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Review



## Nanoparticles in clinical trials of COVID-19: An update

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## ABSTRACT

Once the World Health Organization (WHO) declared the COVID-19 (Coronavirus Infectious Disease-19) outbreak to be pandemic, massive efforts have been launched by researchers around the globe to combat this emerging infectious disease. Strategies that must be investigated such as expanding testing capabilities, developing effective medicines, as well as developing safe and effective vaccines for COVID-19 disease that produce long-lasting immunity to human system. Now-a-days, bio-sensing, medication delivery, imaging, and antimicrobial treatment are just a few of the medical applications for nanoparticles (NPs). Since the early 1990s, nanoparticle drug delivery methods have been employed in clinical trials. Since then, the discipline of nanomedicine has evolved in tandem with expanding technological demands to better medicinal delivery. Newer generations of NPs have emerged in recent decades that are capable of performing additional delivery tasks, allowing for therapy via novel therapeutic modalities. Many of these next generation NPs and associated products have entered clinical trials and have been approved for diverse indications in the present clinical environment. For systemic applications, NPs or nanomedicine-based drug delivery systems have substantial benefits over their non-formulated and free drug counterparts. Nanoparticle systems, for example, are capable of delivering medicines and treating parts of the body that are inaccessible to existing delivery systems. As a result, NPs medication delivery is one of the most studied preclinical and clinical systems. NPs-based vaccines delivering SARS-CoV-2 antigens will play an increasingly important role in prolonging or improving COVID-19 vaccination outcomes. This review provides insights about employing NPs-based drug delivery systems for the treatment of COVID-19 to increase the bioavailability of current drugs, reducing their toxicity, and to increase their efficiency. This article also exhibits their capability and efficacy, and highlighting the future aspects and challenges on nanoparticle products in clinical trials of COVID-19.

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## 1. Introduction of nanomedicine: An update

The Chinese COVID-19 outbreak was deemed a Public Health Emergency of International Concern by the World Health Organization (WHO) on January 30, 2020, posing a significant danger to nations with weak health systems [1]. Globally, the COVID-19 pandemic has caused more than 572,239,451 confirmed cases and more than 6,390,401 fatalities as per the WHO Coronavirus (COVID-19) Dashboard (<https://covid19.who.int/>) on 29th July 2022 at 5:30 p.m. While, a total of 12,248,795,623 vaccine doses have been administered as on 25th July 2022. The COVID-19 epidemic has a negative impact on the world's healthcare systems and has repercussions for many facets of modern life [2]. Globally rising instances have brought attention to the need for revised management recommendations [3]. In this context, nanotechnology and nano-based vaccines played an important role in the health care system.

Nanomedicine involves nanotechnology, biomedical and pharmaceutical sciences. The field has evolved rapidly with the formation of new nanoparticle-based formulations for theragnostic uses, therapeutic applications and others [4]. Food and Drug Administration (FDA) defined NPs-based formulations as products integrated with NPs (ranging from 1 to 100 nm) [5,6]. These formulations show several merits compared to free drug agents by exhibiting an elevated solubility and enhanced efficacy, pharmacokinetics, and minimal detrimental effect. Over 50 nano-pharmaceuticals are currently available in the market and they include wide range of nano-formulations with lipid NPs being the predominant [5–9].

Lipid particles are lipid system with several components, mainly consisting of a phospholipid, cholesterol, an ionizable lipid and a PEGylated lipid. Liposome is the major type of lipid NPs (LNPs) and was initially documented in 1961 by Alec D Bangham (a British haematologist). The NPs were observed under an electron microscope when adding a negative stain to dry phospholipids that aligned into spherical structure via a lipid bilayer [5,10,11]. Subsequently, the first liposomes of interest which was modified by active targeting ligands were designed and this led to markedly enhanced liposome action by elevating accumulation at the target cells, tissues or organs with liberating the carried drug to other sites [12]. Thus, nano-formulations have improved the pharmacokinetic, biopharmaceutical and pharmacodynamics features of drugs.

The emergence of coronavirus has brought about the use of nanomaterials in the management of COVID-19. This involves the mechanistic actions that inhibit the virus entry into the host cells, resulting to their inactivation [13]. Metal NPs have indicated the potential to inhibit viral attachment to the host cell surface, resulting to the inhibition of viral internalization and viral inactivation. Vaccines and therapeutic antibodies are the most effective approaches for preventing and treating COVID-19 [14]. As of June 25, 2022, Food and Drug Administration approved 30 vaccines whilst 212 vaccines with 734 trials are still under process. Among these, 52 vaccines are in Phase I, 71 vaccines in Phase 2, and 80 vaccines in Phase 3 (<https://covid19.trackvaccines.org/vaccines/>).

The mode of action in these vaccines is based on the antibodies neutralization of the spike protein that would prevent its uptake by human cells through human angiotensin-converting enzyme-2 (ACE2) receptor [15]. Apart from conventional vaccines like live vaccines, inactivated vaccines, recombinant vaccines, vector based and DNA vaccines, the use of NPs-based vaccines opened the door to the new era of advanced vaccines. It has directed a new, promising and unique approach in the crucial times of pandemic. NPs are small particles ranging in size from 1 nm to 100 nm in diameter [16]. Their small size offers great surface area to volume ratio and therefore these particles possess greater potency, tunability and promising platforms for next generation vaccine development [17]. They are capable of broad antibody-based immune response and can create stronger NPs-Antibody responses. This tendency can be used to determine evolution and

variations of pathogenic viruses [18]. Currently, 26 NPs-based vaccines are being tested in human clinical trials. Apart from these, nearly 60 are passing through their preclinical stage of development [19]. These nanoparticle-vaccines are available in a variety of formats such as virus-like particles (VLPs), micelles, protein NPs and LNPs. NPs-vaccines can be divided into two groups based on the type of antigen loading strategies. (a) NPs that present vaccine antigens on their surface and (b) NPs encapsulating vaccine antigens or nucleic acids within their core [19]. Since NPs with vaccine antigens on their surface are capable of engaging antigen presenting cells (APCs), so they have the tendency to efficiently promote B-cell receptor (BCR) crosslinking those results in immunogenicity. While in the other strategy, the antigen is already encapsulated in the NPs, so this characteristic offers protection and controlled cargo release after immunization [20,21]. This review provides an update on NPs-based drugs in viral infections and insights about COVID-19 in clinical trials. Further, this review provides an overview on nanoparticle vaccines against emerging COVID-19 variants, highlights the future aspects and challenges on nanoparticle products in clinical trials of COVID-19.

## 2. NPs-based drugs in viral infections

Effective antiviral drug development is important for alleviating many manifestations and inhibiting death in persons infected by viruses. Timely antiviral management is a vital measure to decrease the effect on health. Metallic nanoparticles-based medicines have reported to inhibit the replication of viruses owing to cell-virus blocking mechanism. A variety of silver, zinc, and gold based NPs have shown significant therapeutic effect against herpes simplex virus (HSV), influenza A, HIV, Human parainfluenza 3 (HPIV-3), zika virus, monkeypox virus and gastroenteritis virus [22]. One example includes the inhibition of gp120 to CD4 by gold nanoparticles (AuNPs). While silver nanoparticles (AgNPs) are capable of virion protein degradation to prevent Kaposi's sarcoma-associated herpesvirus primary infection. Binding of AgNPs to nuclei or membrane interfere with the virion capacity to attach itself to the host. Also, AgNPs are effective against influenza A, polio type 1 and coxsackievirus B3. CD4-dependent cellular binding/pathogenesis or covalent linking with the sulfhydryl group at the virus level is the mechanism behind the AgNPs action [23–26]. AgNPs possess characteristic antiviral activity and their mechanism of action suggests their physical binding with the glycoprotein of viruses. In this manner, viruses are no longer available to penetrate the host cells. However, agglomeration can be avoided by combining the AgNPs with graphene oxide (GO-). It imparts negative charge to AgNPs. This GO-AgNPs combination has been used to treat deadly feline coronavirus infection. Moreover, this combo inhibits cell proliferation by increasing the production of IFN-stimulating genes (ISGs), and interferon- $\alpha$  (IFN- $\alpha$ ) [27].

In another study, a peptide was found that was capable of mimicking heptad repeat 2 (HR2) in MERS virus S2 protein. As, a result, the process of cell fusion is stopped by the interference of HR1 [28]. This inhibitory effect of a peptide was enhanced ten folds when it was immobilized on the surface of gold nanorods. Thus, gold nanorods coupled with this peptide showed brilliant biocompatibility by blocking the cell fusion reaction. Similarly, silicon nano-particles (SiNPs) also proved to be excellent scavengers of viruses. Therefore, it can be a probable treatment of COVID-19 [29]. Iron oxide NPs can be incorporated with a receptor used by SARS-CoV-2 to infect host cell; called S1-RBD protein receptor domain. This can serve as a potent COVID-19 therapy [30]. Selenium NPs have shown characteristic antiviral effects at higher concentrations. A combination of selenium NPs with the antiviral drug, Arabidol (ARB) significantly inhibited the cell entry of influenza virus. Also, viral entry can be blocked by using cationic chitosan NPs by targeting the dendritic cells [31]. Likewise, graphene quantum dots can inhibit the cell binding tendency of HIV [32]. Also, viral infections can be prevented by graphene and its derivatives via confrontational damage of viral proteins ad

graphene and its derivative tend to compete for cell receptors. Another combination of nano-particles, such as AuNPs combined with peptide triazole conjugates were found effective against HIV-1. This results by the binding of envelope spike glycoprotein of virus with receptor proteins from host. Similarly, an effective treatment was found against Influenza A virus by conjugating AuNPs and AgNPs with antiviral peptide (Flupep) [33,34].

Another mode of transportation of antiviral drugs in nanotechnology is called nanocarriers. Organic NPs can be used to deliver antiviral drugs like acyclovir and zidovudine. This method reduces risk of toxicity and promotes improved drug delivery and bioavailability [35]. Another important aspect of this treatment is that the longer the circulation time a nanocarrier takes, the more is its efficacy against prophylaxis. This could prove beneficial for healthcare workers who are at high risk of COVID-19 [36]. Acyclovir has low bioavailability and short life cycle (below 3 h) in oral administration. So, its encapsulation into poly (lactic-co-glycolic acid) (PLGA)-based NPs can enhance its effectiveness by 2.6 folds [37]. A group of natural and synthetic antiviral molecules have been designed and these include peptides, chemical compounds and essential oils. These molecules show antiviral actions on different forms of virus [38,39].

Other agents approved by Food and Drug Administration include zanamivir, oseltamivir and abacavir and they utilized to managing HIV and influenza infection [40]. Recently, remdesivir is utilized for alleviating COVID-19 and its utilization is linked to remarked decrease in the death rate of infected individuals [41]. In spite of the contributions of antiviral molecules, there are many limitations linked with their application, and these include limited effect as a result of poor solubility, toxicity and minimal biostability. In addition to this, enhancement of the antiviral molecule and this involves the blocking of viral protein and cellular receptors associated with viral infection cascades. Therefore, effective delivery of antiviral molecules is necessitated [38,39,42].

In order to rectify the limitations mentioned above, nanoparticle delivery systems have been used in the development of antiviral agents. The nanoparticle delivery systems enable constant systemic flow and maintained the liberation of antiviral molecules, therefore maximizing their therapeutic actions [38,43]. Different types of NPs have been employed in the development of nanoscale delivery systems and characteristics of these nanoparticles can be changed by regulating the size of the system, conjugating needed groups to the surface and controlling its surface charges [38]. A broad range of NPs, including lipid nanoparticles, AuNPs, polymeric NPs and AgNPs are often used as carriers for embedded antiviral molecules [38,44,45]. These transporters can be functionalized with targeting groups, such as ligands, antibodies and receptors. A delivery molecule utilizing bilayer polymeric vesicles functionalized together with phenylboronic acid, has been shown for the management of influenza A virus [38,46]. The optimal ratio of the phenylboronic acid and carrier was determined through *in vitro* studies, which led to elevated cellular uptake of the antiviral molecules favipiravir and mir-323a that were co-entrapped in carrier [38]. Polymeric vesicles functionalized with phenylboronic acid elevates the therapeutic

action of the antiviral molecules and maintained cell viability when compared to free drug [38]. This showed the synergistic therapeutic actions and remarkably improved biocompatibility of these systems. The synergistic therapeutic actions linked to dual-delivery were further used to inhibit HIV-1 entry into host cells [47].

Liposomes designed with 1,2-dipalmitoyl-sn-glycero-3-phosphoethanolamine-*N*-[methoxy-(poly (ethylene glycol))-2000] and 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine successfully entrapped two important entry inhibitors, which are protoporphyrin IX and enfuvirtide. Liposome with dual-loaded delivery transporters ensured improved antiviral action on HIV-1 than carriers with single load. These outcomes show the merits of using effective delivery systems that produce synergistic actions to abrogate HIV-1. The transportation of dual-loaded inhibitors in one carrier with high efficacy was in this aspect [38]. Table 1 shows antiviral agents with corresponding carrier NPs. Abrogation of viral replication is essential in antiviral therapeutics and several antiviral molecules have been designed in this way. Nanoparticulate systems are majorly employed to complement antiviral molecules as carriers, to enhance curing property [38,48]. Utilizing the knowledge of the basics of NPs, nanoparticulate systems can serve as potential inhibitors of some viral replication phases, including binding to receptor, cellular entry and formation of viral proteins in host cells [49].

The first phase of a virus life cycle is the receptor binding and this is a potential target for nanomedicine. Recently, studies indicated that NPs are formed through facile surface modulation revealed potent binding with viruses. This blocked the binding of viruses to host cell receptor, leading to inhibition of viral replication. For instance, spiky nanostructures with geometry-matching topography abrogate the influenza A virus [38,50,51]. These spiky nanostructures have silica NPs and are synthesized to match the topography and size of influenza A virus. In addition, they were covered with an erythrocyte membrane to match the hemagglutinin of the virus. The aforementioned nanoparticulate system allow for potent interaction with influenza A virus and inhibit viral entry into the host cells, thus decreasing about 84% of cellular disease. This work disclosed a potential characteristic, nanoparticle topography, to consider in the process of viral inhibitors development. Furthermore, mesoporous silica NPs antiviral action grafted with unique organic moieties such as glycidylxypropyl, aminopropyl or phenylethyl groups was estimated against human immunodeficiency virus [38]. Also, silica NPs have several cytotoxicity profiles and virucidal action, depending on the chemicals present on their surfaces [38]. Peptide-polymer NPs with high binding potential for influenza virus was estimated for potent receptor inhibiting by modifying the density of the peptide [52]. The above results indicate that altering the surface of features of NPs may potentially aid in regulating the transduction of a virus. Also, these NPs can be employed as antiviral molecules and as delivery transporters in the treatment of viruses [38]. The synergistic antiviral activities of curcumin-modified silver NPs were determined for the potent abrogation of respiratory syncytial virus disease [53]. The toxic effect of silver NPs and poor water solubility of curcumin were successfully

**Table 1**  
Some antiviral drugs with their nanoparticle carriers.

Drugs	Nanomaterial	Target virus	Advantage of nanomaterial	Reference
Chloroquine	Poly (lactic) acid	Herpes simplex virus-1	Enhanced release and targeted transportation	[57]
Zidovudine	Cellulose poly (ethylene glycol)	Human immunodeficiency virus	Enhanced release, enhanced encapsulation and targeted transportation	[58]
Zidovudine	Poly (vinyl pyrrolidone)/sialic acid, poly (ethylene glycol)	Human immunodeficiency virus	Enhanced cellular internalization	[59]
Latency-reversing molecules	Poly(lactide-co-glycolide)	Human immunodeficiency virus	Reduced toxicity	[60]
Glutathione	Silver sulfide	Porcine epidemic diarrhea virus	Decreased viral titer	[61]
Oseltamivir	Zinc oxide	Influenza A virus	Enhanced the viability of infected cells	[62]
Zanamivir	Selenium	Influenza A virus	Enhanced the viability of infected cells	[63]

ameliorated by combining the two systems. In addition to the virucidal actions of the two agents, their combination enables significant antiviral action on respiratory syncytial virus diseases with less detrimental effects. Biocompatible cell-mimicking nano-decoys formed from cells have been reported to show viral inhibition [38,54]. Rao and co-workers designed nano-decoys consisting of genetically engineered human embryonic kidney 293T/ACE2 cells for managing coronavirus disease. The nano-decoys consisting of cytokine and ACE2 receptors remarkably abrogated the replication of virus by preventing cytokine and virus binding [54]. In another study, ACE2 nano-decoys designed from human lung spheroid cells inhibited coronavirus disease and ameliorated lung injury. In addition to this, human lung spheroid cell-nano-decoys decreased lung injury and enhanced viral clearance through inhalation [38,55].

In this sense, NPs exhibit antiviral action and enable novel strategies for designing antiviral systems using the nanoparticle dual functionality. Nano-systems with virucidal action can be used as antiviral barriers to cover surfaces that are frequently contacted, including public areas, masks and healthcare facilities [56]. The use of antiviral NPs such as zinc oxide, copper, graphene oxide and silver has revealed novel targets in inhibiting the spread of viruses via contact transmission and they can serve an important role in the establishing practical strategies to prevent outbreaks in future [38].

### 3. NPs-based drugs in clinical trials against COVID-19

During last decade, role of nanotechnology in diagnosis, prevention, treatment, and production of vaccine against disease has gained explicit attention of researchers [64]. FDA has authenticated the use of nano-crystal formulations, polymer-based NPs, non-polymer NPs, and lipid-based NPs [19,65]. Further, some other NPs like metallic, inorganic, and protein-based NPs are in process of getting approvals to be used as an effective tool in drug delivery [8]. Currently, vaccines have attained an increased attention of researchers due to their effective results in combating several infections, low cost of production, and decreased death rate around the world [66]. Recently, vaccinations against COVID-19 infection have revealed that purposely designed vaccines are helpful in management of public health and social safety. Coronavirus vaccines have aided community by preserving them from infection owing to their therapeutic effects. Nanoparticle vaccines are broadly divided into two subtypes depending upon their antigen loading strategies: Firstly, vaccine antigen presenting (attached on surface) NPs and secondly, NPs encapsulated on vaccine antigen. A schematic

illustration showing pros and cons of different vaccines classified depending upon the antigen loading strategies are shown in Fig. 1 [19].

Therefore, various platforms are being investigated for the development of COVID-19 vaccine, as it is need of time for the safety of world community [67,68]. However, a main hurdle and concern in designing and developing COVID-19 vaccines is due to mutation of virus original genome structure, which is termed as VOC (variants of concern) [69]. Initially developed COVID-19 vaccines (first generation) were designed keeping in view the original genome of SARS-CoV-2 isolate (Wuhan-Hu-1). On the other hand, various novel strains of SARS-CoV-2 are circulating globally having several mutations in spike protein and are of great concern owing to their probable escape from vaccine produced immunity [69,70]. Vaccines developed using nano-technological methodologies are considered as an innovative approach in advanced vaccine science and ensures the provision of controlled administration in present pandemic situations. NPs are classified as nano-scale and adjustable particles, which features structural mimics of naturally occurring viruses. Adjustable and tunable design characterize them as a potential candidate for development of next generation vaccines, provision of platforms for driving promising natural antibody responses, and therapeutic antibody-based immunity, which may aid in evolution of viruses [19]. Fig. 2 depicts the delivery of nanoparticles carrying SARS-CoV-2 derived antigens to pulmonary system.

To date, according to WHO, nearly 166 vaccines are in clinical development while 198 are in preclinical phases (<https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>; assessed on June 25, 2022). World Health Organization has granted 11 vaccines in Emergency Use Listing (EUL) (<https://www.who.int/news/item/19-05-2022-who-validates-11th-vaccine-for-covid-19>; assessed on June 25, 2022). These include Spikevax, Nuvaxoid, Covovax, Comirnaty, Janssen, Vaxzevria, Covishield, Covaxin, Covilo, CoronaVac, and Convidecia. Coronavirus vaccines are designed depending upon diverse platforms including protein subunits, viral vectors (non-replicating), viral vectors (replicating), DNA-based, RNA-based, virus like particles, inactivated virus, live attenuated virus, viral vector (replicating) + Antigen presenting cell, viral vector (non-replicating) + Antigen presenting cell, and Bacterial antigen spore expression vectors. A total of 189 vaccine candidates are registered in 650 clinical trials across 72 countries worldwide [70]. According to Vu et al. [19], approximately 26 NPs-based COVID-19 vaccines are in human clinical trials while nearly sixty candidates are in different stages of pre-clinical stages.

In the last two years, the field of nanomedicine has gained interest rapidly as a result of global demand for new strategies to enable

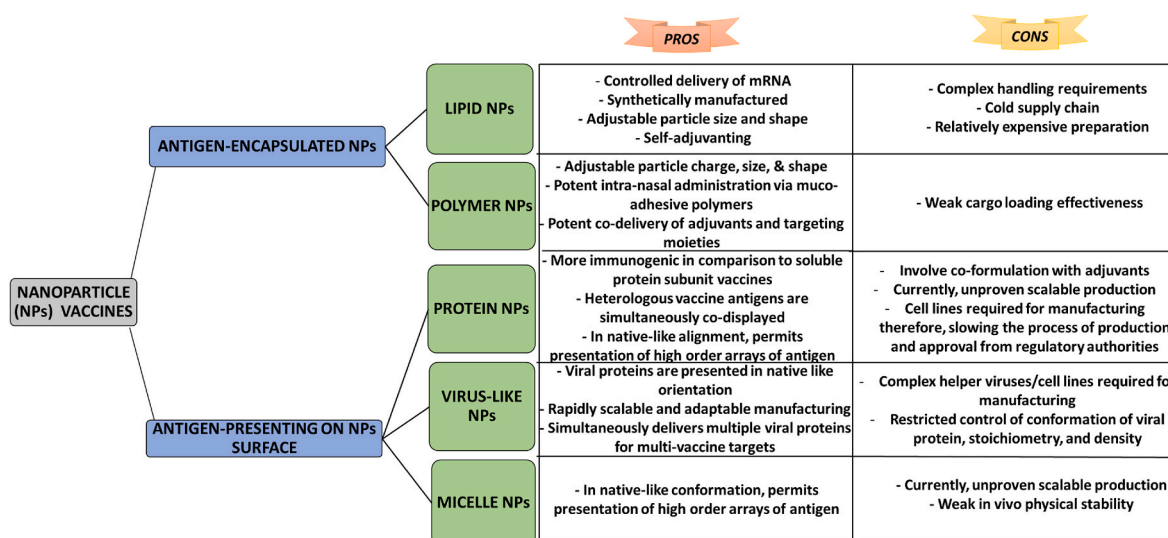
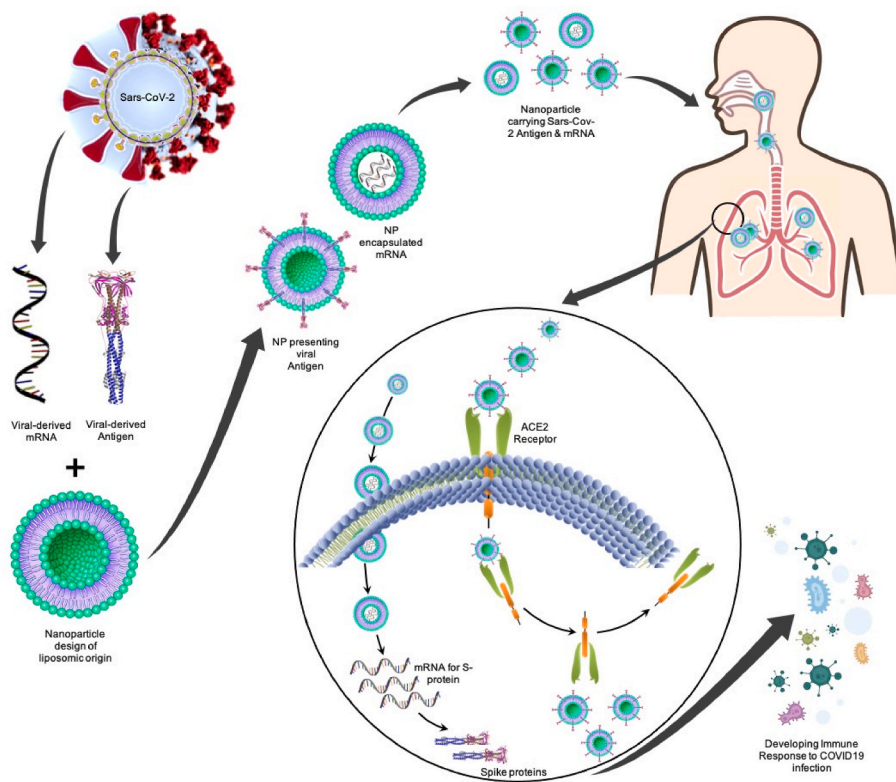


Fig. 1. A schematic illustration showing pros and cons of different vaccines classified depending upon the antigen loading strategies.



**Fig. 2. Delivery of nanoparticles carrying embedded mRNA for S-protein and nanoparticles presenting SARS-CoV-2 derived antigens to a pulmonary system:** The specific mRNA that encodes for spike protein is being embedded in a liposomic nanoparticle where another type of nanoparticles is presenting the viral derived antigen. These nanoparticles will work as an immune booster that can either be delivered orally or intravenously into the COVID-19 patient. The mRNA-carrying NPs enter the cells where it releases the specific mRNA that will go on to translate spike protein. The antigen-presenting nanoparticles attaches to the ACE2 receptors in alveoli where it gets endocytosed and the nanoparticle is released from the receptor. As a result of the antigen exposure, the immune response is developed against SARS-CoV-2 infection.

preventive and therapeutic measures against COVID-19 [71–73] which is induced by the virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [74]. Among the available strategies in fighting COVID-19, LNPs are the delivery molecule employed in the Moderna and Pfizer-BioNTech coronavirus infection vaccines. In 2020, these two companies were given Emergency Use Authorization in USA [75]. On November 9th, 2021, Pfizer (New York) and BioNTech (Germany) reported that their designed COVID-19 vaccine has an efficacy of nearly 90%. Later, FDA permitted its emergency use in United States. Back in January 2020, BioNTech's scientists started the work on potential COVID-19 vaccine that was based on mRNA (messenger RNA). Basically, this vaccine encompasses genetic instruction for development of spike protein. This vaccine aid cells in producing spike proteins that on release into the circulation provokes immunity response. Lately in March, BioNTech joined with Pfizer to expand the study for which a clinical trial was registered and started in May [76,77]. Generic name of this vaccine is tozinameran and branded under name Comirnaty. This vaccine contains PEGylated liposomes (PEGLips) or LNPs encapsulated Tozinameran [78]. In Comirnaty, LNPs formulation allows mRNA to be stable [79,80]. LNPs-formulated mRNA-based vaccine helps provision of correct genetic information to antigen-presenting cells together with an adjuvant [81]. Preclinical trials revealed prophylactic effectiveness of this technique against different viral targets [82–84]. Clinical trial showed 94.1% effectiveness at suppressing the illness induced by COVID-19 and this study involves 30,420 participants [85]. BNT162b2, a vaccine from Pfizer-BioNTech, is a lipid nanoparticle and has cationic lipid ALC-0315 ((4-hydroxybutyl) azanediy) bis(hexane-6,1-diyl) bis(2-hexyldecanoate), cholesterol, DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), PEGDMA (2 [(polyethylene glycol)-2000]-N, N-ditetradecylacetamide) [86]. On December 11th, 2020, U.S. FDA granted BNT162b2 emergency use authorization based on a number of clinical investigations, and this include the one that showed both immunogenicity and safety of BNT162b2 [87]. Also, another clinical investigation including 43,548 individuals showed that BNT162b2 has 95% efficacy in preventing coronavirus disease [88]. Vaccines

consisting of LNPs are administered (intramuscular route) in two different doses and are employed to encapsulate mRNA that encodes for spike glycoprotein found on SARS-CoV-2, which regulates the entry of the virus into the host cell [89]. After the spike glycoprotein encoding, the host organism initiates an immune response to the available virus antigenic proteins. Subsequently, the formation of host antibody against the coronavirus is initiated [90]. mRNA molecules transfer into the cytoplasm are enable by lipid nanoparticle, thus, this NPs has rectify the challenges of translation in mRNA technologies [91]. After using the LNPs to overcome the limitations of intracellular delivery, another possibility is antigen presentation and antibody stimulus neutralization against COVID-19. Both BNT162b2 and mRNA-1273 use employed in more than 35 countries with an estimated 1 billion for mRNA-1273 and two billion for BNT162b2 doses to be produced for the whole of 2021 [92–94].

Nearly after a week BioNTech and Pfizer developed their COVID-19 vaccine-Comirnaty, FDA permitted the use of Spikevax, another COVID-19 vaccine, produced by Moderna on 18th December. Spikevax was the second successful vaccine that was approved by FDA for use in emergency. Moderna's Spikevax is also an mRNA based COVID-19 vaccine similar to that produced by BioNTech& Pfizer. Moderna started production of COVID-19 vaccine in January 2020 [78,95]. Like Comirnaty, Moderna's vaccine also contains LNPs or PEGLips loaded mRNA as this assist in preserving mRNA and conferring its lability [79]. The Moderna vaccine (mRNA-1273) is a nanoparticle in liquid form made up of ionizable cationic lipid SM-102 (heptadecan-9-yl 8 ((2 hydroxyethyl) (6 oxo 6-(undecyloxy) hexyl) amino) octanoate), cholesterol, DSPC (1, 2-distearoyl-snglycero-3 phosphocholine), and PEG-DMG (1 monomethoxypolyethyleneglycol-2,3-dimyristylglycerol containing polyethylene glycol) [86]. On December 18th, 2020, USA food and drug administration gave emergency use of authorization on mRNA-1273, in respect to number of clinical trials. This includes one that displayed anti-SARS-CoV-2 immune stimuli in individuals without trial-limiting safety concerns [89].

Another COVID-19 vaccine known as Vaxzevria is manufactured

jointly by collaboration of University of Oxford and AstraZeneca. Results of clinical trials demonstrated that administration of 2-doses of Vaxzevria twelve weeks apart had 82.4% effectiveness. In December 2020, United Kingdom approved the use of Vaxzevria for emergency in spite of certain misperceptions. Later in January 2021, Serum Institute of India started manufacturing and supplying this vaccine having brand name as Covoshield under the sub-license agreement with AstraZeneca. Vaxzevria carries genetic instruction for development of spike protein (SARS-CoV-2 protein) encapsulated in another non-replicating virus. Purposely, scientists of Oxford-AstraZeneca team attached gene encoding SARS-CoV-2 spike protein with a modified chimpanzee adenovirus (ChAdOx1). Generally, Adenoviruses are naturally occurring viruses causing flu like symptoms. In this vaccine, adenovirus aids in protecting the genetic material via its protective protein coating. Therefore, Vaxzevria needs no frozen storage and can last up to 6 months if refrigerated at 2–8 °C [96–100]. An America biotechnology company named Novavax manufactures and supplies a COVID-19 vaccine named Nuvaxoid. It is a protein subunit-based vaccine and contains part of SARS-CoV-2 spike protein. This vaccine was developed using recombinant nanoparticle technology and contains an ingredient known as Matrix-M™ adjuvant, which aids in creating an effective immune response to the vaccine. Currently this protein-based vaccine is being manufactured and supplied by Serum Institute of India under a trade name Covovax [101].

Ad26.COV2, a COVID-19 vaccine, which is being manufactured by Janssen Pharmaceutical (Johnson & Johnson) with the collaboration of Beth Israel Deaconess Medical Center. Clinical trials have shown efficacy of single dose of this vaccine up to 72%. Like Oxford-AstraZeneca vaccine (Vaxzevria), this is also a non-replicating viral vector type of vaccine. In this vaccine, scientists have genetically modified an adenovirus by placing a gene for making of SARS-CoV-2 spike protein. WHO has permitted its use in case of emergency use [102]. By the end of 2020, Beijing Institute of Biological Products developed an inactivated type of COVID-19 vaccine. This vaccine is also known as BIBP-CorV or by its trade name *i.e.* Covilo. Clinical trials conducted by Sinopharm have reported an effective of 79% against COVID-19. This vaccine comprises of an inactivated form of SARS-CoV-2, which is not capable of replicating. However, the spike protein remains intact in this inactivated virus that results in triggering the immune response for the production of respective antibodies so that it cannot replicate, but it keeps the surface spike protein intact to trigger the body's immune system to create antibodies for protection against the live virus [103–107]. Some other vaccines namely Covaxin and Coronavac being produced by Bharat Biotech and Sinovac, respectively are also inactivated vaccines. Table 2 shows the details of some nanoparticle-based vaccines for COVID-19 that are in phase-4, and phase-3 of clinical trials or have qualified for WHO Emergency use authorization.

Inorganic and LNPs are the mainly NPs recommended clinically. Anselmo and Mitragotri [94] stated that the first clinically approved particle in 1989 and the most recent clinically recommended NPs show how NPs that are lipid in nature enable regulated interactions between complex microenvironments and encapsulated therapeutics in patients. NPs that are lipid base are used for protecting and carrying sensitive molecules such as mRNA after their production, during their storage and during their use as intramuscular injection. This is in addition to their use as clinically approved intravenous applications [94] and based on this report, the use of NPs for managing COVID-19 is gaining more attentions. There is an increment in the number of clinical trials for recommended nanoparticle from 1220 (2016) to 1935 (2021). They revealed the success recorded in the use of NPs against COVID-19 and continuous progress made on other NPs for their use in clinics [94], though more investigations are required in wake of emerging strains of COVID-19 [109].

#### 4. Nanoparticle vaccines against emerging SARS-CoV-2 variants

Around the globe, the vaccines against COVID-19 have been

effectively being formulated but threat of SARS-CoV-2 and its variants still persists [110]. Scientists around the world have identified polymorphic changes in code sequences of COVID-19 genome [111]. These mutations in genome sequence of SARS-CoV-2 have affected the effectiveness of viral transmission, vaccine sensitivity, and pathogenicity and therefore known as VOCs. Emergence of VOCs has been a significant threat and hurdle in development of effective SARS-CoV-2 vaccines. Various VOCs have been identified and reported till now that are commonly known as Alpha, Beta, Gamma, Delta, and Omicron variants [112–115]. In spite of significant success in development of SARS-CoV-2 vaccines, it is need of time for development of vaccines having broad spectrum mechanism of action to overcome infections caused by emerging variants of SARS-CoV-2 and reduced immunity.

For this purpose, Li et al. [116] revealed that immunization of SARS-CoV-2 RBD-scNP (receptor binding domain sortase A-conjugated ferritin nanoparticle) induced potential nAbs (neutralizing antibodies) in NHPs (non-human primates) against 8 variants of SARS-CoV-2 such as Omicron, Delta, and Beta. As compared to SARS-CoV-2 D614G, the RBD-scNP-induced antibodies neutralized Omicron variant as ID<sub>50</sub> titers reduced on an average of 10.6-folds. RBD-scNPs immunization helped in protection non-human primates against SARS-CoV-2 Beta, WA-1, and Delta variants, further mice were also protected from SARS-CoV-2 Beta variant. They were of the view that RBD-scNPs induces neutralizing antibodies against different variants of SARS-CoV-2 and protected non-human primates & mice from SARS-CoV-2 variants. This type of vaccine may be helpful in providing immunity against different variants (Omicron & Delta) of SARS-CoV-2 [116].

In 2021, a variant of SARS-CoV-2 known as Delta variant emerged and became a variant of concern. As compared to its original strain, Delta variant have twice the transmission capacity, short incubation time, and elevated viral content. Thus, development of vaccine against Delta variant of SARS-CoV-2 was an urgent need. Purposely, Chen et al. [117] reported that RBD-conjugated NP vaccines, when administrated according to single dose and prime boost approach, induced ample amount of NAbs (neutralizing antibodies) as they protected mice (hACE2) against Delta variant. Moreover, in rhesus macaques, third re-boost of trivalent vaccine resulted in production of broader cross-protective neutralizing antibodies. They concluded that RBD-conjugated NP vaccines are potent 2nd generation vaccines against VOCs of SARS-CoV-2 [117]. Third dose of Walvax COVID-19 vaccine (ARCoV) lead to robust elevation in NAbs against wild type SARS-CoV-2 and Omicron variant. Administration of homologous booster vaccination of ARCoV might be a significant rational approach against current emergence of Omicron [118].

Owing to the emergence of VOCs of SARS-CoV-2, the need of next generation vaccines having broad spectrum protective effect against COVID-19 has escalated around the world. In non-human primates, adjuvant SpFN (SARS-CoV-2 spike ferritin nanoparticle) vaccine have been manufactured and evaluated. SpFN (50 µg) administrated twice 28 days apart resulted in induction of T<sub>H</sub>1 (T helper cell 1)-biased CD4 T<sub>H</sub> response and evoked NAbs against wild type and VOCs [119]. Both alone and heterologous booster of wild type mRNA vaccine along with Omicron-specific LNP mRNA-based vaccine candidate have been experimented in animals. In vaccination-naive mice, developed Omicron-specific LNP mRNA vaccine evoked significant and specific Ab response. Double dose wild type mRNA vaccinated mice receiving a booster single dose of either homologous booster shot of wild type LNP mRNA or heterologous booster shot of Omicron LNP mRNA helped in restoring diminishing Abs response against Omicron variant. Results showed 40-fold elevation in Abs post two weeks of administration of booster doses. Furthermore, heterologous administration of booster dose of LNP mRNA resulted in 10-to-20-fold increase in NAbs as compared to homologous administration of wild type booster against the Omicron variant [120]. On the other hand, Glycosite-deleted SARS-CoV-2 spike protein mRNA vaccine specifically in S2 (subunit 2) domain for exposing more conserved epitopes evoked strong Abs and

**Table 2**

Some nanoparticle-based SARS-CoV-2 vaccines that are in phase-4, phase-3 of clinical trials or have qualified for WHO Emergency use authorization [94,108].

Sr. No.	Vaccine Name	Type of vaccine	Developer	Registered Trial Number (s)
<b>WHO-EUA qualified COVID-19 vaccines</b>				
1	Covilo	Inactivated Virus	Sinopharm	NCT05204589; NCT04984408; NCT04560881; NCT04917523; NCT04612972; ChiCTR2000034780; IRCT20201214049709N3; IRCT20210206050259N3
2	CoronaVac		Sinovac	NCT04800133; NCT04582344; NCT04651790; NCT04992260; NCT04456595; NCT05156632; PHRR210210-003308; NCT05077176; NCT05137418; NCT05225285; NCT04617483; NCT04508075, 669/UN6.KEP/EC/2020; NCT05204589
3	Covaxin		Bharat Biotech	CTRI/2020/11/028976, NCT04641481; NCT04918797
4	Ad26.COV2.S	Non-replicating viral vector	Janssen (Johnson & Johnson)	NCT05220397; NCT05148845; NCT05048940; NCT05047640; NCT05091307; NCT04505722; NCT04838795, PACTR202102855526180; NCT04614948, ISRCTN14722499
5	Vaxzevria		Oxford/AstraZeneca	NCT04540393; ISRCTN89951424, NCT04536051; NCT04864561; NCT05007951; NCT04516746; EUCTR2020-001228-32, NCT04400838; CTRI/2020/08/027170; NCT05059106; NCT05236491; NCT04756271; NCT05011526; NCT04885764; NCT05198596; NCT04800133; NCT05017792
6	Covishield		Serum Institute of India	CTRI/2020/08/027170
7	Comirnaty	mRNA	Pfizer/BioNTech	NCT05124171, EUCTR2021-004550-33; jRCT2071210106; NCT05022329; NCT04805125; NCT05142319; NCT05228730; NCT04368728, EUCTR2020-002641-42; NCT05225285; NCT05047640; NCT04754594; NCT04816669; EUCTR2020-005442-42; NCT04951323; NCT04713553; NCT05029245; NCT04800133
8	Spikevax		Moderna	NCT04806113; NCT04860297; NCT04811664; NCT05168813; NCT05236491; NCT05048940; NCT04470427; NCT04927065; NCT05249829; NCT04805125; jRCT2071210106; NCT05230953; NCT05228730; NCT05022329; NCT05119855; NCT05142319; NCT05158140; NCT04649151; NCT04796896
9	Nuvaxovid	Protein subunit	Novavax	EUCTR2020-004123-16, NCT04583995; CTRI/2021/02/031554; NCT05236491; NCT04611802
10	Covovax		Serum Institute of India:	CTRI/2021/02/031554
<b>Phase 4</b>				
11	Covilo	Inactivated Virus	Sinopharm	NCT04863638; NCT05105295; NCT05104216
12	CoronaVac		Sinovac	NCT04756830; NCT04747821; NCT04775069; NCT04789356; NCT04754698; NCT04801888; NCT04911790; NCT04953325; NCT04962308; NCT05057169; NCT04892459
13	Ad5-nCoV-IH	Non-Replicating	CanSino	NCT05057169; NCT05037266; NCT05030974
14	Ad26.COV2.S	Viral Vector	Janssen (Johnson & Johnson)	NCT04775069; NCT04760132; NCT04914832
15	Vaxzevria		Oxford/AstraZeneca	NCT04775069; NCT04760132; NCT04969250; NCT04780659; NCT05057182; NCT05047718; NCT04955626; NCT04952766
16	Comirnaty	mRNA	Pfizer/BioNTech	NCT04760132; NCT05030974; NCT04792567; NCT05047718; NCT04952402; NCT04885907; NCT04969250
17	Spikevax		Moderna	
<b>Phase 3</b>				
18	Nanocovax	Protein subunit	Nanogen Pharma	NCT04922788
19	Zifivax		Anhui ZhifeiLongcom	ChiCTR2100050849; NCT05107375; ChiCTR2000040153, NCT04646590; NCT05091411; NCT05128643
20	MVC-COV1901		Medigen Vaccine Biologics Corporation	NCT05198596; NCT05011526
21	V-01		Livzon Mabpharm Inc	NCT05096845; NCT05096832
22	ReCOV		Jiangsu Rec-Biotechnology Co Ltd:	NCT05084989
23	RaziCov Pars		Razi Vaccine and Serum Research Institute	IRCT20201214049709N3
24	Recombinant Protein		Sanofi/GSK	NCT04904549; PACTR202011523101903
25	Soberana Plus		Instituto Finlay de Vacunas Cuba	IFV/COR/09
26	SP/GSK subunit B.1.351 vaccine		Sanofi/GSK	NCT05124171, EUCTR2021-004550-33
27	SCTV01C		Sinocelltech	NCT05043285; NCT05043311
28	S-268019		Shionogi	NCT05212948; jRCT2031210383
29	GBP510		SK Bioscience Co Ltd	NCT05007951
30	UB-612		Vaxxinity/DASA	NCT04683224
31	SCB-2019		Clover Biopharmaceuticals	NCT04672395; NCT05188677; PHRR210209-003334; NCT05193279
32	AKS-452		University Medical Center Groningen	CTRI/2021/10/037269
33	Abdala		Center for Genetic Engineering and Biotechnology (CIGB)	RPCEC00000359
34	SpikoGen		Vaxine/CinnaGen Co.	NCT05175625, IRCT20150303021315N26; NCT05148871; NCT05005559, IRCT20150303021315N24
35	EpiVacCorona		Vector State Research Center of Virology and Biotechnology	NCT05021016; NCT04780035
36	Corbevax		Biological E Limited	CTRI/2021/10/037066; CTRI/2021/08/036074; CTRI/2021/06/034014
37	Recombinant (Sf9 cell)		West China Hospital	NCT04904471; NCT04887207
38	Noora vaccine		Bagheiat-allah University of Medical Sciences	IRCT20210620051639N3
39	Recombinant SARS-CoV-2 Vaccine (CHO Cell)		National Vaccine and Serum Institute	NCT05069129

(continued on next page)



Table 2 (continued)

Sr. No.	Vaccine Name	Type of vaccine	Developer	Registered Trial Number (s)
WHO-EUA qualified COVID-19 vaccines				
40	Covifenz	Virus like particles	Medicago	NCT05040789; NCT04636697
41	LYB001		Yantai Patronus Biotech Co Ltd	NCT05137444
42	AG0302-COVID19	DNA	AnGes	NCT04655625
43	ZyCoV-D		Zydus Cadila	CTRI/2021/01/030416
44	INO-4800		Inovio	NCT04642638; PACTR202110626944896
45	GX-19		Genexine	NCT05067946
46	BNT162b2s01	mRNA	Pfizer/BioNTech	NCT04368728, EUCTR2020-002641-42
47	ARCT-154		Arcturus Therapeutics Inc	NCT05012943
48	DS-5670a		Daiichi Sankyo Co Ltd	JRCT2071210106
49	mRNA-1273.529		Moderna	NCT05249829
50	GRAd-COV2	Non-Replicating	ReiThera	NCT04791423; EUCTR2020-005915-39
51	AZD2816	Viral Vector	Oxford/AstraZeneca	NCT04973449
52	Sputnik Light		Gamaleya	NCT04741061
53	Convidecia		CanSino	NCT04540419; NCT05169008; NCT04526990
54	Sputnik V		Gamaleya	NCT04656613; NCT04530396; NCT04640233; NCT04642339; NCT04564716; NCT04954092
55	Ad5-nCoV-IH		CanSino	NCT05204589; NCT05169008; NCT05124561
56	Brilife	Replicating Viral Vector	Israel Institute for Biological Research (IIBR)	NCT04990466
57	DelNS1-2019-nCoV-RBD- OPT1		WantaiBioPharm	ChiCTR2100051391; PACTR202110872285345
58	Turkovac	Inactivated virus	Health Institutes of Turkey	NCT04942405; NCT05077176
59	VLA2001		Valneva SE	NCT04956224; NCT04864561
60	COVIranBarekat		Shifa Pharmed Industrial Co	IRCT20201202049567N3
61	KCONVAC		Minhai Biotechnology Co	NCT05204589; NCT04852705

CD8<sup>+</sup> T cell response thus resulting in broad-spectrum protection against VOCs including alpha variant, beta variant, gamma variant, and omicron variants [121,122].

## 5. Conclusion and future prospects

The crucial times of pandemic and hard situations calls for innovative strategies. Therefore, nanotechnology emerged as a promising field in the cure of COVID-19. This article not only highlighted the facts, mechanisms and stable delivery of nanoparticle products to human system but has also demonstrated their efficacy and capability. Apart from, absorption, digestion, circulation and functioning of NPs, excretion of nanomedicines is also a subject of great interest. Thus, nanotoxicological studies are a pre-requisite in the process of nano-products formulation and design. Apart from this, the size, morphology and surface area of NPs also play a key role in design and manufacture of NPs along with their commercial production on large scale.

Nanotechnology have played a vital role in diagnosis, treatment, prevention, and vaccination related to various diseases including SARS-CoV-2. Nanotechnology may be consolidated as a significant tool for ensuring safety of healthcare personals and general public. To date, various vaccine platforms including protein subunits, viral vectors (non-replicating), viral vectors (replicating), DNA-based, RNA-based, Virus like particles, inactivated virus, live attenuated virus, viral vector (replicating) + Antigen presenting cell, viral vector (non-replicating) + Antigen presenting cell, and Bacterial antigen spore expression vectors have been developed. To enhance the effectiveness of vaccines, nano-systems like lipid, polymeric, micelles, and metallic NPs are in practice. Synthetic NPs having close morphology and physiochemical similarities of SARS-CoV-2 are an efficacious interventional technique. NPs are functionalized using various functional groups and polymers to perform specific functions.

Owing to extensive research in development of different vaccine platforms, it was possible today that NPs based clinical studies initiated within 2 months post public availability of genome sequence of SARS-CoV-2. Practically, the swift response in production and effectiveness of developed vaccines against SARS-CoV-2 helped in saving countless lives. Nonetheless, time will tell how these NPs based vaccines will

evolve during the next phase of COVID-19 and/or in combating upcoming pandemic situations. Different NPs vaccines have their own advantages and disadvantages like mRNA-based vaccines are considered to be more expensive as compared to whole-inactivated virus vaccines as they require an additional ultra-cold supply chain facility too. Further, mRNA and protein NPs vaccines require highly equipped production facilities and therefore is an area of concern in low-income countries. Protein NPs have their own challenges like complex purification, stability issues, and rigid GMP-grade requirements of cell line are hurdles in attaining regulatory approvals. There is dire need for technology transfer to scale up production and associated benefits of NPs vaccine for ensuring ample supply of manufactured vaccines around the globe. NPs vaccines results in offering controlled antigen release, and viral entry inference for treatment and prevention against COVID-19. The safety, stability, and effectiveness of NPs vaccine may be evaluated through clinical outcomes. Ongoing trials to further authenticate the safety and effectiveness of NPs vaccines must be continued.

## Ethical approval

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Conceptualization and writing-original manuscript, A.R.; Data collection, T.A., A.A.K., N.H., A.O., and M.M.R.; Editing and proof reading, R.S., P.S., Y.S.A., O.S.B., I.N.K., and M.A.K. All authors approved submission of the final manuscript.

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#### Declaration of competing interest

The authors declare that they have no conflicts of interest.

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