TOPICAL REVIEW

Nanotechnology based approaches for combatting COVID-19 viral infection

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Abstract

The novel coronavirus pneumonia pandemic was declared as ‘public-health emergency of international concern’ by the World Health Organization on 30 January 2020. The sudden emergence of the viral pathogen responsible for this outbreak, the novel coronavirus, SARS-CoV-2, has triggered alarm for their instant management using anti-viral measures and diagnostic tools. Early diagnosis will enable containment of COVID-19 (coronavirus disease 2019), allowing quick implementation of control measures for limiting the spread of this disease. Due to high human to human transmission, the development of effective anti-SARS-CoV-2 therapeutics for treating affected patients will help to slow down the transfer of viruses from patients to healthy individuals. However, till the time any effective therapeutic or vaccine is developed, preventing exposure to SARS-CoV-2 virus is the best way out. The development of more effective personal protective equipments (PPEs) is essential to maintain the safety of healthcare professionals and the public at large. Taking into consideration the current severity of this disease and the imperative need of SARS-CoV-2 specific treatment and diagnostic tools, nanotechnology-based approaches can provide promising alternatives to conventional ways of disease diagnosis, treatment, and preventing exposure to SARS-CoV-2. In this review, we inform about the different ways in which nanotechnology can help in the detection and treatment of prevailing SARS-CoV-2 infection as well as help to improve the PPE devices.

1. Introduction

SARS-CoV-2 is a member of the coronaviruses (CoV), which is a family of single-stranded RNA viruses. Six coronaviruses have been identified till date in humans. These include HCoVs-229E and HCoVs-NL63 (alpha-CoVs); HCoVs-OC43 and HCoVs-HKU1 (beta-CoVs); SARS-CoV (severe acute respiratory syndrome-CoV) [1]; and MERS-CoV (Middle East respiratory syndrome-CoV) [2]. The emergence of new coronaviruses in humans has been known to occur periodically. This is primarily attributed to the wide distribution and high prevalence of coronaviruses, the high genetic diversity of CoVs coupled with frequent genome recombinations, and human-animal interface activities [3, 4]. Using the metagenomic sequencing technology, the SARS-CoV-2 virus was identified as a novel coronavirus in bronchoalveolar lavage fluid samples collected from the seafood market in Wuhan, China [5].

SARS-CoV-2 possesses a positive sense, single-stranded RNA genome [6, 7]. The virus particles have an approximate diameter of 60–140 nm and appear crown-shaped as observed under an electron microscope [3]. The host cell receptor for SARS-CoV-2 is human angiotensin converting enzyme 2 (hACE2) to which the virus binds in order to gain cell entry [8]. The main symptoms of COVID-19 are dry cough, fever and fatigue. Some patients may have sore throat, runny nose and diarrhoea. The severe form of COVID-19 may lead to coagulation dysfunction, acute respiratory distress syndrome and septic shock [9, 10]. Currently, only symptomatic treatment is adopted for COVID-19 patients, and no SARS-CoV-2 specific antiviral drugs or even vaccines are
available. Also, the current methods employed for COVID-19 detection fail to identify the mild or asymptomatic cases, which are capable of further spreading the disease [11].

Exploring nanotechnology-based approaches for combating COVID-19 will help to overcome the limitations associated with conventional methods of viral disease management [12]. Many previous studies have reported the successful application of nanostructures in developing virus detection systems and treatment modalities. In this review, we will first discuss the nano-based diagnostics followed by a discussion on the nano-based therapies and vaccines, which have proved to be effective against viruses, closely related to SARS-CoV-2 in terms of pathogenicity, tissue tropism, or viral structure. We will also discuss nanotechnology-based strategies for preventing environmental contamination and exposure to the SARS-CoV-2 virus.

2. Nanotechnology in SARS-CoV-2 detection

The current method for the detection of COVID-19 infection is nucleic acid testing by reverse transcription-polymerase chain reaction (RT-PCR). There are three main issues with RT-PCR based SARS-CoV-2 detection. First, RT-PCR is unable to detect asymptomatic patients, as it requires the presence of detectable SARS-CoV-2 in collected samples. Second, healthcare centres in non-urban settings lack sufficient PCR infrastructure in order to accommodate high sample throughput. Third, the availability for RT-PCR kits and reagents is unable to meet the increased demand. A recent WHO report, mentions the immediate need for point-of-care diagnostics and the development of protein and nucleic acid detection tests for SARS-CoV-2 [13]. In this section, we will review some of the various ways in which nanotechnology can help to realize the COVID-19 testing demands (table 1).

2.1. Nucleic acid testing

Amplification of nucleic acid under isothermal conditions helps to eliminate the requirement for sophisticated instruments that are needed in RT-PCR based detection. Loop-Mediated Isothermal Amplification (LAMP) is an isothermal amplification method and is highly sensitive, specific and rapid [23]. Zhu and Wang et al combined Reverse transcription loop-mediated isothermal amplification (RT-LAMP) with nanoparticles-based biosensors for COVID-19 diagnosis [24]. They used two primer sets for isothermal amplification of nucleoprotein (np) and opening reading frame 40a/b(F1ab) genes of the SARS-CoV-2 virus. The result of the amplification reaction was visually assessed as a simple readout on a nanoparticles-based biosensor platform. When used to diagnose clinical samples, this sensor demonstrated high sensitivity and specificity, with no cross-reactivity from non-SARS-CoV-2 templates. Likewise, Wang et al combined RT-LAMP with chemiluminescence, using nanoparticles, for virus detection [25]. Nanoparticles conjugated with probe molecules would bind to RT-LAMP amplified viral DNA. The amplification products of RT-LAMP were biotin labelled (prior to hybridization with the probe) to allow binding of streptavidin modified alkaline phosphate (ALP) enzyme. ALP caused the conversion of the substrate to emit a chemiluminescence signal which was recorded to detect the presence of the virus. Nanoparticles can also simplify the viral extraction procedure for RT-PCR, making the detection process less labour-intensive and less time-consuming. Zhao et al used magnetic nanoparticles to extract SARS-CoV-2 viral RNA for detection by real time-polymerase chain reaction (RT-PCR) [26]. The magnetic nanoparticles were functionalized with poly (amino ester) carrying multiple carboxyl groups. The extracted viral RNA was efficiently absorbed onto magnetic nanoparticles due to the strong interaction between the carboxyl groups. The RNA-nanoparticle complex can be directly used for RT-PCR amplification without the prior need of eluting viral RNA from the magnetic beads. This helped to significantly reduce the operation time and contamination risk, enabling faster diagnosis with less false-negative results. The high sensitivity (10-copy) of this method highlights that nanoparticle-based viral RNA extraction protocols can be employed for developing high-throughput COVID-19 molecular diagnosis. In an alternative approach, Chen et al utilized magnetic nanoparticles to separate the virus particles as such, instead of the viral RNA. The group reported that how biomimetic nanoparticles were employed for enriching virus particles for enhanced detection [27]. The nanoparticles mimicked the host cell membrane and were functionalized with target receptors to allow virus-binding to the nanoparticles (figure 1). Magnetic nature was imparted to the nanoparticles by encapsulation of superparamagnetic iron oxide nanoparticles (SPIONs), which helped to separate out the nanoparticle bound virus pathogen using an external magnet. The extracted virus retained their infectivity and could be detected using multiple virus diagnostic assays such as immunochromatographic strip test, cell-based tittering assays and qRT-PCR (quantitative reverse transcription-polymerase chain reaction). The virus sample enrichment by biomimetic magnetic nanoparticles resulted in significantly improved virus detection. Fluorescent nanoparticles such as quantum dots also allow the development of rapid, easy and sensitive viral detection methods. Roh et al conjugated RNA aptamers (specific for SARS-CoV nucleocapsid protein) to fluorescent quantum dots. The presence of the virus leads to the interaction of RNA aptamers with the viral
| Type of Sensor | Virus/antigen | Nanomaterial for detection                                                                 | Limit of detection | References |
|---------------|---------------|--------------------------------------------------------------------------------------------|-------------------|------------|
| Optical/colorimetric | SARS-CoV-2 N gene | Gold nanoparticles functionalized with thiol modified antisense oligonucleotides | 0.18 ng μl⁻¹      | [14]       |
|               | MERS-CoV      | Thiol modified probes conjugated to gold nanoparticles                                      | 1 pmol μl⁻¹       | [15]       |
|               | MERS-CoV DNA  | Gold nanoparticles functionalized with pyrrolidinyl peptide nucleic acid (paper based)         | 1.53 nM           | [16]       |
|               | SARS-CoV- nucleocapsid protein | RNA aptamers conjugated to quantum dots                                                    | 0.1 pg mL⁻¹      | [17]       |
| Electrochemical | SARS-CoV-2 spike protein | Graphene sheet of field-effect transistor                                                 | 2.42 × 10^7 copies/ml (in clinical samples) | [18]       |
|               | MERS-CoV      | Gold nanoparticle functionalized carbon electrode                                           | 1.0 pg ml⁻¹      | [19]       |
|               | HCoV          | Gold nanoparticle functionalized carbon electrode                                           | 0.4 pg ml⁻¹      | [19]       |
|               | SARS-CoV      | Thiolated oligonucleotides self-assembled onto gold nanostructured screen-printed carbon electrodes | 2.5 pmol l⁻¹   | [20]       |
| Chiral        | Infectious bronchitis virus (IBV) | Self-assembled chiroplasmonic gold nanoparticles and quantum dots | 47.91 EID/50 μl | [21]       |
|               | Infectious bronchitis virus (IBV) | Zirconium quantum dots and magnetic nanoparticles                                           | 79.15 EID/50 μl  | [22]       |
protein causing variation in optical signal of quantum dots. This method was suitable in detecting even 0.1 pg.ml\(^{-1}\) the concentration of viral protein [17].

2.2. Point-of-care testing (POCT)

POC testing helps to diagnose infected individuals, without the need of sending patient samples to laboratories. This is especially important in communities that lack suitable laboratory infrastructure for sample testing. Colorimetric biosensors are attractive POCTs, as they allow detection of the analyte via simple color changes that are visible to the unaided eye (figure 2). Kim et al developed a colorimetric assay using gold nanoparticles to detect the MERS-CoV virus [15]. This assay uses two thiol modified probes (complementary either to the upstream of the E protein gene (upE) or open reading frames (ORF) 1a of viral DNA) and citrate capped gold nanoparticles (AuNPs). The probes are conjugated to AuNPs via strong Au-S interactions. In the absence of a target, the AuNPs aggregate (in the presence of a positive electrolyte), leading to colour change, which can either be visualized with the naked eye or detected by localized surface plasmon resonance (LSPR) shift. However, the presence of viral target induces extended self-assembly of double-stranded DNA (formed due to binding of probe DNA with viral DNA), preventing aggregation of gold nanoparticles in the presence of positive electrolytes, preventing transition in optical properties of AuNPs. This assay has a potential detection limit of 1 pmol \(\mu\text{l}^{-1}\), allowing the detection of lower amounts of the viral target. Such a colorimetric based assay allows low-cost and fast disease diagnosis without the need for sophisticated instruments. Paper-based analytical devices (PADs) are also low-cost and portable detection technology. They are being widely used for diagnostic assays [28]. Teengam et al developed a paper-based colorimetric DNA sensor for the detection of MERS-CoV [16]. A cationic pyrrolidinyl peptide nucleic acid (acpcPNA) probe was used for the detection of MERS-CoV DNA. PNA probes serve as a better alternative to DNA and RNA probes because they are biologically and chemically stable and also hybridize efficiently to the complementary target. The presence of a lysine moiety at the C-terminus imparted the positive charge to the probe. Positively charged acpcPNA could interact with either negatively charged citrate capped silver nanoparticles or negatively charged target DNA. In the absence of viral DNA, the PNA probe binds to silver nanoparticles allowing aggregation of the nanoparticles. However, in the presence of the MERS-CoV virus, the probes form a complex with viral DNA, protecting the aggregation of silver nanoparticles (due to electrostatic repulsion between the particles). The presence or absence of viral DNA is read out as a colour change. This assay is coupled with a paper-based analytical device (PADs), allowing it to serve as a point-of-use diagnostic tool. This device offers a detection limit of 1.53 nM under optimized conditions.

2.3. Electrochemical sensors

Owing to the high sensitivity and possibility of miniaturization, electrochemical sensors are also an appealing choice for detection. Modification of electrochemical sensing interfaces with gold nanoparticles (AuNPs) offers added advantages such as immobilization of biomolecules retaining their functionality, AuNPs act as conducting interfaces possessing electrocatalytic property and also allows amplification of the electric response. Combining the potential of electrochemical sensors and gold nanoparticles, Layqah et al developed an immunosensor for the detection of the MERS-CoV virus [19]. The sensor consists of an array of carbon
electrodes coated with gold nanoparticles to increase the sensitivity of the sensor and signal response. The recombinant spike (S1) protein of MERS-CoV was immobilized to the gold nanoparticles. The immobilized S1 protein competes with virus particles in the sample for binding to the antibody (which is added in limited amounts to the sample). The binding event is detected by measuring the current changes. For instance, in the absence of virus infection, the antibody binds to the immobilized spike protein leading to a drop in the SWV (square wave voltammetry) reduction peak current. However, in the presence of virus particles, less amount of antibody binds to the immobilized viral antigen. Since this sensor contains an array of electrodes, it allows multiplexed detection of different coronaviruses. The sensor was able to simultaneously detect MERS-CoV and HCoV viruses in spiked nasal samples. The detection limit was 0.4 pg ml$^{-1}$ for HCoV and 1.0 pg ml$^{-1}$ for MERS-CoV. Electrochemical sensors can serve as detection platforms for viral nucleic acid as well. Paredes et al. developed an electrochemical genosensor for the detection of the SARS virus [20]. The sensor consists of a monolayer of thiolated oligonucleotides, which are self-assembled onto gold nanostructured screen-printed carbon electrodes. The oligonucleotide sequence is specific to a short region of SARS nucleocapsid protein. The presence of the virus is detected by enzymatic amplification of the viral DNA-probe hybridization signal. This causes a highly sensitive detection of the SARS target sequence. A suitable enzyme-conjugate, along with a blocking agent (casein) was utilized to minimize the non-specific signals. The detection limit reported was 2.5 pmol l$^{-1}$. In addition to gold nanoparticles, nanowires also hold potential in sensing applications. Ishikawa et al developed In$_2$O$_3$ nanowire sensors for the detection of SARS-CoV nucleocapsid (N) protein [30]. They utilized fibronectin based antibody mimic proteins (AMP) as capture agents. AMPs possess higher binding affinity and higher selectivity compared to antibodies and aptamers. The presence of viral N protein affected the electronic properties of the In$_2$O$_3$ nanowire and was detected as an electronically readable signal. The nanosensor was capable of detecting sub-nanomolar concentrations of the viral N protein (even in the presence of 44 μM bovine serum albumin as a background).

2.4. Chiral biosensors

Chiral biosensors with rapid response time may prove to be especially useful in the SARS-CoV-2 pandemic. Ahmed et al. fabricated chiral zirconium quantum dots for the detection of coronavirus [22]. Zirconium quantum dots and magnetic nanoparticles were conjugated with coronavirus specific antibodies and mixed together. In the presence of a viral target, both the quantum dots and nanoparticles will bind to the viral target.
and form magneto plasmonic-fluorescent nanohybrids, which can be separated by an external magnet. The analyte concentration was then determined by measuring the fluorescence intensity of the separated nanohybrids. This sensing method has a limit of detection of 79.15 EID/50 μl. In another study, Ahmed et al. reported chiro-immunosensor using self-assembled chiroplasmonic gold nanoparticles and quantum dots [21]. The immunosensor was able to detect coronavirus infection in blood samples. The virus sample was added to antibody conjugated chiral gold nanostructures followed by the addition of antibody conjugated quantum dots. The change in the chiro-optical response was measured by circular dichroism (CD). Asymmetric plasmonic chiral gold nanostructures created by self-assembly, enabled extension of the spectral range of CD response. This helped to obtain an improved plasmonic resonant coupling with an excited state of quantum dots. The reported chiro-immunosensor had a lower LOD (limit of detection) value of 47.91 EID/50 μl for coronavirus.

3. Nanotechnology in SARS-CoV-2 treatment

Currently, no SARS-CoV-2 specific antiviral drugs are available in the clinic. The development of anti-viral drugs takes many years before it can be made available for the treatment of patients [31]. The drug has to pass through various regulatory and safety measures before its clinical use [32]. Moreover, the development of viral resistance seen in the case of other viral infections is another challenge of employing drugs for viral infection treatment. In this section, we will explore the potential of nanotechnology in addressing these concerns. We will review some of the previous studies which have successfully demonstrated the application of nano-based therapies in targeting SARS-CoV-2 related viruses, such as SARS-CoV, MERS-CoV, and other members of the coronavirus family.

3.1. Blocking viral entry into the host cell

The first step of the viral infection cycle involves the binding of the virus to the host via cell surface receptors. Blocking the entry of viruses has been found to be a successful anti-viral strategy in many viral infections (figure 3). By virtue of their properties, nanostructures are suitable to competitively bind and inhibit viral entry into cells [33]. Some nano-based approaches are targeted to binding the virus particles directly, preventing them from approaching the host cell in the first place. For instance, carbon quantum dots were found to interact with the S protein of human coronavirus (HCoV-229E strain), preventing the viral protein interaction with the host cells. This reduced viral replication (figure 4). When the carbon quantum dots were functionalized with boronic acid, they exhibited even higher antiviral activity [34]. Huang et al. demonstrated the benefit of utilizing gold...
nanorods in developing anti-viral therapy for the Middle East Respiratory Syndrome (MERS) virus, which is also a member of the coronavirus family. MERS virus utilizes its surface spike (S) protein to mediate the fusion of the viral membrane with the host cell membrane in order to facilitate entry of the viral genome into the host cell. However, a small α-helix peptide, pregnancy-induced hypertension or PIH was effective in blocking the membrane fusion mediated by the S protein. Conjugation of the S protein to gold nanorods not only increased the therapeutic potential of PIH but also improved its biocompatibility, biostability and pharmaceutical profiles in vitro and in vivo [35].

Some natural compounds possessing anti-viral potential can be coupled with nanoparticles for synergistic therapeutic effects. Du et al reported the antiviral potency of hypericin (HY) loaded graphene oxide (GO) complex (GO/HY). Hypericin, which is an anthrone derivative, obtained from Hypericum perforatum, exerts anti-viral effect against a wide range of viruses. The low cytotoxicity and high loading capacity of GO helped to improve the anti-viral efficacy of hypericin. The GO/HY complex inhibited viral replication, which can be attributed to either suppression of viral attachment to the host cell or due to the inactivation of the virus itself [36]. Not only hypericin but graphene oxide also possesses intrinsic anti-viral properties [37]. Akhavan et al found that graphene tungsten oxide composite film inactivated viruses when irradiated under visible light. The inactivation of the virus was reported due to photo-degradation of viral capsid protein followed by the subsequent release of viral RNA [38]. Curcumin also possesses broad-spectrum antiviral activity and exerts its viral inhibitory actions by various mechanisms. However, the low water solubility of curcumin limits its application in clinics. Yang et al improved the solubility and biocompatibility issue of curcumin by loading them into graphene oxide nanoparticles (GSCC). Functionalization with sulfonate groups allowed curcumin loaded graphene oxide to mimic cell surface and inhibit viral attachment by a competitive inhibition mechanism. Moreover, the GSCC exhibited antiviral activity, both pre- and post-viral infection of the host cell [39].

Furthermore, carbon quantum dots synthesized from curcumin possess superior anti-viral properties and greater water solubility, compared to natural curcumin. These carbons dots were effective in inhibiting viral binding to the cell surface [40]. Du et al reported that curcumin based cationic carbon dots act as multi-site viral inhibitors [41]. The study involved porcine epidemic diarrhea virus (PEDV), which is a member of the coronavirus family. The curcumin carbon dots altered the structure of the viral surface protein, thereby inhibiting the cell entry of the virus. The carbon dots also suppressed the formation of negative-strand RNA of virus and viral budding. The carbon dots stimulated the production of pro-inflammatory cytokines and interferon-stimulating genes (ISGs) to inhibit viral replication. Yang et al also reported that curcumin modified silver nanoparticles were effective antiviral agents and inhibited the virus prior to cell infection [42].

It has been reported that many viruses, including coronaviruses, utilize HSPG as a receptor to mediate the first step of the virus replication cycle [43]. Therefore, many HSPG mimicking materials, including heparin have been utilized to prevent viral infection [44, 45]. However, most of these substances exhibit reversible binding with the virus and hence the inhibition is lost upon dilution, exerting virustatic effects in vitro and no anti-viral...
effects in vivo. Cagno et al synthesized heparin sulfate proteoglycan (HSPG) mimicking nanoparticles to irreversibly inhibit viral binding to host cells [46]. Gold nanoparticles coated with mercapto-1-undecanesulfonic acid (MUS-AuNPs) bound irreversibly to the virus, eventually leading to viral deformation. The long backbone of MUS allows flexibility to the terminal sulfonate groups to bind in a multivalent fashion. The MUS-AuNPs were virucidal in vivo in mice infected with the respiratory syncytial virus. Viana et al developed glycodendrinnanoparticles to competitively inhibit viral binding to the glycan receptors. Using nested layers of multivalency, highly valent glycodendrimeric constructs were fabricated which mimicked the virus both in size and the high surface glycosylation present on the virus. These nanoparticles were able to successfully block host-pathogen interaction at picomolar concentrations [47].

3.2. Inhibiting viral replication
Once the virus enters the cell, it hijacks the cellular biochemical machinery to produce more copies of itself. If the virus is able to successfully execute the second step of the infection cycle, it is able to spread in the body and cause infection. Thus, therapeutic strategies targeting this step are extremely essential to contain the infection. Nanostructures have mainly been utilized as carriers to deliver the anti-viral molecules. The benefits which the nanoparticles provide in this regard are- higher specificity and bioavailability of the viral drug, combining different drug molecules in a single particle, improved solubility of the drug and decreased toxicity to the host. However, recently a number of nanoparticles are shown to intrinsically inhibit viral replication, such as Ag$_2$S nanoclusters, which were reported to exert an inhibitory effect on coronavirus replication, thereby preventing the budding of new viral particles from the host cell. In addition, Ag$_2$S nanoclusters also enhance the expression of pro-inflammatory cytokines, which might also play a role in combating viral infection. The study was carried out using the porcine epidemic diarrhea virus (PEDV) as a model for coronavirus infection [48]. Similarly, zinc oxide (ZnO) nanoparticles have also been reported to possess antiviral activity. ZnO nanoparticles have been effective against H1N1 influenza virus infection, and studies have also reported the ability of zinc to inhibit SARS-CoV replication [49, 50]. Zinc modulates host immune response, inducing the production of antiviral cytokines and suppressing inflammation. Other studies have also highlighted the role of antiviral efficacy of zinc oxide nanoparticles, and exploring the anti-SARS-CoV-2 potential of these nanoparticles might provide an early therapeutic solution for COVID-19 [51, 52]. RNA dependent RNA polymerase (RdRP) is an important SARS-CoV-2 protein, which helps to maintain genome fidelity, together with some other non-structural proteins. Inhibiting viral RdRP enzyme will provide a therapeutic advantage against COVID-19. A similar strategy employed by Shiang et al to inhibit HIV reverse transcriptase may be utilized for inhibiting SARS-CoV-2 RdRP. His research group developed aptamer functionalized gold nanoparticles to inhibit viral reverse transcriptase. The conjugation of aptamers to gold nanoparticles protected them from nuclease degradation and increased their in vivo lifetime. Also, the conjugation allowed a multivalent display of aptamers, resulting in greater antiviral activity. Two different aptamer-Au nanoparticle conjugates were synthesized, one containing aptamers specific for the polymerase region and other containing aptamers specific for the RNaseH of HIV reverse transcriptase [53]. Silver nanoparticles have also been found to exert anti-viral effects on coronavirus as well. Xiaonan’s research group reported that silver nanoparticles and silver nanowires inhibited TGEV (a type of coronavirus) multiplication and also inhibited TGEV-induced host cell infection. These nanomaterials also downregulated host cell apoptosis triggered by TGEV infection [54].

3.3. Nano-delivery systems for COVID-19 treatment
Drug delivery via nanocarriers helps to overcome several challenges associated with the traditional method of antiviral drug administration. Poor bioavailability, susceptibility to in vivo degradation of drug, systemic toxicity, and short half-life in the body are some of the drawbacks associated with antiviral therapeutics. However, nano-delivery systems resolve these issues and enable higher bioavailability, reduction in effective drug dosage, lower toxicity, protection from degradation, improved half-life in circulation and ability to cross the biological barriers to target viral infection in sheltered body sites [55]. Stealth technology, specific tissue or cell targeting, and desired drug release profiles are some other advantages of nano-delivery systems. Specific targeting of nanocarriers can be achieved by targeting moieties like monoclonal antibodies for cell surface antigens or by employing stimuli-responsive nanoparticles [56]. The stimuli sensitive nano-delivery systems can be triggered by some intrinsic abnormal factors at the viral infected tissue such as temperature values or pH. On the contrary, these smart nanocarriers can also be sensitized to external stimuli like applied magnetic field or ultrasound waves [56]. Liposomes, dendrimers, micelles, microspheres and other organic nanoparticles have been successfully used for improved and targeted delivery of different antivirals such as dapivirine, efavirenz, acyclovir and zidovudine [56].

Given that COVID-19 is a respiratory disease, inhalable nanoparticles can be a non-invasive method of delivering anti-SARS-CoV-2 therapeutics directly to their site of action. This can help in the preferential
deposition of nanoparticles in the SARS-CoV-2 infected lung tissues. To administer drugs in respirable form, devices such as nebulizers are used, which deliver the drug as a solid or liquid, suspended in a gaseous medium [57, 58]. It has been reported that many therapeutic molecules, when administered alone, are not stable in aerosolized form. However, when combined with nano-delivery systems, they can be easily administered in inhalable forms with enhanced lung deposition and retention [59, 60]. Nanocarriers are especially important delivery of poorly soluble drugs, which exhibit bolus formation and subsequent lung toxicity when given as free drugs [61]. Both inorganic as well as polymeric nanoparticles have been studied as nanocarriers for drug delivery in the respirable form [62, 63]. Mucociliary clearance and phagocytosis by alveolar macrophages are the physiological barriers that must be taken care of when developing inhalable nanomedicines.

### 3.4. Nano-based vaccine

Conventional vaccines such as live attenuated viruses, inactivated viruses, or subunit vaccines, all have certain limitations. The risk of reversion of viral virulence (live attenuated vaccines), weak immune response (inactivated viruses), and limited immunogenicity (subunit vaccines) are some of the concerns of conventional vaccines. However, advances in biological and chemical engineering allow designing nano-based vaccines with strong immunogenicity and enhanced antigen presentation. Nanoparticles can serve as platforms for displaying the viral antigen to host immune cells such as the small nanovesicles expressing MERS virus S protein on its surface, mimicking MERS-CoV pathogen. Recombinant viral proteins, namely, Spike (S), Envelope (E), and membrane (M) proteins, were transfected into Bm5 cells, and S-protein displaying nanovesicles were obtained by both surfactant treatment as well as mechanical extrusion method [64]. Raman et al and FIMENTEL et al reported that peptide nanoparticles could act as potent immunogens and serve as a vaccine for SARS and other enveloped viruses. They designed a polypeptide that self-assembles into icosahedral nanoparticles. The polypeptide sequence corresponded to a C-terminal region of viral S protein which plays an important role in the entry of the viral genome into the host cell. The icosahedral nanoparticle repetitively displayed the B-cell epitope and elicited an adequate antibody response with the use of any adjuvants. The potent immunogenic effect of the vaccine is due to the small size of the immunogen and the repetitive presentation of the epitope, both of which were met by virtue of utilizing nanoparticles [65, 66]. Functionalizing the antigen-loaded nanoparticle with ligands targeting the antigen-presenting cells of the immune system helps to enhance significantly the vaccine potential. For instance, RAGHUWANSHE et al developed plasmid DNA loaded chitosan nanoparticle formulation as a potential vaccine for immunization against the SARS-CoV virus. The plasmid DNA encoded the nucleocapsid (N) protein of SARS-CoV, as it is highly conserved compared to other SARS-CoV proteins and is also abundantly shed during viral infection. The chitosan nanoparticles surface contained bifunctional fusion protein which specifically recognized the DEC-205 receptor of nasal dendritic cells to elicit an immune response at the site of the viral entry itself. When these nanoparticle vaccines were delivered intranasal along with anti-CD40 dendritic cell maturation stimuli, they stimulated mucosal IgA response and systemic IgG response against viral N protein. However, when the naked plasmid DNA was delivered intranasal, it did not elicit mucosal or systemic immune response [67]. Many studies have reported that, in case of respiratory infections, vaccination via the intranasal route leads to better immune-mediated protection [68, 69]. Intranasal vaccination induces higher levels of antigen-specific IgA antibody, higher cytokine production and a more increased proliferation of antigen-specific lymphocytes. Shim et al developed a SARS vaccine, comprising of DNA encoding for viral spike protein (pci-S), complexed with polyethyleneimine (PEI). Intranasal delivery of the PEI/pci-S vaccine nanoparticle elicited antigen-specific antibody and cellular immune response. Mice vaccinated with PEI/pci-S had a high number of B220+ cells as well as elevated levels of class II major histocompatibility complex molecules (I-A^d) and costimulatory molecules (CD80 and CD86) on CD11c+ dendritic cells of cervical lymph nodes [70]. Nano-based vaccines allow loading the adjuvant along with the viral antigen, accelerating the development of safe and effective vaccines. LIN et al reported virus-like polymeric nanoparticles as a vaccine for the MERS-CoV. A suitable adjuvant (STING agonist) was encapsulated in a shell layer of poly (lactic-co-glycolic acid) (PLGA), and the MERS-CoV RBD antigen was displayed on the nanoparticle surface to mimic the viral morphology. The viromimetic nanoparticle vaccine-elicited RBD antigen-specific T-cell and potent neutralization antibody responses in mice. Moreover, the transgenic mice model (permissive for MERS-CoV) immunized with the nanoparticle vaccine was safely protected when challenged with a lethal MERS-CoV infection [71].

### 3.5. Current SARS-CoV-2 nanotherapies under development

Many therapy candidates currently in development for COVID-19 infection are utilizing nano-based approaches. iBio and Beijing CC-Pharming are developing SARS-CoV-2 virus-like particles using iBio’s FastPharming System (ibioinc; see Related Links). The Virus-like particles (VLPs) will be purified from plants and tested further as vaccine candidates. Moderna has developed a lipid nanoparticles encapsulating
mRNA vaccine. The mRNA codes for SARS-CoV-2 spike protein (Moderna, Inc., see Related links). This nanoparticle-based vaccine has already entered the clinical trials. NanoViricides, Inc. has developed nanoviricides capable of binding and engulfing the SARS-CoV-2 virus particle. The nanoviricides comprise of a nanomicelle conjugated with ligands that can bind to the virus. These ligands are derived from the host receptor angiotensin converting enzyme type 2 (ACE2) of SARS-CoV-2.

4. Nanotechnology for improvement of personal protection equipment (PPE)

In the present pandemic situation, when no definite therapy or vaccine is available, the people at the highest risk of infection are the healthcare professionals, in addition to the aged people and those with other comorbidities and immunodeficiency [72]. Thus, the protection of healthcare workers for catching the infection is not only imperative for proper patient care but also to prevent healthcare workers from unknowingly serving as SARS-CoV-2 carriers [73]. Thus, highly effective personal protective equipments (PPEs) are imperative for healthcare workers. In areas or situations where social distancing cannot be strictly practised, PPEs can be effective measures.

It has been reported that SARS-CoV-2 persists for many hours on frequently touched surfaces (such as doorknobs, public toilets, light switches, tables etc) and aerosols [74–77]. Since the surface and aerosol contamination play a significant role in the spread of SARS-CoV-2, the development of antiviral surface coatings and efficient air filtering devices may help reduce viral contamination [78]. Also, it has been found that the PPE kits currently in use also frequently carry SARS-CoV-2 contamination [79].

Nanotechnology-based solutions can be promising approaches for improving the effectiveness of PPEs, given that many nanoparticles have been proven to exhibit potent antiviral properties. For instance, the controlled release of metal ions such as copper, for a long-duration, helps to modulate the antiviral properties of surfaces, and metal nanoparticles serve as a reservoir for ensuring the controlled release of metal ions [80, 81]. The metal nanoparticles can be loaded into a polymer matrix to develop highly efficacious anti-viral surface coatings. Similarly, Bhattacharjee et al reported the antimicrobial properties of metal grafted graphene oxide, and the same has been explored for utilization in PPEs [82]. Graphene oxide loaded with copper or silver nanoparticles possess antiviral potential against enveloped and non-enveloped viruses [83, 84]. Borkow and colleagues demonstrated that polypropylene masks loaded with copper oxide are useful in protection against the influenza virus [85]. In order to prevent contamination of the facial masks, Balagna et al deposited a coating of silver nanocluster/silica composite on face masks. When tested for SARS-CoV-2, this coating successfully reduced the viral titres on the mask. Such coatings can also be utilized on frequently exposed surfaces in public places to protect from environmental contamination of the SARS-CoV-2 virus [86]. Similarly, Ahmed et al incorporated copper oxide nanoparticles and graphene oxide into electrospun nanofibres for inactivating the viral particles trapped in the face mask [87]. Graphene oxide has been reported to exhibit antiviral activity against porcine epidemic diarrhea virus, which is also a coronavirus [88]. The use of graphene can offer the possibility of sterilizing facemasks allowing their re-use [38, 89]. The thermal and electrical properties of graphene can enable sterilization of the filters and fabric of the facemasks and respirators. Thus, the nanomaterials can help to significantly improve the current PPEs, helping prevent exposure to the virus in the first place.

5. Conclusion

The SARS-CoV-2 pandemic is claiming a large number of human lives and is a serious health concern for the international community. Precaution is best to measure available currently to fight this infection. Those affected with the disease only receive symptomatic treatment or supportive therapy. Presently, a cure is not available for this highly contagious infection. But scientists world-over are working extensively to quickly develop a safe and effective drug treatment or a vaccine for COVID-19. Efforts are also underway in developing more sensitive, specific, and easy to use diagnostic kits for detecting the pathogenic virus. The scientific community is also working on ways to develop highly protective tools for personal protection and environmental decontamination, which is also a smart way to manage the current pandemic situation. Nanotechnology has been able to provide promising solutions for some other human health problems and diseases. Nanomaterials offer the advantage of incorporation of conventional anti-viral or viral detecting modalities with new modifications that are unique to nano-sized systems. Taking advantage of the unique properties of nano-sized materials for COVID-19 detection and treatment will help to provide immediate relief from the ongoing pandemic.
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