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DIAGNOSIS AND VARIOUS APPROACHES IN TREATMENT OF COVID-19 USING NANOPARTICLE CARRIER SYSTEM

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ABSTRACT

The novel coronavirus disease 2019 (COVID-19) is by far the deadliest pandemic of the new millennium, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARSCoV2) that has afflicted worldwide health and economies. In the current article a panoply of nanotechnology approaches explored in detection, treatment and vaccination are elaborated. SARS-CoV-2, can be regarded as a functional core-shell nanoparticle (NP), which has the tendency to bond with adverse components in its vicinity and remain intact also maintaining its activity. In each category, we detail how nanoparticles are custom-made to bio-interface with the host and virus. We highlight the structure-function link for each nanoparticle design that permits effective antiviral activity. In addition to this the history, pathogenesis and impact on humans are discussed. Special emphasis and detailing are done on silver nanoparticle, gold nanoparticles, chitosan nanoparticles, copper nanoparticles, zinc nanoparticles and iron nanoparticles. Spotlight is put on future prospects and current trends with regards to work done on treatment of the novel coronavirus. Overall, the review should help researchers better grasp the role of nanomaterials in the diagnosis and treatment of COVID-19 and it could pave the way for advancements in this field.

KEYWORDS

Nanoparticles, Spike protein, SARS-CoV-2, Gold nanoparticles, Silver nanoparticles and Zinc nanoparticles.

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INTRODUCTION

The aim of this work was the investigation of nanoparticles for the treatment and diagnosis of COVID-19. Coronaviruses are enclosed and spherical viruses with a single-stranded RNA genome that belong to the *Coronavirinae* subfamily (order: *Nidovirales*, family: *Coronaviridae*)[1]. The new virus that causes COVID-19 (dubbed SARS-CoV-2) has a genomic sequence that is 96.2 percent

identical to that of bat coronavirus RaTG13 and 79.5 percent similar to that of SARS-CoV. With a concentrated mass of nucleic acid and nucleocapsid protein beneath a well-defined lipid bilayer envelope, this 80-160 nm virus has a broadly spherical or fairly pleiomorphic form[2]. The genomic sequence of SARS-CoV-2 reveals that replicase ORF1a/1b, which encodes 16 non-structural proteins and translates two polyproteins, makes up roughly two-thirds of the RNA, followed by approximately 13 downstream ORFs. Spike (S), envelope (E), membrane (M), and nucleocapsid (N) are crucial structural proteins encoded by the rest of the viral genome (N) S. The incubation period for viral infection ranges from 1 to 14 days, with 3 to 7 days being the most noticeable. People having a history of hypertension, diabetes, obesity, chronic lung illness, or cardiovascular problems have been found to be more susceptible to SARS-CoV-2 infection and mortality. Patients above the age of 80 are also at a higher risk, with a death rate of 14.8%[3]. 229E (-CoV), NL63 (-CoV), OC43 (-CoV) and HKU1 (-CoV) are four common human CoVs with low pathogenicity that cause mild illnesses. However, SARS-CoV, MERS-CoV, and the newest developing CoV all have major side effects that can be fatal (SARS-CoV-2)[4]. The α- and β-coronaviruses appreciably infect mammals, whereas the γ and δ-coronaviruses infect birds, fish and, at times, mammals. SARSCoV-1 and -2 are β-coronaviruses and, thus, share similar structural and molecular architecture. The β-coronaviruses have projecting spike proteins that help them bind to receptors and fuse to membranes. The virion's membrane glycoproteins shape it and maintain the nucleocapsid, whereas the envelope protein is involved in viral assembly, release, and pathogenesis. The viral genomic RNA, as expected, contains the virus's replicative identity, whereas the nucleocapsid encases the genome into the virus. During infection, the spike protein binds to the ACE2 receptor on the cell surface and fuses with the cell membrane with the help of host cell proteases like cathepsin L and TMPRSS2[5].

From the above flow chart, the clear progression and activity is known where attachment of SARS-CoV-2 viral S protein with ACE2 receptor present on the host cell membrane[6]. Binding of viral S protein with the ACE2 receptor permits the entry of the virus into the host cell[7]. After entry of the virus into the cell, the viral envelope undergoes proteolytic cleavage and releases its genomic RNA into the cytoplasm[8,9]. The genomic RNA is then converted into smaller sub genomic mRNA, which is translated to S, E, M and other proteins that are required for the assembly of the virus[10,11]. Next, the S, E and M proteins enter the endoplasmic reticulum (ER), followed by the formation of mature virion by their combination with nucleocapsid (N) protein and positive-strand genomic RNA in the ER-Golgi compartment[12]. Finally, the completely formed virus particles are released out of the cells through exocytosis, to repeat the same cycle by infecting another cell.

Nanotechnology is defined as "the study, manipulation, control, design, synthesis, and development of various systems by manipulating matter at the nm (nanometre scale) scale of 1-100nm, where 1nm=10-9, i.e., at the molecular and atomic level, and utilising unique phenomena and properties at that scale[13]. The size of the nanoparticle can have a significant impact on protein adsorption, cellular internalisation, and biodistribution. Release of drugs under strict control: Understanding matrix erosion, diffusion, and desorption of connected drugs is a substantial release of drug cargos. By lowering the amount of drug carrier used, drug loading can lessen carrier toxicity. Surface characteristics, shape, size, treatment efficacy, drug system release, and loading are only a few of the physicochemical aspects of nanoparticle drug delivery systems. Nanoparticle surface characteristics influenced drug molecule biocompatibility, biodistribution, and pharmacokinetics[13]. The development of a sensitive, rapid, and specific diagnostic tool for COVID-19, the use of nanomaterials to deliver antiviral agents, improving contact tracing tools, coating nanomaterial surfaces to inactivate the virus, and

the preparation of effective environmental disinfectants are all examples of nanotechnology-based techniques that can be used to combat COVID-19 pandemics[14]. Because of their huge surface-to-volume ratios, nanomaterials can produce effective interactions between the analyte and the sensor, enabling for quick and precise virus detection. Nanotechnology has the potential to improve virus targeting in biological fluids like nasal, throat, and blood samples. On the surface of magnetic nanoparticles, specific viral receptors can be painted. Because viruses are nanoparticles, their features can be utilised to create virus-like structures that deliver targeted drugs and gene alterations. Nanomaterials can alter the pharmacokinetic parameters of an encapsulated drug and reduce the needed drug concentration through a controlled release mechanism. Furthermore, by binding a specific ligand to the surface of the nanoparticle containing the drug for recognition of molecular components of the target tissue/organ, the antiviral effects of the developed nano-drug can be improved[14]. Nanoparticle surfaces can be easily changed with multivalent ligands or other biomolecules for signal augmentation and readout for disease diagnosis. Nanoparticle-based vaccinations can either encapsulate antigens within or carry antigens on their surface for disease prevention, shielding antigens from premature degradation[12]. Silver, copper, and titanium dioxide are metal nanoparticles that have unique antiviral activity, durability, and efficacy in low concentrations, making them a viable alternative to commonly employed chemical disinfectants. These photo-dynamic and photo-thermal metal nanoparticles can be used. Because of their low toxicity, distinctive size, programmable charge, and chemical alteration capabilities, nanomaterials have been shown to be an emerging platform for point-of-care diagnosis carriers for medicines and vaccine development

Diagnosis of SARS-CoV-2 using Nanoparticles

Diagnosing is the most important aspect and basically revolves around structural protein of the virus and its genetic material, the presence of C-reactive protein and serological components is the current method for detecting SARS-CoV-2. CRP detects the presence of viral particles by reacting with a fragment of SARS-CoV-2 genetic code, whereas the serological approach is based on the severity of the virus's immune response. Nanoparticles are often used as detection components in immunoassays, known colloquially as lateral flow immunoassays (LFIA), that are being used to detect antigens or antibodies[8]. In US scientist designed tests using nanoparticles of gold, The researchers' concept is to link a specific molecule to gold nanoparticles that can identify a specific protein from the SARS-CoV-2 virus's genomic sequence. Nanotechnology-based probes have been widely used in the development of biosensors, in which the incorporation of nanomaterials improves the sensor's response via gaining electrical, optical, or catalytical attributes, leading to enhanced diagnostic sensitivity[1]. This interaction begins whenever the biosensor binds to the virus's genetic sequence, as well as the gold nanoparticles cause the liquid reagent to change colour from purple to blue at 400nm. They facilitate the coupling of biomolecules to form hybrid bridge is made of biological Au nanoparticles, enabling for virus target detection. The Bio-Au nanoparticle-based detection method has a greater level of test sensitivity and a broader detection range[7], Nanomaterials featuring high specific surface area and volume ratios strengthen the interactions between the sensor and the analyte, minimizing the detection limit and expediting the detection process[1]. Because of their ability to locate and recognise specific pathogens, molecular techniques are more effective for accurate diagnosis versus syndromic testing and CT scans[9].

A COVID-19 Rapid POC CE IVD test has now been designed by Nano Composix, a firm based in the United States, that integrates Au-NPs with lateral flow devices which use AU-NP. This kit is for *in vitro* diagnosis and is available on the market. Sure Screen Diagnostics Ltd, U.K.-based, designed the COVID-19 Rapid Test Cassette, which is now in the market. Au-NPs are coupled with lateral flow

devices in this assay, COVID-19 biomarkers (IgG and IgM) are detected by Au-NPs embedded in the nitrocellulose test strip, which are released once these interact with antibodies inserted in the strip, resulting in a change in colour[3].

In one trial, 3, 3′, 5, 5′-tetramethylbenzidine had been used to encapsulate polylactic-co-glycolic (PLGA) nanoparticles (TMB). The nanoparticles were then linked with antibodies against the SARS-CoV-2 S protein 'TMB-PLGA NPs'). They were performed to recognize S protein in a microplate-based assay. The S proteins were first collected by antibodies immobilised in the plate in this assay. The TMB-PLGA NPs were then functionalized with anti-S protein antibody and bound to isolated S proteins. Once the isolation of unbound TMB-PLGA NP'S this was then reacted with dimethyl sulphoxide which dissolved the nanoparticles and therefore released the TMB. Oxidation of TMB using hydrogen peroxide and copper nanoparticles possessing peroxidase-like properties was done. The oxidised product's absorbance was influenced by the concentration of S protein. S protein was detectable in the femtogram ml^{-1} range using this technique[12].

S9.6 antibodies were coupled to fluorescent europium-chelate nanoparticles (FNPs), which bind preferentially to RNA-DNA hybrid strands (S9.6-FNPs). The SARS-CoV-2 pseudo virus was cultured with S9.6-FNPs and DNA probes that particularly targeted SARS-CoV-2 RNA. The viral RNA bonded to the DNA probe during incubation, produced RNA-DNA hybrid strands. S9.6-FNPs then joined to the RNA-DNA hybrids, yielding a RNA-DNA-S9.6-FNP complex. This was put onto an LFIA strip after incubation. S9.6 antibodies mounted at the test line caught the RNA-DNA-S9.6-FNP complex on the strip. The accumulation of FNPs at the test line culminated in a fluorescent signal, that was used to quantify the viral RNA load quantitatively[12].

The limitations of this techniques are the mutations that are seen and the possibility of cross-reactivity of the antibodies used can increase the risk of false positives, diminishing the efficiency, validity, and selectivity of these tests[1]. Results have shown that it causes detrimental action on human health such as nanotoxicities where more often than not oxidative stress responses caused by reactive oxygen species (ROS) generation is seen leading to fibrosis and genotoxicity. As a result, a thorough regulatory approval process for nanotherapeutics for COVID-19 is required in order to ensure safety and efficacy[15].

Approaches in treatment of COVID-19 using Nanoparticle carrier system

Nanotechnology is concerned with the design and engineering of materials with dimensions of 1-100nm SARS-CoV-2 has a similar size range (60-140nm) and form (spherical)[5]. Nanoparticles have been successfully used in the prevention, detection, therapy, control of a range of infectious diseases due to its multifaceted nature. Nanomaterials are being used as carrier systems and/or adjuvants in the development of possible vaccine candidates under clinical review to combat SARS-CoV-2 and COVID-19 disease using nanotechnology-based approaches. The use of nanoparticles in COVID-19 sickness treatment focuses on suppressing one or more viral processes such as viral particle interface with host cell, fusion of both viral and host cell membranes, viral protein synthesis, viral genome replication, and so on[6]. Some of the most commonly use nanoparticle carrier system in treatment of COVID-19 are;

Chitosan nanoparticle
Silver nanoparticles
Iron oxide nanoparticles
Zinc oxide nanoparticles
Copper nanoparticles
Gold nanoparticles etc,

The benefits of using nanoparticles include efficient drug encapsulation, gradual drug release, and assisting in the improvement of drug molecular characteristics. Modifying the different functional groups on the surface and bonding with certain receptors can also enhance the effectiveness of nanoparticles. This method can be used to prevent the virus from making contact with the target cell[7]. Nanoparticle virucidal nature is associated with the

physical attributes such as small particle size, high specific surface area for contact and surface charge, which aids membrane penetration, antiviral payload uptake, and antiviral payload binding, respectively. Secondly, they have biomimetic capabilities that allow them bind to viral particles and host cells. Lastly, nanoparticles can encapsulate antiviral actives and carry them to the targeted area, enhancing dosage, bioavailability, distribution time, and its stability[8]. Nanomaterials have been shown to be promising tools for immunological regulation to trigger the immune response against a disease, according to growing research. In T cells, for example, graphene oxide treated with amino groups regulated the STAT1/IRF1 interferon signalling pathway, promoting T cell chemo attractant production. Nanomaterials that imitate viruses' innate immunostimulatory properties enable the development of next-generation vaccines. To combat SARS-CoV and MERS, a messenger RNA (mRNA) lipid nanoparticle vaccination has been explored[15].

Chitosan nanoparticle

Chitosan is a cationic, highly basic, and mucoadhesive natural polysaccharide that is biocompatible. It's commonly used in nano applications including medicine delivery, Blending, which comprises the physical mixing of two or more substances to eventually get the optimum NP size and morphological qualities to make it perfect for use as a drug nano carrier, produces specific physical alterations[16]. Cyprus researchers have made significant progress in developing chitosan nanoparticles for aerosol application, which allow medications to be targeted on the epithelial tissues of the lungs, ensuring controlled release and lowering toxicity. Chitosan nanoparticle under the brand name of Novochizol, allows various medications to be encapsulated and transported to the lungs for efficient treatment of severe COVID-19 infections. Novochizol aerosols can give a patient a therapeutic dose for 25 minutes to 3 hours. In both an *in vitro* and an *in vivo* paradigm, using chitosan as a nanoparticle has a number of advantages, including low toxicity and biodegradability. Furthermore, studies on chitosan reveal that it has a lot of potential for drug delivery to the lungs. Furthermore, chitosan has excellent mucoadhesive qualities, which aid in the mitigation of COVID-19-related intestinal reactions[7].

The goal of combining Epigallocatechin gallate (EGCG) and ChitosanNanoparticles (NPs) is to increase the benefits of chitosan as a nanocarrier for antiviral medication delivery. Chitosan, along with other polysaccharides such chitosan carrageenan, has been demonstrated to have powerful antiviral activities in numerous investigations. Sulphated polysaccharides, for example, can impede virus entry by reducing the positive charge of pathogen surface receptors, stopping them from attaching to the host cell's heparan sulphate proteoglycans (HSPGs)[16].

Silver Nanoparticles

Since ancient times, silver has been used to treat illnesses. Inhibiting cellular respiration and disrupting metabolic pathways, resulting in increased production of reactive oxygen species; forming pores and punctures on a bacterial cell wall by interacting with peptidoglycan molecules; and disrupting microbial DNA, thereby inhibiting viral replication, are all reported mechanisms for its antimicrobial activity. Taking action in this direction SHEPROS, a Malaysian company, has developed Nano Silver sanitizer, which contains a suspension of silver nanoparticles with a size of 25nm and kills a wide range of microorganisms, including viruses, by disrupting cellular metabolism and inhibiting cell growth by suppressing the electron transport system's basal metabolism[3]. When compared to other metal NPs, silver NPs have demonstrated the surface plasmon resonance (SPR) effect, which produces a significant photo thermal effect as well as greater biocompatibility[10]. A prior analysis revealed that bare AgNPs have antiviral efficacy against the monkey pox virus by preventing viral particle entrapment. AgNPs have been shown to have effective antiviral properties against RNA viruses, therefore they could be a good choice for testing to inhibit the novel SARS-CoV-2 virus. AgNPs have a great affinity for sulphur-

containing groups, which explains its strong interaction with cysteine, methionine, and glutathione, all of which are found in the active areas of many proteins. As a result of the inactivation of related proteins, AgNPs may interfere with viral genome replication as well as protein synthesis, contributing to its antiviral potential[6]. AgNPs work by preventing the virus from entering the host and also preventing the virus from attaching to the cell receptor. By denaturing the surface proteins, AgNPs deactivates the virus. The virus is then inhibited from binding to the receptor of the host cells by interacting with the glycoprotein (gp120) of the sulphur carrying groups that are dispersed on the lipid membrane of the viral cells[7]. Silver nanoparticles bind to SARS-CoV-2 surface proteins that have a lot of sulfhydryl groups. They cleave the disulphide links and alter the protein structure to kill it after binding. Silver nanoparticles' virucidal effect was greatly influenced by their size, with 2-15nm nanoparticles having the best protein affinity and virucidal activity[12]. The antiviral activity of AgNPs functionalized with polyvinylpyrrolidone has been shown to be size and dose dependent. Two cell lines, one of non-human origin (VeroE6/TMPRSS2) and the other of human lung epithelial origin (Calu-3) were infected with SARS-CoV-2 at varying viral concentrations (MOI) and then evaluated for cell viability and viral load after treatment with PVP-AgNPs. Using real-time reverse transcriptase quantitative polymerase chain reaction, the amount of viral load contained in Calu-3 cells was further measured (RT-qPCR). In triplicate testing, PVP-AgNPs were found to have a strong antiviral impact, as evidenced by an increase in the vitality of infected VeroE6/TMPRSS2 cells at doses between 1 and 10ppm[6,17].

The presence of reactive oxygen species on the surface of the nanoparticles causes the viral surface to be disrupted. AgNP's antiviral potential is enhanced by this modification of viral surface[6]. Inhaled silver nanoparticles (Ag NPs) have recently been employed as a first-line therapy and preventative strategy for COVID-19 infection progression. Ag NPs' antiviral action may be due to their adhesion to RNA virus surface glycoproteins, which prevents the virus from integrating into host cells[15].

Gold Nanoparticles

Due to its related special attributes like as surface chemistry, configurable size and shape, high biocompatibility, simplicity of design, and facile functionalization, gold nanoparticles are widely used in biomedical applications. The antiviral properties of AuNPs increases multi folds when coated with sulfonated polysaccharides and surface ligands have been attached[2]. In contrast to silver nanoparticles, gold nanoparticles (AuNPs) have a better tolerance on healthy normal cells, making it more suitable for in vivo applications. When AuNPs react with the glycoprotein haemagglutinin (HA), the Au oxidise the disulphide link, rendering the virus inactive. Porous AuNPs have a greater surface area than nonporous AuNPs, which favours contact with the capsid and boosts their antiviral effectiveness. In the presence of gallic acid, gold ions create homogeneous AuNPs that prevent viral infection. The functionalized AuNPs have a number of advantages, including a longer circulation period and a low concentration, as well as particular patterns to target the virus. Gold nanoparticles can enter a variety of cells and tissues, including the central nervous system, and stay there for a long time. Researchers created a vaccine adjuvant using gold NPs combined with the NALP3 inflammasome against SARS-CoV, which was capable of activating dendritic cells (DCs) in a similar manner toalum (aluminium hydroxide), the most common adjuvant, synergistically promoting an antigen-specific cellular immune response[7]. To limit herpes simplex virus type 1 (HSV-1) attachment to cells, experts used gold nanoparticles capped with mercaptoethanesulfonate (Au-MES NPs) to imitate the heparan sulphate proteoglycans (HSPGs) receptor. This method prevents the virus from attaching to and entering cells, as well as spreading from one cell to another. This tool could also be used to stop SARS-CoV-2 from infecting cells, as HSPGs are one of the virus's entrances path[1].

Sulphonate and organic sulphates were utilised to engage with the viral cell's capsid proteins and block HA activity. When compared to the succinic acid functionalized AuNPs, the sulphonate functionalized AuNPs had a higher viral inhibition. The thiol functionalized AuNPs showed a very effective suppression of virus in in vitro settings, according to a study. Even at low concentrations, functionalized AuNPs are capable of preventing viral multiplication[7]. Because of their potential to act as adjuvants in immunisation as well as antigen carriers, gold nanoparticles (AuNPs) are extensively employed in nano vaccines. VLPs can be made by incubating AuNPs as a core with CoV S proteins (such as avian CoV S protein), which naturally functionalize the surface (S-AuNPs). When compared to free antigens, S-AuNP-based vaccines can improve lymphatic antigen transport and increase both cellular and humoral responses. 0.1g of S protein electrostatically binds to 40-nm AuNPs, producing a S protein corona, in an S-AuNPs vaccine (94 1nm) against SARS-CoV. Due to alterations in the structure of S proteins following binding to AuNPs, this vaccine was able to produce a high IgG response but had a low affinity to neutralise CoVs, resulting in lung eosinophilic immunopathology[4].

Zinc oxide (ZnO) Nanoparticles

Several nanomaterials, such as Ag2S nanoclusters and ZnO nanoparticles, have an inherent ability to prevent viral propagation. These are said to promote the release of antiviral cytokines and decrease inflammation by modulating the host immunological response. Investigating these types of nanomaterials in COVID-19 could lead to a successful therapeutic response[3]. ZnO nanoparticles (ZnO NPs) are recognised to have distinct physicochemical, optoelectronic, and mechanical properties. Zinc is a trace element in the human body that is required for critical metabolic activities such as protein synthesis, DNA/RNA synthesis, haematopoiesis, neuron growth, and so on. As a result, administering ZnO NPs is not an issue because these nanoparticles are easily digested[6]. According to physical mechanisms such as virus adhesion, infection, and uncoating, Zinc (Zn)-containing compounds have antiviral effects toward a variety of viruses. In addition to viral protease and polymerase inhibition, ZnO NPs are more easily absorbed by the body than zinc itself[18]. Zinc supplementation has also been used to help create host resistance to SARS-CoV-2 infection by reducing the severity of symptoms and lowering viral load due to its antiviral properties. This is due to prior studies that zinc has an inhibiting effect on SARS-CoV replication. Zinc-based supplements have been shown to reduce the number of SARS-CoV infections by inactivating RNA-dependent RNA polymerase and proteolytic enzymes that are required for viral genome replication[6]. Because SARS-CoV-2 illness mostly affects the respiratory tract, airborne nanoparticles can be employed for direct pulmonary distribution, which has the advantages of quick absorption due to high vascularization and bypassing the first-pass metabolic effect[3]. Using ZnO NPs would not only assist inactivate SARS-CoV-2, but would also increase antiviral immunity in the host by increasing the concentration of Zn2+ in the human body once these ZnO NPs are digested, and so might be employed in COVID-19 therapies[6]. When PEGylated ZnO NP were used, virus proliferation was inhibited by the zn2+ ion dissolution. Zn2+-induced RNA polymerase inhibition in SARS-CoV-2 was studied by recent evidences[8].

Zinc has also been found in cell culture tests on VeroE6 cells to suppress the replication of the severe acute respiratory syndrome (SARS) coronavirus. When the intracellular concentration of zinc was high, the replication of the SARS coronavirus was suppressed using both zinc ions and zinc-ionophore (pyrithione). A proposed mechanism of SARS coronavirus replication suppression is zinc-mediated inactivation of the RNA-dependent RNA polymerase (RdRp; main replication enzyme). SARS-CoV-2 replication also requires two important enzymes, RdRp and 3C-like proteinase (3CLpro). Molecular modelling revealed that the zinc-binding sites in RdRp and 3CLpro are conserved and zinc-binding can lower the

enzymatic activity of 3CLpro and RdRp to impede viral propagation[19].

Copper oxide Nanoparticles

Copper has been known for its antiviral and antibacterial properties, also known as oligodynamic activity, since ancient Egypt. The steady release of Cu2+ cations on the surface, which can damage the membrane and nucleotides of viruses, is one of these metals' primary mechanisms[8]. Copper is a trace element that is necessary in trace amounts in the human body for immune system function and maintenance. Copper is required for the proper operation of immune cells such as natural killer cells, T cells, B cells, macrophages, monocytes, neutrophils, and dendritic cells, which are involved in the killing of infectious pathogens and the elicitation of immunological responses via innate and adaptive immunity. Copper nanoparticles have been shown to have antiviral properties against a variety of viruses, including the human immunodeficiency virus, poliovirus, influenza virus, retroviruses, and others[6]. Cu is significantly more cost-effective than Ag, and it is simple to use in the production of NPs and has great stability. As a result, the most appropriate technique for inactivating SARS-CoV-2 in the external environment is to generate and apply NPs containing Cu or copper oxide (CuO)[11]. Copper's antiviral action against human coronavirus 229 (HuCoV 229) was established by the destruction of the virus's RNA genome as well as irreversible damage to the virus's structural proteins such the envelope protein and spike protein. When compared to other smooth surfaces such as Teflon, glass, stainless steel, ceramic tiles, polyvinyl chloride, and so on, surfaces coated with a minimum of 70% copper, HuCoV 229 was shown to be inactivated irreversibly in less than an hour. or Cu–Ni alloys that contain more than 90% copper[20]. Intercalation of copper nanoparticles between DNA strands irreversibly damages the viral genome, preventing it from replicating further and thereby suppressing the virus. Cu2+ ions irreversibly damage viral proteins and lipids, resulting in viral inactivation, in the case of the severe acute respiratory syndrome coronavirus[6].

In an experiment done by Gharpure S *et al*, it was observed that the virus was found to endure 4 hours on a copper-containing surface, compared to 24-48 hours on plastic and stainless steel, and up to 24 hours on cardboard. Cu2+ ions act on viral proteins and lipids, causing irreversible damage to viral proteins as well as the formation of reactive oxygen species (ROS), resulting in viral particle inactivation. According to studies, surface pollution plays a crucial influence in virus transmission. When combined with polymers and textiles, some nanomaterials can inhibit the survival of viruses on surfaces, especially when exposed to light. Copper 3D, a Chilean/American business, has created the Nano Hack nanocomposite face mask, which contains 5% copper oxide nanoparticles impregnated in three layers of nonwoven polypropylene filters and has high antiviral efficacy against SARS-COV-2 because the mask's filter is enriched with accelerated copper oxide nanoparticles, it not only intercepts but also actively kills viruses. Furthermore, by depositing a few layers of graphene on a low-melting-temperature unwoven mask, a reusable and recyclable mask can be created. Graphene's outstanding hydrophobic and photothermal characteristics aid to reject incoming aqueous droplets while also allowing for sunlight sterilising[3]. The fundamental mechanism of action of copper nanoparticles in the treatment of herpes virus was increased ROS generation, which caused oxidative damage to the viral DNA[6].

Another study team from Ben-Gurion University of Negev (BGU) developed a polymer-based coating that used copper and other metal NPs to enable for regulated and delayed release of antiviral NPs, allowing them to remain effective for long periods of time[10]. Copper oxide nanoparticles Face mask made by ReSpimask R VK (RESPILON) with a 99.9% viral filtering efficiency; also inactivates the virus[3].

Iron and iron oxide Nanoparticles

The severity of COVID-19 is often determined by iron metabolism. Ferritin is a protein that controls

iron metabolism in the body. Hyperferritinemia, or a rise in ferritin levels in the blood, has been linked to life-threatening COVID-19 problems. To treat COVID-19, we propose ferritin as a therapeutic target," Dr. Muhammed said in an article published in THE HINDU newspaper. Iron oxide nanoparticles (IONPs) have already proven antibacterial activity through many studies. It has also been approved by the US Food and Drug Administration (FDA) for the treatment of anaemia because of the excellent biocompatibility of IONPs. The interaction between IONPs and the S protein of SARS-CoV-2 has been identified in recent studies and the potential antiviral activity of IONPs has been reported.325 In addition, the ability of IONPs to produce ROS can be applied to inactivate SARS-CoV-2 in the external environment[7]. Metal nanoparticles in the form of ions, such as copper and iron, will create radicals through Fenton-like processes, oxidising capsid proteins and inhibiting virus replication in the early stages[7]. Higher iron levels have been linked to respiratory disorders such pulmonary fibrosis and acute respiratory distress syndrome (ARDS), which may hasten the viral infection's progression. COVID-19 patients have been documented to develop ARDS. The US Food and Drug Administration (FDA) has approved a few iron chelators for clinical usage, including Deferasirox and Deferoxamine. These drugs have a strong affinity for iron ions and can bind free iron to remove it from proteins that store iron[22]. MS2 bacteriophage, Herpes simplex virus, viral haemorrhagic septicaemia virus, Infectious pancreatic necrosis virus, and other viruses were treated with superparamagnetic iron oxide nanoparticles, which irreversibly destroyed the viral genome and hindered viral genome replication[6]. Iron oxide particles have also been reported to have detrimental properties *in vitro* and *in vivo*, owing to the formation of reactive oxygen species (ROS). The vitality of cells was greatly increased by a polymer coating on the surface of iron oxide nanoparticles. Another method for reducing the detrimental effects of nanoparticles is to modify their surface[21]. Because of their multi-faceted features, iron oxide nanoparticles (IONPs) are widely used in bio-applications such as antibacterial agents, medication transport, cell separation, photo-thermal treatment, regenerative medicine, bio-imaging, and so on. Different kinds of IONPs, such as magnetite (Fe3O4), maghemite (-Fe3O4), and hematite (-Fe3O4), have been the most chosen magnetic nanoparticles for diverse biomedical applications due to their superior magnetic characteristics, biocompatibility, and stability, among others. The interactions of Fe2O3 and Fe3O4 IONPs with the receptor binding domain of the spike protein (S1-RBD) present in SARS-CoV-2, which is crucial in the virus's anchoring upon host cell receptors, were studied using a molecular docking technique. These molecular docking analyses demonstrated that both Fe2O3 and Fe3O4 nanoparticles engage effectively with the S1-RBD, with Fe3O4 nanoparticles creating a more stable complex than Fe2O3 nanoparticles. The binding of IONPs with SARSCoV-2 S1-RBD is thought to cause permanent conformational changes in the virus, resulting in its inactivation[6]. Several natural compounds that act as iron chelators and viral protease inhibitors, according to the researchers, could help reduce the inflammatory condition and relative oxidative stress after SARS-CoV-2 infections. The researchers used docking studies to find certain natural compounds that can fight SARS-CoV-2 infection by acting as both iron chelators and protease inhibitors. Quercetin has also been proven to be effective against viruses including enterovirus, Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS CoV) in investigations[22].

When utilising IONPs to treat SARS-CoV-2, patients with COVID-19 should be aware of potential risks. Iron dysregulation has been detected often in COVID-19 patients. Recent publications describe the connection of SARS-CoV-2 spike protein with haemoglobin (Hb) via cell receptors such as CD147, CD26, and others found on erythrocytes and other blood cell precursors, as well as ferroportin blocking due to the viral spike

protein's hepcidin mimicking function. Due to ROS formation and lipid peroxidation, these pathogenic conditions led in decreased Hb, increased iron load in cells and tissues, and ferroptosis (Cavezzi *et al*, 2020). As a result, increasing the iron concentration in COVID-19 patients may exacerbate these problems, which must be addressed while utilising IONPs for COVID-19 treatment[6]. Cagno *et al*. have reported antiviral NPs (Au and iron oxide core) with long and flexible linkers that strongly attach and inactivate viruses like respiratory syncytial virus *in vitro* and *in vivo* in a lung infection model, resulting in irreversible viral deformation (16).

Martins E.S *et al*. developed DMSA-Fe3O4 as a possible drug-delivery platform for COVID-19 treatment and characterised it. The nanoparticles were produced via co-precipitation and then coated with the DMSA molecule, resulting in a stable aqueous dispersion of thiolated nanoparticles. The free thiol groups of DMSA can be employed as covalent binding sites for antibiotics or other medications in the treatment of COVID 19[23].

Recent trends and future prospects

The creation of nano-based formulations that can successfully target exact regions of viral infection, limit medication toxicity in other tissues, and potentially have some intrinsic antiviral efficacy will be the key focus of future research into nano-based antiviral medicines[1]. Comirnaty (BNT162b2), Moderna COVID-19 Vaccine (mRNA-1273), COVID-19 Vaccine Astrazeneca (AZD1222), CoronaVac, and Convaxin are presently the only vaccines available for nCoV infection. NVX-coV2373, ZyCov-D, and VIR-7831 are among the therapy options currently being tested in other trials. In addition, there are over 50 MERS and/or SARS inhibitors available, including galidesivir, compound 3k, GC813 protease inhibitors, and helicase inhibitors (SSYA10-00). As potential therapy options, a wide range of antiviral medicines, immunotherapies, and vaccines are being investigated[9]. The completion of Phase 3 clinical trials of Pfizer's liposomal mRNA vaccine (BNT162b) can be considered a significant success in nanomedicine[11].

Pfizer's tablet is the first FDA-approved oral antiviral medicine designed specifically to combat Covid. Dosage: 300mg nirmatrelvir (two 150mg pills) combined with 100mg ritonavir (one 100mg tablet) taken twice daily for five days. For mild renal impairment (eGFR 30 to 60mL/min), the dose is reduced to 150mg nirmatrelvir (one 150mg tablet) plus 100mg ritonavir (one 100mg tablet), given twice daily for five days. Paxlovid will continue to be highly effective in treating those who have the omicron version of the virus. The tablet inhibits an enzyme required for virus replication. It's quite difficult for the virus to change in such a way that it no longer requires the protease enzyme. Paxlovid is a combination of two drugs: nirmatrelvir and ritonavir. Nirmatrelvir [PF-07321332] is an inhibitor of the SARS-CoV-2 main protease (Mpro) (also known as SARS-CoV2 3CL protease inhibitor) that prevents the disease from progressing to severe COVID-19 by suppressing viral replication in the early stages. Ritonavir is given in combination with nirmatrelvir to assist reduce its metabolism so that it can be active in the body for longer periods of time and at higher concentrations, which aids in the fight against the virus.

BNT162b2 (Comirnaty®; BioNTech and Pfizer) is a nucleoside-modified mRNA vaccine formulated in lipid nanoparticles for the prevention of the new coronavirus. BNT162b2 is made up of nucleoside-modified mRNA formulated in lipid nanoparticles. The full-length membrane-anchored SARS-CoV-19 spike protein is encoded by the mRNA, which contains mutations that keep the spike protein in an antigenically favourable prefusion conformation. The non-replicating RNA is protected from destruction by the lipid nanoparticles, which allows it to be transported into host cells following intramuscular injection. The mRNA is translated into SARS-CoV-2 spike protein, which is produced on the surface of the host cells once inside the cells. The transitory production of this spike antigen elicits anti-neutralizing antibodies and cellular immune responses, which may provide protection

against COVID-19. It shows about 95% of accuracy[24].

For patients with severe or critical COVID-19, baricitinib is strongly advised. It belongs to a class of medications known as Janus kinase (JAK) inhibitors, which reduce immune system overstimulation. It is recommended by the WHO that it be used in conjunction with corticosteroids. The use of sotrovimab, a monoclonal antibody medication, for treating mild to moderate cancer has also been conditionally approved by the WHO. COVID-19, Sotrovimab is a monoclonal antibody cocktail that was suggested by the World Health Organization in September 2021 as an alternative to casirivimab-imdevimab.

Spikevax's clearance by the FDA is a crucial step forward in the fight against the COVID-19 pandemic, as it is the second COVID-19 vaccine to be approved. Spikevax complies with the FDA's stringent safety, efficacy, and manufacturing quality requirements for any vaccine authorised for use in the United States. Spikevax is administered in two doses, one month apart, and has the same formulation as the EUA Moderna COVID-19 Vaccine. Spikevax was found to be 93 percent effective in preventing COVID-19.

Table No.1: Nanoparticles-based vaccination against coronaviruses

S.No		Platform	Antigen component	Virus	Notes
1	Self Assembled NP'S	Spike protein NP's	Spike protein	SARS-CoV, MERS-CoV	Induce high level of neutralizing antibodies Adjuvants (Alum, Matrix) improved safety and immunogenicity
		Spike protein-displaying VLPs	-	MERS-CoV	Spike protein attaches DPP4 receptors, stimulating immune system
		RBD-displaying VLPs	Gene of RBD of spike protein	MERS-CoV	Induced RBD-specific immune responses Antisera protected host cells from CoV infection
		Chaperna-based NPs	-	MERS-CoV	Induced mice immunization via interfering with binding of RBD to DPP4 receptors
2	AuNPs	Polypeptide NPs	HRC1 epitope of spike protein	SARS-CoV	Specific, work against SARS-CoV and any enveloped virus
		S-AuNPs	Spike protein of avian CoV	Avian CoV	Significant improvement in vaccination potency
		S-AuNPs	Spike protein	SARS-CoV	Induced strong IgG responses Lung eosinophilic immunopathology

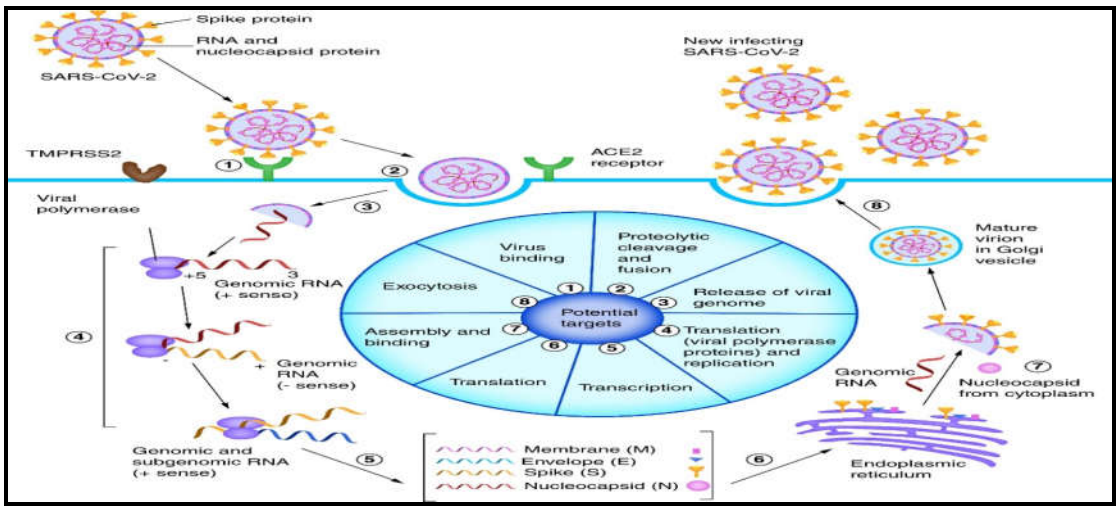

Figure No.1: Progression and activity of SARS-CoV-2 on host cell membrane

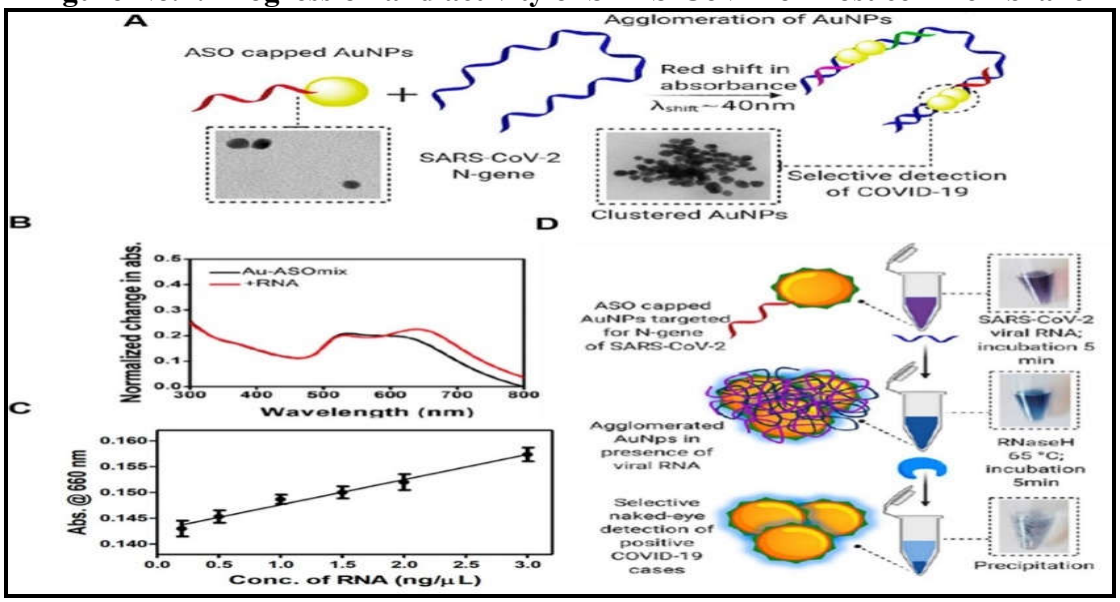

Figure No.2: Detection of biomarkers using Au-NPs

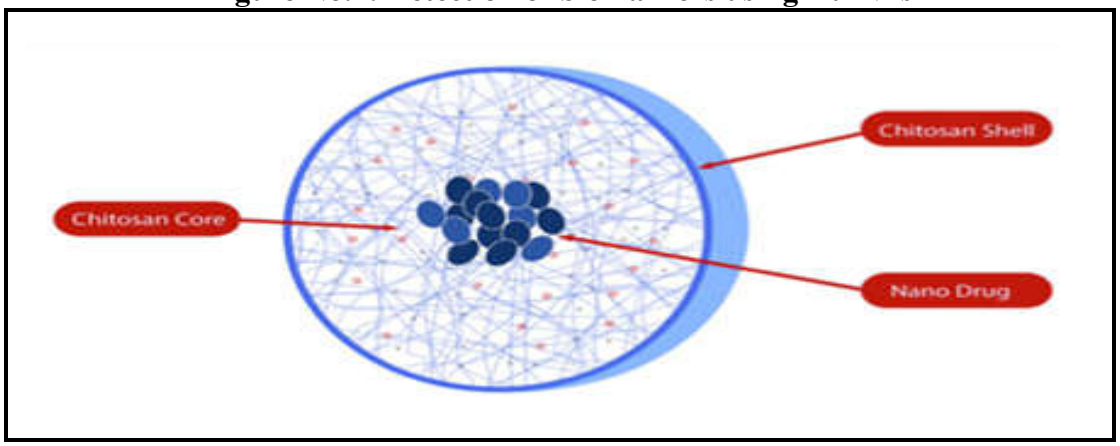

Figure No.3: Model of incorporation of nano-drug into chitosan

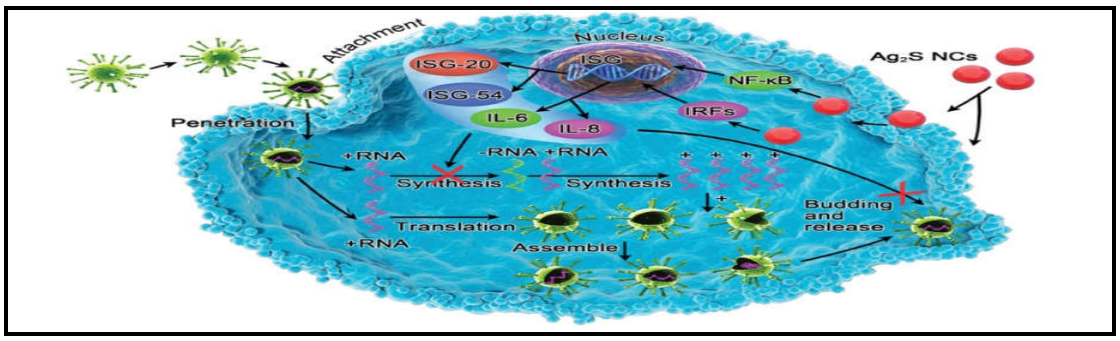

Figure No.4: MOA of AgNPs

CONCLUSION

To mitigate the effects of the COVID-19 health catastrophe, academics and industry around the world are working on everything from basic science to advanced technologies. Nanoscience and nanotechnology concepts and methods are currently a good approach within the present global focus. Nanotechnology has already been used to diagnose and treat various viral infections, and it could provide pre-existing medications and treatments a "new start" against COVID-19 by addressing toxicity, poor stability, and low bioavailability. Nanotechnology-based antiviral medications are chosen over traditional antiviral therapy in the current pandemic crisis due to their ease of synthesis, facile manipulation of characteristics, high stability, inertness, minimal cytotoxicity, and cost-effective nature. Nanotechnology-based medications, unlike standard antiviral treatments, help to reduce antiviral resistance due to their unique physio-chemical, mechanical, and opto-electronic capabilities. Nano-based formulations could potentially be tailored to target a specific tissue and have controlled-release capabilities, increasing treatment efficacy and, as a result, reducing the time and dose required to control the virus. Overall, these techniques have the potential to simplify multiple medicines now used to treat infectious illnesses. Nanotechnology has so far demonstrated considerable promise in terms of preventing, diagnosing, and potentially treating COVID-19 infections. Clinical trials are under underway for several immune-mediated, antigen-based and gene-based nano vaccine candidates. The capacity to build biomolecular pattern recognition for multiple categories of biomolecules is a fundamental advantage of nanotechnology-based approaches over traditional diagnostic testing. This pattern recognition is critical for a quick and accurate diagnosis of COVID-19 infections that are deadly. The perception of patterns is predicated on the phenomenon of biomolecules being linked to adaptive plasma discrepancy and/or comorbidity. The findings of this analysis will aid pharmacologists, biomedical engineers, and nano-systems engineers who are researching efficient manipulative nanomedicine as a potential COVID-19 infection treatment, where the goal is to manage medication delivery and release without causing side effects. It is concluded that gold nanoparticles are used to detect a specific protein from the SARS Cov-2 viruses genomic sequence they enabled the virus target detection these nanomaterials has high specific surface area and volume ratios Nanomaterials have been successfully used in the prevention of various infectious diseases they focus on suppressing one or more viral process like viral protein synthesis, replication and so on using gold, silver, iron, zinc, copper etc nanoparticle carrier systems.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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