Insights of Nanotechnology in COVID-19: Therapy, Detection and Prevention

2021-07-12

The Covid-19 outbreak has fueled an urgent demand for effective and advanced diagnosis and treatment while mitigating the spread of the infection. In this regard, nanotechnology seems to be highly applicable in this outbreak, due to the unique characteristic features and physicochemical properties of nanomaterials.

These properties offer a variety of approaches through the versatile chemical functionalization of nanoengineered materials which would be beneficial in coping up with this pandemic. Nano-intervention with rapid and cost-effective diagnostics and therapeutics against the Covid-19 infection is significant in this pandemic situation.

Emerging pandemic disease: Covid-19

The recent pandemic – Covid-19 has affected the whole world and it is caused by a virus that was first detected in Wuhan, located in the Hubei Province, China. This virus was named as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) on 11 February 2020 while the World Health Organisation (WHO) named the disease caused by SARS-CoV-2 as the coronavirus disease 2019 (Covid-19). Initially, this disease was reported as pneumonia of unknown origin and it spread among people widely. This omnipresent human infection and the transmission of SARS-CoV-2 triggered an alarm in the whole world and the WHO declared this as a pandemic in March 2020.

Moreover, Covid-19 is a highly communicable disease and it has been evidenced from scientific findings that SARS-CoV-2 can spread through direct and indirect or close contact with an infected person. It is mainly caused by inhaling virion particles consisting of respiratory fluid droplets which are expelled through sneezing, coughing or face-to-face talking. Furthermore, it has been found that these viruses can be active for hours on inanimate and tangible surfaces like metals, furniture, stationary, plastics and cloths, depending on the temperature, humidity and the chemical and topological nature of the solid surface. Then, the infection can be transmitted by touching these surfaces containing viruses and then touching one's eyes, nose or mouth. Common symptoms of the disease include fever, dry cough and tiredness, while body pain, nasal congestion, headache, conjunctivitis, sore throat or diarrhoea, are also observed in some reported cases. Serious symptoms, like difficulty in breathing or the shortness of breath, chest pain and the loss of speech or movement are also observed in a few cases. In addition to these, symptoms and syndromes like dizziness, ataxia (lack of muscle control), neuropathic pain, headache, myopathy (muscle disease), epilepsy and ischemic (restriction in blood supply to tissues) stroke are also commonly manifested in patients with severe Covid-19. However, it is important to mention that all SARS-CoV-2-infected people do not show symptoms while these asymptomatic patients act as carriers of the virus. However, it has been reported that these carriers have a common symptom of the decreased sense of smell which can act as a marker for identifying asymptomatic patients.

It is well noticed that people with a history of diabetes, hypertension, chronic lung diseases, asthma, cardiovascular issues and kidney diseases are at a higher risk of SARS-CoV-2 infection and mortality. Further, patients aged more than 60 years are at a higher risk, with 14.8% mortality. These reports mean that elderly people with chronic diseases have higher mortality than healthy individuals when infected with SARS-CoV-2. At the time of writing (June 2021), SARS-CoV-2 has infected 180 million people, among whom 3.89 million have died due to the disease. Further, 'second and third waves' of the disease are taking place, with a variety of mutant strains of SARS-CoV-2 spreading in more countries. Statistics clearly show that the mutant strain emerging in India is more infectious than the previous strains: each infected individual could infect an average of six other people, rather than the 1.1 average for the earlier strain. However, as of now, there is no indication as to whether it could cause more severe disease related complications or deaths. This continued rise of both cases and deaths, with the emergence of variant strains, necessitates the development of new treatment methodologies to control and treat the infection. Although scientists have discovered the complete structural details of SARS-CoV-2, they are still struggling to develop a cure for the disease. This is mainly because the development of new drugs requires clinical trials and a long approval process to prove their efficacy and safety in clinical trials, whereas the effectiveness of conventional antiviral treatments is not applicable with the emergence of viral mutations. In this scenario, multidisciplinary research efforts are quite essential to fight against this pandemic. In this context, nanotechnology can offer several beneficial impacts due to its unique physicochemical properties.

How nanotechnology can be used to mitigate Covid-19?

In the current Covid-19 pandemic situation, nanotechnology can be used in various aspects in the fight against Covid-19, such as prevention, diagnosis and therapy. For warding off the spread of the virus, it can be used in the development of effective disinfectants, antimicrobial surface coatings, self sterilizing personal protective equipment (PPE) for health care personnel, and protective masks. As Covid-19 is a highly infectious disease, it is essential to develop specific and sensitive sensors that can quickly identify the infection and monitoring of the disease. Here, nanotechnology can be used with its potential to develop simple, fast and cost effective assays (a testing of a method to determine its quality) using gold based nano-particles and other inorganic nano-particles. Mainly, it can be used to design assays to monitor the presence of SARS-CoV-2 and related biomarkers. Apart from this, nanotechnology can be used to develop new antiviral drugs, promote the co-delivery of multiple drugs, enhance circulation time and achieve the slow and sustained release of drugs. Moreover, it can also be used for pulmonary (related to lungs) targeting, which can reduce the side effects of drugs. Further, it is essential to develop a vaccine since spreading is taking place very fast. Here, nanotechnology can be used as a delivery agent for messenger ribonucleic acid (mRNA) and deoxyribonucleic acid (DNA) vaccines as a means of protecting them from enzymatic degradation.

Nanotechnology for the prevention of Covid-19

As Covid-19 is a highly communicable disease and presently there is a severe shortage of effective treatment and vaccination for the disease, therefore, preventing the spread of infection is one of the most important factors. Several efforts and strategies have been made to prevent the transmission of the virus through social distancing, the use of masks and gloves and PPE and the reinforcement of hygiene methods. In this context, several companies are investing in nanotechnology based products for the development of effective sanitary products and PPE. In early research studies, it has been proven that silver nano-particles have enhanced antimicrobial effects and are used as disinfectants against viruses, bacteria and other microorganisms. Silver has been used to control infections since ancient times. Silver nano-particles inhibit cellular respiration and disrupt metabolic (chemical processes within the body required for life) pathways, leading to the enhanced production of reactive oxygen species (ROS) and punctures on a bacterial cell wall by interacting with peptidoglycan (polymer that makes up the cell wall of most bacteria) molecules. As a result of that, it will disrupt microbial DNA by inhibiting viral replication. Silver nano-particles are better antimicrobial agents than their macro counterparts due to the larger surface to volume ratio that results from their nano size, which increases the area of reactivity with microbes and enhances cellular uptake and infiltration into biological membranes. Further, the toxicity of silver nano-particles is size and shape dependent. It has been found that the smaller the size, the higher the toxicity due to higher reactivity and ion (an atom or molecule with a net electric charge due to the loss or gain of one or more electrons) release in cells.

In this regard, a Malaysian company named SHEPROS, has developed a nano-silver sanitiser containing a suspension of silver nano-particles of size 25 nanometres (nm) that kills a broad spectrum of microorganisms, including viruses, by adversely affecting cellular metabolism and inhibiting cell growth through the suppression of the basal (fundamental) metabolism of the electron (subatomic particle) transport system. This product is available in the market and can be used as a sanitiser against SARS-CoV-2. Further, WeInnovate Biosolutions, the Indian Department of Science and Technology and the Department of Biotechnology, has developed a nonalcoholic aqueous based colloidal (a gelatinous or mucinous nature) silver solution which shows its antiviral effect by preventing the synthesis of viral negative strand RNA and viral budding (a method of the release of a virus from a cell after replication has taken place). NanoTouch Materials, LLC, a US-based company, has developed NanoSeptic® Self Cleaning Surface, which helps in the disinfection of public touch points, such as door handles, elevator buttons and even the rear of phones, protecting them against SARS-CoV-2. This disinfectant is composed of mineral nanocrystals, which act as a catalyst in the presence of light to create a powerful oxidation (a process in which a chemical substance changes because of the addition of oxygen) reaction that oxidises organic contaminants.

It has been revealed that surface contamination plays a significant role in the transmission of

Covid-19. In this regard, several nano-materials (titanium dioxide, copper oxide and silver nano-particles), when associated with surfaces and textiles, can reduce the viability of viruses on surfaces. As an example, a Chilean-US-based company, Copper 3D, has developed a nano-composite face mask named NanoHack in which 5% copper oxide nano-particles are impregnated in three layers of nonwoven polypropylene (a type of synthetic plastic) filters with excellent antiviral activity against SARS-COV-2. This face mask is popular throughout the globe. Promethean Particles Limited in the United Kingdom is developing copper nano-particle-embedded polymers (a class of natural or synthetic substances composed of very large molecules that are multiples of simpler chemical units) fibres in collaboration with leading research facilities and textile companies for use in PPE kits. Further, the development of protective materials that can not only capture the viruses but also kill them would have a far reaching effect in preventing the spread of Covid-19. For this, nano-materials that have an inherent antiviral activity, such as silver nano-particles, graphene oxide (GO), copper oxide nano-particles, two dimensional carbides and nitrides can be employed. It was found that coating these nano-materials on masks, gloves and PPE enhances their ability to capture and inactivate viruses. In this regard, RESPILON Group (Czech Republic based Company) has developed ReSpimask® Virus Killer (VK), which is available in the market and has 99.9% filtration efficiency for viruses/bacteria. The filter of the mask is enriched with accelerated copper oxide nano-particles and it actively kills virus/bacteria. Further, nanotechnology has also been employed in the development of air purifiers to prevent the airborne transmission of the SARS-CoV-2 Virus. In this context, the TeqAir 200 air ioniser (a device which produces ions) developed by TEQOYA is already in the market. As the size of SARS-CoV-2 is close to the median (the size that is in the middle of the series of sizes) of the particle sizes for which TEQOYA air purifiers are efficient, they would be expected to reduce the concentration of SARS-CoV-2 in the air.

Looking back to the past global experiences of viral outbreaks, immunising individuals is the most significant prevention from the future influence of viral infections. Therefore, biomedical intervention toward vaccination should be the prime focus of research at this time. Vaccination has served as the most effective public health programme that can eradicate or control the spread of pandemic disease and the situation is the same in Covid-19 as well. The unexpected increase in the number of SARS-CoV-2 infected cases and the emergence of new mutants of SARS-CoV-2 has emphasised the urgent global need for vaccine development. Vaccination is the process of immunisation whereby the host immune system is activated to induce long term immune memory, which protects against future infection by a pathogen (a bacterium, virus, or other microorganism that can cause disease). It prevents infectious diseases by inducing a controlled immune response against the pathogen by mimicking its natural interaction with the host immune system. Vaccines consist of two major components: an antigen (substance that is capable of stimulating an immune response), which targets the immune system to activate it, and an adjuvant (a substance which enhances the body's immune response to an antigen), which is co-administered with vaccines to potentiate or modulate the immune system against the antigen.

Conventional vaccines include either live attenuated pathogens which have a risk of reversion to virulent strains, or inactivated pathogens which generally display weak immunogenicity (ability of a foreign substance to provoke an immune response in the body). This has led to the development of next generation subunit vaccines like RNA/DNA encoding viral antigens, which could overcome these limitations. Because all of these are proteins which are easily degraded in the body, successful vaccines are still difficult to achieve for various infectious diseases. Nanotechnology based platforms have been used for targeted delivery and for the slow and sustainable release of antigens, adjuvants and immunoregulatory agents as they can control improper immune stimulation, the loss of bioactivity of immuno-active agents during circulation, and off-target side effects. In this regard, pharmaceutical companies are mostly using nanoparticles for vaccine development and delivery. BioNTech/Pfizer and Moderna have encapsulated their mRNA vaccines in lipid nano-particles, while Oxford/AstraZeneca and CanSino Biologics have incorporated the antigen encoding sequence into the DNA of the adenovirus (a group of viruses that cause any different illnesses). On the other hand, Novavax, Inc., a nanotechnology based Company, has conjugated the S protein of SARS-CoV-2 onto the surface of nano sized virus like particles for the effective delivery of vaccines to the host body. The next generation vaccines like subunit (a distinct component of substance) vaccines rely on adjuvants that can enhance the vaccine's potency in elevating the immune response against specific antigens. In this regard, the nano scale adjuvant can be of great potential in encapsulating and presenting these antigens to the immune cells to improve the immunogenicity in groups that respond poorly to vaccines. Recently, Novavax marked the entry of its Coronavirus vaccine candidate NVX-CoV2373, which includes the Company's proprietary Matrix-M™ adjuvant, to clinical trials. Thus, owing to the flexible nature of nanotechnology, nano-particles can be engineered to strengthen immune stimulation with desired adjuvant activities.

Nanotechnology in the detection of SARS-CoV-2

Most of the time, Covid-19 patients exhibit a wide range of clinical symptoms that are similar to other respiratory diseases, and therefore, the accurate detection of the exact disease is vital to initiate required treatments and to take necessary actions to prevent the spread of the infection. Nucleic acid based testing is the primary detection tool for SARS-CoV-2, whereby nasopharyngeal (relating to the upper part of the pharynx)/oropharyngeal (relating to the oropharynx) swabs are used for detecting the presence of the virus using Reverse Transcription Polymerase Chain Reaction (RT-PCR). On the other hand, this technique is more time consuming and labour intensive and requires expensive instruments. As Covid-19 cases are unexpectedly increasing, with almost 180 million people already affected across the globe by the end of June 2021, the current situation urgently requires the development of detection techniques that are accurate, rapid and cost effective with the ease of handling. Therefore, research should be centered on developing rapid, sensitive and accurate nucleic acid or protein based tests and point of care testing (POCT). In this scenario, nanotechnology can offer a great enhancement in the sensitivity of existing detection techniques like RT-PCR and immunofluorescence (the labeling of antibodies or antigens with dyes) assays by virtue of the nano-particles' quantum size effects, high surface to volume ratio, high adsorption (the adhesion of atoms, ions or molecules from a gas, liquid or dissolved solid to a surface) capacity, and high reactivity. These properties allow for efficient interaction with sample analytes (a substance whose chemical constituents are being identified and measured). Moreover, nano-particles offer the ease of surface functionalization and it facilitates the binding of ligands (a molecule that binds to another molecule) to surface receptors via covalent or noncovalent (types of chemical bonding) bonding, which invariably enhances selectivity and specificity by greatly reducing the time of detection. Further, nanomaterials can be employed as nano labels for enhancing the signals, which helps in achieving the detection of very low magnitude signals. This nano labeling is normally done by attaching metal nano-particles, such as silver or gold nano-particles or quantum dots on targeted bio recognising probes and thereby the significant enhancement of signals can be obtained. Silver nano-particles have been incorporated in designing a wide range of virus detection tools due to their unique catalytic and electric properties, coupled with biomolecules such as antibodies, RNA aptamers (short, single stranded DNA or RNA) and single stranded DNA. In addition to this, they have excellent multiplexing capabilities, which further render them suitable for incorporation into futuristic technologies for virus detection.

Nanotechnology in the treatment of Covid-19

Although pharmaceutical science has been improved to higher levels, still there is no specific drug recommended to prevent and treat Covid-19. But, the US Food and Drug Administration (FDA) has approved the ‘remdesivir’ drug for emergency use, which could be administered to patients who have severe effects in Covid-19 disease. Covid-19 adversely affects the respiratory system, so it would be beneficial to conduct research in the field of cytokines (a large group of small proteins important in cell signaling) that protect the respiratory system and promote lung homeostasis (self regulating process to maintain stability) during viral infections. One of the important cytokines is the leukemia inhibitory factor, which modulates severe adverse events during acute respiratory distress syndrome. Although it has not been studied in Covid-19, leukaemia inhibitory factor nano-particles have shown a greater clinical importance in animal models of autoimmune encephalomyelitis (a collection of related conditions in which the body’s immune system attacks the brain, causing inflammation).

The most successful strategy in many viral infections is blocking the entry of viruses into the host. As previously described, the virus enters into the host via the interaction of the receptor binding domain of its spike (proteins having protruding spikes from the surface) protein, therefore any drug which could disrupt the binding of SARS-CoV-2 to the ACE2 (a cell surface protein found on tissues) receptor has the potential to inhibit the Virus. As an example, researchers have chemically synthesized SBP1, a 23 mer peptide (short strings of amino acids) fragment of the ACE2 peptidase (an enzyme) domain α1 helix composed entirely of proteinogenic (which produces proteins) amino acids, which specifically and strongly binds to the SARS-CoV-2 spike protein, and inhibits the virus. The delivery of this peptide based drug is very challenging due to enzymes in the body because enzymes rapidly degrade and finally reduce the efficacy. In this regard, a group of researchers from the Northwestern University’s Simpson Querrey Institute have discovered the delivery of the peptide drug in nanostructures having water filled channels that are prepared by ‘gluing’ millions of peptides. These nanostructures can protect the peptide drug from enzymatic degradation while it circulates in the body. These peptide nanostructures against the SARS-CoV-2 spike protein are in the preclinical trial stage. Furthermore, researchers have found that nanomaterials can bind to viral particles and prevent their interaction with the host cell. As an example, carbon quantum dots are able to prevent the entry of another human Coronavirus (HCoV-229E strain) into the host cells by interacting with the protein of the virus. As a result of that, the coronavirus is not available to bind with the host cells by inhibiting the entry of SARS-CoV-2 in the host. Several nanomaterials exhibit an intrinsic ability to inhibit viral replication, such as Ag2S nanoclusters, ZnO nano-particles and Co nano-particles. Further, these nanomaterials have proven their ability to enhance the secretion of antiviral cytokines and suppress inflammation by modulating the host immune response. The suitability of these types of nanomaterials in Covid-19 should be explored as an effective therapeutic response.

In SARS-CoV-2 infection, the respiratory tract is the main target and airborne nano-particles can be used for direct pulmonary delivery, which offers the benefits of rapid absorption due to high vascularisation (excessive formation of blood vessels). The drug delivery of nano-particles to the lungs depends primarily on the particle size, surface area, electrical charge and surface morphology of the nanoparticles, and therefore, these properties can be tailored by using nanoparticles and to cross mucosal (rich in mucous substance) membranes through the transmucosal (route of administration in which the drug is administered across mucosa) route using endocytosis (cellular process in which substances are brought into the cell), carrier mediated or receptor mediated transport processes. The other nano-formulations, such as solid lipid (macro bio-molecule) nanoparticles, polymeric nanoparticles and liposomes (spherical lipid vesicle), have been evaluated for various pulmonary diseases. These are coupled with devices such as nebulisers (a device used to deliver medicine in the form of a mist), pressurized metered dose inhalers, dry powder inhalers and soft mist inhalers for their delivery. An aerosol (Novochizol) based on chitosan nano-particles has been synthesized by Bioavanta LLC/Bosti Trading Ltd. The importance of this nano-formulation is the strongly adhering to lung epithelial (sheets of cells covering blood vessels) tissues and it ensures sustained release without systemic distribution, making it an ideal intrapulmonary delivery system. Due to the above properties, the respective production Company is in the process of developing drug loaded Novochizol for the treatment of Covid-19, and this is in the preclinical evaluation stage.

The future perspective of nanotechnology in the prevention of Covid-19

Although we have developed technologies and treatment methodologies to fight against Covid-19, we still do not have proper strategies and treatments to prevent and treat the infection. Protection and diagnosis are the most important factors for preventing the spread of infection. Currently, drug repurposing is in high demand for therapy against SARS-CoV-2 infection, but it has not been effective in all reported cases. So far, the most significant strategy to control the pandemic situation is the development of an effective vaccine that can mitigate the severe conditions of the infection. In this regard, nanotechnology seems to be highly effective due to the physicochemical properties of nano-particles that provide an opportunity to cope against the SARS-CoV-2 infection. In this scenario, nanotechnology plays a big role in developing PPE, anti-bacterial surface coatings, face masks and hand sanitisers which can help to prevent the transmission of the infection. As the symptoms of Covid-19 are very similar to those of other respiratory diseases like asthma (respiratory disease), it is essential to have accurate and rapid diagnostic tools with improved sensitivity to detect the infection at an early stage. In this context, it is reasonable to believe that due to their smaller size and larger surface area, nanotechnology related findings can detect the disease with high accuracy. With the growing demand for drug repurposing to find therapeutics against SARS-CoV-2 infection, it is equally important to develop nano-platforms for the effective delivery of the same to the target site. Furthermore, it is important to develop strategies whereby nano-particles can themselves be used as therapeutics or immune modulating agents upon the SARS-CoV-2 infection. Therefore, we firmly believe that vaccination can give effective results to fight against Covid-19, and therefore, the role of nanotechnology in the development of suitable vaccines is emphasised. We firmly believe that broad spectrum nano-formulations will be developed for vaccination and therapeutics that can be easily modified according to the need of the moment.

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