Recent Advancement in SARS-CoV-2 Diagnosis, Treatment, and Vaccine Formulation: a New Paradigm of Nanotechnology in Strategic Combating of COVID-19 Pandemic

Sushil Kumar Upadhyay 1 • Siddhartha Dan 2 • Mansi Girdhar 1 • Kartikey Rastogi 3

Abstract

Purpose of Review The coronavirus disease-2019 (COVID-19) is a global pandemic which has not been seen in recent history, leaving behind deep socioeconomic damages and huge human losses with the disturbance in the healthcare sector. Despite the tremendous international effort and the launch of various clinical trials for the containment of this pandemic, no effective therapy has been proven yet.

Recent Findings This review has highlighted the different traditional therapeutic techniques, along with the potential contribution of nanomedicine against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Repositioning of the drugs, such as remdesivir and chloroquine, is a rapid process for the reach of safe therapeutics, and the related clinical trials have determined effects against COVID-19. Various protein-based SARS-CoV-2 vaccine candidates have successfully entered clinical phases, determining positive results. The self-assembled and metallic nanovaccines mostly based on the antigenic properties of spike (S) protein are also approachable, feasible, and promising techniques for lowering the viral burden.

Summary There are number of NP-based diagnostic systems have been reported for coronaviruses (CoVs) and specifically for SARS-CoV-2. However, extensive studies are still necessary and required for the nanoparticle (NP)-based therapy.

Keywords COVID-19 • SARS-CoV-2 • Nanomedicine • Nanovaccines • Nano-based diagnosis

Introduction

The outbreak of coronavirus disease-2019 (COVID-19) began in Wuhan, China. The corona virus global crisis is posing unprecedented difficulties to humans [1]. This new social landscape requires collective consideration, where our actions are interrelated, interdependent, to trans-boundaries and cultural diversity [2, 3]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was recognized as the causative agent of this revolution and grown by smooth tissues such as the muzzle, mouth, and nose [4, 5]. The SARS-CoV-2 is a single-stranded ribonucleic acid (ssRNA) virus having a short genome of 26–32 kb with a diameter of 65–125 nm, and earlier known to be a 2019-novel coronavirus (2019-nCoV) [6, 7]. The infection expanded quickly everywhere in China within a month, and according to the World Health Organization (WHO), it is recently expanded to over 212 countries, regions, and provinces worldwide [8, 9]. Based on clinical evidence, there are two major requirements to control the COVID-19 pandemic: first to overcome infection rates and second to reduce mortality [10]. Recently, no approved drugs or vaccines are prepared for the treatment or prevention of COVID-19 [11]. Still, the ongoing vaccines are in the second and third phases of clinical trials. As the accessible therapies, including nonspecific antivirals, antibiotics, to treat secondary bacterial diseases, sepsis, and corticosteroids to decrease inflammation fail to treat the severe illness with COVID-19 [12, 13]. This appears as inflammatory lesions with ground-glass ambiguity on computed tomography (CT) scans. The current accessible drugs have been able to moderately handle indications. Therefore, the appropriate and effective medical treatment for the current COVID-19
infection is an immediate demand for mankind [10]. Early detection of the infection is essential for defence among all states including symptomatic and asymptomatic populace [3, 11, 14]. Numerous forthcoming drugs that are thought to be unsuervingly appropriate, as well as new therapeutic drugs are being produced, including viral entry inhibitors, replication inhibitors, protease inhibitors, heterocyclic antivirals, nanodrug delivery systems, and biological therapeutic drugs [15].

In the name of health as our primary necessity, the common interest should be addressed in the future, keeping in mind the “One Health” concept, relying on the belief that the well-being of humans is stringent with animals’ connections and environment [16]. To tackle such a complex challenge, the collaboration between diverse researchers with complementary expertise is needed. The current challenge should be taken as an incredible opportunity to remind us of our globalized world, as shown in other scientific contexts, a multi-disciplinary methodology involving transversal disciplines of knowledge between countries [17]. Promoting exchanges and increasing diversity in teams will all be necessary to obtain new and important scientific solutions [18]. From this point of view, nanotechnology is inherently an area in which scientists with incredibly diverse backgrounds have converted into valuable cooperations for multifaceted difficulties. Now, nanotechnology is required to lay new foundations towards combating the recent global public health threat and rethinking a more sustainable future based on science [19]. Nanoparticles (NPs) are small, but have a large surface-to-volume ratio, giving them unprecedented, unique features. Because of these characteristics, nanoparticles have been used in the fields of biotechnology, medicine, drug delivery, sensors, and DNA labelling and are treated as a bridge between bulk materials [20]. The nano-strategies have been widely applied to enhance antiviral drug delivery and efficiency, individually in combination with nucleoside analogues which have potential applications against drug-resistant human immunodeficiency virus disease also [15, 21]. There are several available nano delivery systems can be used with newly developed drug formulations to efficiently deliver drugs with rapid therapeutic indices for COVID-19. However, this work is in growth phase, and no nanotechnology is recently available for the treatment of COVID-19 so far. Even nanotechnology plays a pivotal role in the analysis of COVID-19 [22]. In this review, authors explain the possible role of nanotechnology in the diagnosis, investigation, vaccine formulation, and reasonable treatment of COVID-19.

Nanoparticle-Based Diagnosis of Coronavirus

The diagnosis of coronaviruses (CoVs) including SARS-CoV-2 is primarily based on computing tomography scans and nucleic acid testing that utilize reverse transcription polymerase chain reaction (RT-PCR) technique [23, 24]. The rapid analysis and recognition of infected patients are the most ideal approaches to contain surges and typical-to-traditional diagnostic methods because of inaccessibility of facilities, instruments, reagents, low yield, and technical speciality. Because of urgent need for fast, sensitive, and economic testing of COVID-19, nanotechnology can play a crucial role in the diagnosis of SARS-CoV-2 using nanoparticle-based (NP-based) electromagnetic properties (Table 1) [35]. The test procedures require robotized extraction of nucleic acids from samples to prevent cross-contamination or false-negative outcomes. Magnetic nanoparticles (MNPs) are also employed in separation of nucleic acids. For instance, Zhao et al. built up a one-step nucleic acid isolation procedure utilizing amino-adjusted MNPs along with polycarboxyl groups (PC-coated NH2-MNPs) to tie viral RNA [25]. Under influence of magnetic fields, nucleic acid combines easily and delivered from MNPs by the expansion of buffer. Utilizing COVID-19 pseudoviruses, polycarboxyl MNPs (10 ± 3 nm, −39 ± 1 mV) indicated superior retention and paramagnetic properties at a magnetic capture of 30 s. Superparamagnetic NPs were set up to give a magnetite core secured with silica of 80 nm combined with probe that is corresponding to the target cDNA (complementary DNA) of SARS-CoVs. The functionalized superparamagnetic NPs had the option to strengthen and separate target cDNA from samples utilizing magnetic field [26]. This separated DNA was intensified with polymerase chain reaction (PCR) so that it could be effectively detected through sandwich hybridization assessment through silica-coated fluorescence NPs (40 ± 5 nm) bringing about fluorescence intensity, which is legitimately identified with the target cDNA concentration.

Gold nanoparticles (AuNPs) were investigated for developing nano assays for two reasons: (i) simplicity of electrostatic surface-design with different moieties, for example, antigens and antibodies; and (ii) SPR transition and change in colour [35, 36]. The AuNPs are most commonly utilized in colorimetric hybridization tests such as disulfide bond-based colorimetric assay designed by Kim et al. [27]. Utilizing thiolated single-stranded deoxyribonucleic acid (ssDNA) probes for targeting sites of Middle East respiratory syndrome coronavirus (MERS-CoV) genome for envelope protein (E) gene and open reading frame-1a (ORF-1a), framing a long self-assembled hybrid. This structure shields citrate ion-headed AuNPs from salt-actuated assembly. However, when target genes are absent, this protection is nonexistent, bringing about accumulation of AuNPs [27]. AuNP-based elementary hybridization assay was accounted for utilizing a DNA probe, which comprises thiolated-DNA comb immobilized on AuNP carbon terminal to hybridize biotinylated target DNA of SARS-CoV (Fig. 1) [28]. As a consequence of this, basic phosphatase streptavidin was formed through streptavidin-biotin association, catalyzing silver (Ag) ions and statement displacement of metallic Ag on anode surface. Metallic Ag
| Nanoparticles          | Virus               | Platform and ligand                                           | Target                                      | Description                                                                 | Ref. |
|------------------------|---------------------|---------------------------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------|------|
| Magnetic nanoparticles (MNPs) | SARS-CoV-2          | Polycarboxyl-functionalized magnetic nanoparticles in polycarboxyl groups | Viral RNA                                   | One-step, simple, sensitive, excellent paramagnetic characteristic, high purity and fertility, no toxic reagents | [25] |
|                        | SARS-CoV            | Superparamagnetic nanoparticles in probe (complementary to cDNA) | Targeted cDNA                               | Quick process, high specificity, and sensitivity                              | [26] |
| Gold nanoparticles (AuNPs) | MERS-CoV            | AuNP-based colorimetric assay in thiolated ssDNA probe        | Upstream of envelope protein gene and ORF-1A | Visible detection, cheap, quick (within 10 min), limit of detection is 1 pmol/μl | [27] |
|                        |                     | AuNP-modified carbon electrodes in thiolated ssDNA probe      | Targeted DNA                                | Quick, sensitive, simplistic                                                  | [28] |
|                        |                     | Array of AuNP-modified carbon electrodes in MERS-CoV protein  | Antibodies                                  | Extremely selective, individual-step, genuine and sensitive                  | [29] |
|                        |                     | Streptavidin-AuNP conjugates in streptavidin                   | Fluoresce in isothiocyanate and biotin-labelled RNA of MERS-CoV (nucleocapsid gene) | Upward flow detection, simple to operate, low-priced, quick                  | [30] |
|                        | SARS-CoV-2          | SARS-CoV-2 antigen-AuNP conjugates (immunoassay strip)         | IgG1 IgM against SARS-CoV-2                 | Chromatographic immunoassay is membrane-based, quick, affordable             | [31] |
|                        |                     | in SARS-CoV-2 antigens                                        |                                             |                                                                               |      |
|                        | Antigens- SARS-CoV-2 conjugates (immunoassay strip)            | IgG1 IgM for SARS-CoV-2                       | Oblique flow detection, sturdy readout signal                                 | [32] |
|                        | Silica-coated fluorescence nanoparticle in probe (complementary to cDNA) | Target cDNA                                   | Quick process, high specificity and sensibility                                | [33] |
|                        | AI-A, AV, CoV       | Self-assembled star-shaped chiroplasmonic AuNP-quantum dot in virus-specific antibodies | Target virus                                | Chiro-immunosensor with exciton-plasmon interaction in chiral AuNP ultrasensitive | [34] |

*SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; AI-A, avian influenza-A; AV, adenovirus; CoV, coronavirus; cDNA, complementary DNA; AuNP, gold nanoparticle; ORF, open reading frame*
can be estimated and it is in proportion to the concentration of alkaline phosphatase that target viral DNA [28].

Chiral gold nanohybrids (CAuNPs) with quantum dots (QDs) have been recently utilized to build star-shaped chiroplasmonic AuNPs that can detect distinctive viral infections including CoVs [34]. In this technique, each of CAuNPs and QDs were conjugated to two distinctive target virus-targeted antibodies. When target virus is present, a nanosandwich configuration was produced, bringing about predominant plasmonic resonant coupling with the beta particle of QD [34]. In addition, AuNPs can be intended to identify CoV-specific antibodies utilizing electromagnetic immunosensor assay consisting of a chip and a C-terminal that contains a variety of AuNPs to identify CoV-explicit antibodies (Fig. 1) [29]. Over the surface of AuNP-anodes, MERS-CoV protein was immobilized in the presence of antibodies with specific concentration; emulation took place between the free viruses in the prototype with immobilized MERS-CoV protein. A ferrocyanide probe was utilized for electrochemical estimation. This chip was utilized for multiplexed recognition simultaneously through numerous terminals on a similar chip, with every electrode connected to various viral antigens [29]. New indicative tests for SARS-CoV-2, for example, NP-based flow detection strips, were too augmented to accelerate detection and also eliminate the prerequisite to send samples at laboratories. Vertical stream (VF) detection was done to visually recognize nucleoprotein (N) gene of MERS-CoV in association with reverse transcription loop-interceded isothermal amplification method (RT-LAMP-VF) [30]. RNA of MERS-CoV was enhanced by RT-LAMP; the amplicons were labelled with

Fig. 1 Nanoparticle-based assays for coronaviruses. a Colorimetric hybridization assays, b Electrochemical hybridization assays, c Electrochemical immunosensor assays
Coronavirus is one of the deadliest respiratory infections which is quickly propagating overseas and has caused global concern. Presently, it is analyzed by SARS-CoV-2 nucleic acid through reverse transcriptase loop-mediated isothermal amplification (RT-LAMP) combined with a nanoparticle-based biosensor (NBS) [41]. Other approaches are time-tedious and complex and require skilled specialists. Therefore, Yang et al. built up a RT-LAMP test to recognize triple genes for rapid diagnosis of SARS-CoV-2 [37]. In 2003, this technique was utilized to test for the SARS coronavirus and found to be simple and quick [42]. RT-LAMP, NBS-LAMP amplification method, and reverse transcription with nanoparticle-based biosensors enable diagnosis of COVID-19 in a single step. This technique requires 30 min for the amplification of nucleic acid at a consistent 60–65 °C utilizing various primers to distinguish the N, E, and ORF1ab gene sequence. Around ten sets of such primers have been configured per gene. The specificities of the COVID-19 RT-LAMP-NBS test was investigated by analysis of genomic sequence obtained from different microbes, including bacteria, fungi, and virus [22, 43].

**Point-of-Care Testing**

Purpose-of-care test procedure is followed when the patient samples are not sent to research facilities; this method does not require lab network to recognize patients who are infected. Lateral-flow antigen detection for SARS-CoV-2 is a consideration point being used for diagnosing COVID-19 [44]. Business lateral flow assays consist of a paper-like film strip covered with two lines: one consists of gold nanoparticle-antibody conjugate and another is used for antibody detection. Patient sample like blood, sputum, and urine are placed on the film; capillary movement attracts the protein through the line. At the point when the first line moves, antigens bind to the nanoparticle-antibody conjugate, after binding the complex streams across the film. The captured antibodies immobilize the complex after entering second side where the blue or red side is evident. Singular gold nanoparticles are red, while the coupled plasmon groups trigger the solvent enclosing the bundled gold nanoparticles to appear blue [23]. In research centres, numerous stages, for example, electrochemical sensors, paper-based frameworks, and surface-upgraded Raman spectrum-based systems are also established [22].

**Optical Biosensor Nanotechnology**

Optical biosensor nanotechnology is a new field of technology that enables the detection of the COVID-19 in only 30 min instantly from patients’ samples. This new innovation could undoubtedly decide if a patient is infected with the COVID-19 or flu infection [22]. This method will conceivably be utilized for procurement of patients and dealing with current pandemic situation. This novel biosensor device is also utilized for the analysis of different types of coronavirus diseases existing in animal body, for example, bats, cats, dogs, and sea animals, to identify and trace the possible evolutionary mechanism of these viruses for controlling such kinds of future outbreaks [22, 45].

**Nanopore Target Sequencing**

The nanopore target sequencing (NTS) technology detects SARS-CoV-2 with ten additional respiratory infections just in 6–10 h. This method is required contemporary for the diagnosis of COVID-19. Furthermore, the blueprint can also be extended to analyze different viruses and microorganisms. The NTS depends on intensification of eleven SARS-CoV-2 virulent virus.
and distinctive genomic sequence (e.g. ORF1ab) utilizing an essential band continued by sequencing of amplified section on a nanopore membrane [46]. This technique is based on a nanopore platform that sequences fragments of nucleic acid and simultaneously investigates the information near-real-time affirming SARS-CoV-2 diseases in few minutes by mapping the sequence read of SARS-CoV-2 genome for the analysis of identity and validity of outputs. The virulence locale (genome 21,563–29,674 bp; NC 045512.2) encoding spike (S, 1273 amino acid; AA), ORF3a (open reading frame 3a, 275 AA), envelope (E, 75 AA), membrane (M, 222 AA), ORF6 (66 AA), ORF7a (121 AA), ORF8 (121 AA), nucleocapsid (N, 419 AA), and ORF10 (38 AA) are helpful for the identification of SARS-CoV-2-virulent genomic sequence. The NTS is performed on one MinION sequencer chip (Oxford nanopore technique) to detect all test samples, the sequence info is determined through bioinformatics channelling at regular interval of timeframes. To expand plasmid concentration, all high-element reads were resolute by output reads on SARS-CoV-2 genome. As a norm for qPCR, NTS cannot decide that sample is positive for contagion via testing at one or two different domains; discoveries and information from all possible regions must be taken into consideration for further investigation [22, 47, 48].

Mechanism of Action of Antiviral Nanomaterials

Preclinical investigations have indicated virus nanoparticle reactions induce antiviral activity. Nanomaterials that work indirectly do not restrain virus alone; rather, they enhance the pharmacological action of antiviral medicines, and utilized for stability and better bioavailability [49–51]. Additionally, nanomaterials can likewise initiate an immune reaction for developing short-term immunity [52]. Interestingly, nanomaterials with direct activity act as dynamic compound, since they resist the viral infection alone, typically by changing the hereditary information of viral DNA. In 2005, Lara et al. demonstrated that receptors of HIV interact with AgNPs, restraining its infectivity [53]. They proposed that AgNPs bind to gp120 glycoproteins (GP) that prevent the virus to bind with cells, as noticed in the in vivo outcomes. Morris et al. has shown that AgNPs attach to surface GP of the virus preventing the association phenomenon by dropping its capability to attract cells [54]. Also, Cagno et al. proved that gold and iron oxide NP-coated ligands dislocate the configuration of numerous viruses [55], flattening the viral molecule that leads to denaturation of virus. Kim et al. exhibited that viral genes are suppressed by nanomaterials, the in vivo administration of anti-CCR5 siRNA/LFA-1 I-ts NPs silenced genes in leukocytes for approximately 10 days, inhibiting human immunodeficiency virus (HIV) disease [56]. Cojocaru et al. depicted the possible mode of action that permits nanomaterials to halt both DNA and RNA virus [57]. Among all the existing fundamental methods, inhibition of viral DNA/RNA is the major mechanism [58]. Nanomaterials show different characteristics of clinical intrigue, for example, upgraded chemical interactions, bio-compatibility, and controlled and targeted drug release, and were found safer when contrasted with the non-nanomaterials [59, 60].

Role of Nanotechnology in COVID-19 Treatment

COVID-19 outbreak requires impactful healthcare approaches for combating lethal lung infection. Until now, no particular medication is affirmed for the treatment of COVID-19 [61]. According to clinicians and therapeutic systems, a few immunomodulatory and antiviral drugs have been recommended and a number of drug verities are presently in phases of clinical trials. They include remdesivir, baricitinib, oseltamivir, EIDD-2801, favipiravir, darunavir/cobicistat, mRNA-1273, mycophenolate, tocilizumab, methylprednisolone, interferon, teicoplanin, ribavirin, hydroxychloroquine, and azithromycin [62]. On 28 March 2020, the Food and Drug Administration (FDA) permitted the use of hydroxychloroquine sulphate and chloroquine phosphate as an emergency prescription to fight against COVID-19 [63, 64]. As indicated by the most recent studies, regulations in Belgium, which additionally involved recommendations from Netherlands, Switzerland, France, and Italy, put forward the use of remdesivir, ritonavir/lopinavir, chloroquine or hydroxychloroquine, and tocilizumab for additional support; they also included use of O₂ ventilator as a life support system and to save lungs from failure [65]. Favipiravir another antiviral medicine endorsed in China and Japan for curing flu is currently under audit for COVID-19 [66]. In addition to these prescriptions, Chinese drugs assume significant function to deal with coronavirus. The Chinese Academy of Sciences in collaboration with Shanghai Institute of Materia Medica recommended that SARS-CoV-2 can be treated utilizing an oral dose of Shuanghuanglian [67, 68]. The chemical composition of this fluid consists of baicalin, chlorogenic acid, and forsythin also demonstrated antiviral and bactericidal effects [69]. At present day 20 September 2020, none of the vaccine is approved for COVID-19; researches are ongoing in almost every country and are under pipeline, some are in phases I, II, and III. A vaccine developed by Oxford when tested on participant during clinical trial indicated serious neurological symptoms. Nanotechnology could have high chances for curing COVID-19 [69]. These can be utilized to decrease the severity and lethality of the disease (Table 2). Experimentations are under process and nano-based drugs will ideally be accessible soon.

Nano systems with that work against SARS-CoV-2 have been summarized in Table 1. There are two main approaches to deactivate enveloped viruses. The first includes interaction between viral surface and nanomaterial for its inactivation. Nano system consists of hydrophobic layer that interacts with
| Target virus | Nanocomposites | Inhibition action | Inference or findings | Ref. |
|--------------|----------------|-------------------|----------------------|-----|
| Poliovirus type-1 | Silver nanoparticles (AgNPs) | – | AgNP-based merchandises were absolute for biomedical utilization and to fight viral contagions | [70] |
| Human immunodeficiency virus-1 (HIV-1) | Silver nanoparticles | The basic relationship between thiol residues and Ag | Ag nanoparticles showed antiviral activity against HIV-1 bound to carbon coated, PVP coated, and bovine serum albumin. The interactions of Ag nanoparticles and viruses were size-dependent and involved thiol groups of glycoprotein 120. | [71] |
| Human immunodeficiency virus (HIV) | Amantadine (Ada), on the outermost layer of PVP-PEG-coated silver nanorods (Ada-PVP-PEG silver nanorods) | Amantadine surface-modified silver nanorods enhance HIV vaccine-triggered cytotoxic lymphocyte to generate approximately eight times more potent tumor necrosis factor-alpha in vivo. | Surface alterations of nanomaterials in essentially enhancing immunotherapy of the HIV vaccine towards HIV-infected cells | [72] |
| Polyvinylpyrrolidone (PVP)/stearic acid (SA)-polyethylene glycol (PEG) NP | – | Meritorious cellular internalization | Convenient loading, sustained deliverance, hemocompatibility and nontoxicity | [73] |
| Lactoferrin NPs | – | — | — | [74] |
| Enterovirus 71 (EV71) | Amide functionalized alginate NPs | Represses viral transcriptase | — | [75] |
| Porcine epidemic diarrhea virus (PEDV) as a model of coronavirus | siRNA-modified Polyelectrolyne (PEI) encapsulated AgNPs | Prevent fragmentation of DNA, chromatin Condensation and activation of caspase-3 and obstacle approach of EV71 in the host cell | — | [76] |
| Respiratory syncytial virus (RSV) | Glutathione-capped Ag2S nanoclusters (NCs) | Represses the synthesis of viral negative-strand RNA and viral budding | — | [77] |
| Rabies virus | Nonlinear globular G2 dendrimer | — | — | [78] |
| Hepatitis C virus (HCV) | Ammonium-terminated amphiphilic Janus dendrimers | Repress HCV replication by combining with viral proteins | Nontoxic drug-loaded nano groups repress HCV replication at lowering camptothecin concentration. | [79] |
| Venezuelan equine encephalitis virus (VEEV) replicon RNAs Zika virus | Modified dendrimer NPs | Activation of both CD8+ T-cell. Viral E protein-specific IgG responses | This strategy can be utilized to evaluate fresh antigen antigens and recognize immune correlates without the usage of a live virus. | [80] |
| Pseudo typed viral particles (Ebola virus glycoprotein) H1N1, norovirus | Glycodendrofullerenes Carbohydrate moieties (Mannose, Galactose) | Dendritic cell-specific blocking Intracellular adhesion molecule 3 Non-integrated receptor grabbing DNA hybridization | Prohibition of viral attachment. Interrupted leading to the viral approach | [81] |
| Herpes simplex virus | Gold (Au)/iron oxide magnetic NP-decorated carbon nanotubes (CNTs) | — | — | [82] |
| Porcine reproductive and respiratory syndrome virus (PRRSV) | Monodispersed gold nanoparticles | — | — | [83] |
| Glycyrrhizic-acid-based carbon dots | Gly-CDs can repress PRRSV invasion and replication, stimulate antiviral innate immune responses, and prevent the accumulation of intracellular reactive oxygen species (ROS) due to PRRSV contamination. | Gold nanoparticles obtained recommended as a safer alternative in virus chemotherapy Gly-CD has exceptional antiviral action with a multisite inhibitory mechanism, giving an encouraging applicant | — | [84] |
| Target virus                                                                 | Nanocomposites              | Inhibition action                                                                 | Inference or findings                                                                 | Ref.  |
|------------------------------------------------------------------------------|-----------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------|
| Porcine epidemic diarrhea virus and pseudorabies virus                       | Gt, GtO, GO, rGO, GO-PDDA, GO-PVP | Electrostatic interaction and hydrophobic interaction with the sharp edged structure | The antiviral action accompanied the sequence: GO ≈ rGO > GO-PVP > GtO. Gt and GO-PDDA did not exhibit antiviral action. GO represses viral infection by inactivating the virus before inserting the cell. The envelope and routine spikes were damaged upon virus incubation with GO for both viruses. | [85]  |
| Porcine epidemic diarrhea virus                                              | Ag2 S NC                    | Cerium oxide demonstrated better at reducing virus titer when correlated to the control CD. The nanosystem can repress viral approach, the synthesis of negative-stranded RNA, the budding of the virus, and the reactive oxygen species (ROS) produced by PEDV | CD based on curcumin Electrostatic interaction CD based on curcumin resulted in better at reducing virus titer when correlated to the control CD. The nanosystem can repress viral approach, the synthesis of negative-stranded RNA, the budding of the virus, and the reactive oxygen species (ROS) produced by PEDV | [86]  |
| Feline coronavirus and infectious bursal disease virus                       | GO and GO-Ag                | Electrostatic interactions and hydrophobic interactions within the lipid and the aromatic plane of GO. The basic relationship between thiol residues and Ag | GO and GO-Ag exhibited repression of FCoV with better results for the latter (only GO-Ag exhibited inhibition for IBDV). For clogged viruses, GO acts as a support and contributes towards the inhibition of the virus. No hydrophobic interactions exist for non-enveloped viruses and virus inhibition requires a divert bond. | [87]  |
| Bacteriophages MS2 and ΦX174, murine norovirus, and adenovirus serotype 2     | Ag-MHC                      | The basic relationship between thiol residues and Ag. Ag⁺ ions can produce ROS and contribute towards virus inactivation | The Ag-MHC operation produced significant antiviral effects towards bacteriophages ΦX174 and MNV, but not towards AdV2. Antiviral actions were diminished at pH 2 and 12. When estimating bacteriophage inactivation in tap and surface waters, Ag-MHC maintained its activity towards butX174, but it was diminished for MS2 correlated to regulators (distilled water). | [88]  |
| Human coronavirus-229E                                                        | CQD modified with boronic acid moieties | Glycan borono-lectin interaction involving the S protein | CQDs were reactivated with boronic acid, phenylboronic acid, and 4-aminophenyl boronic acid, which determined antiviral action with better results for the latter. Viral repression action in the replication phase was determined. | [90]  |
| Influenza A/PR/8/34 (H1N1)                                                   | SNP-DDAB                    | Electrostatic interaction                                                         | Nanosystems show antifungal, antibacterial, and antiviral action when applied to surfaces. The existence of any virus was not detected when contacted with nanosystems and influenza virus-coated glass coverslips. | [91]  |
| Influenza strain X-31, A/Aichi/2/68 (H3N2)                                   | NT-P                        | ROS upon irradiation                                                              | When NCI cells were treated with NT-P in the presence of a virus, the percentage of infection was reduced to 1% after 90 hours. | [92]  |
the lipid membrane present on viral surface encouraging denaturing. Examples possibly will be 1 (rGO) and 5 (CD); electrostatic interactions, 2 (SNP-DDAB), 4 (NCC), and 6 (GO); 3 (CQD modified with boronic acid); borono-lectin-sugar interaction, 7 (GO-Ag); combined dative bond and 8 (Ag-MHC); and dative bond interaction. Second approach deals with the nano system that entirely executes the virus. Both approaches are effective to act against SARS-CoV-2 [96]. Another approach using nanosystems, as previously mentioned, has an additional feature in them that can be used to kill viruses. In this regard, electromagnetic radiation has been employed to activate this additional characteristic either by reactive species or by photothermal heating. Therefore, viruses can be killed by oxidation or denaturation processes [96].

Miyako et al. [97] shaped carbon nanohorns (CNH) operationalized with a PEG derivative with PL (distearoylphosphatidylethanolamine) at one end and a T7 tag antibody (Ab) at the other end, NP sizes were of 50–150 nms. PEG has been incorporated to provide stability, PL to solubilize nanoparticles, and Ab to target T7 bacteriophage (T7 phage) as prototype virus. The overall impression (Fig. 2) signifies virus binding to the CNH, site-specific exclusion of the T7 phage exist via

| Target virus, dengue virus serotype 2, and influenza A | Nanocomposites | Inhibition action | Inference or findings | Ref. |
|--------------------------------------------------------|----------------|------------------|----------------------|-----|
| Japanese encephalitis virus                            | NCa, NCh, and NCc | Electrostatic interaction | NCNanosystems essentially obstructed JEV infection at the onset of viral contamination. NCNanosystem protected mice (80–100% protection) when vaccinated with JEV or DEN-2 prefabricated with NCh. In clinical studies, 6 lpi with JEV, a treatment with NCh, resulted in 60–80% protection of mice. | [93] |
| T7 bacteriophage                                        | CNH-PL-T7       | Antibody-antigen interaction + photothermal effect | Both nanosystems (with and without antibodies) were able to eliminate T7 phage upon NIR irradiation. When using a thin suspension of nanohorns, only the targeted nanohorns were able to eliminate the T7 phage. | [94] |
| Hepatitis C virus                                       | SNP-BA, MNP-BA, and ND-BA | Glycan borono-lectin interaction | None of the nanosystems exhibited important cell viability after 2 h, 58, 47, and 60% of viral repression were recorded for ND-BA, MNP-BA, and SNP-BA, sequentially. The nanosystems analyzed were able to diminish virus penetration. | [95] |

Gt, graphite; GtO, graphite oxide; GO, graphene oxide; rGO, reduced graphene oxide; GO-PDDA, graphene oxide/poly (diallyldimethylammonium chloride) composite; GO-PVP, graphene oxide-polyvinylpyrrolidone composite; GO-Ag, graphene oxide-silver nanocomposite; Ag-MHC, magnetic hybrid colloid decorated with Ag nanoparticles; CQD, carbon quantum dots; NC, nano-clusters; CD, carbon dots; SNP, silica nanoparticles; DDAB, didodecyldimethylammonium bromide; SNP-BA, silica nanoparticles-boronic acid; MNP-BA, iron oxide nanoparticle-boronic acid; ND-BA, nanodiamond-boronic acid; NCh, carbon nanotube functionalized with C18 tallow alkyl amine; NCb, nanoclay with triton X100; NCh, nanoclay with sodium dodecyl sulphate; CNH-PL-T7, carbon nanohorns functionalized with PEG distearoylphosphatidylethanolamine (PL) and T7 tag antibody; NT-P, multi-walled carbon nanotubes (MWNT) functionalized with protoporphyrin (PPIX)
crosslinks protein-RNA [99]); it could likely work against all types of influenza virus strain.

**Nano Vaccine Models of Relevance in the Fight Against COVID-19**

The nanotechnology can play a prime role to fight against COVID-19 utilizing nano vaccines, which contain nanoparticles and act as carriers of Ag that could activate defensive immune reactions. Antigen processing cells have ability of capturing microparticulate Ag complex to boost adaptive autoimmune responses that subsist with pathogen after entering inside an organism. Nanomaterials have inbuilt immunomodulatory properties that can impact therapeutic action of vaccine [100]. Hence, these can be a good choice to evade viral diseases. In this context, VLPs could be a leading approach for the development of safer nano vaccines due to highly immunized macromolecular complex, imitating antigenic effects of microorganism. The recombinant vaccines based on VLPs (vaccines against hepatitis B virus and human papillomavirus) are very much commercialized [101]. In addition to VLPs, other NPs have also been utilized in the field of vaccinology; some examples are liposome, gold NPs, chitosan, and PLGA [102]. Many researchers are targeting vaccines for SARS-CoV-1 and MERS-CoV and described in the works; these reports can be preliminary facts to develop SARS-CoV-2; among all, VLPs were utmost discovered strategy. Real-time expression of S (spike), E (envelope), M (membrane), and N (nucleocapsid) proteins of SARS-CoV serve to produce VLPs engaging baculovirus/insect cells; they depicted similar homologous characters with that of SARS-CoV virion when observed under an electron microscope [103, 104]. One report suggested that VLPs are formed within insect expressing M and E protein barely [105]. A set of four subcutaneous doses of VLP (mixed with Freund’s adjuvant) immunized to mice model leads to release of high Ab titers counter to SARS-CoV. VLPs provoked cellular resistance by enhancing IFN-γ and IL-4 production [106]. In another in vitro research, DCs triggered production of IL-6 and TNF-α after VLPs concocted with E and M proteins from SARS-CoV and S protein from a bat-isolated CoV. Furthermore, DCs pre-exposed to VLPs bring about an upsurge in the quantity of IFN-γ + IL-4 + CD4 + T cells [107]. For mucosal immunization (being documented as the most relevant), VLPs from SARS-CoV were examined in a mouse prototype exposed to intraperitoneal or intranasal vaccination. Both lead to SARS-CoV-specific IgG upregulation with increased levels in case of intraperitoneal route (i.p. route). Contrasting parenteral administration, intranasal delivery prompts IgA response that can be traced in the GIT and lungs. IgA level was higher for the i.p. immunization in the intestinal tract rather than intranasal route (i.n. route). However, secretions from the venereal region for mice vaccinated intranasally exhibited low response [108]. A number of studies indicate that VLPs are synthesized in the baculovirus/insect cell system by co-expression of M1 influenza protein and the S protein from SARS-CoV. The resultant chimeric VLPs remained analogous to the wild-type SARS-CoV when linking size and structure. The major troublesome task is to develop immunogenicity and defensive effectiveness, the chimeric VLPs totally saved mice after i.m. and i.n. immunization of S protein S [104, 109]. Rhesus macaques when immunized with VLPs and Al adjuvant exhibited release of T-helper 1 (Th1) cell-mediated immunity [104, 110]. Silkworm larvae and Bm5 cells were confirmed to synthesize vaccine contenders with the help of MERS-CoV inherent protein S, E, and M. Despite that E and M proteins are released and secreted to the culture supernatant, the S protein is absent as VLPs. Nanosized vesicle (100–
200 nm through immune-TEM) displayed that S protein was produced from Bm5 cells stating operational proteins of the S protein via surface active agent processing and physical ejection [111]. Thus, the nanoformulation of COVID-19 vaccines might be more effectively helpful in the immunization against the current pandemic among students of higher education and under-studies stakeholders in school education system too [112].

Conclusions

The data presented in the current review depicted that nanotechnology has allowed development of various biosensors, nanovaccines, and antiviral composites that are highly effective for close-related viruses; thus, it is a valuable guide for the agent’s development against SARS-CoV-2. Therefore, there is much more that nanotechnology has to offer in the fight against COVID-19 pandemic and the following months will be critical for the exploitation of unique characteristics of nanosized sensors, antiviral composites, and vaccines in the fight against this unprecedented global health crisis at multiple levels, especially for viral spread prevention and establishment of infection, but also in an accurate and timely diagnostic. For the proper containment of COVID-19 or any other emerging coronaviral pandemic, the detailed understanding of the virus virulence and the transmission are required which will enable a better understanding of virus transfer between species along with the identification of the differently encoded nanostructural enzymes and proteins and the related mechanism of action. Accordingly, new therapeutic targets can be recognized and targeted by the use of surface-functionalized NPs. Also, the study of the lifecycle of the virus and the host’s response will help us to produce effective nanovaccine. Based on these studies, the future aspect of a broad-spectrum ‘universal’ NP-based vaccine or therapeutic is expected to be ready for the current and future CoV pandemics. It can be predicted interestingly that microfluidics will have the contribution in CoV detection, taking the benefits of miniaturization, rapid detection, and portability. As the infection and spread of the viruses is way faster than the effective vaccines, vaccines and drug study should be complementary to what has already been achieved in the previous CoV-related research. The infection-to-mortality ratio because of current global health emergency has crossed the limits, making it different from other viral infections. The tools of nanotechnology can be modified and used for detecting, treating, and preventing the spread of COVID-19. Nanotechnology offers a unique set of tools which can help in the contribution and in the understanding of viral diseases and towards the critical development of therapeutic and diagnostic platforms.

Acknowledgements Authors would like to express their gratitude to the facilities provided by Maharishi Markandeshwar (Deemed to be University) Mullana-Ambala (Haryana), India, for carrying out this work.

Compliance with Ethical Standards

Conflict of Interest None.

Human and Animal Rights and Informed Consent The article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Adhikari SP, Meng S, Yu-Ju W, Yu-Ping M, Rui-Xue Y, Qing-Zhi W, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. Infect Dis Poverty. 2020;9:29. https://doi.org/10.1186/s40495-020-00646-x.

2. Upadhyay SK, Singh R, Babita KG, Singh G. The outbreak and challenges of novel coronavirus (COVID-19): The global pandemic emergency of early 2K20 and Indian scenario. Int J Biol Pharm Allied Sci. 2020;9:1173–99. https://doi.org/10.31032/IJBPPAS/2020/9.5.5126.

3. Yadav R, Parihar RD, Dhiman U, Dhamija P, Upadhyay SK, Imran M, et al. Docking of FDA approved drugs targeting NSP-16, N-protein and main protease of SARS-CoV-2 as dual inhibitors. Biointerface Res Appl Chem. 2020;11:9846–61. https://doi.org/10.33263/BRIAC113.98489861.

4. Waris A, Khan AU, Ali M, Ali A, Baset A. COVID-19 outbreak: Current scenario of Pakistan. New Microbes New Infect. 2020;100681:100681. https://doi.org/10.1016/j.mni.2020.100681.

5. Sood S, Aggarwal V, Aggarwal D, Upadhyay SK, Sak K, Tuli HS, et al. COVID-19 pandemic: From molecular biology, pathogenesis, detection and treatment to global societal impact. Curr Pharmocol Rep. 2020;6(5):212–27. https://doi.org/10.1007/s40495-020-00229-2.

6. Kaul D. An overview of coronaviruses including the SARS-2 coronavirus-Molecular biology, epidemiology and clinical implications. Curr Med Res Pract. 2020;10(2):54–64. https://doi.org/10.1016/j.cppv.2020.04.001.

7. Upadhyay SK, Singh R, Singh M, Kumar V, Yadav M, Aggarwal D, et al. COVID-19 in republic of India: A report on situation and precautionary strategies to global pandemic. Bull Environ Pharmacol Life Sci. 2020;9:39–48.

8. Curley M, Thomas N. Human security and public health in Southeast Asia: The SARS outbreak. Aust J Int Aff. 2004;58:17–32. https://doi.org/10.1080/1035771032000184737.

9. Kumar G, Singh G, Bhatnagar V, Gupta R, Upadhyay SK. Outcome of online teaching-learning over traditional education during covid-19 pandemic. Int J Adv Trends Comput Sci Eng. 2020;9(5):7704–11. https://doi.org/10.30534/ijatcse/2020/113952020.

10. Kumar S, Rathi B. Coronavirus disease COVID-19: A new threat to public health. Curr Top Med Chem. 2020;20(8):599–600. https://doi.org/10.2174/1568026620999200305144319.

11. Dan S, Pant M, Upadhyay SK. The case fatality rate (CFR) in SARS-CoV-2 patients with cardiovascular disease (CVD): A global health risk paradigm in COVID-19 pandemic. Curr Pharmocol Rep. 2020;6:315–24. https://doi.org/10.1007/s40495-020-00239-0.

12. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020;19(3):149–50. https://doi.org/10.1038/d41573-020-00016-0.

13. Jha D, Sharma V, Sharma JK, Kumar S, Sharma V, Kamboj P, et al. Plausible state-specific plans and recommendations to avert COVID-19 pandemic and the following months will be critical for the exploitation of unique characteristics of nanosized sensors, antiviral composites, and vaccines in the fight against this unprecedented global health crisis at multiple levels, especially for viral spread prevention and establishment of infection, but also in an accurate and timely diagnostic. For the proper containment of COVID-19 or any other emerging coronaviral pandemic, the detailed understanding of the virus virulence and the transmission are required which will enable a better understanding of virus transfer between species along with the identification of the differently encoded nanostructural enzymes and proteins and the related mechanism of action. Accordingly, new therapeutic targets can be recognized and targeted by the use of surface-functionalized NPs. Also, the study of the lifecycle of the virus and the host’s response will help us to produce effective nanovaccine. Based on these studies, the future aspect of a broad-spectrum ‘universal’ NP-based vaccine or therapeutic is expected to be ready for the current and future CoV pandemics. It can be predicted interestingly that microfluidics will have the contribution in CoV detection, taking the benefits of miniaturization, rapid detection, and portability. As the infection and spread of the viruses is way faster than the effective vaccines, vaccines and drug study should be complementary to what has already been achieved in the previous CoV-related research. The infection-to-mortality ratio because of current global health emergency has crossed the limits, making it different from other viral infections. The tools of nanotechnology can be modified and used for detecting, treating, and preventing the spread of COVID-19. Nanotechnology offers a unique set of tools which can help in the contribution and in the understanding of viral diseases and towards the critical development of therapeutic and diagnostic platforms.

Acknowledgements Authors would like to express their gratitude to the facilities provided by Maharishi Markandeshwar (Deemed to be University) Mullana-Ambala (Haryana), India, for carrying out this work.

Compliance with Ethical Standards

Conflict of Interest None.

Human and Animal Rights and Informed Consent The article does not contain any studies with human or animal subjects performed by any of the authors.

References
19 community transmission. Bull Pure Appl Sci Zool. 2020;39A(2):447–54. https://doi.org/10.9589/2320-3188.2020.00051.0.

14. Hashmi HAS, Asif HM. Early detection and assessment of COVID-19. Front Med. 2020;7:311. https://doi.org/10.3389/fmed.2020.000311.

15. Agarwal HK, Chihkara BS, Doncel GF, Parang K. Synthesis and anti-HIV activities of unsymmetrical long chain dicarboxylic esters of dinucleoside reverse transcriptase inhibitors. Bioorg Med Chem Lett. 2017;27:1934–7. https://doi.org/10.1016/j.bmcl.2017.03.031.

16. Capua I, Cattoli G. One Health (r) evolution: Learning from the past to build a new future. Viruses. 2018;10:725. https://doi.org/10.3390/v10120725.

17. Sumaryada T, Pramudita CA. Molecular docking evaluation of some Indonesian’s popular herbs for a possible COVID-19 treatment. Biointerface Res Appl Chem. 2020;11:9827–35. https://doi.org/10.3326/BIJRIAC11.98279835.

18. Why interdisciplinary research matters. Nature. 2015;525:305. https://doi.org/10.1038/525305a.

19. Weiss C, Carriere M, Fusco L, Capua I, Regla-Nava JA, Pasquali M, et al. Toward nanotechnology-enabled approaches against the COVID-19 Pandemic. ACS Nano. 2020;14(6):6383–406. https://doi.org/10.1021/acs.nano.0c03697.

20. Gnanasangeetha D, Sarala TD. One pot synthesis of zinc oxide nanoparticles via chemical and green method. Res J Mater Sci. 2013;2320:6055.

21. Chhikara BS. Corona virus SARS-CoV-2 disease COVID-19: Infection, prevention and clinical advances of the prospective chemical drug therapeutics. Chem Biol Lett. 2020;7:63–72.

22. Waris A, Ali M, Khan AU, Ali A, Baset A. Role of nanotechnology in diagnosing and treating COVID-19 during the pandemic. Int J Clin Virol. 2020;4:665–70. https://doi.org/10.29328/journal.ijcvi.1001017.

23. Uduyama B, Kadhiyans P, Kozlowski RN, Malekjahani A, Osborne M, Li VYC, et al. Diagnosing COVID-19: The disease and tools for detection. ACS Nano. 2020;14(4):3822–35. https://doi.org/10.1021/acs.nanolett.0c02624.

24. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223):470–3. https://doi.org/10.1016/S0140-6736(20)31085-9.

25. Zhao Z, Cui H, Song W, Ru X, Zhou W, Yu X. A simple magnetic nanoparticles-based viral RNA extraction method for efficient detection of SARS-CoV-2. Bio Rxiv. 2020. https://doi.org/10.1101/2020.02.22.961268.

26. Gong P, He X, Wang K, Tan W, Xie W, Wu P, et al. Combination of functionalized nanoparticles and polymerase chain reaction-based method for SARS-CoV gene detection. J Nanosci Nanotechnol. 2008;8(1):293–300.

27. Kim H, Park M, Hwang J, Kim JH, Chung DR, Lee KS, et al. Development of label-free colorimetric assay for MERS-CoV using gold nanoparticles. ACS Sens. 2019;4(5):1306–12. https://doi.org/10.1021/acssensors.9b00175.

28. Martinez-Paredes G, Gonzalez-Garcia MB, Costa-Garcia A. Genosensor for SARS virus detection based on gold nanostructured screen-printed carbon electrodes. Electroanalysis. 2009;21(3–5):379–85. https://doi.org/10.1002/elect.200804399.

29. Layqah LA, Eissa S. An electrochemical immunosensor for the corona virus associated with the Middle East respiratory syndrome using an array of gold nanoparticles-modified carbon electrodes. Microchim Acta. 2019;186(4):224. https://doi.org/10.1007/s00604-019-3345-5.

30. Huang P, Wang H, Cao Z, Jin H, Chi H, Zhao J, et al. A rapid and specific assay for the detection of MERS-CoV. Front Microbiol. 2018;9(1101):1–9. https://doi.org/10.3389/fmicb.2018.01101.

31. Genie A. Rapid COVID-19 antibody detection tests: Principles and methods. http://www.assaygenie.com/rapid-covid19-antibody-detection-tests-principles-and-methods. Accessed Mar 2020.
83. Halder A, Das S, Ojha D, Chattopadhyay D, Mukherjee A. Highly monodispersed gold nanoparticles synthesis and inhibition of herpes simplex virus infections. Mater Sci Eng. 2018;89:413–21. https://doi.org/10.1016/j.msec.2018.04.005.

84. Tong T, Hu H, Zhou J, Deng S, Zhang X, Tang W, et al. Glycyrrhizin-acid-based carbon dots with high antiviral activity by multisite inhibition mechanisms. Small. 2020;16:1–12. https://doi.org/10.1002/smll.201906206.

85. FDA. Cellex qSARS-CoV-2 IgG/IgM rapid test. 2020. https://www.fda.gov/media/136625/download. Accessed Apr 2020.

86. EDP™. Novel coronavirus COVID-19 ELISA kits. Epitope Diagnostics Inc. 2020. http://www.epitopediagnostics.com/covid-19-elsa. Accessed Apr 2020.

87. SYBCIL. SARS-CoV-2 solution. Shenzhen Yhlo Biotech Co.-Ltd. 2020. https://www.amp-asbach.de/index_files/flyer_cov2.pdf. Accessed Apr 2020.

88. FDA. COVID-19 IgM/IgG system. DPP®. 2020. https://www.fda.gov/media/136963/download. Accessed Apr 2020.

89. USFDA. US food and drug administration VITROS immunodiagnostic product anti-SARS-CoV2 total reagent pack. Ortho-Clinical Diagnosis Inc. 2020. https://www.fda.gov/media/136970/download. Accessed Apr 2020.

90. Sure Biotech. Coronavirus (COVID-19) rapid test. 2020. https://www.surebiotech.com/rapid-test/coronavirus-covid-19-rapid-test/. Accessed Apr 2020.

91. Ye S, Shao K, Li Z, Guo N, Zuo Y, Li Q, et al. Antiviral activity of graphene oxide: How sharp edged structure and charge matter. ACS Appl Mater Interfaces. 2015;7(38):21571–9. https://doi.org/10.1021/acsami.5b06876.

92. Loechezina SK, BarnsA, et al. Functional carbon quantum dots as medical countermeasures to human coronavirus. ACS Appl Mater. 2019;11(46):42964–74. https://doi.org/10.1021/acsami.9b15032.

93. Ellechiguera JL, Burt JL, Morones JR, Camacho-Bragado A, Gao X, Lara HH, et al. Interaction of silver nanoparticles with HIV-1. J Nanobiotechnol. 2005;3(1):6. https://doi.org/10.1186/1477-3155-3-6.

94. Galdiero S, Falanga A, Vitelli M, Cantisani M, Marra V, Galdiero M. Silver nanoparticles as potential antiviral agents. Molecules. 2011;16(10):8894–918. https://doi.org/10.3390/molecules16108894.

95. Chen YN, Hsieh YH, Hsieh CT, Tzou DY, Chang PL. Antiviral activity of graphene-silver nanocomposites against non-enveloped and enveloped viruses. Int J Environ Res Public Health. 2016;13(4):430. https://doi.org/10.3390/ijerph13040430.

96. Palestino G, García-Silva I, González-Ortega O, Rosales-Pérez SC, Barras A, et al. Functional carbon quantum dots as effective antiviral agents. Nanotechnology. 2012;23(10):105101. https://doi.org/10.1088/0957-4484/23/10/105101.

97. Miyako E, Nagata H, Hirano K, Sakamoto K, Makita Y, Nakayama KI, et al. Photoinduced antiviral carbon nanohorns. Nanotechnology. 2008;19(7):6. https://doi.org/10.1088/0957-4484/19/7/077106.

98. Banerjee I, Douaisi MP, Mondal D, Kane RS. Light-activated nanotube–porphyrin conjugates as effective antiviral agents. Nanotechnology. 2012;23(10):105101. https://doi.org/10.1088/0957-4484/23/10/105101.

99. Schneider JE, Tabatabaie T, Maidt L, Smith RH, Nguyen X, Pye Q, et al. Potential mechanisms of photodynamic inactivation of virus by melittine blue I. RNA–protein crosslinks and other oxidative lesions in Qb Bacteriophage. Photochem Photobiol. 1998;67(3):350–7. https://doi.org/10.1111/j.1751-1097.1998.tb05299.x.

100. Bharchdawaj P, Bhatia E, Sharma S, Ahamad N, Banerjee R. Advancements in prophylactic and therapeutic nanovaccines. Acta Biomater. 2020;108:1–21. https://doi.org/10.1016/j.actbio.2020.03.020.

101. Gilca V, Sauvageau C, Boulianne N, de Serres G, Coquillard M, Krajdem M, et al. Immunogenicity of quadrivalent HPV and combined hepatitis A and B vaccine when co-administered or administered one month apart to 9-10 year-old girls according to 0-6 month schedule. Hum Vaccine Immunother. 2014;10(8):2438–45. https://doi.org/10.4161/hv.29617.

102. Singh R, Upadhyay SK, Singh M, Sharma I, Sharma P, Kamboj P, et al. Chitin, chitinases and chitin derivatives in biopharmaceutical, agricultural and environmental perspective. Biointerface Res Appl Chem. 2021;11(3):9985–10005. https://doi.org/10.33263/BRIAC11.99851005.

103. Mortola E, Roy P. Efficient assembly and release of SARS coronavirus-like particles by a heterologous expression system. FEBS Lett. 2004;576(1-2):174–8. https://doi.org/10.1016/j.febslet.2004.09.009.

104. Wang C, Zheng X, Gai W, Zhao Y, Wang H, Wang H, et al. MERS-CoV virus-like particles produced in insect cells induce specific humoral and cellular immunity in rhesus macaques. Oncotarget. 2017;8(8):12686–94. https://doi.org/10.18632/oncotarget.8475.

105. Ho Y, Lin PH, Liu CY, Lee SP, Chao YC. Assembly of human severe acute respiratory syndrome coronavirus-like particles. Biochem Biophys Res Commun. 2004;318(4):833–8. https://doi.org/10.1016/j.bbrc.2004.04.111.

106. Lu X, Chen Y, Bai B, Hu H, Tao L, Yang J, et al. Immune responses against severe acute respiratory syndrome coronavirus induced by virus-like particles in mice. Immunology. 2007;122(4):496–502. https://doi.org/10.1111/j.1365-2667.2007.02676.x.

107. Bai B, Hu Q, Hu H, Zhou P, Shi Z, Meng J, et al. Virus-like particles of SARS-like coronavirus formed by membrane proteins from different origins demonstrate stimulating activity in human dendritic cells. PLoS One. 2008;3(7):e2685. https://doi.org/10.1371/journal.pone.0002685.

108. Lu B, Huang Y, Huang L, Li B, Zheng Z, Chen Z, et al. Effect of mucosal and systemic immunization with virus-like particles of severe acute respiratory syndrome coronavirus in mice. Immunology. 2010;130(2):254–61. https://doi.org/10.1111/j.1365-2667.2010.03231.x.

109. Liu YV, Massare MJ, Barnard DL, Kort T, Nathan M, Wang L, et al. Chimeric severe acute respiratory syndrome coronavirus (SARS-CoV) S glycoprotein and influenza matrix 1 efficiently form virus-like particles (VLPs) that protect mice against challenge with SARS-CoV. Vaccine. 2011;29(38):6606–13. https://doi.org/10.1016/j.vaccine.2011.06.111.

110. Schijsn V, Fernandez-Tejada A, Barjaktarovic Z, Bouzas I, et al. Modulation of immune responses using adjuvants to facilitate therapeutic vaccination. Immunol Rev. 2020;296:169–90. https://doi.org/10.1111/imr.12889.

111. Kato T, Takami Y, Kumar Deo V, Park EY. Preparation of virus-like particle mimetic nanovesicles displaying the S protein of Middle East respiratory syndrome coronavirus using insect cells. J Biotechnol. 2019;306:177–83. https://doi.org/10.1016/j.jbiotec.2019.10.007.

112. Garg S, Aggarwal D, Upadhyay SK, Kumar G, Singh G. Effect of COVID-19 on school education system: Challenges and opportunities to adopt online teaching and learning. Hum Soc Sci Rev. 2020;8(6):10–7. https://doi.org/10.18510/hssr.2020.862.