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Applications and Challenges of Nano Medicine for Covid-19 Outbreak: The Potential Relevance of Therapeutic and Diagnostic Approaches for Treatment

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Abstract

The recent coronavirus 2019 (COVID-19) outbreak was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Finding newer therapeutic targets is necessary because, despite the fact that pandemics like SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) have been around for almost 20 years, no effective medication against the CoV family has been approved. Compared to conventional PCR tests, nanoparticle-based biosensors and point-of-care testing kits yield faster and more accurate issues with toxicity. In order to successfully incorporate nanotechnology into standard medical practice and improve readiness for upcoming pandemics, several problems must be resolved. With an emphasis on medication administration, diagnostics, vaccinations, and protective gear, this study investigates several nanotechnology-based strategies for COVID-19 management. Engineered nanoparticles (NPs) are used in Nano medicine to improve immunological response, targeting, and medication stability while lowering toxicity. The research emphasizes how important Nano medicine is in the fight against COVID-19 by improving drug delivery, diagnostics, vaccinations, and protective gear. The findings show that, in comparison to traditional methods, nanotechnology offers better efficacy, tailored distribution, and fewer adverse effects. To assurance the wellbeing, effectiveness, and moral application of Nano medicine in healthcare, stringent regulations are required.

Keywords: Covid 19; Homoeopathy; Nano Medicine; Nanoparticles; Vaccination

Abbreviations

ACE: Angiotensin Converting Enzyme; CRS: Cytokine Release Syndrome; TNF: Tumour Necrosis Factor; SMPN: Super Paramagnetic Nanoparticle; SLNs: Solid Lipid Nanoparticles; APCs: Antigen-Presenting Cells; EUL: Emergency Use Listing.

Introduction

The recent coronavirus 2019 (COVID-19) outbreak was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first verified and documented cases of COVID-19 in China in 2019 quickly escalated to a global

state of emergency that hasn't been seen since the Spanish Flu pandemic in 1918. The inability to stop the spread of COVID-19 has brought attention to how urgent it is to create diagnostic and treatment strategies for extremely contagious diseases [1]. To reduce the pathogenicity, morbidity, and mortality of SARS-CoV-2, numerous novel treatments are being developed that combine both conventional and cutting-edge techniques. One new area of study that has expanded into the medical field is nanotechnology. Nano medicine can overcome the challenges that conventional medicine faces because of its progressive nature. The most significant of all is that it should help transform drug-based medicine in the twenty-first century. If properly utilized, the features of nanomaterials may enhance medications and vaccinations and offer safer and more effective means of combating illnesses [2].

Anatomy of Virus

The CoV are enveloped positive single-stranded RNA viruses, and their 8.4–12 kDa genomes are the biggest known viral RNA viruses. The 5C and 3C terminals make up the viral genomes. A significant portion of the genome is made up of the 5C terminal, which has open reading frames that encode the proteins needed for viral replication. The spike protein (S), membrane protein (M), nucleocapsid protein (N), envelope protein (E), and hemagglutinin-esterase (HE) are the five structural proteins found in the 3C terminal. [1] The S protein facilitates the attachment and fusion of the virus with the membrane of the host cell as well as between the infected and nearby uninfected cells. In a vaccine, they are the main inducers of neutralizing antibodies [3]. RNA complexes formed by the N protein help in the transcription and assembly of viruses. The most prevalent structural protein, the M protein, also determines the form of the viral envelope. During the viral replication cycle, the E protein—the tiniest and most mysterious of the key structural proteins—is widely expressed within the infected cell. The HE protein is in charge of host specificity and receptor binding [2].

Transmission Method

Common methods of human-to-human transmission include direct transmission, contact transmission, aerosol-borne transmission, and transfer during medical procedures. Common ways of transmission include coughing, sneezing, inhaling droplets, and coming into touch with mucous membranes of the mouth, nose, and eyes. Other viral sources propagate as a result of viral shedding from the respiratory system, saliva, faces, and urine [4]. Patients with severe COVID-19 have a greater and longer-lasting viral burden. There have also been reports of COVID-19 spreading from patients to medical personnel and airline attendants who had close contact with the affected patients [2]. Common COVID-19 symptoms include fever, coughing, sputum production, myalgia, lumbago, diarrhoea, rhinorrhoea, headache, loss of taste and smell, and dyspnoea [5].

Structures Intricate in Covid-19

Angiotensin converting enzyme II (ACE2), a surface receptor found in human cells that is crucial for SARS-CoV-2's efficient uptake in the host cells, is one of the virus's primary targets. The viral spike glycoprotein attaches itself to the host cell's ACE2 (ACE2 peptidase domain) during infection. Disrupting this binding pathway is a crucial therapy strategy since the attachment of S protein to ACE2 is a crucial and first stage of infection. SARS-CoV-2 first affects the respiratory system before spreading to the heart, liver, and kidneys. The airways have significant levels of ACE2 expression [4].

Because ACE2 is highly expressed in the lungs and respiratory tract, the respiratory system is the primary entrance point and binding location for SARS-CoV-2. Therefore, SARSCoV-2 can readily enter the body via interacting with ACE2 in the alveolar cells. This is thought to be the cause of acute pneumonia, which in extreme cases results in ARDS and multiple organ failure. The cardiovascular system's cells express ACE2, which is essential for controlling blood pressure and myocardial contractility. Heart fibrosis and inflammation may develop as a result of SARSCoV-2 binding to ACE2. Both direct infection harm and hypoxia injury are ways that the CoV-2 might infect the central nervous system. A cytokine storm and significant brain damage can result from the activation of brain immune cells caused by astrocyte, macrophage, and microglia infections [6].

The BBB's integrity may be impacted by SARS-CoV-2's interaction with the ACE2 of brain capillary endothelial cells, which facilitates the virus's entry. The liver and pancreas are possible targets of CoV-2 because they contain higher levels of ACE2 and TMPRSS2 (transmembrane serine protease 2) than other intestinal epithelial cells. More ACE2 is expressed in the reproductive system, specifically in pregnant women's uterus, placenta, and foetus interface. Foetal tissue that expresses ACE2 may be a key target site for CoV-2 binding, which increases morbidity and death. [4] Patients with COVID-19 have high levels of inflammatory chemokines and cytokines, which leads to cytokine release syndrome (CRS). Severe multi-organ damage can result from advanced types of CRS, especially when paired with ARDS. failure, followed by death. Tumour necrosis factor (TNF) or interleukins 1 or 6 (IL-1, IL-6) are the chemokines and cytokines that are involved [7].

Nano Medicine Procedure

Although there are numerous treatment options available, the application of different Nano medicine

techniques has been effective in accurately treating a number of illnesses; nonetheless, its application in pulmonary drug/therapeutic targeting as an adjuvant therapy is still pending. Improved lung infection treatment approaches are made possible by Nano engineering with possible medications. Pulmonary Nano-drug delivery systems are the perfect drug delivery system for treating COVID-19-like pulmonary infections because of their special physicochemical characteristics, which include mucosal penetrability, ease of ligand functionalization, enhanced permeation because of their small size, increased local concentrations of drugs, and high adjuvant properties for vaccine applications [5].

Nanoparticles' Antiviral Properties

Antiviral compound delivery has demonstrated notable potential benefits with nanoparticles. Furthermore, nanoparticles exhibit direct antiviral action. Silver nanoparticles, functional gold nanoparticles, and quantum dots are among the different types of nanoparticle systems that have been shown to have antiviral properties thus far. For example, the majority of "antiviral" nanoparticles employ the well accepted tactic of preventing the virus from attaching itself to or entering the host cells. The suggested medications' Nano encapsulation may result in a safer way to treat COVID-19 and other viral illnesses.

By permanently harming different viruses, these particles can stop their transcription, translation, and replication. To target infected cells, drugs can be enclosed in Nano carriers [8]. When compared to free medicines, these nanoparticle-based systems have demonstrated improved therapeutic efficacy and decreased related toxicity. It's interesting to note that their mucoadhesive quality is one of these characteristics that is highly valued while developing treatments for respiratory infections using nanoparticles.

Numerous nanomaterial modifications using different functionalization techniques have been created in order to obtain this high mucoadhesive characteristic [6].

Nanoparticles in COVID-19 Investigation

identify SARS-CoV-2, nanoparticles can be designed as biosensors for the detection of biomarkers, such as nucleic acids (DNA, RNA), certain antigens (proteins, enzymes), or antibodies. A SARS-CoV-2 detection tool that employs graphene coupled to an anti-spike antibody has been made available thanks to recent developments in nanotechnology. Graphene oxide particles coated with fluorophore-bound DNA target strands that may detect viral helicase and dual-functioning plasmonic biosensors that utilize the energetics of DNA-RNA hybridization are examples of alternative detection techniques that have been developed [7]. NPs that are magnetic (MNPs): Due to their great magnetic efficiency, iron oxide nanoparticles are the most often employed MNPs. Similar to the technique employed, these nanoparticles can be utilized to enhance the detection of the SARS-CoV virus. in silica-coated superparamagnetic nanoparticle (SMNP) PCR-based tests [5].

Nano Medicine Interconnected with Covid-19:

Cascade molecules: Cascade molecules are three-dimensional, highly branching, monodispersed, radially symmetric, nanoscale polymeric scaffolds. The delivery of antiviral medications by cascade molecules has been investigated. Inhibiting virus absorption into host cells is one method of controlling viral infections, and NPs may be employed to stop SARS-CoV-2 and ACE2 from interacting and causing infection.

Dendrimers can increase the efficacy of medications and bioactive substances because of their tree-like branching nature. According to a study, pamam (polyamidoamine) dendrimers functioned as an antagonist for viral infection via binding with angiotensin receptors. Angiotensin converting enzymes are easily bound by NPs functionalized with ligands that are unique to these enzymes. Because of their ability to prevent viral attachment to ACE2, these NPs acquisition and spread of SARS-CoV-2 and to support preventative measures based on vaccination.

Drugs' antiviral efficacy can be increased by using polynomic dendrimers. Cascade molecules may therefore be investigated as a possible delivery system for antiviral medications to combat COVID-19 [9].

Gold Nanocrystals

Because gold nanoparticles (AuNPs) imitate a target binding receptor for the virus, they can cause viral deformation. These lipid-based nanoparticles can be utilized to treat lentivirus, dengue, respiratory syncytial virus (RSV), human papillomavirus, and HSV [5]. Graphene exhibits intriguing antiviral capabilities and a two-dimensional (2D) planar sheet. They are appropriate for the transportation of antiviral medications due to their excellent mechanical strength and surface loading characteristics [10].

Lipid Stranded Nano Probes

Liposomes, solid lipid nanoparticles (SLNs), Nano emulsions, and Nano suspension are the different types of lipid-based nanoparticles. Their vast surface area, high drug-loading capacity, regulated release, and improved drug delivery make them useful for a variety of therapeutic purposes. Antiviral medications such as Ritonavir, Maraviroc, Darunavir, Efavirenz, Zidovudine, and Lopinavir have been administered by SLNs [11].

Methods of Liposome Preparation

Liposomes, which are vesicles with one or more lipid bilayers surrounding aqueous spaces, are among the most researched Nano medicines utilized for drug targeting. There aren't many liposome-based goods on the market, and liposomes are primarily composed of natural or synthetic phospholipids. Because they can deliver medications intracellularly, they may be able to provide antiviral medications for COVID-19. Liposome surface functionalization with hydrophilic compounds and proteins enhances specificity. Unspecific protein adsorption is decreased by PEG functionalization.

Drugs are administered to the respiratory system using soft mist inhalers, dry powder inhalers, jet nebulizers, and metered dose inhalers. Following intranasal delivery, NPs effectively transported medications to organs like the brain and lungs [9]. Corticosteroid-containing NPs demonstrated deep lung penetration. when used to treat asthma in aerosol form. Therefore, the delivery of antiviral medications into the lungs using NP-based aerosols seems promising. It has been investigated if NPs can boost the antiviral efficacy of medications used to treat respiratory infections. Chitosan nanoparticles conjugated with influenza (H1N1) antigen enhanced the antigen's immunogenicity in a study following intranasal delivery [11].

Ultrafine Emulsions

Nano emulsion droplets are stable when diluted, they can be employed in parenteral applications. Nano emulsions are primarily made up of water, oil, and surfactant. Antiviral medications and vaccinations have been investigated for delivery via Nano emulsions. Monoclonal antibodies that neutralize SARS-CoV-2 have both preventative and therapeutic uses [12].

For the treatment or prevention of infectious disorders such as respiratory syncytial virus, anthrax, and Clostridium difficile, the FDA has approved three monoclonal antibodies. Products containing monoclonal antibodies decreased the death rate from Ebola virus infection.

This demonstrates that monoclonal antibodies are effective in treating COVID-19. However, they have drawbacks, including problems with viral diversity and bioavailability. Therefore, it's critical to monitor the development of resistant virus transmutation.

Nano Medicine for Vaccine Distribution

Before the virus infects the host, vaccines stop it in its tracks. Vaccines offer sustained protection against the infection. The adaptive immune system depends on the delivery of certain viral antigens via vaccines, which are frequently displayed on the cell surface of antigen-presenting cells (APCs). When the adaptive immune system detects such antigens, it either releases antibodies against them or activates T cells to eliminate them [13].

Additionally, memory B cells create viral-specific antibodies on the cell membrane that identify the virus and trigger an instant immunological response to eradicate it. The creation of COVID-19 vaccines has begun with the discovery of the genetic sequence of SARS-CoV-2. Vectored vaccines, recombinant proteins, fully attenuated vaccines, and other vaccines can be created using viral antigens inactivated virus and can also be created from viral antigens encoded in DNA or RNA.

The WHO Emergency Use Listing (EUL) includes the COVID-19 vaccines, including the Sinopharm COVID-19 vaccine, the Pfizer/Biotech Comirnaty vaccine, the Covishield and AstraZeneca vaccines (produced by AstraZeneca/Oxford), the Janssen/Ad26.COV 2.S vaccine (created by Johnson & Johnson), and the Modern COVID-19 vaccine [8].

The spike glycoprotein of SARS-CoV-2 is encoded by the mRNA vaccine BNT162b2, which is packaged as lipid nanoparticles. The full-length S protein of SARS-CoV-2 is encoded by the mRNA-1273, a lipid NP-encapsulated mRNA-based vaccine [14].

The ribosomes create antigens when antigen-encoding mRNA is delivered to them by mRNA vaccinations. Following vaccination, different cell types absorb the mRNA vaccine, which subsequently triggers the immune system through the MHC-I and MHC-II pathways.

APCs that have absorbed the mRNA vaccination express the target protein as an endogenous antigen, which in turn triggers CD8+ T cells through the MHC-I pathway. The target protein is translated and secreted by the non-APCs if they absorb the mRNA vaccine, and the APCs then internalize it. After then, the APCs activate the CD8+ through the MHC-II pathway in cells.

Compared to traditional vaccines, both DNA and RNA vaccines provide some benefits, such as affordability and ease of purification. However, there are certain problems with medication distribution, including quick bodily removal, low bioavailability, and degradation. Drug targeting strategies based on Nano medicine can solve these issues. NPs have demonstrated efficacy in delivering small interfering RNA (siRNA) to treat autoimmune diseases, neurological disorders, cancers, and infections [10].

Nano Medicine Intended for Vaccine Tributary Provision

Adjuvants are occasionally needed to increase the immunogenicity of recombinant and inactivated protein vaccines. NPs can carry molecular adjuvants, and they frequently exhibit adjuvant properties for the integrated antigen on their own [15].

The drawbacks of the conventional method of administering molecular vaccination adjuvants can be addressed using vaccine adjuvant nanoparticles. Alum (aluminium salts), MF59 (a squalene-based emulsion adjuvant), AS01 (a liposome-based adjuvant), AS03 (a squalene-based emulsion adjuvant), AF03 (a squalene-based emulsion adjuvant), AS04 (which contains the TLR4 agonist MPL (3-O-desacyl-4′-monophosphoryl lipid A), and virosomes are among the adjuvants that have been licensed for use in vaccines.

As a Nano adjuvant, MF59 demonstrated strong adjuvant action, including humoral and T helper type 1 immunological. DTap, Hib, hepatitis A, and hepatitis B are among the licensed vaccines that contain alum. Virosomes are utilized in the hepatitis A and influenza vaccines Invivac and Inflexal V. For influenza vaccinations intended for older adults, MF59 and AS03 have licenses [12].

The adjuvant qualities of virus-like particles, PLGA NPs, cationic liposomes, Nano emulsion, and cholesterol-bearing Nano gel are also being investigated. By enhancing antigen presentation and utilizing their innate immuno activation capabilities, several nanomaterials on their own exhibit adjuvant activity [16].

The properties of cyclic dinucleotides (CDNs) make them useful as vaccine adjuvants. CDNs were transported to the draining lymph nodes by cyclic di-GMP (cdGMP) loaded PEGylated lipid NPs (NP-cgGMP), which also enhanced the adjuvant activity of CDNs as an adjuvant to induce CD4+ and CD8+ T cell responses. Adjuvants may be helpful for individuals with compromised immune systems and those with additional comorbidities that lead to immune dysfunctions in the case of SARs-CoV-2.

It is anticipated that vaccine adjuvants will lower the COVID-19 antigen dose needed. Matrix-M adjuvant, a saponin-based adjuvant, along with a SARS-CoV-2 recombinant spike protein NPs vaccine, is in a phase I clinical study to assess its immunogenicity and safety.

Therefore, it is thought that a combination of vaccine and adjuvants is crucial, particularly for elderly and immunocompromised patients [14].

Defensive Achievement Through Nano Medicine

Because of their additional layers of nanofibers and tiny holes, Nano masks can keep viruses from accessing the respiratory system. As a result, Nano masks are far more effective than regular masks at preventing the spread of viruses. Without sacrificing the material's structure or breathability, face masks, lab or surgical aprons, and other items have been Nano engineered to incorporate novel qualities including hydrophobic and antibacterial activity [15]. In addition to providing comfort, nanomaterials, including nanofibers, can lower pressure and breathing resistance while protecting against tiny particles (less than 50 nm). Comparing this to traditional surgical face masks, the protection is far higher.

Conversely, the mucous membrane serves as the coronavirus's entryway into the human body. Therefore, the strategies for preventing and providing Medication that passes through the mucosa is essential. When it comes to transport across mucosal membranes, nanotechnology has demonstrated enormous promise [17].

Dares and Restrictions

One of the biggest challenges will be producing nanoparticles on a large scale, particularly when attempting to make these treatments reasonably priced. Although total health care costs could be reduced if nanomaterials and Nano-vaccines are successful in preventing COVID-19, the cost of nanoparticles may increase due to the complexity of their manufacturing methods and intellectual property rights [16].

Unwanted tissue interactions and toxicity, as well as unintended systemic dissemination and deposition, including unintended blood-brain barrier crossing, are additional drawbacks of nanoparticles.

Depending on the size and chemical makeup of the nanoparticles, accidental inhalation into the lungs is thought to result in fibrosis, pulmonary inflammation, and epithelial damage. Furthermore, it has been demonstrated that nanoparticles disrupt biological functions such as oxidative stress, inflammation, mitochondrial activity, and macrophage phagocytosis. as well as platelet activity. ROS production, cell membrane binding, DNA damage, altered cell cycle control, and protein denaturation are some of the ways that nanoparticles can be harmful, either acutely or over time.

The lack of knowledge regarding the long-term impacts of nanoparticles on people and the environment is another significant problem [17].

Grouping	Nano medicine Tactic	Task in COVID-19	Illustrations	Benefits	Tasks
Analysis	Nanoparticle-based biosensors	Rapid detection of SARS-CoV-2 over biomarkers	Graphene oxide sensors, Quantum dots	Great kindliness, rapid fallouts	Budget of mass invention, monitoring endorsements
Drug Transport	Nanoparticle-emanate transferors	Boosts drug solidity, besieged distribution to diseased cells	Lipid nanoparticles (LNPs), Dendrimers, Gold nanocrystals	Condensed toxicity, better-quality value	Prospective toxicity, intricacy in amalgamation
Antiviral Assets	Implemented nanoparticles	Undeviating antiviral exploit by precluding viral access	Silver nanoparticles, Functional gold nanoparticles	Constrains viral repetition, enriches drug bioavailability	Peril of inadvertent immune retort
Vaccine Provision	Lipid-based nanoparticles	Well-organized supply of mRNA vaccines	Pfizer-BioNTech, Moderna mRNA vaccines	Better exempt retort, stability	Cold stowing requirements, extraordinary production expenses
Special Fortification	Nano-engineered facades & layers	Affords antiviral and antibacterial safeguard	Nanofiber masks, Nano-coated PPE	Advanced filtration efficiency, enduring safety	Frame manufacture scalability, cost limitations
Therapeutics	Nano medicine for immune accent	Develops immune reaction and shrinks infection	Nano liposomes Monoclonal antibody-loaded NPs	Compact cytokine squall possessions	Long-standing well-being unidentified

Table: 1: Assessment of Nanomedicine Methods in COVID-19.

Conclusion

Because they improve antigen stability, antigen processing, and immunogenicity as well as the sustained and targeted administration of antigens, Nano medicines like NPs, lipid NPs, and VLPs have drawn attention from researchers as therapeutic molecules and vaccine delivery vehicles [18]. However, a significant obstacle is the reproducibility and large-scale industrial manufacturing of target-specific ligand coupled Nano medicines loaded with drugs or vaccines. It is anticipated that Nano medicine will be a potent platform for repurposing current antiviral medications to enhance the treatment of COVID-19. In several phases of COVID-19 prevention, diagnosis, treatment, vaccine, and research, Nano medicine and its constituent parts can be crucial [19]. Personal equipment can use Nano-based antibacterial technologies to increase patient and healthcare worker safety stated in table 1. Nanoparticles' exciting promise extends beyond their use in medicine and diagnosis. strategies, but they can also be used for worldwide preventative actions that try to reduce the symptoms and spread of SARS-CoV-2 infection. By enhancing medication delivery, diagnostics, vaccine effectiveness, and preventative measures, Nano medicine has become a ground-breaking strategy in the fight against COVID-19. By tackling the issues with conventional treatments, the incorporation of nanoparticles (NPs) into medical applications has resulted in notable breakthroughs. The concludingstance of treatment of infectious diseases could be drastically altered in the future because to nanotechnology. Maximizing Nano medicine's potential to effectively manage future pandemics will need ongoing study, technological improvements, and regulatory reforms [20].

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