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A Concise Review of The Role of Nanotechnology, Nanoparticles and Nanomedicine Play in The Diagnostics, Vaccination and Treatment Options For COVID-19

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Abstract

Since the end of 2019, we have been combating the health challenges caused by the multiple waves of COVID-19 (coronavirus disease 2019) pandemic caused by the mutated variants of concern of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The key to successfully combating the COVID-19 pandemic remains prevention by vaccination, rapid as well as timely detection and diagnosis, with proper treatment of infection cases. The previously used and standardized viral diagnostics and therapeutics have not been effective in combating the SARS-CoV-2 virus as observed during this ongoing COVID-19 pandemic. Nanotechnology and it's applications in nanomedicine have been very effective and valuable as applied in drug delivery, vaccines and nanosensor technology in various diseases. In the last three years, nanotechnology, nanoparticles and nanomedicine have played a very significant role in the prevention, diagnostics, treatment options and vaccination associated with the COVID-19 infection. In this concise review, the most recent developments on the role played by nanotechnology, nanoparticles and nanomedicine in the diagnostics, vaccination and treatment options for COVID-19 have been highlighted. .

Keywords: Nanotechnology; COVID-19 nanotechnology-based vaccines; COVID-19 and nanoparticles; Nanomedicine in COVID-19; Nanoparticles

Abbreviations: COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; WHO: World Health Organization

Introduction and Background

In March 2020, the World Health Organization (WHO) characterized the spread of the COVID-19 (coronavirus disease 2019) to have become a global pandemic. COVID-19 is the third world-wide pandemic in human history and the causative agent is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that is transmitted through the oral route (mouth) and through contact of infected fluids via the eyes and the nose [1,2]. The WHO documented figures have validated that the COVID-19 pandemic has caused over 633 million cases of active infections and 64.9 million mortalities until the end of the year 2022 [3]. SARSCoV-2 is from the *Corona viridae* family of viruses and has a single stranded RNA and exists in the beta form. The origins of the human disease of COVID-19 continue to be debatable but the epidemic started in Wuhan China and then spread all over the world.

The COVID-19 virus structure shows it to an enveloped, positive-sense, and single-stranded RNA virus while the genome is 30kb with a diameter of just between 60 to 140nm, thus confirming the very tiny size of this virus [4,5]. The genomic structure of the SARS-CoV-2 virus has been found to have a 79.5% match with the SARS-CoV-1 virus which was the causative agent of an epidemic in the year 2002 [3,4]. In addition, the SARS-CoV-2 virus exhibits a 96% genome similarity to RaTG13 which is a species of a bat coronavirus [3,4,6]. As validated by evolutionary research and due to the genomic similarity, the bat is now considered to be the main biological host of SARS-CoV-2 virus. In order to successfully prevent and manage COVID-19 infections, there is need to understand it's viral protein structure as well as the links between its functions and the interactions with the human host machinery during pathogenesis [4-8].

Structurally the SARS-CoV-2 virus has been documented as being a sphere in shape while the diameter as mentioned above is in a nanoscale measure although a bigger and pleomorphic particulate shape is also prevalently found (see Figure 1 below) [3]. Since the COVID-19 infection is highly transmissible, there is need for efficient measures of prevention, timely diagnosis, treatment of active infections and containment of the spread through use of effective PPE (personal protective equipment). As the conventionally used viral drugs, testing methodologies and vaccines proved to be ineffective against the SARS-CoV-2 virus, since 2020 there has been an ongoing research and innovative nanotechnology, nanoparticle and nanomedicine based solutions for tackling the COVID-19 infection.

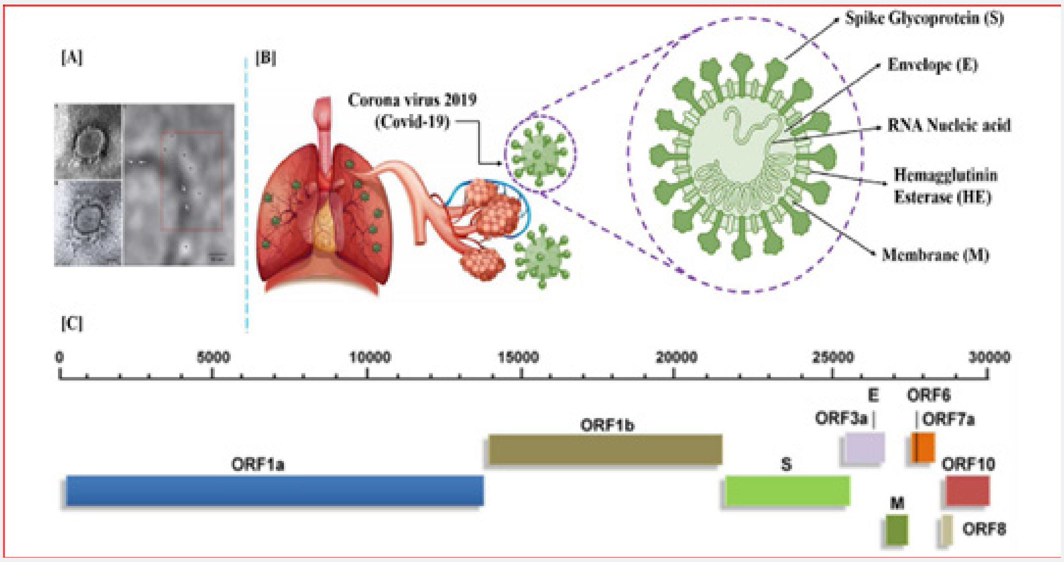

Figure 1: (A) Structural details and tiny size of the SARS-CoV-2 virus as seen via the transmission electron microscope (B) A schematic figure showing the surface structural proteins of SARS-CoV- 2 virus (C). The genome of the SARS-CoV-2 virus (Source 3).

Nanotechnology, Nanoparticles and Nanomedicine

Due to the extremely tiny size of the SARS-CoV-2 virus, all prevention, containment, diagnostics, therapeutics as well as management methodology has to be correspondingly within the "nano" measure as it is then targeted and very efficacious [4-8] In the last two decades, nanotechnology, use of nanoparticles and nanomedicine clinical approaches have given viable options to counteract viral diagnosis, vaccines and therapies [9-21]. Nanotechnology refers to the field that studies and applies nanomaterials and nanoparticles (materials that have a diameter of less than 100nm). Nanotechnology-based uses in COVID-19 medicine include the field of drug discoveries, targeted drug delivery testing, prevention and containment. Nanotechnology has found applications in different methods of designing and developing tools, testing kits, detection protocols and strategies, COVID-19 diagnostics as well treatment drugs and the innovative development of mRNA and other COVID-19 vaccines and PPE [3,9-21].

Since 2020, nanotechnology has boosted the designing of special sensors for the quick and extremely sensitive diagnosis of COVID-19 infections [15,19,21], the creation of effective sanitizers [11], the development and delivery mechanisms of extracellular antigenic components in the form of the mRNA-based vaccines [3,13,14,16,17] as well as the development and targeted delivery of COVID-19 specific antiretroviral drugs for human use (see Figure 2 below) [9-21].

The use of nanotechnology and nanoparticles based nanomedicine is vast in clinical practice because of the unique characteristics of nanomaterials like provision of increased surface area to volume ratios (attributed to the nano measure size), helping with multifunctional clinical protocols, enhanced ability to dissolve and capacity of better surface adaptability. These characteristics of nanomaterials have been very useful in the development of targeted COVID-19 treatments, the innovative creation of novel drugs, improved as well as swift COVID-19 diagnostic tools and nanomedicine applications for patient personalized treatment. All these nanotechnologies based COVID-19 management aspects are far more efficient in mitigation and containment of the SARS-CoV-2 virus [1,7-9]. In this concise review article, we present the most current as well as in trial developments in the last 2-3 years in terms of the use of nanotechnology, nanoparticles and nanomedicine in the management of the ongoing COVID-19 pandemic.

Literature Review Search Methodology and Analysis

In this review article, we have carried out a quick review of

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the latest published research on COVID-19 nanotechnology-based viral prevention, treatment and containment protocols. The aim is to present a summary of how nanotechnology based applications have been useful in the following three perspectives of COVID-19 management. We have reviewed the use of nanotechnology and nanoparticles in swift, accurate and easy detection of the SARS-CoV-2 virus (COVID-19 diagnostics). Next, we have reviewed the use of nanotechnology and nanoparticles in the development of COVID-19 specific antiviral treatments. Thirdly, we have reviewed the use of nanotechnology and nanoparticles in COVID-19 prevention strategies (vaccines) and containment (PPE, sanitizers, air filters etc).

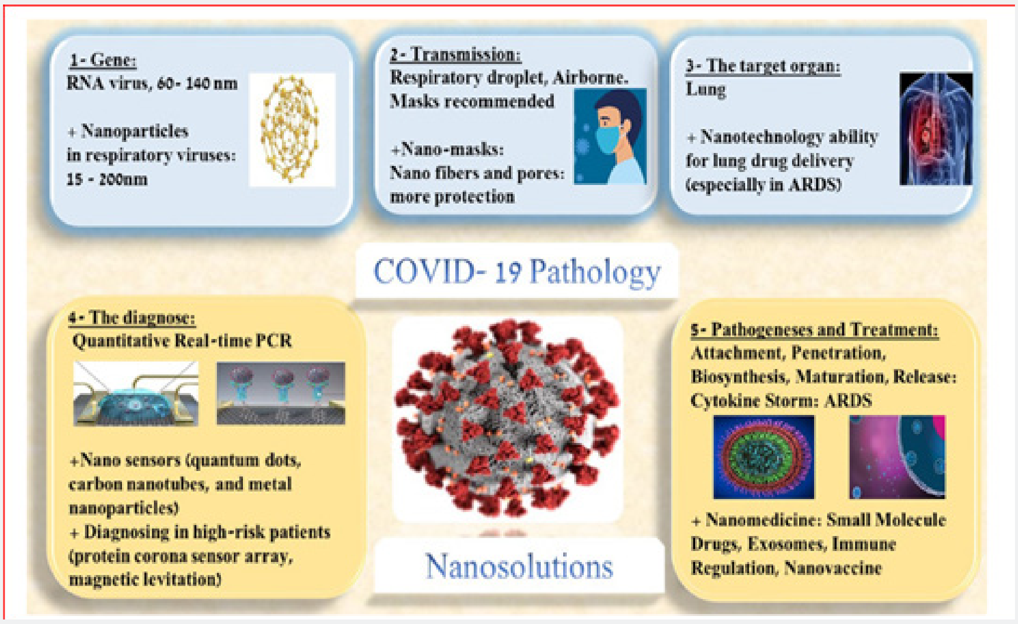

Figure 2: Nanotechnology, nanoparticles and nanomedicine based applications for combating the COVID-19 infection (Source 4).

This research study methodology made use of the follows the Preferred Reporting Items for Systematic Reviews (PRISMA) checklist requirements to carry out a qualitative review of appropriate published articles to provide findings for the three nanotechnology-based COVID-19 aspects mentioned above [22-24]. A search was carried out on PubMed as well as Google Scholar databases for relevant articles (published in peer-reviewed journals) on the role of nanotechnology, nanoparticles and nanomedicine in the management of COVID-19 infection as well as pandemic.

A number of MeSH (medical subject headings) and terminology were utilized to carry out the search on the two databases (PubMed and Google scholar) and these were: combinations of these key search phrases and synonyms "nanotechnology, nanoparticles and nanomedicine in COVID-19," "nanotechnology-based applications in COVID-19" and "Nanomedicine in COVID-19." The abstracts of all the obtained titles from the search results were assessed for relevance in terms of the most current findings. After this, the articles were examined to ensure that they examined one of these aspects: role of nanotechnology, nanoparticles or nanomedicine based aspects of COVID-19 diagnostics, vaccines, treatment or prevention and containment strategies. The abstracts of the relevant reviewable articles were than examined once again to exclude duplicates. The final set of qualifying articles was reviewed for the purposes of this concise review.

Inclusion and Exclusion Criteria

Only studies published between 2020- 2023 on the three nanotechnology-based COVID-19 aspects were included. Furthermore, only studies published in the English were included in this concise review.

Results

The PRISMA flowchart (see Figure 3 below) and the key emerging themes with validated findings are presented below. The findings from the reviewed articles showed that the following key themes emerged in the perspective of the role of nanotechnology, nanoparticles and nanomedicine based approaches in COVID-19 management.

Nanotechnology, Nanoparticles and Nanomedicine in COVID-19 Diagnostics

Nanotechnology, nanoparticles and nanomedicine based applications in faster and cost effective COVID-19 diagnostics are

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an emerging field with many clinical trials of COVID-19 specific diagnostics and detection strategies underway [3,5,9,11,21]. PCR (Polymerase chain reaction) as well as real time reverse-transcription polymerase chain reaction (RT-PCR) are the most accurate testing and diagnosis protocols with a very high sensitivity and specificity for detection of the SARS-CoV-2 virus. The main drawback as seen in the ongoing COVID-19 pandemic is that these diagnostic tests need multiple use and are quite long in duration, making them costly. In a pandemic situation, high-cost and lengthy diagnostics that also have limitations like providing false-negative results often cause delays in isolation and treatment of active COVID-19 infections. Thus, the need for low-cost, faster and more accurate COVID-19 diagnostics have brought use of nanotechnology in this aspect into focus [3,5,9,11,14-18,21].

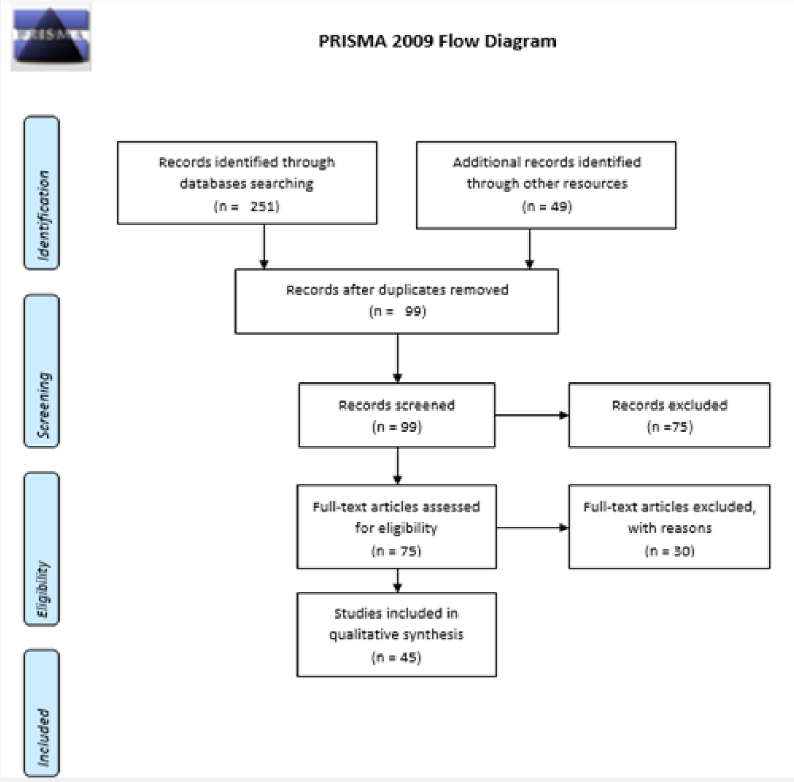

Figure 3: The PRISMA flowchart of systematic analysis of articles included in this review (24).

The use of plasmonic nanoparticles as the basis of developing cutting-edge, novel and highly sensitive COVID-19 detection tools is an emerging field [2,3,10,12,13,19,22-27]. These new biosensors may become a low-cost and reliable option in future COVID-19 diagnostics. Many clinical trials are underway for the testing of real-time biosensor platforms made using the special features of plasmonic nanoparticles including gold, copper and silver nanoparticles as their working principle (see Figure 4 below) [3]. Many nanomaterials have been used to make detection platforms which can provide fast as well as precise detection of the SARS-CoV-2 virus. These include colorimetric assays made using nanoparticles, new optical sensors, nano immune-sensors for COVID-19, novel immune-chromatographic assays, aptamer based COVID-19 assays as well as bio-barcode assays [3]. Some of the nanotechnology, nanoparticles and nanomedicine based other applications as well as uses of in COVID-19 diagnostics and detection are presented in (see Figure 5 and 6 below) (see Table 1 below) [28-38].

Nanotechnology, Nanoparticles and Nanomedicine in COVID-19 Treatment

Although we have a much better understanding of antiviral protocols as well as the structural details of COVID-19's causative virus, the SARS-CoV-2 virus in 2023, the currently conventional antiviral drugs that have been used in COVID-19 treatment are not very effective and they have massive side effects. Nanotechnology and nanoparticle-based protocols have found a lot of overlapping use in many of the COVId-19 management aspects strategies of treatment, disinfection, prevention, diagnosis and containment (see Figure 7 below) [3]. Nanotechnology makes use of nanoparticle-based nanomaterials that fall in the 1 to 100 nm size region. Nanotechnology utilizes cutting-edge technology which

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customizes the synthesis and application of various nanomaterials based on the special physical, chemical, mechanical, optical and electronic characteristics as compared to the larger particles used in clinical medical applications [2,3].

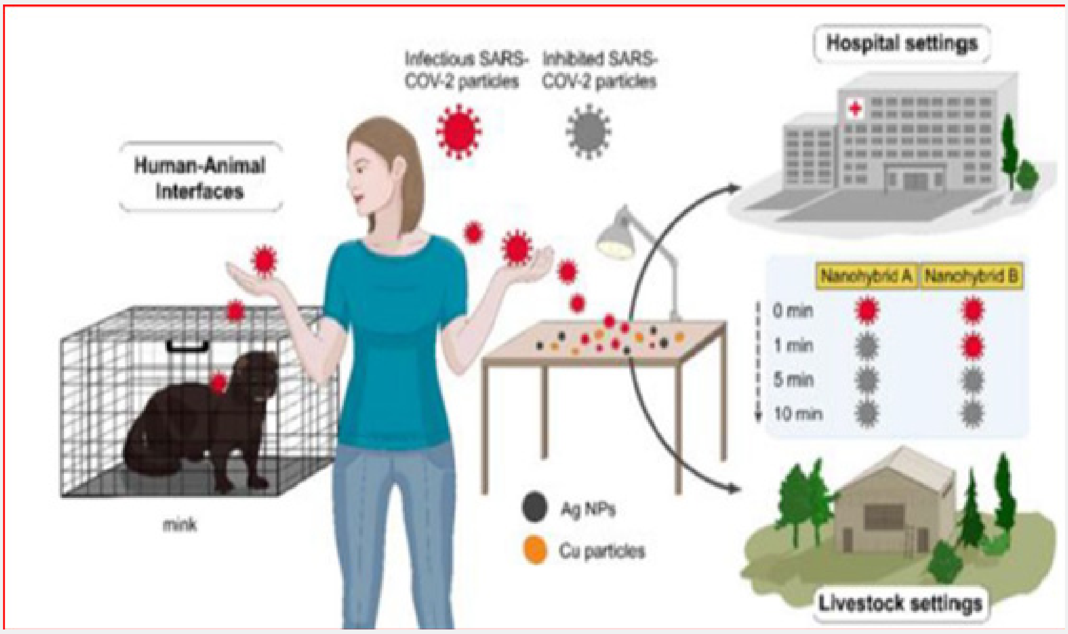

Figure 4: Out-of-the-box surface use of copper-silver nano-hybrid materials that show fast inhibition of the SARS-CoV-2 within 1-5mins and can disrupt the SARSCoV-2 transmission chains thus limiting the transmission of the virus in vulnerable settings like hospitals & public reservoirs (Source 3).

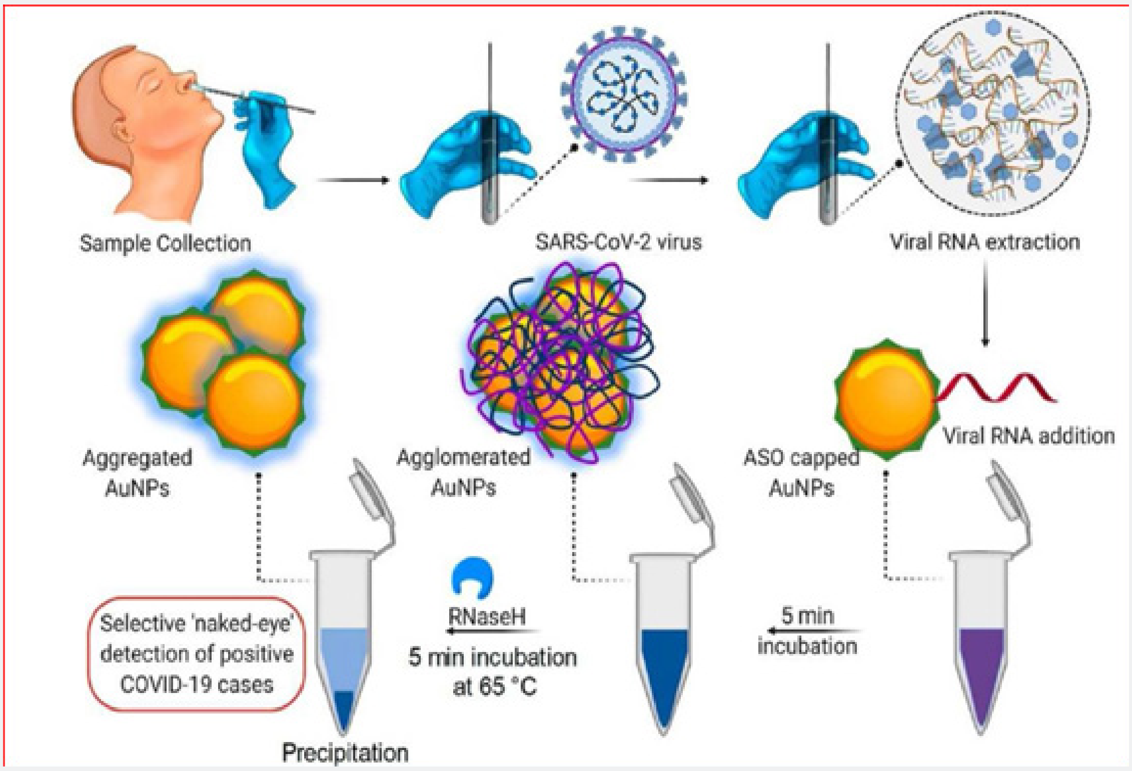

Figure 5: A schematic diagram showing antisense oligonucleotide-capped gold nanoparticles utilized in detection of the SARS-CoV-2 RNA (Source 3).

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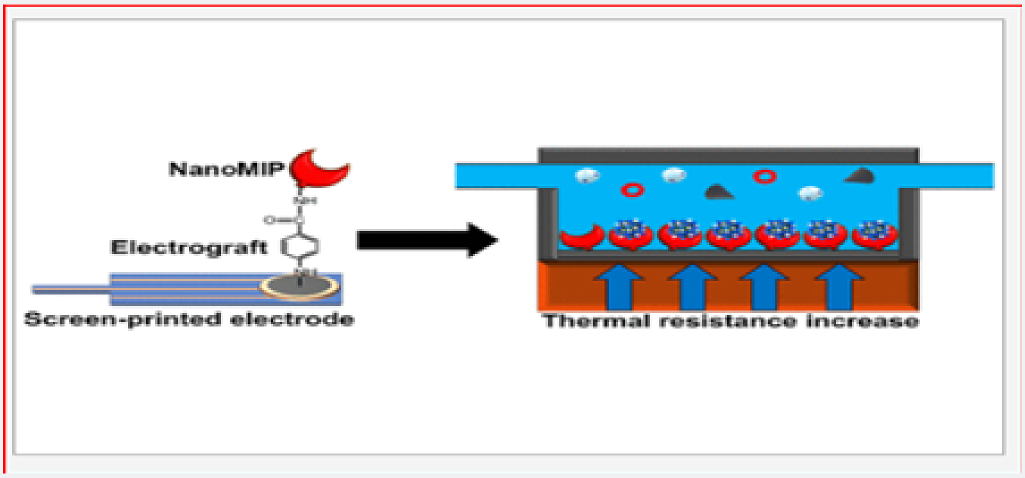

Figure 6: A schematic diagram showing molecularly imprinted nanoparticles (NanoMIP) sensors that can be used in detection of the SARS-CoV-2 virus (Source 32).

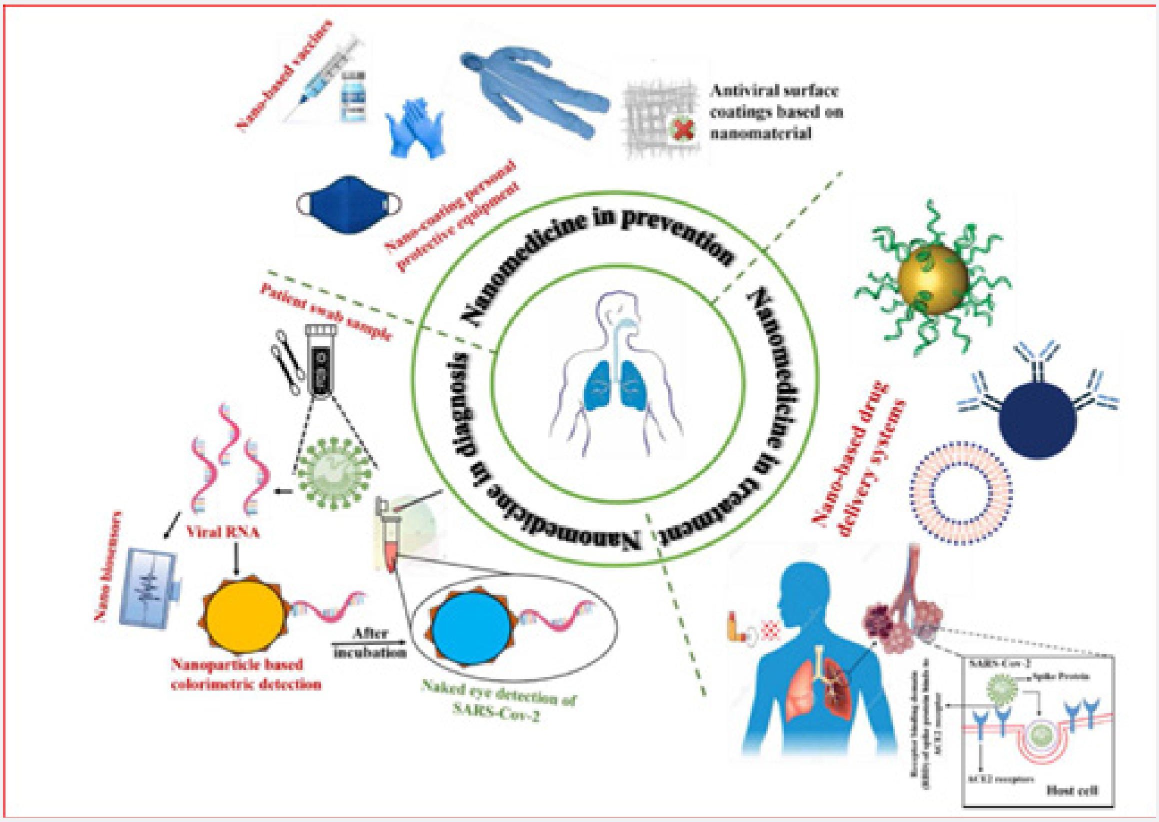

Figure 7: The different nanotechnology, nanoparticles and nanomedicine-based applications in COVID-19 prevention, diagnostics and treatment strategies (Source 3).

Nanoparticle-based materials have found use in creation of advanced COVID-19 bio-sensors, bio-imaging protocols, targeted drug delivery systems, COVID-19 therapeutics [2]. Nanomaterials have found use both as drug delivery systems and in the nano-encapsulation of antiviral active compounds that need timed as well as targeted release to work as treatment options. Utilization

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of nanotechnology-based strategies in COVID-19 therapy usually emphasize on attaining the inhibition of one or several viral pathogenesis pathways such as disruption of the interaction of viral proteins with the host cell, preventing the fusion process of the viral with the host cell membranes, deactivating viral protein synthesis that allows them to stick to human cell surfaces and ultimately mitigating the viral replication pathways [3,5,6,9,11,21]. One of the major issues faced in the clinical use of existing anti-viral drugs in treating the COVID-19 infection is their non-specificity and the fact that they have severe cytotoxic effects in human cells.

Most of the anti-COVID-19 drugs (examined for clinical use in trials) such as remdesivir, chloroquine, favipiravir, atazanavir, lopinavir or ritonavir as well as daclatasvir have not shown any validated potential for either being efficient cures or even appropriate prophylaxis [3]. The combination of such drugs with nanomaterials-based drug delivery systems has the potential of increasing the solubility, bio-distribution, as well reducing the half-life of the drug when used in COVID-19 therapy. As the need arose, new nanotechnology based therapeutics have been developed for treatment of active COVID-19 infections. The most prevalent nanoparticles that have until date been utilized in antiviral treatment are metal and metal oxide nanoparticles, carbon-based nanoparticles, quantum dots, polymeric nanoparticles and lipid-based nanoparticles that have validated antimicrobial, antiviral characteristics as well as serving as effective drug delivery carriers [2,21].

The use of nanotechnology-based nanomedicine has been instrumental in the development of drugs for the treatment of COVID-19 disease that have lower cytotoxicity, higher specificity and improved efficiency. Nanoparticle use contributes to attainment of desirable features like higher biocompatibility, improved efficacy and highly targeted specificity in COVID-19 drugs [2,21]. Nanotechnology-based solutions and nanoparticles have proven to be very versatile as targeted drug carrier systems and given the needed options in COVID-19 nanomedicine practice. Inactivating pathways of the SARS-CoV-2 virus right at the entry point to the human host cell is a potential, highly potent mechanism that has been explored with use of nanoparticles. Furthermore, nanotechnology provides improved pharmacokinetics with better bio-distribution, which gives overall effective antiviral drugs [3].

The US FDA (Food and Drug Administration) has given approval for the following nanomaterials to be used in COVID-19 drug development: polymeric nanoparticles, lipid-based nanoparticles, metallic nanoparticles and dendrimers [3]. These are being used in the encapsulation of antiviral drugs for delayed release and long-term circulation, the combined delivery of many drugs to get effective action against the SARS-CoV-2 virus (see Figure 8 and 9 below) (see Table 2 below) [3,5,6,9,11,21].

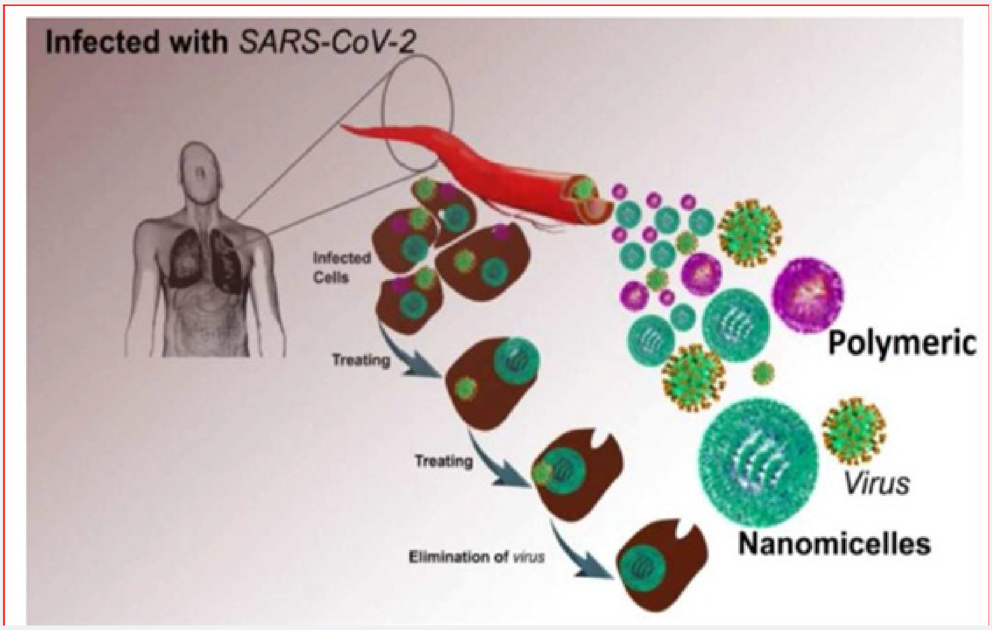

Figure 8: Two examples of nanosystems (polymeric nanoparticles and nano micelles) for the delivery of hydroxychloroquine and azithromycinhe in COVID-19 treatment strategies (Source 3).

Nanotechnology, Nanoparticles and Nanomedicine in COVID-19 Prevention (Vaccination) Measures

Most of the strategies designed to fight the SARS-CoV-2 virus in treatment protocols make use (to some degree) of nanotechnology-based nanoparticles that serve as adjuvants or medicine carrier systems in COVID-19 vaccines [3,6]. The main aim in this COVID-19 aspect has been development of an effective vaccine which can provide high levels of boosted immunity and has low levels of cytotoxicity or other undesirable side effects to

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fight the infection without causing any side effects [2]. Several clinical trials are using lipid-based nanoparticles as the carrier of the vaccine parts in a stable and efficient nano delivery system, examples are the BioNTech & Pfizer developed the nucleoside-modified mRNA vaccine, BNT162b2 (Comirnaty®) fort COVID-19. BNT162b2 refers to an mRNA vaccine that uses lipid-based nanoparticles and this resulted in an improved 95% efficiency against the SARS-CoV-2 virus. Moderna utilized lipid-based nanoparticles in the delivery platform for their COVID-19 vaccine mRNA-1893 (see Figure 10 below) [1-7,10,13,14,16-21,25-28].

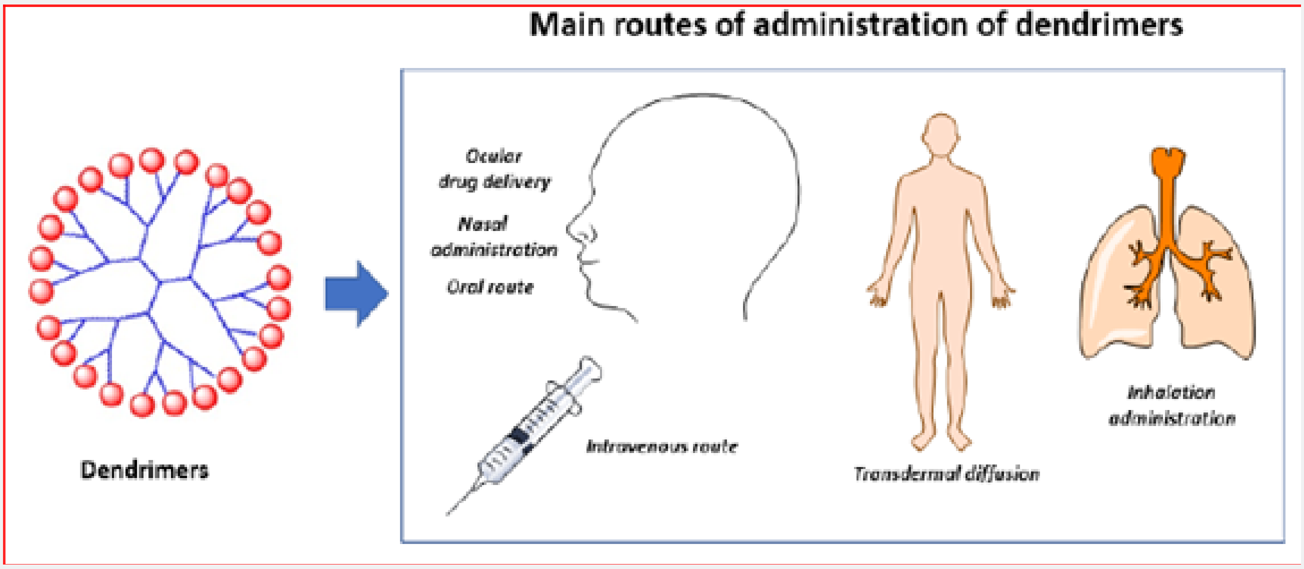

Figure 9: Potential of dendrimers as anti-COVID-19 therapeutics with ability for versatility in route of administration (Source 29).

In the last three years, the role of nanotechnology, nanoparticles and nanomedicine in the prevention and development of nanotechnology-based COVID-19 vaccines has been phenomenal. The FDA has authorized utilization of nano-crystal formulations, polymer-based nanoparticles, lipid nanoparticles and non-polymer nanoparticles as well as metallic, inorganic, and protein-based nanoparticles as COVID-19 vaccine and drug delivery applications [11-13,15-18,21]. At present, COVID-19 vaccines have been developed to mitigate the spread of the SARS-CoV-2 virus. The use of nanoparticle-based vaccines is of two kinds on the basis of their antigen loading protocols.

The first kind are the antigen presenting (attached to the surface) nanoparticles while the second type are the nanoparticles which are encapsulated onto the vaccine antigen. A schematic illustration showing pros and cons of different vaccines classified depending upon the antigen loading strategies are shown in (see Figure 11 below). Many types of COVID-19 vaccines including the BioNTech & Pfizer mRNA vaccine, the Moderna lipid-nanoparticles based COVID-19 vaccines (already in clinical use) and some experimental nanoparticles-based nasal vaccines are still in various phases of clinical trials [3,11,21].

Nanotechnology, Nanoparticles and Nanomedicine in COVID-19 Containment Measures

As with any viral pandemic, the SARS-CoV-2 virus needs effective containment measures to prevent further spread of the infection and to provide protection to those who have to work in close quarters with high exposure to the virus. Nanotechnology and nanomaterials based PPE gear have played an important role in the containment aspects of the COVID-19 pandemic. Preventive and containment measures for the SARS-CoV-2 virus without vaccines have been attained through use of traditional viral infection control standards like maintaining hand hygiene with soaps and sanitizers, carrying out environmental sanitization using strong surface disinfectants, implementing social distancing and above all the use of personal protective equipment (PPE) for healthcare workers and caregivers who have exposure to high viral loads from active COVID-19 patients.

The use of PPE serves as the provision of a physical barrier against the SARS-CoV-2 virus. The most frequently utilized PPE gear include filtering face piece respirator masks (N kinds, R kinds and P kinds), surgical face masks, surgical gowns, nurse aprons, gloves, eye shields, goggles as well as totally closed work shoes and boots (see Figure 12 below) [1,5,6,8,9,12-14,23,39]. The uses of nanotechnology and nanoparticle-based materials in the amplifications of the protective features of the PPEs provide enhancements like UV (ultraviolet) protection, antiviral characteristics as well as fire retarding properties [9]. Furthermore, nanotechnology-based applications help in the production of hydrophobic as well as comfortable PPE gear that is better in protection against the COVID-19 infection (see Figure 12 below) [6,9,17]. In this ongoing COVID-19 pandemic,

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face masks have emerged as being the first line of defence and vital for preventing exposure to the SARS-CoV-2 virus and other pathogenic organisms through the oral and nasal route.

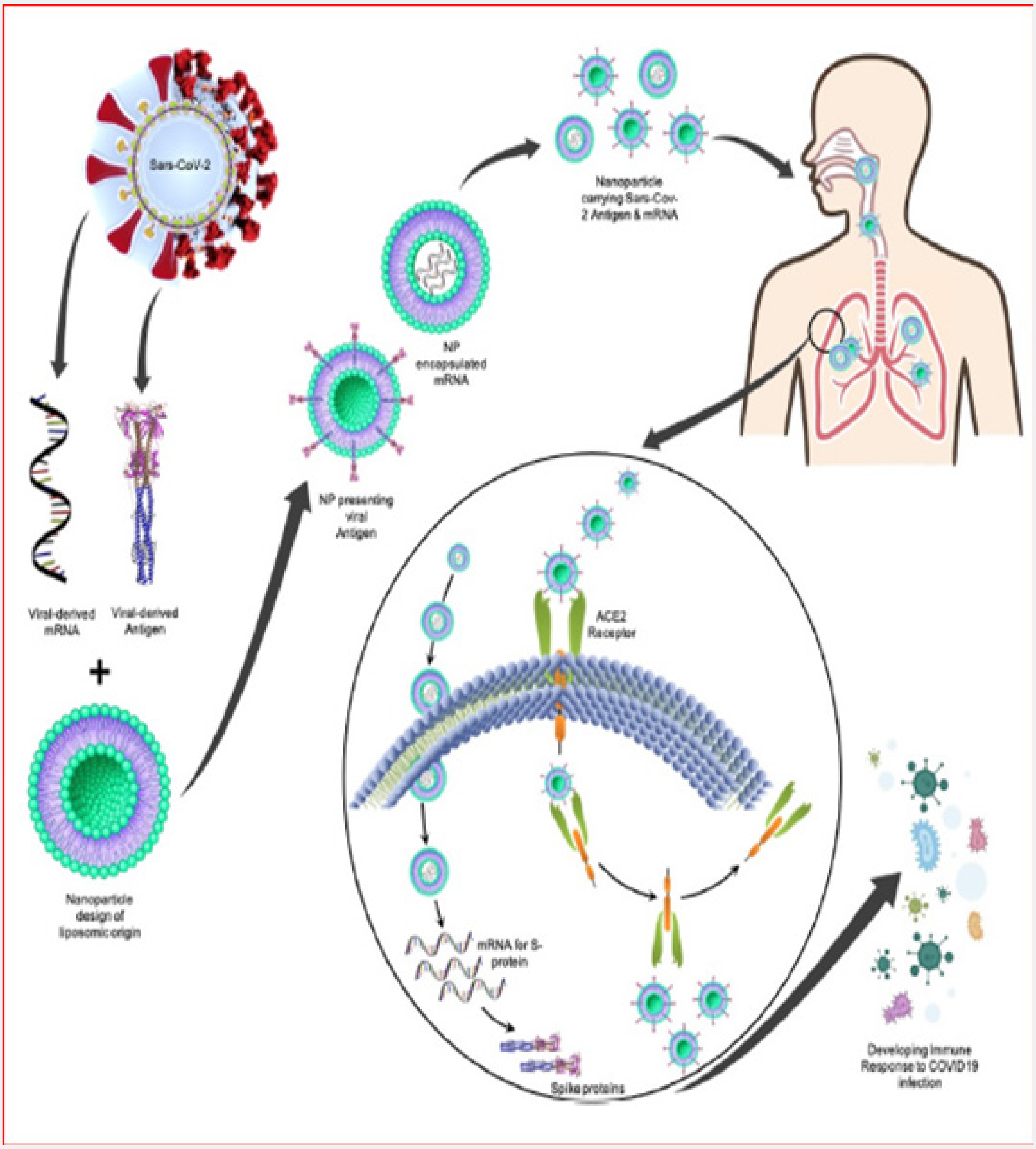

Figure 10: Schematic figure showing the delivery of nanoparticles carrying embedded mRNA for S-protein and nanoparticles presenting SARS-CoV-2 derived antigens to a pulmonary system: The specific mRNA that encodes for spike protein is being embedded in a liposomic nanoparticle where another type of nanoparticles 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 nanoparticle 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 (Source 6).

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Table 1: Nanotechnology, nanoparticles and nanomedicine based COVID-19 diagnostics & detection strategies being developed currently.

#	Nanotechnology-Based Diagnostics Options	Nanoparticle Based Use in Detection or Diagnostics of the SARS-CoV-2 virus	References
1	Colorimetric assays	- The nanoparticle -based assay that was used in the detection of MERS-CoV virus had a detection range of 1 pmol/L, showing that it has the sensitivity to detect targets even in low concentrations. At present, a recent study has used a gold binding polypeptides protein for a microscale-to nanoscale-regulated immobilization of proteins on top of a bare gold surface that has a highly selective and specific affinity. This helps in the interaction between two proteins (gold binding polypeptides and fusion proteins) due to the gold nanoparticle and as such detection of a viral analyte is improved colorimetrically - Work has been done on worked on gold nanoparticles for making a SARS-CoV-2 detection nanotechnology that can detect the SARS-CoV-2 virus RNA. This approach used the complementary binding principle wherein gold nanoparticles were coated with the SARS-CoV-2 N-gene specific antisense oligonucleotides and this was thiol modified. The antisense oligonucleotides have the ability to complementarily bind the target RNA. As such this colorimetric assay based on the gold nanoparticle's anisotropic, plasmonic characteristics that allow for targeted binding and thus giving this assay the needed high specificity for detection of the SARS-CoV-2 virus (Figure 5)	[2,3,10,12,13,19,22-27]
2	Photothermal biosensors	- Work has been done to make a photothermal biosensor using a dual function plasmonics approch. In this sensor, there is amalgamation of the localized surface plasmon resonance & use is made of plasmonic photo thermal nanotechnology to detect and give a potentially sensitive detection of the SARSCoV-2 virus in clinical diagnostics. The developed biosensor shows a higher level of sensitivity as well as selectivity for the SARS-CoV-2 genomic sequences & thus helps in detection even in fairly low concentrations of 0.22pM.	[3,11,15,18,30,31]
3	Molecularly imprinted nanoparticles sensors	- Molecularly imprinted nanoparticles sensors nanoparticles utilize small fragment of the SARS-CoV-2 virus. They can give vast benefits due to their ability to work exceptionally well in tough media having a smaller range. In order to provide a quantitative measure of the SARS-CoV-2 antigen, a thermal test has been made wherein screen-printed electrodes are used onto which the molecularly imprinted nanoparticles sensors are electrographted. This thermal strategy was able to detect both the Alpha & Delta strains' spike proteins even in measures as small as 9.9fg/mL & 6.1fg/mL each. This molecularly imprinted nanoparticles sensors-based detection protocol has been found to have more sensitivity than the currently used the SARS-CoV-2 commercial antigen testing kits& also various antigen assay tests too. Such a detection assay which can test the clinical character of patient samples in just 15 min while providing higher specificity at even in low numbers is desirable (Figure 6).	[3,11,15,18,32]
4	Electrochemical nano-immunosensors	-Electrochemical nano-immunosensors are being made for detecting the SARS-CoV-2 virus. Nano-immunosensors refer to high sensitivity, low-cost with capacity for miniaturization. Researchers have created a nano-immunosensor in which a sample, the free virus as well as the MERS-CoV immobilized protein indirectly compete for binding within this test which is still in the experimental stage.	[3,11,15,18,32]
5	Aptamer based & other biosensors	- Aptamers refer to oligonucleotides which have the ability to carrying out binding of specified targets like proteins, peptides, carbohydrates& tiny molecules. As such, they have an application as a specialized group of molecules in molecular diagnostics & therapy. Aptamers provide the benefits of being a recognition molecule and playing the role of the chemical equivalent of antibodies. - Aptamers permit higher sensitivity as compared to enzymes or antibodies. Therefore, they are the option of choice in the development of vast arrays of aptamer-based biosensors. The combination of RNA aptamers with quantum dots & use in faster as well as sensitive quantification of the SARS-CoV-2 N protein has been validated for future clinical applications. - Colloidal gold-immunochromatographic assay & enzyme-based immunoassays also show the ability of detecting the SARS-CoV-2 virus.	[3,11,15,18,33-38]

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Table 2: Nanotechnology, nanoparticles and nanomedicine based COVID-19 treatment options being developed currently.

#	Nanotechnology-Based Treatment Solutions	Nanosystem Developed to Combat the SARS-CoV-2 virus	References
1	Polymeric nanoparticles	-Natural polymers like chitosan, dextran, alginates, hyaluronic acid albumin, gelatin, and collagen have antiviral characteristics. -Synthetic polymers including polyethylene glycol, N-(2-hydroxypropyl)-methacrylamide copolymer, Poly (lactic-co-glycolic acid) (PLGA), poly-1-glutamic acid, polystyrene maleic anhydride copolymer found use in nano-drug delivery systems. -Self-assembled copolymers, virus-like polymers as well as cell membrane-coated nanoparticles have been used for polymeric-based nano-drug delivery options (see Figure 8 below for 2 examples)	[2-7,19-21,25,26]
2	Lipid-based nanoparticles	-Lipid-based nanoparticles have found applications as the COVID-19 mRNA vaccine that is a nanotechnology-based drug delivery.	[1-7,10,13,14,16-21,25-28]
3	Metallic nanoparticles	- Use of metallic nanoparticles as potential therapy for the SARS-CoV-2 virus. - Studies have indicated that some metallic nanoparticles including silver & Au nanoparticles exhibit antiviral action. - Silver nanoparticles have the ability to inactivate viruses as they bind to their genetic material leading to prevention of viral cell replication. Most of the metallic nanoparticle therapy against COVID-19 is in development and not in clinical practice yet. - Use of inorganic polyphosphate that underwent encapsulation using polyphosphate nanoparticles in clinical antiviral treatments is being explored also.	[3-8,10,13,14,16-21,25- 27]
4	Dendrimers	-Dendrimers refer to synthetic homogeneous nano-sized symmetric macromolecules having a monodisperse structural detail. Application of dendrimers in nanomedicine is new but due to the fact that they have the potential of multiroute administration, they can help in controlling the cytokine storm in active COVID-19 infections. They are being explored in experimental drug delivery and other anti-COVID-19 aspects (see Figure 9 below).	[3,29]

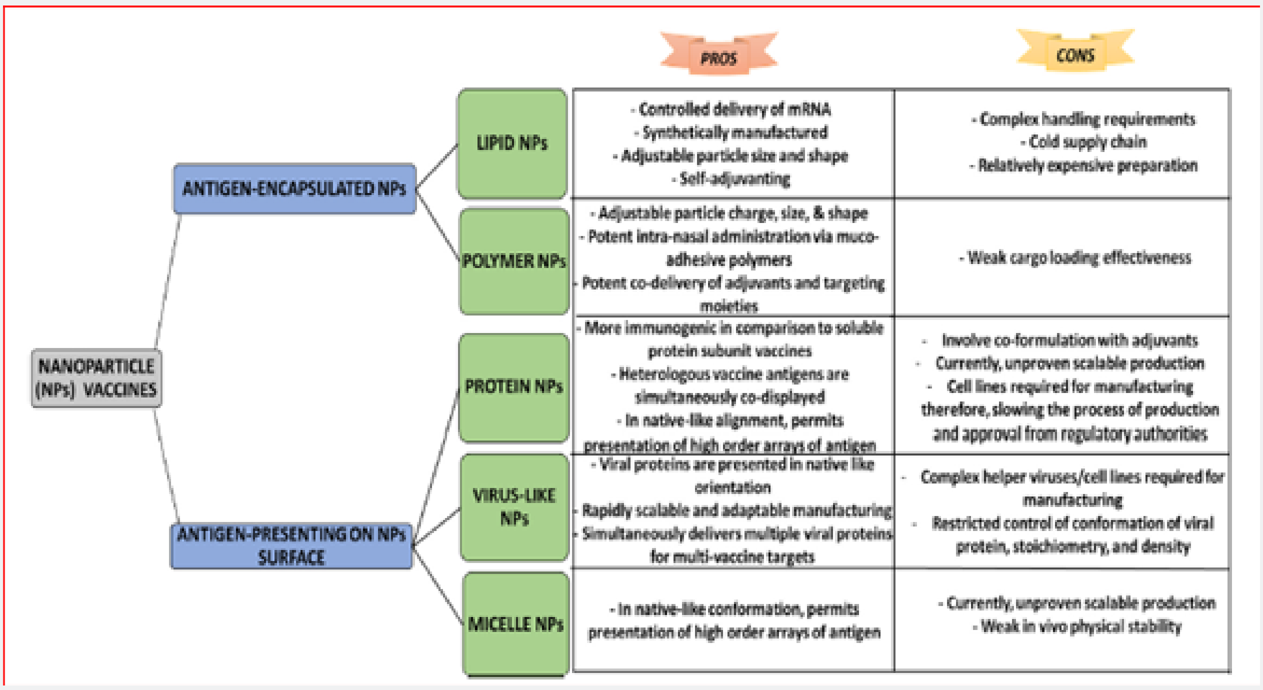

Figure 11: The advantages and disadvantages of the various nanoparticles-based COVID-19 vaccines (Source 11).

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Figure 12: Nanotechnology-based application range in PPE gear used to provide protection against contracting the COVID-19 infection in high exposure situations (Source 6).

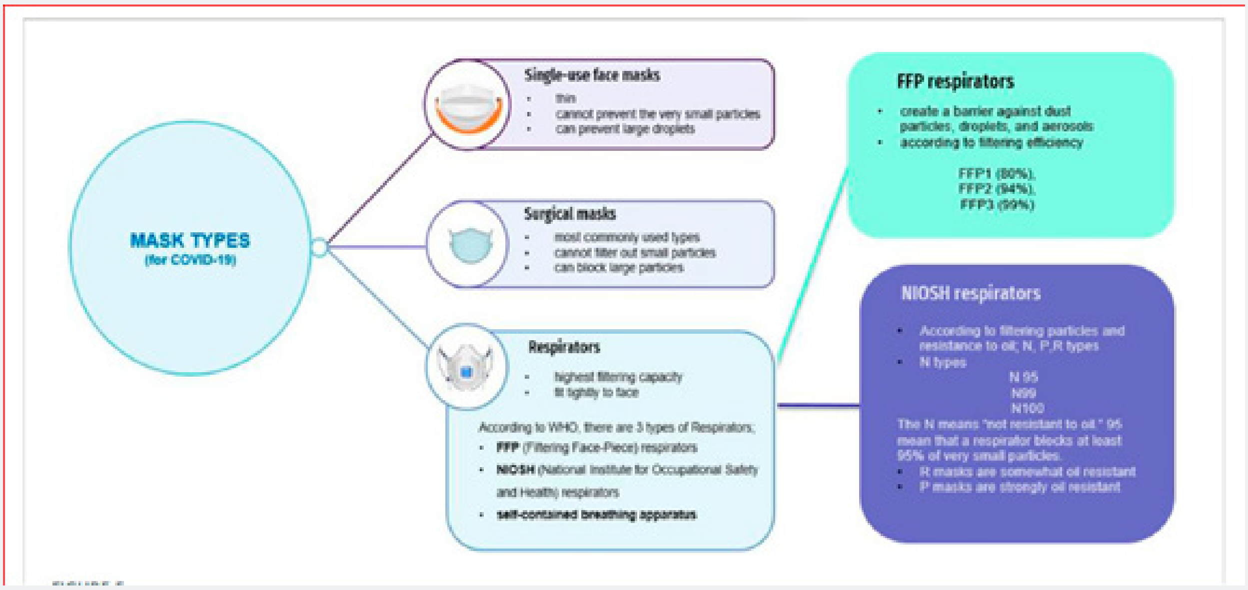

Figure 13: Application of nanotechnology in masks and respirators used as PPE against the SARS-CoV-2 virus (Source 11).

The mask provides protection to the person wearing it and also gives some degree of protection the surroundings. Masks used as PPE have been placed into 3 groups as per the types of filters they have: disposable one-use masks, respirator masks as well as surgical masks (see Figure 13 above) [5,6,40-45]. The gold standards in a mask have the ability of filtering out bio-aerosols efficiently while giving the person wearing it proper comfort. At the same time, when designing a PPE mask, several other factors

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such as levels of humidity, ambient temperature, the airflow patterns and most importantly the properties of the material used as all this has a significant impact on the mask's filtration effectiveness and quality. In the ongoing COVID-19 pandemic, nanomaterials combined with textiles of choice, provided efficient options for constructing effective masks [5,6,40-45].

Furthermore, they showed a direct effect on the survival times and rates of the SARS-CoV-2 virus after coming into contact with the surface of the mask. As an example, nano-fibers and nanoparticles were able to enhance the antiviral characteristics, filtration ability and the breathability features of the COVID-19 masks. Nano-fibers produced through electro-spinning technologies have proven to be extremely useful materials as their average fiber diameters fall within the nanometer range and they have high surface area to volume ratio which gives the needed functional properties of an ideal anti-COVID face mask [5,6,40-45]. The different types of nanotechnology-based nanoparticles being used in the various prevention and COVID-19 PPE gear is shown in summary in (see Figure 14 below) [1,43].

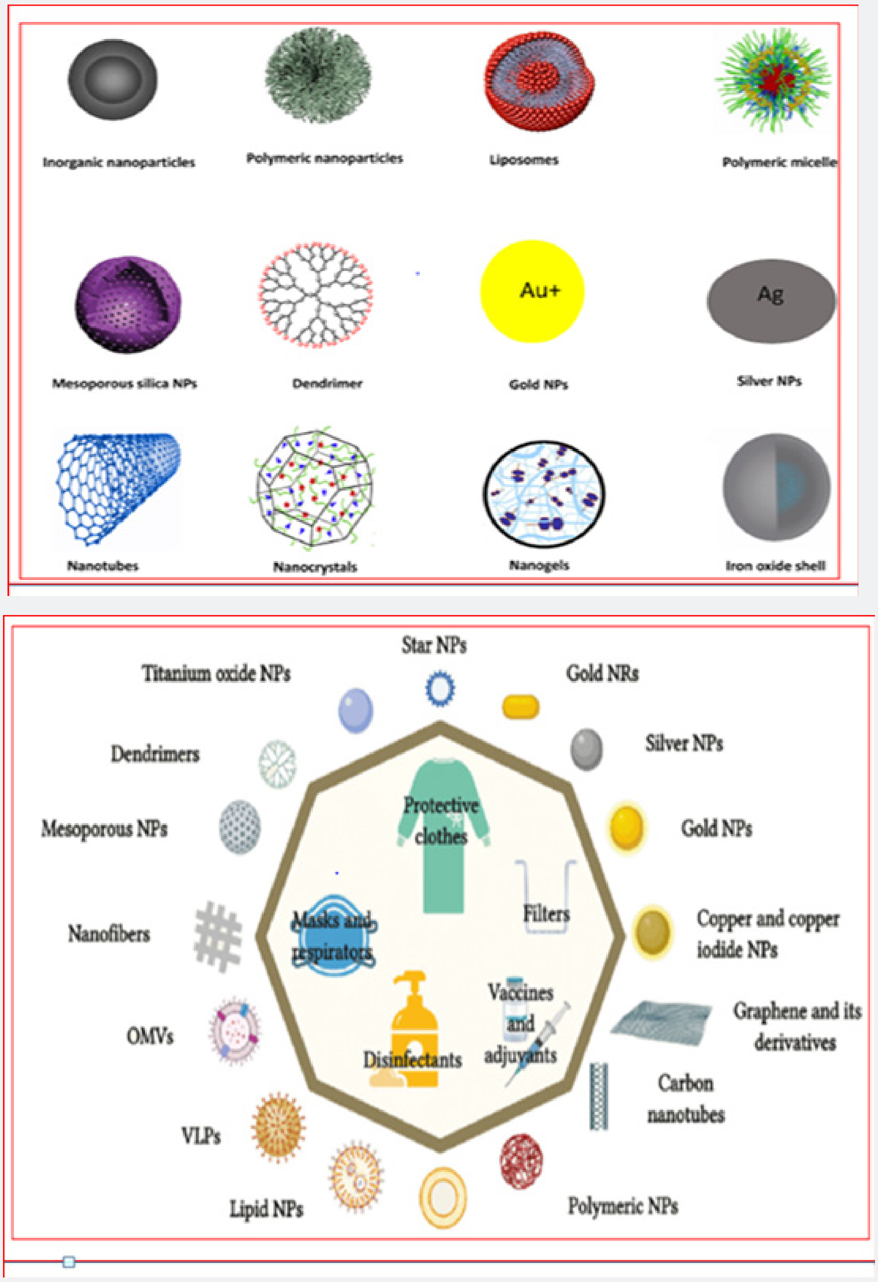

Figure 14: Application of nanotechnology in masks and respirators used as PPE against the SARS-CoV-2 virus (Source 11).

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Conclusion and Future Prospects

As shown in this concise review, the most recent applications of nanotechnology, nanoparticles and nanomedicine in combating the ongoing COVID-19 pandemic are many and in different aspects. Due to the very unique properties of nanoparticles, they are able to be provided desirable features against like the SARS-CoV-2 virus in clinical nanomedicine practice. These properties include their incredibly small nanoscale size and the consequent extra surface area to a volume ratio, providing multifunctional uses, enhanced solubility as well as the capacity to adapt to different media and surfaces.

The potential of harnessing these properties in the development of targeted COVID-19 treatment regimes, examination of new, novel drug options, faster, low-cost detection and COVID-19 diagnostic tools, use of nanomedicine protocols to personalize patient therapy medicines have all improved our chances against the SARS-CoV-2 virus. The possibilities of enhanced COVID-19 clinical practice, better vaccines and PPE gear, as well as effective drugs in the future are unlimited using applications of nanotechnology. The most important applications of nanotechnology in the ongoing COVID-19 pandemic which have emerged from the findings of this review are:

1. Useful in multi-route administration of water-insoluble drugs, vaccines and other pharmaceuticals.

2. Nanoparticles help in increasing the duration of circulation and timed release of drugs in the human body fluids.

3. The use of nanoparticles as delivery platforms of both drugs as well as vaccines is one of the best preventive strategy uses against the SARS-CoV-2 virus.

4. The development and use of a variety of nanoparticles in the form of nanofibers has helped in making of enhanced PPE gear that is more efficient in filtering out bio-aerosols containing the SARS-CoV-2 virus while simultaneously being comfortable, long-lasting and antiviral in nature (thus reducing the viral load in the ambient environment also).

At present, we do have improved insights on the application of nanotechnology, nanoparticles and nanomedicine applications against the SARS-CoV-2 virus. Nanotechnology-based strategies can be utilized in a variety of ways for combating the ongoing COVID-19 pandemic including prevention, diagnostics, containment and treatment strategies or options. However future innovation, development and studies are required in the fields of the safety of nanotechnology-based COVID-19 uses.

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