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Abstract: Several lines of treatment for COVID-19 are being used worldwide, but to date, the perfect line of therapy is not available. Nanomedicines received success rates in past in treating various viral complications like HCV, HSV1, IAV, HuNoV, IBV, EBOV and HIV1, which could be a game-changer for COVID-19. Various manufacturing units are looking towards nanotechnology and evaluating different nanomedicines and vaccines for treating corona infection. Recently Pfizer achieved great success in developing liposome-based messenger ribonucleic acid vaccine called BNT162b. There are few nanoparticles (NPs) under clinical trials capable of neutralising SARS-CoV-2 in outer surrounding, e.g., GDs-NPs (Gold nanoparticles), Ag-NPs (Silver nanoparticles), CuO-NPs (Copper oxide nanoparticles). The mutation of virus is challenging for treating COVID-19 and intense discovery in field of nanoscience and clinical manifestation of COVID-19 is required. Authors described the significant role of lipid nanoparticles (LNPs) in different vaccine formulations and their utility in nanomedicines for management of COVID-19.

Keywords: SARS-CoV-2 vaccines; graphene derivatives; GDs; virus-like particles; VLPs; ZnO/Ag/Cu-NPs; nanomedicines; NPs-based-formulations; inhalation aerosols.

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1 Introduction

Nanomedicines, an exceptionally incredible system having the possibility of alleviating the load of illness, is a nanoparticles-based carrier system now employed for immunisation purposes (Vu et al., 2021). It is well documented that nanotechnology-based devices have been viable in preclinical examinations for classifying microorganisms, including respiratory infections, herpes infections, human papillomavirus, and HIV (Kaittanis et al., 2010; Pan et al., 2021). Amid these corona circumstances, nanotechnology attracted the concentration of scientists to develop effective drug delivery systems to help out against COVID-19 (Vahedifard and Chakravarthy, 2021). The nanotechnology-based systems for COVID-19 treatment incorporate modern and improved testing devices for an expeditious, precise, and direct determination of the virus, creating powerful sanitisers, delivering the mRNA vaccine into human cells, and transportation of antiviral vehicles into the desired site

(Rashidzadeh et al., 2021; Weiss et al., 2020). Nanomaterials are smaller (10–100 nm) particulate materials, somewhat equivalent to the size of the virus. This smaller nano size is responsible for better penetration into the virus cell (Cavalcanti and Nogueira, 2020). The smaller size delivers a high surface-to-volume proportion and enhanced nanomaterial with excellent load-carrying moieties, improving drug transportation, targeting, and interaction among analyte and sensor (allowing fast and accurate virus detection) (Milovanovic et al., 2017; Singh et al., 2017; Ivanov et al., 2018). Due to nanoparticles' special physical and compound properties, they play a crucial role in treating COVID-19 (Dheyab et al., 2021; Chowdhury et al., 2021).

1.1 Significance of nanoparticles for the detection of SARS-CoV-2

Metal associated with nanoparticles is generally proposed for diagnostic purposes instead of the treatment of COVID-19 because of their toxicity (Vahedifard and Chakravarthy, 2021). Researchers prepared a diagnostic kit containing the gold nanoparticles coated with antisense oligonucleotides; when this interacted with viral ribonucleic acid, some changes could visually identify the presence of the COVID-19 virus. This kit can analyse and recognise the quantity of COVID-19 virus without having any highly equipped tools and techniques (Moitra et al., 2020; Alafeef et al., 2020). Recently, a metal-oxide-semiconductor has been developed with a silicon-on-insulator nanowire detector that helps to detect COVID-19 antibodies in a short time (Wasfi et al., 2022). The sensor has graphene capping, which detects SARS-CoV-2 in biological samples. It also has a transistor that produces the field-effect towards a specific antibody in anticipation of COVID spike protein, PBS 100 fg/ml is used as a biological transporter medium that can evaluate the COVID-19 spike protein at 1 fg/ml concentration (Seo et al., 2020). Another later flow-based testing tool using nanoparticles is also prepared, where a glyconanoparticle scaffold is used to identify the COVID-19 S protein, the glyconanoparticle scaffold forms a bond with spike protein in place of sialic acid; therefore, no antibodies are required for diagnosis. That phenomenon is also used in detecting SARS-CoV-2 due to its cost-effectiveness and less time-consuming properties (Baker et al., 2020).

1.2 Significance of nanoparticles in the treatment of Covid-19

The nano-techniques involved in COVID-19 treatment, consisting of polymer-coated nanoparticles, exhibit a high mucus penetration rate (Prasher et al., 2022). Formulations containing biodegradable, safe, and stable nano molecules are widely used in pulmonary disease with fewer complications (Mangal et al., 2017). The toxic effects of treatments can be minimised by changing the surface of nanoparticles with the help of conjugated polyethylene glycol and other capping substances (Emami et al., 2019; Suk et al., 2016). The use of nanoparticles (NPs) has arisen as momentous in the clinical field and permits exact conclusions and expedient treatment of a few illnesses (Rezaei et al., 2019). Due to their dimensions, less noxiousness, and surface charge properties, they could be used in several kinds of manifestations with diverse routes of application. The SARS-CoV-2 virus penetrates the host body by the fusion of S protein to the host cell membrane, and the NPS binds to the targeted cells and downregulation of S protein (He et al., 2021). Lipid-based nanoparticles or liposomes have great utility in nanoscience because of their biocompatibility and lipidic nature. Generally, liposomes are found in a globular shape

(Bozzuto and Molinari, 2015). They contain a hydrophilic layer enclosed in a phospholipid bilayer and can be administered satisfactorily through the intranasal route (Hong et al., 2019). The advantages and disadvantages of nanoparticles are summarised in Table 1.

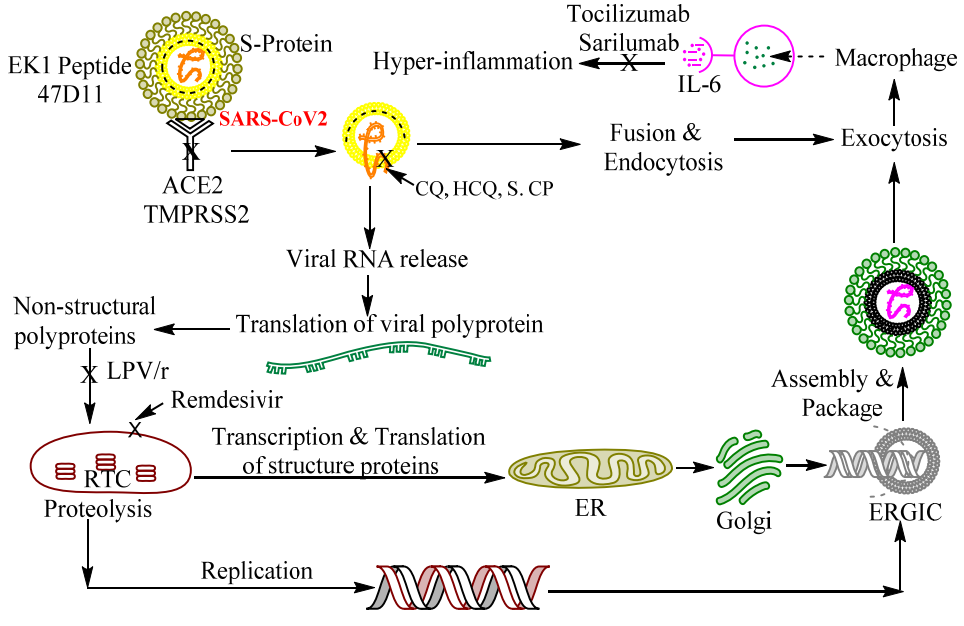
Table 1 Advantages and disadvantages of nanoparticles for the management of COVID-19

Nanoparticles	*Advantages*	*Disadvantages*
Cell-derived vesicles (Veerman et al., 2019; Hazrati et al., 2022; Snell et al., 2019)	Low immune rejection Low inherent toxicity Low apparent risk of aneuploidy	Contribution to tumour cell survival Promoting metastasis formation in tumour cell
Liposomes (Alyane et al., 2016; Bozzuto and Molinari, 2015; Leitgeb et al., 2020)	Improved pharmacokinetics and pharmacodynamics Enhancement of drug activity against pathogens Selective target specificity Reduced toxicity	Rate of removal from the bloodstream Short shelf life due to instability The difficulty of sterilisation Low drug entrapment
Dendrimer nanoparticles (Abbasi et al., 2014; Lee et al., 2005; Singh et al., 2008; Chauhan, 2015; Tomalia et al., 2007)	Controllable synthesis and degradation High miscibility and solubility High structural homogeneity High cell penetration	High production cost The need for quality management improvement The difficulty of clinical application in research
Polymer nanoparticles (Ahmad et al., 2014; Qi et al., 2019)	Controllable synthesis and degradation High cell penetration High miscibility and solubility High structural homogeneity	The need for quality management improvement The difficulty of clinical application in research High production cost
Gold nanoparticles (Yeh et al., 2012; Bansal et al., 2020)	High biocompatibility The convenience of synthesis and conjugation of various bioactive agents	High cost of large-scale production Impossible biodegradation Nanoparticle aggregation
Virus-like particles (Bundy and Swartz, 2011; Lu et al., 2015; Bundy et al., 2008)	Functionalisation of antibody fragment display for specific cell targeting Produced by cell-free protein synthesis Stabilisation by disulfide bonds Small molecule nucleic acid and protein loading capacity	Extravasate from the blood vessel Low stability Phagocytes avoidance

2 Antiviral drugs and their target site

Antiviral drugs and their target site of action have been illustrated in Figure 1 and how SARS-CoV-2 infects the lungs and heart is illustrated in Figure 2.

Figure 1 Antiviral drugs and their potential target site of action in SARS-CoV-2 virus (see online version for colours)



Note: Endocytosis is a process by which the SARS-CoV-2 penetrates the host cell ACE 2 target and interacts with S protein. RTC – replication transcription complex, ER – endoplasmic reticulum, ERGIC – endoplasmic reticulum-Golgi intermediate cavity. Antiviral drugs – chloroquine (CQ), hydroxychloroquine (HCQ), lopinavir/ritonavir (LPV/r), and remdesivir, S protein and ACE2 interaction inhibitors; EK1 peptide, neutralising antibodies: 47D11. Immunotherapy [anti-interleukin (IL)-6 Drugs]: tocilizumab and sarilumab and convalescent plasma therapy: convalescent plasma (CP).

Source: Yang (2021)

Table 2 Nanomedicine and its mechanism of action (MOA) for the treatment of viruses

Viruses	*Characteristics of viruses*	*Disease*	*Nanomedicine and their MOA*
HBV (De Clercq et al., 2010; Woo et al., 2017; Kim et al., 2010)	No subjective symptoms	Hepatitis B	Tenofovir (Viread)-reverse transcriptase inhibitor of HBV Interferon (INF)-α-inhibit HBV replication Adefovir (Hepsera)-blocking reverse transcriptase

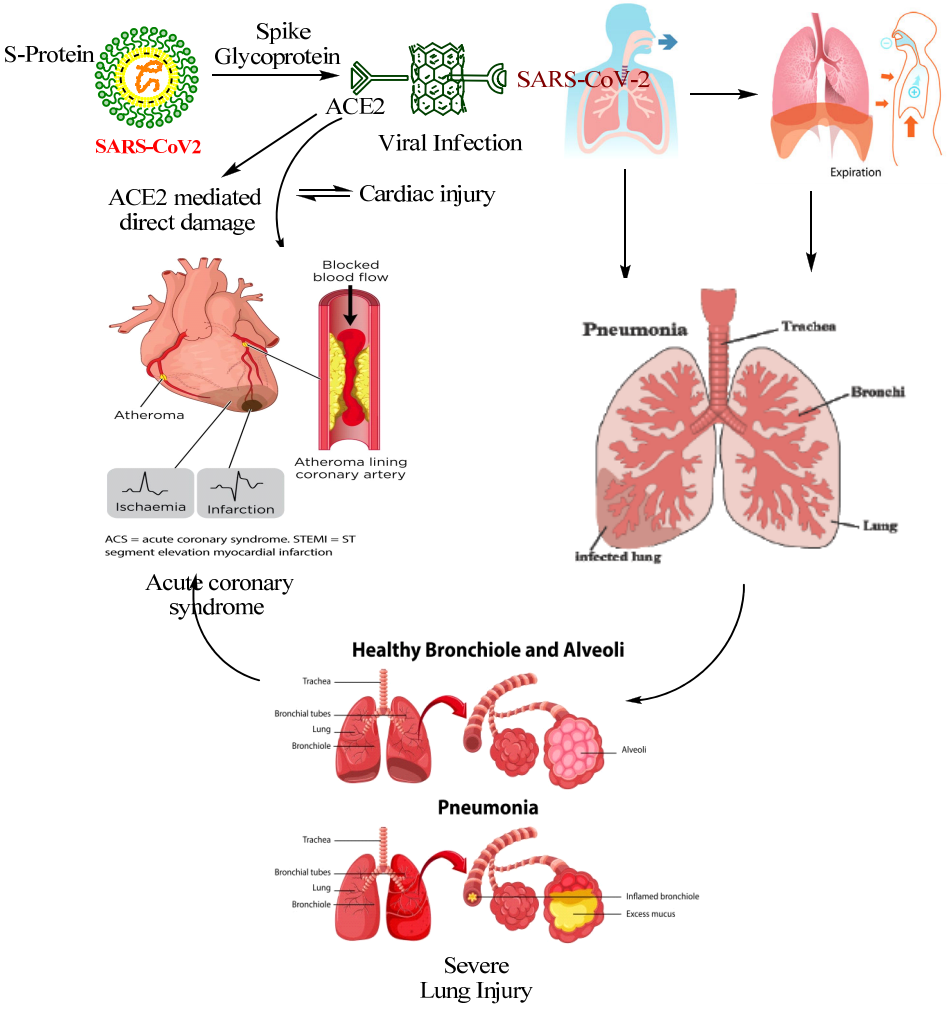
Table 2 Nanomedicine and its mechanism of action (MOA) for the treatment of viruses (continued)

Viruses	*Characteristics of viruses*	*Disease*	*Nanomedicine and their MOA*
IBV and IAV (Barik, 2012; Levina et al., 2016; Hendricks et al., 2013)	Antigenic drift Muscle pain Headache High fever	Influenza	STP702 (Fluquit)-RNA interference TiO_2 nanoparticles-Photolytic inactivation of the virus Oseltamivir modified silver nanoparticles-signalling pathway inhibitor
HSV2 and HSV1 (https://starpharma.com/news/story/spl7013-shows-significant-activity-against-sars-cov-2-coronavirus; Hassan et al., 2020)	Herpes simplex	Herpes	Viva Gel- blocked the interaction between viral spike protein and the human cell proteins Acyclovir loaded nanoparticles-enhance drug distribution
EBOV (Dunning et al., 2016)	A lethal viral hemorrhagic fever	Ebola hemorrhagic fever	TKM-130803-RNA interference
HIV2 and H1V2 (Pereira de Oliveira et al., 2005; Rodriguez et al., 2013; Orkin et al., 2019; Price et al., 2011)	Targeting CD4-positive T-cells to attack the immune system resulting in AIDS	AIDS	Indinavir nano capsules-enhancing drug distribution Doravirine (MK-1439)-non-nucleoside reverse transcriptase inhibitors Viva gel-blocking the interaction
SARS-Cov-2 (Lammers et al., 2020)	Breathing difficulty Cough and fever	COVID-19	Nano-formulating dexamethasone-anti-oedema activity and anti-fibrotic effects

3 Nanotechnology in vaccine formulation

Several types of vaccines have been formulated for combating COVID-19, based on the phenomenon of non-technological sciences. Some of the vaccines are described in brief below.

Figure 2 SARS-CoV 2 caused infection and injury in the lungs and heart (see online version for colours)



3.1 Subunit vaccines

Nano vaccines have been formulated with the help of nanocarriers and delivered the attenuated antigens to the host body. Nano vaccines have the potential to target both the innate (neutrophils, macrophages and monocytes) and adaptive (B cells and T cells) types of the body's defence system. Nanoparticles (NPs) are an inseparable adjuvant that can deliver antibodies into the host system (Zhang et al., 2020; Pati et al., 2018). Moderna and Pfizer-BioNTech developed mRNA-based vaccines for the SARS-CoV-2, which contained cationic lipid nanoparticles (LNPs) and were not affected by the RNase enzymes and could be injected through a different route of administration. Subunit vaccines have the potency to empower immunity by generating immune retaliations (Mascellino et al., 2021; Tenchov et al., 2021; Ewert et al., 2021; Palgen et al., 2021).

The S protein of the virus-cell has a special receptor-interacting and membrane attachment site. Therefore, it is important to formulate a vaccine with high binding efficiency toward the S protein of SARS-CoV-2 and prevent its attachment with the membrane by stimulating antibody formation (Jiang et al., 2012). Novavax developed a nanoparticles (NPs) vaccine that interferes with the S protein of SARS-CoV-2 (Australia, 2022). Queensland University in Australia has also developed a COVID-19 vaccine through the molecular clamp technique, which inhibits the S protein's attachment during the infection's starting phase. Few vaccines, like protein NPs and vaccines containing NPs are also in the clinical phases (The University of Queensland, 2022). The receptor binding domain (RBD) spike protein has a high affinity towards the ACE2 in COVID-19. For that reason, the SARS-CoV-2 vaccine could be helpful in the treatment of COVID-19 infection (Tai et al., 2020).

3.2 Nucleic acid vaccines

When any person gets infected, in that person, the antigen activates the nucleic acid for protein synthesis; as a result of this, the cell-mediated response along with antibody formation takes place (Marshall et al., 2018). These nucleic acid phenomena can be utilised in developing the vaccine; the vaccine contains synthetic nucleic acid that activates the desirable immune response similar to the live or attenuated vaccine. The messenger RNA is also now an integral part of vaccine development, and the mRNA enhances the immunogenic responses (Pardi et al., 2018; Zeng et al., 2020). Combining various mRNAs into one vaccine is required to achieve the maximum therapeutic effect. The mRNA-1273 vaccine is still in phase-1 trial for the SARS-CoV-2 manufactured by the US-based Cambridge, Moderna that contains a synthetic messenger RNA strand and has the binding ability to S protein of COVID virus (World Health Organization, 2021; Baden et al., 2021). Unlike regular vaccines, mRNAs do not contain any virus in the live or attenuated form. Pfizer has manufactured another vaccine called BNT162b1, a codon-boosted messenger RNA vaccine coded with the SARS-CoV-2 receptor-binding domain (Mulligan et al., 2020). In addition, Inovio Pharmaceuticals has manufactured the INO-4800 deoxyribonucleic acid vaccine (Andrade et al., 2021), which can produce immunity through the translation process in the host cell. Nucleic acid-based vaccines have been made by applying polymeric nanoparticles (PNs), NPs and cationic liposomes, through nanotechnology (Guo et al., 2019). Nano-sized virus-like particles have the potential to activate the B cell using penetration into the human cell; therefore, virus-like particles act as a vaccine base. Nano-sized virus-like particles have revealed therapeutic safety and efficacy and have enormous utility in the treatment of COVID-19 (Perotti and Perez, 2019; Nasr et al., 2021).

4 Intranasal therapy

Ongoing research examinations revealed that epithelium cells of the nasal cavity and olfactory system contain receptors such as priming proteases like TMPRSS2 and ACE2. Impairment in the olfactory modality is a primary marker in SARS-COV-2 contaminations (Butowt and von Bartheld, 2021). It has been suggested that the harm in sustentacular cells that contains the ACE2 receptor prompts olfactory impairment in the

COVID-19 population (Fodoulian et al., 2020). Now a day, numerous experiments are being focused on developing nanoparticles, which can be administered through the nasal route due to their various advantages over oral formulations (Arya et al., 2015). However, the COVID-19 infection started from the mucus membrane nasal cavity; therefore, a targeted mucosal approach could be the better strategy to treat the infection (Russell et al., 2020). The nasal drug delivery system is simple, cost-effective, and less toxic than other systems. Nanoparticles can be absorbed expeditiously from the nasal cavity because of the rich blood supply and surface area (Arya and Juyal, 2017). Nasal spray is also a component of the nasal drug delivery system. Sanotize nitric oxide (SaNOtize) is delivered through the nasal spray, which restricts the entry of the COVID-19 virus into the upper airways and averts the incubation and escalation to the lungs. Nitric oxide is a natural Nano molecule generated in humans and showed an immediate impact on COVID-19 (https://www.biopharminternational.com/view/nitric-oxide-nasal-spray-for-covid-19-to-be-distributed-to-india-and-other-asia-markets). SaNOtize spray formed a layer that helps to treat the infection at the earliest phase by inhibiting viral replication in the nasal cells. Nitric oxide also blocks the ACE2 receptor, which is crucial for causing infection (AbdelMassih et al., 2021). Human monoclonal antibody (mAb) acts as a precautionary antagonist toward COVID-19 infections. mAb nasal spray has been designed to counteract the SARS-CoV-2 that inhibits the infection in the nasal cavity (Quiros-Roldan et al., 2021). The mAb blocked the ACE2 by binding the S1-protein on the respiratory tract. This phenomenon prevents the entry of infection into cells (Chen et al., 2020). Nano-spray containing zinc oxide (ZnO-NPs) has been evaluated as effective germicidal action for treating SARS-CoV-2. Zinc oxide nanoparticles have shown antiviral effects at a minimum concentration (IC50 = 526 ng/mL). It has been proven that ZnO-NPs have accumulated intracellularly, effectively impairing replication of SARS-CoV-2 (El-Megharbel et al., 2021; Rohani et al., 2022).

4.1 Pulmonary delivery using NPs inhalation aerosols

When treatment with intranasal delivery did not show a desirable therapeutic effect and infection passed to the lungs, we have another approach called pulmonary delivery of aerosols to block the infection (Ahamed et al., 2013a). Lung endothelial cells contain ACE receptors, mainly angiotensin II, responsible for regulating pulmonary vascularity (Ahamed et al., 2013b). For the prevention of SARS-CoV-2 infection, the lungs are one of the most important target sites; for that reason, inhaled aerosols are prescribed as an efficacious and safer route of delivery (Lavorini et al., 2021). The application of different nanotechnologies has formulated aerosols containing NPs. The particle size of NPs in inhalation aerosols remains in the range of 10–30 nm so that they can effortlessly be transported to the lungs in the form of dry powder or the dispersible colloidal spray solid form of compressed metered-dose inhaler (MDI) (Muralidharan et al., 2015). The Novochizol technology formulates chitosan nanoparticles, and those NPs are highly biologically compatible, show great affinity towards the epithelial cells of lungs, and have prolonged released tendencies (Cavalcanti and Nogueira, 2020). Systemic distributions of those NPs are less, so they can maintain an effective concentration around the targeted site. Preclinical testing of chitosan nanoparticles showed promising intranasal delivery (Arya et al., 2015; Arya and Juyal, 2017).

5 Nanotechnology for the neutralisation of SARS-CoV-2 in the outer environment

SARS-CoV-2 is enacted at temperatures 1 to 35°C and is neutralised in the acidic and high alkaline environment. The solidity of SARS-CoV-2 depends on its surface structure and is readily inactivated by currently accessible disinfectants. In this way, surface processing utilising NPs demonstrated antagonistic action towards the SARS-CoV-2 (Coleman et al., 2014). The utilisation of nanotechnology in surface disinfectants can be a system of more viable choices than the traditional sterilisation method (Rasmi et al., 2021). Additionally, by utilising NPs, one can openly control the delivery pace of metal particles, which have been demonstrated to be good and effective surface antibacterial (Joe et al., 2016). Antiviral effects of silver nanoparticles (Ag-NPs) have been now revealed, and the antiviral activity showed basically through faster disintegration and donating Ag^{+} ions, responsible for microbial-lysis (Orlowski et al., 2014). Ag^{+} ions bind with protein on the virus surface, piled up in the host cells, and inhibit virus replication with thiols containing enzymes (Galdiero et al., 2011). Due to the size of Ag-NPs, which is about 10 nm, they can easily bind with the surface of the virus and show greater physical interconnection and antiviral potency (Lara et al., 2010). On the other hand, Ag-NPs generate free oxygen radicals after attachment to the virus's surface. The uses of Ag-NPs have effectively been explored, and they are used in the air channels and face masks to immobilise SARS-CoV-2. The Ag-NPs are also used in filters to restrict the entry of MS2 bacteriophages from the outer environment, particularly from dirt (Allawadhi et al., 2021). SARS-CoV-2 was also neutralised by the application of copper, and its antiviral effect on HuCoV-229E has been proved. Cu^{2+} has the genome-breaking ability, thus making the virus disable (Govind et al., 2021). Cu^{2+} ions bind with surface proteins of the virus and release hydroxyl radicals, which cause impairment of viral proteins, and finally, agitation of virions occurs (Raha et al., 2020). As far as economics and stability are concerned, Cu^{2+} is superior to Ag+. Hence the development of Cu-NPs like CuO is the best option to neutralise the SARS-CoV-2 in outer surroundings. It has already been proven that the influenza virus got disabled by wearing the CuO-NPs coated mask (Cortes and Zuñiga, 2020; Behzadinasab et al., 2020). SARS-CoV-2 is also neutralised by combining graphene derivatives (GDs) and metal NPs. With the help of electrostatic interactions between GDs and viral surface, the positively charged viral surface interacts with negatively charged GDs ion (Bundy et al., 2008). The GDs nanoparticles containing antibodies already have proved their antiviral action against influenza and rotavirus infections (Palmieri and Papi, 2020). As per the previously mentioned distinguished character of GDs, they could be used to improve, diagnose and manage the COVID-19 viruses (Park et al., 2021a). Numerous techniques have evaluated the antimicrobial properties of iron oxide nanoparticles (IONPs). Due to its better biostability, USFDA has been approved for anaemic management (Coyne, 2009). In outer surroundings, the iron oxide nanoparticles interact with the S protein present in SARS-CoV-2 and generate reactive oxygen species, which causes the inactivation of SARS-CoV-2 (Arias et al., 2018; Abo-zeid et al., 2020).

6 Future of nanoscience in the management of COVID-19

Nanoscience is a novel technology for the treatment of COVID-19. The expeditious interpretation of these nano-formulations in the preclinical, clinical, and regulatory authorities gained more faith in the success of nanotechnology (Campos et al., 2020; Yin et al., 2014). Nanomedicine provides a generic platform, so it could be a cost-effective treatment option, despite the possibilities mentioned above, it is also a bitter truth that Nanomedicine still has to take full regulatory approval before being a part of the treatment, which is a time-consuming process (Foulkes et al., 2020). The main challenge in the treatment of COVID-19 is the mutation of the virus that is needed to be resolved, or else intense discovery in the field of nanoscience is indubitable to COVID-19 therapy (Yayehrad et al., 2021). There are a few challenges for nanomedicine including toxicological studies, therapeutic index, physicochemical stability, bioavailability, regularity requirements, and good manufacturing practice (Soares et al., 2018).

7 Recent advancements in vaccines formulations

Virus-like particles (VLPs) and nanoparticles have given rise to good vaccines. Molecules that activate innate immunity can be enclosed within the VLP to elevate the immune response and stimulate type 1 immunity (Kanekiyo and Buck, 2017). Around 79 COVID-19 candidate vaccines are in clinical trials, four vaccines are in phase IV, and 12 are in the phase III clinical trial process, per the report published on 5 March 2021. Besides these, about 182 other vaccines are in the progress of preclinical studies. Moreover, 90% of preeminent patients administered intramuscular injections (Kyriakidis et al., 2021; Gordon, 2021). Apart from these, the concept of DNA vaccines also seems crucial, in which delivering genes or fragments encode immunogenic antigens to the host cells by employing DNA plasmids as a vector. This approach stimulates a cell-mediated and humoral immune response. The vaccine is synthesised, so the genetic content is translocated to the host cell nucleus (Silveira et al., 2021).

7.1 Inactivated virus vaccines

In this sort of vaccine, the genetic content of the virus has been impaired to prevent the disease-causing efficiency. Inactivated virus lacks the potency to replicate inside the body, so a large dose is required. An adjuvant, i.e., aggravated the immune system, is employed to boost the immune system efficiently. It has been commonly seen that inactivated virus vaccines can aggravate the antibody mediate immunity but cannot elicit cell-mediated immunity inactivated. Some common examples of these vaccines are the rabies vaccine, hepatitis A virus vaccine, whole-cell pertussis (whooping cough) vaccine, and poliovirus (IPV) vaccine (Sanders et al., 2015).

Chinese state-owned biopharmaceutical company Sinopharm developed the inactivated COVID-19 vaccine called BBIBP-CorVin in collaboration with the Beijing Institute of biological products. The private Chinese company Sinovac developed an inactivated COVID-19 vaccine called Corona Vac, while Bharat Biotech, the National Institute of Virology, and the Indian Council of Medical Research jointly developed Covaxin. All three vaccines contain an adjuvant viz. aluminium hydroxide, which can enhance the vaccine's effectiveness. Moreover, Covaxin contains an additional adjuvant

known as a toll-like receptor (TLR) 7/8 agonist that facilitates a sturdy immune response. All three vaccines are administered in two prescribed doses (Kumar et al., 2021).

7.2 Viral subunit vaccine

This vaccine uses antigen of the virus without any genetic content, commonly provided with an adjuvant for showing good immune response. Most childhood schedule vaccines are subunit, protecting people from diseases such as whooping cough, tetanus, diphtheria, and meningococcal meningitis. An adjuvant can stimulate the cell to mediate immunity and cell-mediated immunity. Generally, this vaccine has been formulated by employing a recombinant expression system, i.e., in a cell without using the virus. The antigens have been authenticated through T helper cells during the genuine viral infection with the help of antigen-presenting cells. These vaccines usually produce cell-mediated immunity (Kandeil et al., 2021).

7.3 Viral vector vaccines

Viral vector vaccines use a modified version of a different virus (the vector) to deliver important instructions to our cells. This vaccine elicits its action in the following ways; firstly, the vector (not the virus that causes COVID-19) but a different harmless virus enters into a cell in our body and then uses the cell machinery to produce a harmful fragment of the virus that causes COVID-19. This fragment is known as spike protein and is found on the surface of the coronavirus and causes COVID-19. Spike protein triggers our immune system to produce antibodies and activates other immune cells to fight the infection. Finally, at the end of the process, our antibodies have learned how to protect us against future coronavirus infection, and we get protected from the virus. The vaccine minimised the risk of further disease and its serious consequences or even death. The individual may have some restlessness or uneasiness after the vaccination; this is a typical process experience, and it expresses the proper functioning of the vaccine. The virus vector vaccines can be developed rapidly and show their effect by triggering a sturdy cellular immune response with T cells and forming antibodies with B cells, and an example viral vector vaccine is the rVSV-ZEBOV vaccine against Ebola (Henao-Restrepo et al., 2017).

7.4 Messenger RNA-based vaccine

The messenger RNA (mRNA) vaccine contains instructions for constructing viral or bacterial protein into our cells. The immune mechanism of our body then responds to these proteins and evolves the technique to activate the immune response against the pathogen or infection that comes in the future. The genetically engineered mRNA vaccine instructs our cells on how to make the S protein found on the surface of the COVID-19 virus. After the vaccination, our immune cell initiates the formation of the S protein fragment and displays them on cell surfaces (Kowalzik et al., 2021; Rahman et al., 2021) and our body develops antibodies. If a patient is further infected with the COVID-19 virus, the antibodies formed and fight against the virus. After furnishing instructions, the mRNA is expeditiously broken down and never administered to our

cells' nucleus. Pfizer-BioNTech and the Moderna COVID-19 vaccines are used m-RNA as vaccine targets (World Health Organization, 2021; Park et al., 2021b).

7.5 Subunit vaccine and protein subunit vaccine

Subunit vaccines utilise a small fragment of the pathogen to elicit our immune system to combat future infections. They cannot produce diseases but require the addition of other chemicals to form vaccines to activate the substantial immune reaction. Subunit vaccine-like Novavax COVID-19 candidate possesses either a protein, polysaccharide (sugar moiety), or a combination of both. The protein subunit vaccine exclusively contains the virus that activates our immune system. This kind of vaccine possesses non-detrimental S proteins. Whenever our immune system identifies the S protein, it produces antibodies and protective white blood cells. If a vaccinated individual again gets infected with the COVID-19 virus, the antibodies efficiently combat the virus; examples include the hepatitis B and cellular pertussis vaccines (protein subunit), the pneumococcal polysaccharide vaccine (polysaccharide), and the MenACWY vaccine, which contains polysaccharides from the surface of four types of the bacteria that causes meningococcal disease joined to diphtheria or tetanus toxoid (conjugate subunit) (Ma et al., 2014; Hewings-Martin, 2021).

Table 3 Merit and demerits of the immunogen in different vaccines formulation

Immunogen	*What it is*	*Advantages*	*Disadvantages*	*Examples of vaccines*
Nucleic acids	mRNA coding for a viral protein	Substantial cellular immunity; fast progress	Relatively low antibody response	COVID-19
Viral subunit	A protein emerged from a pathogen	It may have lesser side effects than the whole virus (swelling at injection sides) and redness	It may be a weakly immunogenic; complex process	Influenza
Inactivated virus	Inactivated dead virus	Activates strong antibody response	Desires excess quantities of virus, less or no immune response	Rabies, hepatitis A, influenza
Viral vector	Viral pathogen articulated on a safe virus that is unable to develop the disease	Fast progress, substantial cellular response, comparatively easier to develop	Prior exposure to vector virus (Adenovirus) may alleviate immunogenicity; few vectors desire to boost with a different vector	Ebola

Source: Dai and Gao (2021) and Kashte et al. (2021)

Table 4 Available vaccines for combating COVID-19

Vaccine manufacturer	*Vaccine code/brand name*	*Vaccine target used*	*Composition*	*Dose and incubation period*	*Recommend*
Pfizer, Inc., and BioNTech (COVID-19 Update, 2021; https://en.wikipedia.org/wiki/Pfizer%E2%80%93 BioNTech_COVID-19_vaccine)	BNT162b2/Comimaty	mRNA	It is composed of nucleoside-modified mRNA (mod RNA) encoding a mutated form of the full-length spike protein of SARS-CoV-2, which is encapsulated in lipid nanoparticles	Two doses are given three weeks (21 days) apart	Individuals 12 years of age and older under an emergency use authorisation (EUA)
Moderna TX, Inc. (Moderna COVID-19 Vaccine Overview and Safety, 2021; https://en.wikipedia.org/wiki/Moderna_COVID-19_vaccine)	mRNA-1273, CX-024414, COVID-19 mRNA Vaccine Moderna, TAK-919	mRNA	It is composed of nucleoside-modified mRNA (mod RNA) encoding a spike protein of SARS-CoV-2, which is encapsulated in lipid nanoparticles	Two doses given four weeks (28 days) apart	People 18 years and older
Johnson & Johnson's Janssen (FDA and CDC Lift Recommended Pause on Johnson & Johnson, Janssen; https://en.wikipedia.org/wiki/Johnson_%26_Johnson_COVID-19_vaccine)	JNJ-78436735/ Ad26.COV2. S/Janssen COVID-19 Vaccine	Viral vector vaccine	human adenovirus that has been modified to contain the gene for making the spike protein of the SARS-CoV-2 virus that causes COVID-19	Only one dose is given	People 18 years and older
Oxford/AstraZeneca COVID-19 vaccine (Watanabe et al., 2021; https://en.wikipedia.org/wiki/Oxford%E2%80%93AstraZeneca_COVID-19_vaccine)	AZD1222/Vaxzevria/ Covishield/ChAdOx1 nCoV-19	Spike proteins	It is a viral vector vaccine, using as a vector the modified chimpanzee adenovirus ChAdOx1	Two doses were given intramuscularly with an interval of 8 to 12 weeks.	Priority be given to health workers at high risk of exposure and older people, including those aged 65 or older

Table 4 Available vaccines for combating COVID-19 (continued)

Vaccine manufacturer	*Vaccine code/brand name*	*Vaccine target used*	*Composition*	*Dose and incubation period*	*Recommend*
Novavax and the Coalition for Epidemic Preparedness Innovations (CEPI) (*COVID-19: How the Novavax Vaccine Works – And the Benefits It has over the Three Already Approved*; https://en.wikipedia.org/wiki/Novavax_COVID-19_vaccine)	NVX-CoV2373/ Covovax	Spike protein	It comprises SARS-CoV-2 rS (recombinant spike) protein nanoparticles with Matrix-M1 adjuvant. It is a subunit vaccine, and virus-like particle vaccine, though the producers call it a recombinant nanoparticle vaccine.	Two doses were given intramuscularly at an interval of three weeks apart	Aged 18 to 84, with 27% aged over 65
Sinopharm's Beijing Institute of Biological Products (Kaabi et al., 2021; https://www.who.int/news-room/feature-stories/detail/the-sinopharm-COVID-19-vaccine-what-you-need-to-know; https://en.wikipedia.org/wiki/BBIBP-CorV)	BBIBP-CorV/ Sinopharm-BBIBP	Inactivated SARS-Co V-2 virus	It is composed of one of two inactivated viruses, COVID-19. Inactivated viruses are mixed with an aluminium-based adjuvant	Two doses were given intramuscularly. WHO recommends 3–4 weeks between the first and second dose	The vaccine is not recommended for persons younger than 18 years of age
Sinovac Biotech (https://en.wikipedia.org/wiki/CoronaVac; https://www.who.int/news-room/feature-stories/detail/the-sinovac-COVID-19-vaccine-what-you-need-to-know)	CoronaVac/ Sinovac COVID-19 vaccine	SARS-Co V-2 Inactivated virus	It is an inactivated virus COVID-19 vaccine. The inactivated viruses are then mixed with an aluminium-based adjuvant	Two doses were given intramuscularly; WHO recommends 2–4 weeks between the first and second dose	The vaccine is not recommended for persons younger than 18 years of age

7.6 Nucleic acid vaccines

Nucleic acid vaccines are used the genetic content from a disease-producing virus or bacterium (a pathogen) to aggravate the immune response to combat it. The genetic content may be DNA or RNA based upon the vaccine; in both circumstances, it gives the information for developing a specific protein from the pathogen, which the immune system identifies as foreign (an antigen). While administered to the host cells, this genetic content is prepared by the host cells' protein-making machinery and employed in forming antigens that stimulate the immune system. This newly emerged technique; moreover, RNA or DNA vaccines are formulated to combat several ailments such as COVID-19, Zika virus and HIV. Various kinds of DNA vaccines, but no vaccine has been approved for human use so far. However, many DNA vaccines are validated for animals, e.g., the horse vaccine against the West Nile virus (Dai and Gao, 2021). Some merits and demerits of the immunogen in different vaccine formulations are described in Table 3 and the currently available vaccine for combating COVID-19 is described in Table 4.

8 Conclusions

However, many conventional strategies like antiviral, anti-malarial, ACE inhibitors, and immunosuppressant drugs are used worldwide to treat COVID-19. However, unfortunately, we could not get a proper cure for the infection, and still, we need better strategies for treating COVID-19. The main challenge in the treatment of COVID-19 is the mutation of the virus that is required to be resolved, or else intense discovery in the field of nanoscience is indubitable to COVID-19 treatment. Nanoscience has designed and placed a novel mechanism for the treatment of COVID-19. Nanotechnology can be used in the diagnostic and treatment of COVID-19. Various nano-formulations are under preclinical, clinical trials, or consideration of the regulatory authority. Earlier, the focus of researchers on the nanotechnology-based therapy of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus was very little. Now in this COVID-19 pandemic situation, various approaches are being tested for the development of effective treatment. In the past, nanomedicines have successfully treated various viral complications like HCV, HSV1, IAV, HuNoV, IBV, EBOV, and HIV1 and it could be a game-changer in the treatment of COVID-19. Various manufacturing units and research organisations are looking forward to nanotechnology and trying to manufacture and evaluate different nanomedicines and vaccines, such as nano-formulations of dexamethasone. Recently Pfizer achieved great success in developing a liposome-based messenger ribonucleic acid vaccine called BNT162b. For neutralising the SARS-CoV-2 on the surface and surroundings, some NPs like GDs, Ag-NPs, CuO and NPs are under regulatory trials. Various nano-based vaccines are currently being developed containing the attenuated virus, viral vector fragment, and nucleic acid or synthetic nucleic acid. Despite the possibilities mentioned above, it is also a bitter truth that nanomedicine still has to take full regulatory approval before being a part of the treatment, but it is a long process. From the above discussion, we can conclude that nanoparticles-based diagnostic or COVID-19 treatment can be a miraculous carrier system to combat COVOD-19.

References

Abbasi, E., Aval, S.F., Akbarzadeh, A. et al. (2014) 'Dendrimers: synthesis, applications, and properties', *Nanoscale Res. Lett.*, Vol. 9, No. 1, p.247, DOI: 10.1186/1556-276X-9-247.

AbdelMassih, A., Hozaien, R., El Shershaby, M. et al. (2021) 'The potential role of inhaled nitric oxide for postexposure chemoprophylaxis of COVID-19', *J. Genet. Eng. Biotechnol*., Vol. 19, p.165, DOI: 10.1186/s43141-021-00249-5.

Abo-zeid, Y., Ismail, N.S.M., McLean, G.R. and Hamdy, N.M. (2020) 'A molecular docking study repurposes FDA approved iron oxide nanoparticles to treat and control COVID-19 infection', *Eur. J. Pharm. Sci.*, 1 October, Vol. 153, p.153, DOI: 10.1016/j.ejps.2020.105465.

Ahamed, M., Alhadlaq, H.A., Alam, J., Khan, M.A., Ali, D. and Alarafi, S. (2013a) 'Iron oxide nanoparticle-induced oxidative stress and genotoxicity in human skin epithelial and lung epithelial cell lines', *Curr. Pharm. Des.*, Vol. 19, No. 37, pp.6681–6690.

Ahamed, M., Alhadlaq, H.A., Khan, M.A.M. and Akhtar, M.J. (2013b) 'Selective killing of cancer cells by iron oxide nanoparticles mediated through reactive oxygen species via p53 pathway', *J. Nanopart. Res.*, Vol. 15, No. 1, p.15671.

Ahmad, Z., Shah, A., Siddiq, M. and Kraatz, H.B. (2014) 'Polymeric micelles as drug delivery vehicles', *RSC Adv.*, Vol. 4, No. 33, pp.17028–17038.

Alafeef, M., Dighe, K., Moitra, P. and Pan, D. (2020) 'Rapid, ultrasensitive, and quantitative detection of SARS-CoV-2 using antisense oligonucleotides directed electrochemical biosensor chip', *ACS Nano*., Published online 20 October 2020, DOI: 10.1021/acsnano.0c06392.

Allawadhi, P., Singh, V., Khurana, A. et al. (2021) 'Silver nanoparticle based multifunctional approach for combating COVID-19', *Sensors International*, Vol. 2, p.100101, DOI: 10.1016/j.sintl.2021.100101.

Alyane, M., Barratt, G. and Lahouel, M. (2016) 'Remote loading of doxorubicin into liposomes by transmembrane pH gradient to reduce toxicity toward H9c2 cells', *Saudi Pharm. J.*, Vol. 24, No. 2, pp.165–175.

Andrade, V.M., Christensen-Quick, A., Agnes, J. et al. (2021) 'INO-4800 DNA vaccine induces neutralizing antibodies and T cell activity against global SARS-CoV-2 variants', *NPJ Vaccines*, Vol. 6, No. 1, pp.1–4, DOI: 10.1038/s41541-021-00384-7.

Arias, L.S., Pessan, J.P., Vieira, A.P.M., Lima, T.M.T., Delbem, A.C.B. and Monteiro, D.R. (2018) 'Iron oxide nanoparticles for biomedical applications: a perspective on synthesis, drugs, antimicrobial activity, and toxicity', *Antibiotics (Basel)*, Vol. 7, No. 2, p.46.

Arya, R.K.K. and Juyal, V. (2017) 'Polymer-lipid hybrid nanoparticles for brain targeting through intranasal delivery', *J. Drug Deliv. Ther*., Vol. 7, No. 4, pp.129–136, DOI: 10.22270/jddt.v7i4.1480.

Arya, R.K.K., Juyal, V. and Kunwar, N. (2015) 'Preparation of carbamazepine chitosan nanoparticles for improving nasal absorption', *J. Drug Deliv. Ther*., pp.101–108, DOI: 10.22270/jddt. v5i3.1090.

Australia, H. (2022) *About the COVID-19 Vaccines*, 20 August [online] https://www.healthdirect.gov.au/covid-19/about-the-vaccines.

Baden, L.R., El Sahly, H.M., Essink, B. et al. (2021) 'Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine', *N. Engl. J. Med*., Vol. 384, No. 5, pp.403–416, DOI: 10.1056/NEJMoa2035389.

Baker, A.N., Richards, S.J., Guy, C.S. et al. (2020) 'The SARS-COV-2 spike protein binds sialic acids and enables rapid detection in a lateral flow point of care diagnostic device', *ACS Cent. Sci*., Vol. 6, No. 11, pp.2046–2052.

Bansal, S.A., Kumar, V., Karimi, J., Singh, A.P. and Kumar, S. (2020) 'Role of gold nanoparticles in advanced biomedical applications', *Nanoscale Adv.*, Vol. 2, No. 9, pp.3764–3787, DOI: 10.1039/D0NA00472C.

Barik, S. (2012) 'New treatments for influenza', *BMC Med*., Vol. 10, No. 4, pp.1741–7015, DOI: 10.1186/1741-7015-10-104.

Behzadinasab, S., Chin, A., Hosseini, M., Poon, L. and Ducker, W.A. (2020) 'A surface coating that rapidly inactivates SARS-CoV-2', *ACS Appl. Mater. Interfaces*, Vol. 12, No. 31, pp.34723–34727, DOI: 10.1021/acsami.0c11425.

Bozzuto, G. and Molinari, A. (2015) 'Liposomes as nanomedical devices', *Int. J. Nanomed.*, Vol. 10, No. 2, pp.975–999, DOI: 10.2147/IJN.S68861.

Bundy, B.C. and Swartz, J.R. (2011) 'Efficient disulfide bond formation in virus-like particles', *J. Biotechnol.*, Vol. 154, No. 4, pp.230–239.

Bundy, B.C., Franciszkowicz, M.J. and Swartz, J.R. (2008) 'Escherichia coli-based cell-free synthesis of virus-like particles', *Biotechnol. Bioeng.*, Vol. 100, No. 1, pp.28–37.

Butowt, R. and von Bartheld, C.S. (2021) 'Anosmia in COVID-19: underlying mechanisms and assessment of an olfactory route to brain infection', *Neuroscientist*, Vol. 27, No. 6, pp.582–603, DOI: 10.1177/1073858420956905.

Campos, E.V.R., Pereira, A.E.S., de Oliveira, J.L. et al. (2020) 'How can nanotechnology help to combat COVID-19? Opportunities and urgent need', *J. Nanobiotechnology*, Vol. 18, No. 1, p.125, DOI: 10.1186/s12951-020-00685-4.

Cavalcanti, I.D.L. and Nogueira, M.C.d.B.L. (2020) 'Pharmaceutical nanotechnology: which products are been designed against COVID-19?', *J. Nanopart. Res.*, Vol. 22, No. 9, p.276, DOI: 10.1007/s11051-020-05010-6.

Chauhan, A.S. (2015) 'Dendrimer nanotechnology for enhanced formulation and controlled delivery of resveratrol', *Ann. N.Y. Acad. Sci.*, Vol. 1348, No. 1, pp.134–140, DOI: 10.1111/nyas.12816.

Chen, X., Li, R., Pan, Z. et al. (2020) 'Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor', *Cell. Mol. Immunol.*, Vol. 17, No. 6, pp.647–649, DOI: 10.1038/s41423-020-0426-7.

Chowdhury, N.K., Deepika, C.R. et al. (2021) 'Nanoparticles as an effective drug delivery system in COVID-19', *Biomed Pharmacother*., Vol. 143, p.112162, DOI: 10.1016/j.biopha.2021.112162.

Coleman, C.M., Liu, Y.V., Mu, H.Y. et al. (2014) 'Purified coronavirus spike protein nanoparticles induce coronavirus neutralizing antibodies in mice', *Vaccine*, Vol. 32, No. 26, pp.3169–3174.

Coronavirus (COVID-19) Update: FDA Authorizes Pfizer-BioNTech COVID-19 Vaccine for Emergency Use in Adolescents in another Important Action in Fight against Pandemic (2021) 10 May 2021 [online] https://www.fda.gov/news-events/press-announcements/ coronavirus-covid-19-update-fda-authorizes-pfizer-biontech-covid-19-vaccine-emergency-use.

Cortes, A.A. and Zuñiga, J.M. (2020) 'The use of copper to help prevent transmission of SARS-coronavirus and influenza viruses. A general review', *Diagn. Microbiol. Infect. Dis.*, Vol. 98, No. 4, p.115176, DOI: 10.1016/j.diagmicrobio.2020.115176.

COVID-19: How the Novavax Vaccine Works – And the Benefits It has over the Three Already Approved, 29 January 2021 [online] https://news.sky.com/story/covid-19-what-is-the-novavax-vaccine-and-how-does-it-compare-with-the-others-12201799.

Coyne, D.W. (2009) 'Ferumoxytol for treatment of iron deficiency anemia in patients with chronic kidney disease', *Expert Opin Pharmacother*, Vol. 10, No. 15, pp.2563–2568.

Dai, L. and Gao, G.F. (2021) 'Viral targets for vaccines against COVID-19', *Nat. Rev. Immunol.*, Vol. 21, No. 2, pp.73–82, DOI: 10.1038/s41577-020-00480-0.

De Clercq, E., Férir, G., Kaptein, S. and Neyts, J. (2010) 'Antiviral treatment of chronic hepatitis B virus (HBV) infections', *Viruses*, Vol. 2, No. 6, pp.1279–1305, DOI: 10.3390/v2061279.

Dheyab, M.A., Khaniabadi, P.M., Aziz, A.A. et al. (2021) 'Focused role of nanoparticles against COVID-19: diagnosis and treatment', *Photodiagnosis Photodyn Ther*., Vol. 34, p.102287, DOI: 10.1016/j.pdpdt.2021.102287.

Dunning, J., Sahr, F., Rojek, A. et al. (2016) 'Experimental treatment of Ebola virus disease with TKM-130803: a single-arm phase 2 clinical trial', *PLoS Med.*, Vol. 13, No. 4, p.1001997.

El-Megharbel, S.M., Alsawat, M., Al-Salmi, F.A. and Hamza, R.Z. (2021) 'Utilizing of (zinc oxide nano-spray) for disinfection against 'SARS-CoV-2' and testing its biological effectiveness on some biochemical parameters during (COVID-19 pandemic) ZnO nanoparticles have antiviral activity against (SARS-CoV-2)', *Coatings*, Vol. 11, No. 4, p.388, DOI: 10.3390/coatings11040388.

Emami, F., Yazdi, S.J.M. and Na, D.H. (2019) 'Poly (lactic acid)/poly (lactic-co-glycolic acid) particulate carriers for pulmonary drug delivery', *J. Pharm. Investig.*, Vol. 49, No. 4, pp.427–442, DOI: 10.1007/s40005-019-00443-1.

Ewert, K.K., Scodeller, P., Simón-Gracia, L. et al. (2021) 'Cationic liposomes as vectors for nucleic acid and hydrophobic drug therapeutics', *Pharmaceutics*, Vol. 13, No. 9, p.1365, DOI: 10.3390/pharmaceutics13091365.

FDA and CDC Lift Recommended Pause on Johnson & Johnson (Janssen) COVID-19 Vaccine Use following Thorough Safety Review (2021) 23 April [online] https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough.

Fodoulian, L., Tuberosa, J., Rossier, D. et al. (2020) 'SARS-CoV-2 receptors and entry genes are expressed in the human olfactory neuroepithelium and brain', *iScience*, Vol. 23, No. 12, p.101839, DOI: 10.1016/j.isci.2020.101839.

Foulkes, R., Man, E., Thind, J., Yeung, S., Joy, A. and Hoskins, C. (2020) 'The regulation of nanomaterials and nanomedicines for clinical application: current and future perspectives', *Biomaterials Science*, Vol. 8, No. 17, pp.4653–4664, DOI: 10.1039/D0BM00558D.

Galdiero, S., Falanga, A., Vitiello, M., Cantisani, M., Marra, V. and Galdiero, M. (2011) 'Silver nanoparticles as potential antiviral agents', *Molecules*, Vol. 16, No. 10, pp.8894–8918, DOI: 10.3390/molecules16108894.

Gordon, C. (2021) 'COVID-19 vaccination: intramuscular injection technique', *Br. J. Nurs.*, Vol. 30, No. 6, pp.350–353, DOI: 10.12968/bjon.2021.30.6.350.

Govind, V., Bharadwaj, S., Ganesh, M.R.S. et al. (2021) 'Antiviral properties of copper and its alloys to inactivate covid-19 virus: a review', *Biometals*, Vol. 34, No. 6, pp.1217–1235, DOI: 10.1007/s10534-021-00339-4.

Guo, S., Fu, D., Utupova, A. et al. (2019) 'Applications of polymer-based nanoparticles in vaccine field', *Nanotechnology Reviews*, Vol. 8, No. 1, pp.143–155, DOI: 10.1515/ntrev-2019-0014.

Hassan, H., Bello, R.O., Adam, S.K. et al. (2020) 'Acyclovir-loaded solid lipid nanoparticles: optimization, characterization and evaluation of its pharmacokinetic profile', *Nanomaterials (Basel)*, Vol. 10, No. 9, p.1785, DOI: 10.3390/nano10091785.

Hazrati, A., Soudi, S., Malekpour, K. et al. (2022) 'Immune cells-derived exosomes function as a double-edged sword: role in disease progression and their therapeutic applications', *Biomarker Research*, Vol. 10, No. 1, p.30, DOI: 10.1186/s40364-022-00374-4.

He, L., Lin, X., Wang, Y. et al. (2021) 'Single-component, self-assembling, protein nanoparticles presenting the receptor binding domain and stabilized spike as SARS-CoV-2 vaccine candidates', *Sci. Adv.*, Vol. 7, No. 12, p.eabf1591, DOI: 10.1126/sciadv.abf1591.

Henao-Restrepo, A.M., Camacho, A., Longini, I.M. et al. (2017) 'Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)', *Lancet*, Vol. 389, No. 10068, pp.505–518, DOI: 10.1016/S0140-6736(16)32621-6.

Hendricks, G.L., Weirich, K.L., Viswanathan, K. et al. (2013) 'Sialylneolacto-N-tetraose c (LSTc)-bearing liposomal decoys capture influenza A virus', *J. Biol. Chem.*, Vol. 288, No. 12, pp.8061–8073.

Hewings-Martin, Y. (2021) *COVID-19: How do Subunit Vaccines Work?*, 26 February [online] https://www.medicalnewstoday.com/articles/covid-19-how-do-subunit-vaccines-work.

Hong, S.S., Oh, K.T., Choi, H.G. and Lim, S.J. (2019) 'Liposomal formulations for nose-to-brain delivery: recent advances and future perspectives', *Pharmaceutics*, Vol. 11, No. 10, p.540, DOI: 10.3390/pharmaceutics11100540.

https://en.wikipedia.org/wiki/BBIBP-CorV (accessed 10 November 2021).

https://en.wikipedia.org/wiki/CoronaVac (accessed 13 October 2022).

https://en.wikipedia.org/wiki/Johnson_%26_Johnson_COVID-19_vaccine (accessed 19 February 2021).

https://en.wikipedia.org/wiki/Moderna_COVID-19_vaccine (accessed 5 May 2021).

https://en.wikipedia.org/wiki/Novavax_COVID-19_vaccine (accessed 24 February 2021).

https://en.wikipedia.org/wiki/Oxford %E2%80%93AstraZeneca_COVID-19_vaccine (accessed 19 February 2021).

https://en.wikipedia.org/wiki/Pfizer%E2% 80%93 BioNTech_COVID-19_vaccine (accessed 20 September 2021).

https://www.who.int/news-room/feature-stories/detail/the-sinopharm-COVID-19-vaccine-what-you-need-to-know (accessed 10 June 2022).

https://www.who.int/news-room/feature-stories/detail/the-sinovac-COVID-19-vaccine-what-you-need-to-know (accessed 10 June 2022).

Ivanov, Y.D., Malsagova, K.A., Pleshakova, T.O. et al. (2018) 'Ultrasensitive detection of 2, 4-dinitrophenol using nanowire biosensor', *J. Nanotechnol*., 17 October, https://doi.org/10.1155/2018/9549853.

Jiang, S.B., Bottazzi, M.E., Du, L.Y. et al. (2012) 'Roadmap to developing a recombinant coronavirus S protein receptor-binding domain vaccine for severe acute respiratory syndrome', *Expert Rev Vaccines*, Vol. 11, No. 12, pp.1405–1413.

Joe, Y.H., Park, D.H. and Hwang, J. (2016) 'Evaluation of Ag nanoparticle coated air filter against the aerosolized virus: antiviral efficiency with dust loading', *J. Hazard. Mater.*, 15 January, Vol. 301, pp.547–553, DOI: 10.1016/j.jhazmat.2015.09.017.

Kaabi, N.A., Zhang, Y., Xia, S. et al. (2021) 'Effect of 2 inactivated SARS-CoV-2 vaccines on symptomatic COVID-19 infection in adults: a randomized clinical trial', *JAMA*, 26 May, DOI: 10.1001/jama. 2021.8565, PMID 34037666.

Kaittanis, C., Santra, S. and Perez, J.M. (2010) 'Emerging nanotechnology-based strategies for the identification of microbial pathogenesis', *Adv. Drug Deliv. Rev.*., Vol. 62, Nos. 4–5, pp.408–423.

Kandeil, A., Mostafa, A., Hegazy, R.R., El-Shesheny, R., ElTaweel, A., Gomaa, M.R., Shehata, M., Elbaset, M.A., Kayed, A.E., Mahmoud, S.H. et al. (2021) 'Immunogenicity and safety of an inactivated SARS-CoV-2 vaccine: preclinical studies', *Vaccines*, Vol. 9, No. 3, pp.214–2019, DOI: 10.3390/vaccines9030214.

Kanekiyo, M. and Buck, C.B. (2017) 'Virus-like particle and nanoparticle vaccines', *Human Vaccines*, pp.87–98, DOI: 10.1016/B978-0-12-802302-0.00003-0.

Kashte, S., Gulbake, A., El-Amin III, S.F. et al. (2021) 'COVID-19 vaccines: rapid development, implications, challenges, and future prospects', *Human Cell*, Vol. 34, No. 3, pp.711–733, DOI: 10.1007/s13577-021-00512-4.

Kim, K.H., Kim, N.D. and Seong, B.L. (2010) 'Discovery and development of anti-HBV agents and their resistance', *Molecules*, Vol. 15, No. 9, pp.5878–5908, DOI: 10.3390/molecules15095878.

Kowalzik, F., Schreiner, D., Jensen, C., Teschner, D., Gehring, S. and Zepp, F. (2021) 'mRNA-based vaccines', *Vaccines*, 15 April, Vol. 9, No. 4, pp.390–405, DOI: 10.3390/vaccines9040390.

Kumar, A., Dowling, W.E., Roman, R.G. et al. (2021) 'Status report on COVID-19 vaccines development', *Curr. Infect. Dis. Rep.*, Vol. 23, No. 9, pp.752–753.

Kyriakidis, N.C., López-Cortés, A., González, E.V., Grimaldos, A.B. and Prado, E.O. (2021) 'SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates', *NPJ Vaccines*, Vol. 6, No. 1, pp.1–17, DOI: 10.1038/s41541-021-00292-w.

Lammers, T., Sofias, A.M., van der Meel, R. et al. (2020) ;Dexamethasone nanomedicines for COVID-19', *Nat. Nanotechnol*., Vol. 15, No. 8, pp.622–624.

Lara, H.H., Ayala-Nuñez, N.V., Ixtepan-Turrent, L. and Rodriguez-Padilla, C. (2010) 'Mode of antiviral action of silver nanoparticles against HIV-1', *J. Nanobiotechnology*, Vol. 8, No. 1, p.1, DOI: 10.1186/1477-3155-8-1.

Lavorini, F., Usmani, O.S. and Dhand, R. (2021) 'Aerosol delivery systems for treating obstructive airway diseases during the SARS-CoV-2 pandemic', *Intern Emerg Med.*, Vol. 16, No. 8, pp.2035–2039, DOI: 10.1007/s11739-021-02812-x.

Lee, C.C., MacKay, J.A., Frechet, J.M.J. and Szoka, F.C. (2005) 'Designing dendrimers for biological applications', *Nat. Biotechnol.*, Vol. 23, No. 12, pp.1517–1526.

Leitgeb, M., Knez, Z. and Primozic, M. (2020) 'Sustainable technologies for liposome preparation', *The Journal of Supercritical Fluids*, Vol. 165, p.104984, DOI: 10.1016/j.supflu.2020.104984.

Levina, A.S., Repkova, M.N., Mazurkova, N.A. and Zarytova, V.F. (2016) 'Nanoparticle-mediated nonviral DNA delivery for effective inhibition of influenza viruses in cells', *IEEE T. Nanotechnol*., Vol. 15, No. 2, pp.248–254.

Lu, Y., Chan, W., Ko, B.Y., Lang, C.C.V. and Swartz, J.R. (2015) 'Assessing sequence plasticity of a virus-like nanoparticle by evolution toward a versatile scaffold for vaccines and drug delivery', *Proc. Natl. Acad. Sci. USA*, Vol. 112, No. 40, pp.12360–12365.

Ma, C.Q., Wang, L.L., Tao, X.R. et al. (2014) 'Searching for an ideal vaccine candidate among different MERS coronavirus receptor-binding fragments – the importance of immunofocusing in subunit vaccine design', *Vaccine*, Vol. 32, No. 46, pp.6170–6176.

Mangal, S., Gao, W., Li, T. and Zhou, Q. (2017) 'Pulmonary delivery of nanoparticle chemotherapy for the treatment of lung cancers: challenges and opportunities', *Acta Pharmacol. Sin.*, Vol. 38, No. 6, pp.782–797, DOI: 10.1038/aps.2017.34.

Marshall, J.S., Warrington, R., Watson, W. and Kim, H.L. (2018) 'An introduction to immunology and immunopathology', *Allergy, Asthma & Clinical Immunology*, Vol. 14, No. 2, p.49, DOI: 10.1186/s13223-018-0278-1.

Mascellino, M.T., Di Timoteo, F., De Angelis, M. and Oliva, A. (2021) 'Overview of the main anti-SARS-CoV-2 vaccines: mechanism of action, efficacy and safety', *Infect. Drug Resist*., Vol. 14, pp.3459–3476, DOI: 10.2147/IDR.S315727.

Milovanovic, M., Arsenijevic, A., Milovanovic, J., Kanjevac, T. and Arsenijevic, N. (2017) 'Nanoparticles in antiviral therapy', *Antimicrobial Nanoarchitectonics*, pp.383–410, DOI: 10.1016/B978-0-323-52733-0.00014-8.

Moderna COVID-19 Vaccine Overview and Safety (2021) 5 April [online] https://www.who.int/news-room/feature-stories/detail/the-moderna-covid-19-mrna-1273-vaccine-what-you-need-to-know? (accessed 18 August 2022).

Moitra, P., Alafeef, M., Dighe, K., Frieman, M.B. and Pan D. (2020) 'Selective naked-eye detection of SARS-CoV-2 mediated by N gene-targeted antisense oligonucleotide capped plasmonic nanoparticles', *ACS Nano*., Vol. 14, No. 6, pp.7617–7627.

Mulligan, M.J., Lyke, K.E., Kitchin, N. et al. (2020) 'Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults', *Nature*, Vol. 586, No. 7830, pp.589–593.

Muralidharan, P., Malapit, M., Mallory, E., Hayes, D. and Mansour, H.M. (2015) 'Inhalable nanoparticulate powders for respiratory delivery', *Nanotechnol. Biol. Med.*, Vol. 11, No. 5, pp.1189–1199, DOI: 10.1016/j.nano.2015.01.007.

Nasr, M.J., Alizadeh Khatir, A., Babazadeh, A. and Ebrahimpour, S. (2021) 'The role of ACE2 receptors of the olfactory system in anosmia in COVID-19: an overview', *Neurol. Res. Int*., Vol. 2021, p.5776801, DOI: 10.1155/2021/5776801.

Nitric Oxide Nasal Spray for COVID-19 to Be Distributed to India and Other Asia Markets, BioPharm International, 4 August 2021 [online] https://www.biopharminternational.com/view/nitric-oxide-nasal-spray-for-covid-19-to-be-distributed-to-india-and-other-asia-markets.

Orkin, C., Squires, K.E., Molina, J.M. et al. (2019) Doravirine/Lamivudine/Tenofovir disoproxil fumarate is non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil fumarate in treatment-naive adults with human immunodeficiency virus-1 infection: week 48 results of the DRIVE-AHEAD trial', *Clin. Infect. Dis*., Vol. 68, No. 4, pp.535–544.

Orlowski, P., Tomaszewska, E., Gniadek, M. et al. (2014) 'Tannic acid-modified silver nanoparticles show antiviral activity in herpes simplex virus type 2 infection', *PLoS One*, Vol. 9, No. 8, p.104113.

Palgen, J.L., Feraoun, Y., Dzangué-Tchoupou, G. et al. (2021) 'Optimize prime/boost vaccine strategies: trained immunity as a new player in the game', *Frontiers in Immunology*, 8 March, Vol. 12, https://doi.org/10.3389/fimmu.2021.612747 [online] https://www.frontiersin.org/articles/10.3389/fimmu.2021.612747.

Palmieri, V. and Papi, M. (2020) 'Can graphene take part in the fight against COVID-19?', *Nano Today*, 8 August, Vol. 33, p.100883, DOI: 10.1016/j.nantod.2020.100883.

Pan, L., Li, B., Chen, J., Zhang, H., Wang, X., Shou, J. et al. (2021) 'Nanotechnology-based weapons to combat human papillomavirus infection associated diseases', *Frontiers in Chemistry*, 17 November, Vol. 9, https://doi.org/10.3389/fchem.2021.798727 [online] https://www.frontiersin.org/articles/10.3389/fchem.2021.798727.

Pardi, N., Hogan, M.J., Porter, F.W. and Weissman, D. (2018) 'mRNA vaccines – a new era in vaccinology', *Nat. Rev. Drug Discov*., Vol. 17, No. 4, pp.261–279.

Park, I., Lim, J., You, S. et al. (2021a) 'Detection of SARS-CoV-2 virus amplification using a crumpled graphene field-effect transistor biosensor', *ACS Sens.*, Vol. 6, No. 12, pp.4461–4470, DOI: 10.1021/acssensors.1c01937.

Park, J.W., Lagniton, P.N.P., Liu, Y. and Xu, R.H. (2021b) 'mRNA vaccines for COVID-19: what, why, and how', *Int. J. Biol. Sci.*, Vol. 17, No. 6, pp.1446–1460.

Pati, R., Shevtsov, M. and Sonawane, A. (2018) 'Nanoparticle vaccines against infectious diseases', *Front Immunol*., Vol. 9, p.2224, DOI: 10.3389/fimmu.2018.02224.

Pereira de Oliveira, M., Garcion, E., Venisse, N., Benoit, J.P., Couet, W. and Olivier, J.C. (2005) 'Tissue distribution of indinavir administered as solid lipid nanocapsule formulation in mdr1a (+/+) and mdr1a (-/-) CF-1 mice', *Pharm Res*. 2005, Vol. 22, No. 11, pp.1898–1905.

Perotti, M. and Perez, L. (2019) 'Virus-like particles and nanoparticles for vaccine development against HCMV', *Viruses*, Vol. 12, No. 1, p.35, DOI: 10.3390/v12010035.

Prasher, P., Sharma, M., Singh, S.K. et al. (2022) 'Targeting mucus barrier in respiratory diseases by chemically modified advanced delivery systems', *Chemico-Biological Interactions*, Vol. 365, p.110048, DOI: 10.1016/j.cbi.2022.110048.

Price, C.F., Tyssen, D., Sonza, S. et al. (2011) 'SPL7013 gel (VivaGel (R)) retains potent HIV-1 and HSV-2 inhibitory activity following vaginal administration in humans', *PLoS One*, Vol. 6, No. 9, p.24095.

Qi, F., Wu, J., Li, H. and Ma, G.H. (2019) 'Recent research and development of PLGA/PLA microspheres/nanoparticles: a review in scientific and industrial aspects', *Front Chem. Sci. Eng.*, Vol. 13, No. 1, pp.14–27.

Quiros-Roldan, E., Amadasi, S., Zanella, I. et al. (2021) 'Monoclonal antibodies against SARS-CoV-2: current scenario and future perspectives', *Pharmaceuticals (Basel)*, Vol. 14, No. 12, p.1272, DOI: 10.3390/ph14121272.

Raha, S., Mallick, R., Basak, S. and Duttaroy, A.K. (2020) 'Is copper beneficial for COVID-19 patients?', *Med. Hypotheses*, Vol. 142, p.109814, DOI: 10.1016/j.mehy.2020.109814.

Rahman, M.M., Zhou, N. and Huang, J. (2021) 'An overview on the development of mRNA-based vaccines and their formulation strategies for improved antigen expression in vivo', *Vaccines*, 11 March, Vol. 9, No. 1, pp.244–264, DOI: 10.3390/vaccines9030244.

Rashidzadeh, H., Danafar, H., Rahimi, H. et al. (2021) 'Nanotechnology against the novel coronavirus (severe acute respiratory syndrome coronavirus 2): diagnosis, treatment, therapy and future perspectives', *Nanomedicine*, Vol. 16, No. 6, pp.497–516, DOI: 10.2217/nnm-2020-0441.

Rasmi, Y., Saloua, K.S., Nemati, M. and Choi, J.R. (2021) 'Recent progress in nanotechnology for COVID-19 prevention, diagnostics and treatment', *Nanomaterials*, Vol. 11, No. 7, p.1788, DOI: 10.3390/nano11071788.

Rezaei, R., Safaei, M., Mozaffari, H.R. et al. (2019) 'The role of nanomaterials in the treatment of diseases and their effects on the immune system', *Open Access Maced. J. Med. Sci*., Vol. 7, No. 11, pp.1884–1890, DOI: 10.3889/oamjms.2019.486.

Rodriguez, B., Asmuth, D.M., Matining, R.M. et al. (2013) 'Safety, tolerability, and immunogenicity of repeated doses of Derma Vir, a candidate therapeutic HIV vaccine, in HIV-infected patients receiving combination antiretroviral therapy: results of the ACTG 5176 trial', *J. Acquire Immune Defic*., Vol. 64, No. 4, pp.351–359.

Rohani, R., Dzulkharnien, N.S.F., Harun, N.H. and Ilias, I.A. (2022) 'Green approaches, potentials, and applications of zinc oxide nanoparticles in surface coatings and films', *Bioinorg. Chem. Appl.*, Vol. 2022, p.e3077747, DOI: 10.1155/2022/3077747.

Russell, M.W., Moldoveanu, Z., Ogra, P.L. and Mestecky, J. (2020) 'Mucosal immunity in COVID-19: a neglected but critical aspect of SARS-CoV-2 infection', *Frontiers in Immunology*, 30 November,, Vol. 11, https://doi.org/10.3389/fimmu.2020.611337 [online] https://www.frontiersin.org/articles/10.3389/fimmu.2020.611337/full.

Sanders, B., Koldijk, M. and Schuitemaker, H. (2015) 'Inactivated viral vaccines', in Nunnally, B.K., Turula, V.E. and Sitrin, R.D. (Eds.): *Vaccine Analysis: Strategies, Principles, and Control*, pp.45–80, Springer, DOI: 10.1007/978-3-662-45024-6_2.

Seo, G., Lee, G., Kim, M.J. et al. (2020) 'Rapid detection of COVID-19 causative virus (SARS-CoV-2) in human nasopharyngeal swab specimens using field-effect transistor-based biosensor', *ACS Nano*, Vol. 14, No. 9, pp.12257–12258.

Silveira, M.M., Moreira, G.M.S.G. and Mendonça, M. (2021) 'DNA vaccines against COVID-19: Perspectives and challenges', *Life Sci.*, 15 February, Vol. 267, p.118919, DOI: 10.1016/j.lfs.2020.118919.

Singh, I., Rehni, A.K., Kalra, R., Joshi, G. and Kumar, M. (2008) 'Dendrimers and their pharmaceutical applications – a review', *Pharmazie*, Vol. 63, No. 7, pp.491–496.

Singh, L., Kruger, H.G., Maguire, G.E.M., Govender, T. and Parboosing, R. (2017) 'The role of nanotechnology in the treatment of viral infections', *Ther. Adv. Infect. Dis.*, Vol. 4, No. 4, pp.105–131, DOI: 10.1177/2049936117713593.

Snell, A.A., Neupane, K.R., McCorkle, J.R. et al. (2019) 'Cell-derived vesicles for in vitro and in vivo targeted therapeutic delivery', *ACS Omega*, Vol. 4, No. 7, pp.12657–12664, DOI: 10.1021/acsomega.9b01353.

Soares, S., Sousa, J., Pais, A. and Vitorino, C. (2018) 'Nanomedicine: principles, properties, and regulatory issues', *Front Chem.*, Vol. 6, p.360, DOI: 10.3389/fchem.2018.00360.

Starpharma | SPL7013 Shows Significant Activity against SARS-CoV-2 (Coronavirus), Starpharma, 16 April 2020 [online] https://starpharma.com/news/story/spl7013-shows-significant-activity-against-sars-cov-2-coronavirus.

Suk, J.S., Xu, Q., Kim, N., Hanes, J. and Ensign, L.M. (2016) 'PEGylation as a strategy for improving nanoparticle-based drug and gene delivery', *Adv/ Drug Deliv. Rev.*, Vol. 99, Pt A, pp.28–51, DOI: 10.1016/j.addr.2015.09.012.

Tai, W.B., He, L., Zhang, X.J. et al. (2020) 'Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine', *Cell. Mol. Immunol.*, Vol. 17, No. 6, pp.613–620.

Tenchov, R., Bird, R., Curtze, A.E. and Zhou, Q. (2021) 'Lipid nanoparticles – from liposomes to mRNA vaccine delivery, a landscape of research diversity and advancement', *ACS Nano*, Vol. 15, No. 11, pp.16982–17015, DOI: 10.1021/acsnano.1c04996.

The University of Queensland (2022) *Study Shows Clamp Technology Promising for Future Vaccine Development*, UQ News [online] https://www.uq.edu.au/news/article/2021/04/study-shows-clamp-technology-promising-future-vaccine-development.

Tomalia, D.A., Reyna, L.A. and Svenson, S. (2007) 'Dendrimers as multi-purpose nanodevices for oncology drug delivery and diagnostic imaging', *Biochem. Soc. T*, Vol. 35, No. 1, pp.61–67.

Vahedifard, F. and Chakravarthy, K. (2021) 'Nanomedicine for COVID-19: the role of nanotechnology in the treatment and diagnosis of COVID-19', *Emergent Mater.*, Vol. 4, No. 1, pp.75–99, DOI: 10.1007/s42247-021-00168-8.

Veerman, R.E., Akpinar, G.G., Eldh, M. and Gabrielsson, S. (2019) 'Immune cell-derived extracellular vesicles – functions and therapeutic applications', *Trends in Molecular Medicine*, Vol. 25, No. 5, pp.382–394, DOI: https://doi.org/10.1016/j.molmed.2019.02.003.

Vu, M.N., Kelly, H.G., Kent, S.J. and Wheatley, A.K. (2021) 'Current and future nanoparticle vaccines for COVID-19', *eBioMedicine*, 18 November, Vol. 74, DOI: https://doi.org/10.1016/j.ebiom.2021.103699 [online] https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00493-X/fulltext.

Wasfi, A., Awwad, F., Gelovani, J.G., Qamhieh, N. and Ayesh, A.I. (2022) 'COVID-19 detection via silicon nanowire field-effect transistor: setup and modeling of its function', *Nanomaterials (Basel)*, Vol. 12, No. 15, p.2638, DOI: 10.3390/nano12152638.

Watanabe, Y. et al. (2021) 'Native-like SARS-CoV-2 spike glycoprotein expressed byChAdOx1 nCoV-19/AZD1222 vaccine', *ACS Central Science*, https://doi.org/10.1021/acscentsci.1c00080.

Weiss, C., Carriere, M., Fusco, L. et al. (2020) 'Toward nanotechnology-enabled approaches against the COVID-19 pandemic', *ACS Nano*, Vol. 14, No. 6, pp.6383–6406.

Woo, A.S.J., Kwok, R. and Ahmed, T. (2017) 'Alpha-interferon treatment in hepatitis B', *Ann. Transl. Med.*, Vol. 5, No. 7, p.159, DOI: 10.21037/atm.2017.03.69.

World Health Organization (2021) *mRNA-1273 Vaccine (Moderna) against COVID-19 Background Document*, Draft prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines, 19 January 2021, World Health Organization, License: CC BY-NC-SA 3.0 IGO [online] https://apps.who.int/iris/handle/10665/338738.

Yang, D. (2021) 'Application of nanotechnology in the COVID-19 pandemic', *Int. J. Nanomedicine*, Vol. 16, pp.623–649, DOI: 10.2147/IJN.S296383.

Yayehrad, A.T., Siraj, E.A., Wondie, G.B., Alemie, A.A., Derseh, M.T. and Ambaye, A.S. (2021) 'Could nanotechnology help to end the fight against COVID-19? Review of current findings, challenges and future perspectives', *Int. J. Nanomedicine*, Vol. 16, pp.5713–5743, DOI: 10.2147/IJN.S327334.

Yeh, Y.C., Creran, B. and Rotello, V.M. (2012) 'Gold nanoparticles: preparation, properties, and applications in bionanotechnology', *Nanoscale*, Vol. 4, No. 6, pp.1871–1880, DOI: 10.1039/c1nr11188d.

Yin, H., Kanasty, R.L., Eltoukhy, A.A., Vegas, A.J., Dorkin, J.R. and Anderson, D.G. (2014) 'Non-viral vectors for gene-based therapy', *Nat Rev Genet.*, Vol. 15, No. 8, pp.541–555.

Zeng, C., Hou, X., Yan, J. et al. (2020) 'Leveraging mRNAs sequences to express SARS-CoV-2 antigens in vivo', *bioRxiv*., DOI: 10.1101/2020.04.01.019877.

Zhang, J.Y., Zeng, H., Gu, J., Li, H.B., Zheng, L.X. and Zou, Q.M. (2020) 'Progress and prospects on vaccine development against SARS-CoV-2', *Vaccines-Basel*, Vol. 8, No. 2, pp.351–359.