of their excellent conductivity, the versatility of surface alteration, biocompatibility and they can easily activate the immune system by internalizing the cells and has a lower toxicity than other metallic nanoparticles (Cui et al. 2012; Ramku-

mar et al. 2017). There are many studies that biocompatible polymer-stabilized gold nanoparticles demonstrated an active antiviral agent against several viruses, such as HIV-1, H1N1, H3N2, H5N1, dengue virus, bovine viral diarrhea and Foot-and-mouth virus (FMDV) (Rafiei et al. 2016; Vijayakumar and Ganesan 2014; Ahmed et al. 2016). Due to the existence of a negative charge on gold nanoparticles, it quickly functionalized with various biomolecules such as drug molecules, antibiotics, proteins, genes and a range of targeting ligands without displaying any toxicity found in in-vivo investigations on some human cell lines (Ghosh et al. 2008; Sreejivungsa et al. 2016; Verissimo et al. 2016; Kong et al. 2017). Marques Neto et al. (2017) studied intranasal delivery adaptability and configuration and confirmed that gold nanoparticles are readily disseminated into lymph nodes, triggering CD8+ (T-killer).

**Silver nanoparticles** Among metallic nanoparticles, silver ones are the most successfully studied nanoparticles against bacterial and viral diseases and for detection of infection (Gong et al. 2007). Numerous tests of the NPs had already been carried out to establish a novel approach to either destroy or improve the severity of the infection by releasing of silver ions (Rai et al. 2009), destruction of the cell membrane, and DNA damage (Huh and Kwon 2011).

**Nanosponge** Nanosponges are made from membranes derived from human cells, which are naturally attacked by SARS-CoV-2 (Verissimo et al. 2016). The new approach suggested by Zhang et al. (2020) for drug production, the priority should be on the infected host cells rather than on the causative agent; coronaviruses can't infect their normal cellular targets while bound with nanosponges. Two types of cellular nanosponges were manufactured by the team, probably human lung epithelial type II cell nanosponge (known as "Epithelial-NS") and human macrophage nanosponge (known as "MΦ-NS"). Zhang et al. (2020) confirmed the presence of ACE2, transmembrane protease serine 2 (TMPRSS2), and dipeptidyl peptidase IV (DPP4) viral receptors by Western blot analysis on the epithelial-based nanosponges. To improve the antiviral efficacy of these nanosponges, more work is needed for testing in appropriate animal models, though.

## Nanoparticles-based treatment modalities/Possible nano-based approach for SARS-COV-2 inhibition

### Enhanced drug delivery

Drug delivery system is a method used to deliver drugs to desired cells and organs using a different drug carriers

(Bheemidi et al. 2011). Its major purpose is to overcome problems of the pharmacological activities of drugs like the lack of selectivity, solubility limitation and drug aggregation, and to reduce the therapeutic undesirable effects (Li et al. 2019). During the past few years, drug delivery systems witnessed a great progress. Recently, nanoparticles were considered to be great drug carriers. Drugs can be encapsulated in nanoparticles, including liposomes, dendrimers, micelles, nano capsules, nanospheres and among others. These encapsulations considerably improved the therapeutic index and reduced side effects (Zhang et al. 2010; Zhu et al. 2014). Throughout the past decades, serious and chronic diseases were mainly treated using a simple compound such as pills, tablets, creams and aerosols (Khan and Irchhaiya 2016). The main drawback of these approaches is related to their uncontrolled release of the drug (Liu et al. 2016; Laffleur and Keckeis 2020). A controlled and efficient drug release with reduced administration cost is needed to control the limitations of the conventional drug delivery systems (Laffleur and Keckeis 2020).

Since COVID-19 is a respiratory disease, inhalation exposure nanoparticles may be a non-invasive means of transmitting anti-SARS-CoV-2 drugs directly to their target site. This will lead to the pre-emptive accumulation of nanoparticles in the lung tissue infected by SARS-CoV-2. Tools such as nebulizers that supply the drug as a solid or liquid embedded in the Gas Medium are used in breathing form to deliver medications (Zhou et al. 2014). They can be conveniently delivered in inhalable form with improved lung deposition and retention in conjunction with nano-delivery systems (Abdelaziz et al. 2018). Nanocarriers are particularly essential for poorly soluble medicines, which are developed into bolus and later intoxicated by lung when used as free medications (Beck-Broichsitter et al. 2012). The physiological hurdles to the production of inhalable nanomedicines are the mucociliary clearance and phagocytosis of alveolar macrophages.

### Stimuli-responsive strategy for drug delivery

Currently, stimulus-sensitive transport is considered the most interesting strategy for drug delivery. A wide range of triggers can be used to ensure a controlled and specific delivery. Li et al. (2019) defined the different endogenous and exogenous triggers that can be used to design the stimulus-responsive systems. To ameliorate the penetration ability of drugs into the desired cells, intrinsic and extrinsic stimuli are used to modulate the nanoparticles structure and their surface properties. Canaparo et al. (2019) and Mi (2020) recently provided an overview presenting endogenous and exogenous trigger used to guarantee on antibiotics and antibacterial drug delivery.

Stimuli-responsive strategy showed a great relevance in the field of treating cancer and developing vaccine. However, some limitations need to be controlled in the field of using nonantibiotics such as the limited tissue-penetration depth putting this strategy in the early stages of development. Another issue is the material toxicity, especially for the inorganic materials (Canaparo et al. 2019; Mi 2020).

### Co-delivery strategy and theranostic

Among frequent clinical practice to treat a wide range of diseases, researchers use to combine different drugs. However, the difficulty lies in the combination of the individual pharmacokinetic profiles of the used drugs to get the best synergistic effect. Cell-based tests (Zhang et al. 2017a) are essential to get an optimal dose ratio. Co-delivery using carriers having identical pharmacokinetic properties are useful to get a better combination.

The term theranostics was used about ten years ago to describe diagnostic tests developed to conduct distinctive therapies (Upponi et al. 2018). Lately, the term has been used to designate the fusion of diagnostic and therapeutic strategies in the interest of increasing the efficiency and the safety in a better customized form (MacKay and Li 2010). Thereby, nanoparticles were used as co-delivery strategies for specified theranostics (Mura et al. 2013). Stimuli-sensitive polymeric nanoparticles with multifunctional properties qualify a better drug loading and improve in vivo therapeutic molecules stability. Nonetheless, improvements are still needed to finer identify the mechanism of action between the therapeutic agents and their pharmacological activities (Pan et al. 2019).

### Biomimetic delivery strategy

Biomimetic is an innovative structure of technology inspired from nature to upgrade human life (Hwang et al. 2015). The intention of seeking inspiration from nature has been used for a long time. This idea has also paved the way for actual profits by reducing waste and spending (Barthelat 2007).

The Biomimetic Drug Delivery System is an advanced strategy for nanosystems. It imitates the biological systems such as cell structure or cell membrane (Zhang et al. 2017b). This delivery system presents good biocompatibility and less immunogenicity (Xue et al. 2017). It is well-established in the field of biomedical applications, in particular for targeted drug delivery in addition to the detoxification of cells and blood (Armstrong et al. 2017). The biomimetic strategy is most applicable in nanoparticles concealment in the cell membrane, extracellular vesicles, nanoparticles coated with lipoproteins, virus-like nanoparticles and others (Li et al. 2019).

The Biomimetic Drug Delivery System guaranteed good potential in the biomedical application. But, similar to new emerging technologies, many problems need to be resolved before leading clinical application (Li et al. 2019). These cover incontinent encapsulation of nanoparticles and difficulties in making a normalized protocol for their production and purification (Laffleur and Keckeis 2020).

### Specific small interfering RNAs (siRNAs) delivery

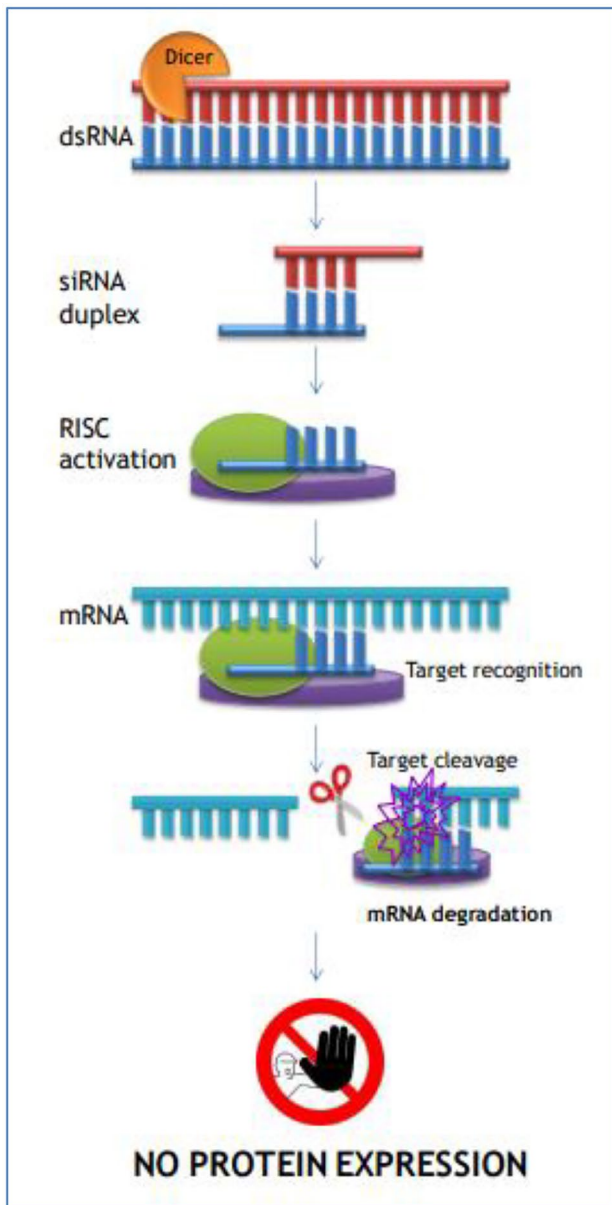
Short interfering ribonucleic acids (siRNA) have attracted attention thanks to their effective function in gene silencing (Cooper and Putnam 2016). The science of siRNA has become of great interest to the pharmaceutical industry, designed as a novel drugs delivery system. siRNA inhibits protein synthesis, and reduces the undesirable side effects compared to the conventional pharmacological therapy. Other advantages are the easy manufacturing in a large scale and a well-developed synthesis with reduced costs (Cavallaro et al. 2017).

#### siRNA structure and mode of action

Approximately, siRNA is a dsRNA of 21–23 pair of complementary bases in a double-stranded nucleic acid molecule in length, with 2-nucleotide extend over the both 3' ends and complementarity to select mRNA (Jackson and Linsley 2010). When synthesized in the cell nucleus and then transferred in the cytoplasm, it's called endo-siRNA (Piatek and Werner 2014), and exogenous, when it is formed outside the aimed cell and then delivered into the cytoplasm (Jeang 2012). But commonly, the siRNA designation in higher organisms refers to exogenous synthesized dsRNA (Cavallaro et al. 2017). Already in the cytoplasm, siRNA partake the formation of a multi-protein complex, the RNA-induced silencing complex (RISC), which breaks down the passenger strand and integrates the guide strand. The RISC complex refers to this strand to recognize and split a complementary mRNA to prevent the synthesis of an encoded protein and to selectively silence the gene expression (Kanasty et al. 2013).

siRNA gained significant attention as an encouraging therapeutic system in the field of gene and protein functions (Kang et al. 2017a; Wang et al. 2016). It is studied to theoretically silence any target gene even the undruggable ones. Researchers are currently developing novel siRNA structures to treat cancer, genetic and viral diseases (Aagaard and Rossi 2007; Iranpur Mobarakeh et al. 2019; Patel and Agrawal 2017). Figure 3 represents the siRNA mechanism in breaking down genes.

In brief, when RNAi is inserted into the cell, it is integrated into a protein complex named the Silencing Complex or RISC (Scaggiante et al. 2011). The multifunctional protein of RISC complex Argonaut 2, unfolds the siRNA.



**Fig. 3** siRNA-mediated gene silencing from Cavallaro et al. Review (Cavallaro et al. 2017)

Subsequently, the sense strand of the siRNA is split. Once the RISC with the antisense strand is activated, it starts scanning to find a complementary mRNA. When attached to its founded mRNA, the single-stranded siRNA causes the mRNA 7 division. The mRNA is subsequently perceived as untypical and consequently degraded (Cavallaro et al. 2017).

### siRNA therapeutic potential

For a well-designed siRNA, the RNAi system can be used to suppress practically any genes in the body, expanding its therapeutic potential larger than small conventional

molecule drugs. With a view to implement these advances in a practical use, delivery systems must be developed in a safe and effective manner. However, non-modified RNAi is contingent to be degraded by endogenous enzymes. Also, its large size (~13 kDa) and its great negative charge decrease the cellular membranes cross ability. Nevertheless, effectiveness and non-toxicity presents the major challenge that should be studied to use the siRNA technology in a practical therapeutic application (Whitehead et al. 2009).

### The biological barriers control in siRNA technology

In vivo delivery of siRNA presents the principal challenge for being applied in clinical therapies. Endogenous nucleases rapidly degrade the unmodified RNAi. One possible technique to inhibit this enzymatic breakdown and to decrease simultaneously the undesirable side effects is the siRNA chemical modification (Shukla et al. 2010). However, there are some issues that still need further efforts to be solved (Serrano-Sevilla et al. 2019): the quite small siRNA size provoke a fast renal emission regarding the corpuscle pore size. The RNA hydrophilicity and its notable molecular weight prevent its penetration into the hydrophobic cell membrane. Solutions consist of enhancing the siRNA transport into the cytoplasm of targeted cells to successfully use the siRNA-based therapeutics (Hong and Nam 2014).

Currently, viral-based carriers are studied in the field of siRNA delivery research. Although, in spite of their promising efficiency for in vivo transfection, their toxicity, inflammatory and immunogenicity potentials remain questionable (Serrano-Sevilla et al. 2019). Moreover, other limitations exist like difficult manufacturing processes and little cell selectivity (Singh et al. 2014). Withal, current progress in nanotechnology sciences is focused on the development of non-viral vectors as substitute for siRNA delivery. Nanostructured delivery systems improve the absorption ability into a targeted tissue and extend the retention time of siRNA (Kumari et al. 2010).

Basically, RNAi therapeutics is being continuously studied since the first confirmation of gene inhibition. siRNA-based vectors shown on table potential as therapeutic agents for a large range of diseases (Whitehead et al. 2009). However, further work is needed to improve the RNAi therapeutic delivery to carry out their application in the clinic.

### Peptide inhibitors

Peptides are active molecules containing at least two amino acids through a peptide bond. Unlike large proteins, peptides are smaller in size and include less than 100 amino acid residues. Their high selectivity and superior safety characteristics make them a good candidate for pharmacological applications (Uhlir et al. 2014). The human body contains



peptides for several biological roles mainly to signal and regulate molecules in different physiological processes. Previously, usage of peptides in drug development was limited because they were easily deactivated by many proteases contained in the human body. Successfully, current technological advances have revoked the previous situation and improved the peptide stability (Chew et al. 2017; Gentilucci et al. 2010).

### The mechanism of action for therapeutic peptides

Several studies are available to describe the mechanism of action of therapeutic peptides. Among these, some peptides presented physical effects causing disordering of the lipid bilayer of the virus envelope or even the viral aggregation. Others bind to and simulate the synthetic viral membrane. There are inhibitory peptides that prevent viruses to bind and/or to fusion to cells.

Numerous studies submit that some processes are involved at the same time (Badani et al. 1838). Chew et al. (2017) discussed the formation of peptide drugs and their mechanism of antiviral activities. Special attention was given to peptidomimetics (modified peptides) viral activity against dengue virus. They also described the use of peptides as inhibitors for viral infection focusing on three principal targets, specially, host cell receptors, viral structural proteins and viral non-structural proteins.

### Implications and future directions

Recently, peptides have gained much attention from the therapeutic drug industry. Several researches were developed to use peptides as therapeutic drugs to treat viral diseases thanks to their high selectivity, low toxicity and little accumulation in tissues. However, peptides have some limitations that could be resolved by chemical modification (Chew et al. 2017; Craik et al. 2013). Advances in the field of materials and chemistry synthesis have improved the purification systems aimed to face challenges in manufacturing peptides in large scale while reducing production cost and making compound modifications.

### Prevention approaches

#### Virus entry into cells

The entry for SARS-CoV in the human body is established through the respiratory system, mostly by droplet transmission. The infection and cells responses are resulted from the spike protein of the surface envelop actions. The interaction between the spike protein (S protein) and the receptor initiate the attachment of the virion to the host cell. Once the attachment and the bonding are established, the S protein

conformation is changed and then followed by cathepsin of L-mediated proteolysis within the endosome. The host cell receptor of SARS-CoV, situated in the lower respiratory system in the human body is called the angiotensin converting enzyme 2 (ACE2) which is found in a large variety of tissues (Xian et al. 2020).

Unfortunately, there is currently no vaccine or drugs available for COVID-19. However, significant researches are under development to get a novel vaccine against COVID-19 as soon as possible (Casella et al. 2020). At the actual situation, several strategies have been adopted worldwide mainly distancing, and wearing masks to reduce the virus spread.

Large amount of research has been performed to search for inhibitors of COVID-19 antiviral agents. Pang et al. (2020) carried out a systematic search to identify the published studies in the field of the fight against coronavirus. A total of 1065 articles were identified in our initial search and 236, 236 and 593 articles related to diagnostics, therapeutics and vaccines, respectively. Equally, Sivasankarapillai et al. (2020) discussed in their recent review the use of nanotechnology to develop novel drugs to treat COVID-19.

### Nanoscience to face Coronavirus

Nanomaterials have proven their efficiency as antiviral materials to treat several diseases by different mechanisms. Their immunological advantages are: small size allowing to transfer drugs to targeted zones, large surface area allowing holding further drug cargos (Nasrollahzadeh et al. 2020). Also, nanomaterials are able to deliver viral therapeutics in a modulated system, to imitate viruses regarding their small size and structure without causing actual infection and to induce immune response. Nanoparticles therapeutics are used in several medical domain such as prevention, detection and treatment and they enhance significantly the drug delivery by targeting specified tissues (Petros and Desimone 2010; Roldão et al. 2010).

The respiratory diseases are also the subject of recent researches in nanoscience (Nikazar et al. 2020). However, little literature is available concerning serious and productive nanotechnology-based therapeutic plans against COVID-19. The use of conventional vaccines is limited because of the toxic return that could lead to a defective immune response and weak immunogenicity. Nanoparticles are used to solve these limitations (Sivasankarapillai et al. 2020). The four major nanoparticles described to be viral against respiratory viruses are given below (Sivasankarapillai et al. 2020; Nikazar et al. 2020).

- Polymeric nanoparticles: They are good candidates for biomedical application because of their controlled properties, easy synthesis and great biocompatibility. Among the well-known members of this category are the Poly

(lactic acid-co-glycolic acid) (PLGA) and chitosan (Carter et al. 2020).

- Self-assembling proteins nanoparticles: Very suitable for biomedical application, produced by monomeric proteins oligomerization (Pillai et al. 2020).
- Inorganic nanoparticles: A large literature is found to study their biological effects mainly the metal oxide nanoparticles. They presented good antibacterial and antifungal characteristics (Du et al. 2005). However, little study is available for inorganic nanoparticles that present antiviral action against respiratory viruses.
- Peptide-based nanoparticles: Previously, short sequenced peptide inhibitors as well as amino acid mutations were proved to potentially act against SARS-COV infections (McReynolds et al. 2008). Recently, a peptide inhibitor isolated from ACE2 showed good evidence for blocking SARS-CoV-2. In addition, binding efficacy is estimated to be increased by multiple binding of linked peptides nanocarrier (Mansoor et al. 2015).

COVID-19 is a pandemic spreading rapidly. Novel methods to diagnose and treat it are under development. Some methods can be inspired from already existent nanomaterials used previously to face earlier SARS-COV.

### Simulation of cells immune system using virus-like nanoparticles

The infectious threats are mainly treated using vaccines which are the most efficacious antidotes that evoke an immune response against particular pathogens. To improve the immune treatment, scientists are incorporating effectively virus-like agent into vaccine conception (Chen et al. 2016). These vaccines have shown better results in eliciting immune responses compared to the conventional vaccine (Noad and Roy 2003) which encouraged researchers to develop novel nanomaterials to mimic virus characteristics to make new vaccines (Moon et al. 2011). The act of displaying several antigens on a single particle makes the access of the antigens to the immune cells more effective (Moon et al. 2012). Vaccine virus-like nanoparticles have capsid without genetic material and rigid structures holding therapeutic molecules in a compact area of nano-distribution (Singh et al. 2006).

The nanocarrier of drugs with different morphology and sizes varying from 10 nm to a few microns are placed in the empty space of the capsid after removing the genetic material (Ma et al. 2012). To avoid unforeseen genetic mutation, capsids from plant viruses are generally used as nano holders as their genomes are unlike the human and animal ones (Hefferon 2018; Jeevanandam et al. 2019). In addition, Virus-like particles made by baculovirus

recombination reveal better immune responses than those particles exhibited by mammals (Quan et al. 2020).

Virus-like particles used as vaccine to fight respiratory viruses like HMPV, RSV infections and influenza have been implemented (Lévy et al. 2013; Cox et al. 2014; Quan et al. 2007). The increasing development in the field of biomedical engineering has increased the use of different virus-like nanoparticles like antigen, drug and vaccine as therapeutic nanocarriers, biosensors and medical imaging (Jeevanandam et al. 2019). As nanoparticles improve the humoral responses versus selected antigens, they equally stimulate the immunity cells and the immunological memory which make them suitable for good vaccine conception (Chattopadhyay et al. 2017). The fact that viruses and nanoparticle vaccine have particularly similar characteristics such size, morphology and immunologic result encourages the scientists to concept nanovaccine and to use it in clinical applications (Singh et al. 2006).

### Nano based products (like masks, Filter, Gowns, etc.)

Within a short span of time of its origin, SARS CoV-2 virus has rapidly spread worldwide (WHO 2020). Healthcare experts are at the frontline, working hardly to limit the epidemic expansion of the virus. New protection protocol is essential to protect the health of people in general and healthcare professionals, and patients in particular. Nanoparticles are also used to simulate mask exposure to the SARS-CoV-2 virus. ReSpimask® is a mask which allows the use of copper oxide nanoparticles and has a filtration potential of 99.9% for viruses and bacteria (Quan et al. 2020). Another designed mask was the MVX Nano Mask™, a self-safe guarding mask that can kill 99.9 per cent of all bacteria and viruses that come in contact and that is powerful against coronavirus, according to the manufacturer (Cavalcanti and Cajubá 2020). Lustig et al. (2020) have produced aerosols that include virus-like fluorescent nanoparticles to monitor transfer across materials that significantly contribute to the accuracy of the detection. They also noted that products with permeable hydrophilic layers and filter layers of hydrophobic materials inhibit the virus from spreading. Recently, research groups have focused on nanofilter masks, and developed a mask with multilayered electrostatically charged polyvinylidene fluoride (PVDF) nanofiber filters that can inhibit the transmission of CoV aerosols smaller than 300 nm (Leung and Sun 2020). Their findings show that the 6-layer charged nanofiber can effectively filter nanoaerosols with sizes ranging from 50 to 300 nm.

## Challenges associated with the personal protective equipment against COVID-19

The personal protective equipment (PPE) used by healthcare professionals caring for patients with COVID-19 are contains gloves, face masks, spill gowns, protective suits, etc. It is estimated that the healthcare workers spends approximately 30 min to dress up properly and they wear the PPE for many hours per day (Kang et al. 2017b). When undressing, special attention is required to prevent infections (Honda and Iwata 2016). The healthcare experts expressed high level of stress when wearing the current PPE. Further improvements are needed. For example, the anti-fog item in goggle could reduce the risk of infection when removed (Han et al. 2018).

Moreover, other discomfort features exist when using the actual PPE such as the use of elastics to place closely the face masks that can result in great feeling of irritation (Locatelli et al. 2014) and the one-size-fits-all aspirators that do not outfit the all users faces. For these reasons, new materials and designs for the PPE is needed to be more adaptive and comfortable especially when used for long periods (Huang et al. 2020b).

Shortages of PPE have been reported worldwide, particularly in the early stages of the epidemic in various regions (Chaib 2020), preventing front-line healthcare professionals from changing their personal protective equipment and keeping use them for extra time. Consequently, the antiviral coatings of the PPE surface (Si et al. 2018), is considered to be efficient in reducing the pandemic spread.

## Solutions to fight against COVID-19

Goel et al. (2020) resumed the three main scenarios that are currently being considered for the control of the COVID-19 disease as indicated below:

- 1) Study and experiments on vaccine: researches are underway worldwide on new vaccines and accelerated acceptance procedures are being rolled out. However, scientists are concerned about the virus mutation that forms new strains, making the vaccine ineffective.
- 2) Therapeutic experiences with actual medicine: The re-use of drugs and advanced formulations is getting attention, such as antimalarial drugs and other immunomodulatory biomolecules.
- 3) Nanotechnology: advanced nanomaterials with low toxicity level are being developed for nanomedicine using previous advances in cancer treatments and cardiovascular therapies for example to treat coronavirus-infected persons.

In this review, the use of nanotechnology to fight against the novel coronavirus is detailed such in the domain of new vaccine development and targeted-drug delivery. Also, nanotechnology is used in filtering blood or in face masks. Recently, the nanotechnology has largely improved the protection effect of the personal protective equipment. Protective performance of these equipment is principally determined by the characteristics of the filtration such the thickness of the nonwoven layer, fiber charge and fiber diameter (Parthasarathi and Thilagavathi 2015). In general, the mask efficacy is conditional to their appropriate usage. Actually, the face protective masks are mainly contaminated with droplets containing infectious contagion. In the actual situation, the coronavirus penetration into the protective layer is established through droplets. Therefore, when removing the masks, the medical care givers hands could get contaminated (Li et al. 2006). For these reasons, nanomaterials are used to make a better filtration system by reducing the infection potential with direct and secondary vectors and producing reusable equipment (Habibzadeh and Stoneman 2020). Antiviral nanomaterials are being incorporated into nonwoven fabrics and into fibers especially in masks (Zhou et al. 2020c).

As being described in the first part of this review, composite, organic and inorganic materials are increasingly being used as functional component. Nevertheless, there are many materials that can be used presenting different antimicrobial resistances and distinct chemical and physical characteristics. The functions are expected to require different applications and manufacturing processes. Researchers are testing different antiviral agents that can be incorporated into the protective equipment all over the globe. Balagna et al. (2020) have proved that face masks with nanocluster/silica composite coating has antiviral effect which reduced the COVID-19 titer, under particular conditions, to zero. The advantage of these coating is the possibility of being deposited on different surfaces like polymeric, ceramic, glass and metallic. Thus, these materials can contribute to the protection against SARS-COV-2. Sportelli et al. (2020) underlined the use of nanotechnology solutions in several fields of the fight against the COVID-19. Nanomaterials showed great efficiency to filtrate coronavirus with diameter ranging from 100 to 60 nm.

Last but not least, development of intelligent PPE with antiviral detection helps to control the transmission rates (Goel et al. 2020). Mutually, they can gather the expanding particles for early detection of contamination (Leung et al. 2020). Several research articles on antibacterial and antiviral agents have been reported using metal particles. For example, they are used for air conditioning filters, packaging products, protective textile, etc. However, their commercialization is still limited for many reasons such their toxicity level, off-target effect, production cost, effectiveness, etc. (Sportelli et al. 2020). In

this actual situation of coronavirus epidemic, turning these researches in a practical application is a very pressing need.

## Conclusion and perspective

COVID-19 has a much higher infection risk than SARS or MERS. To control this disease in a short period of time, research development using novel and effective methods is needed. In the present circumstances, nanomaterials are needed to counter the actual threat to universal public health, to prepare new solutions for contagious diseases and to rethink the use of more sustainable scientific products. Nanomaterials are examined to be good candidates to fight against viral infections, especially coronavirus, because of their easy entry into cells, their rapid interaction with viruses and their genome replication prevention. In addition, improvements, including increasing the biological availability and decreasing the toxicity of typical antiviral therapeutics, can be achieved through breakthrough advances in nanotechnology. Today, scientists are working on significant studies to develop new nano/bio-materials and composites to achieve targeted delivery and nanovaccine against contagious viruses, in particular for the COVID-19. Due to the complicated situation generated by COVID-19, nanotechnology and nanomedicine could be viable alternatives to improve the efficiency of research.

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## Declarations

**Conflict of interest** On behalf of all authors, the corresponding authors state that there is no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** For this type of study formal consent is not required.

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