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Review Article

The Role of Nanotechnology in the Fight against COVID-19

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Abstract

COVID-19 has lately emerged as one of the most difficult pandemics of the twentieth century, with lethal consequences and a high rate of replication. It emphasizes the critical importance of developing effective vaccines to prevent virus infection, early and rapid diagnosis using high sensitivity and selectivity diagnostic kits, and effective antiviral and protective therapeutics to reduce and eliminate viral load and tissue damage-related side effects. As a result, non-toxic antiviral nanoparticles (NPs) are being developed for therapeutic use in the prevention and treatment of COVID-19. Nanoparticles have shown considerable promise in the development of nano vaccines to combat viral diseases. In this paper, we look at the potential of nanoparticles as a medicine or as a platform for drug and vaccine repurposing and development. Meanwhile, sophisticated virus detection methodologies based on NPs will be detailed, with the goal of inspiring scientists to develop cost-effective Nano platforms for prevention, diagnosis, and therapy.

Keywords: Nanotechnology, Fight against, Covid-19.

INTRODUCTION

In recent years, infectious diseases have become the primary cause of death more than ever before. These diseases are spread from person to person since the means of transmission for some of these diseases are still being researched, and coronavirus is not one of them. COVID-19 is caused by the SARS-CoV-2 virus, and it has lately emerged as one of the most dangerous pandemics in history, with fatal results and a high rate of reproduction and transmission. With the emergence of the severe acute respiratory syndrome coronavirus (SARS) in late 2002 and then the Middle East respiratory syndrome (MERS) in late 2012, coronaviruses have become a serious epidemic threat (Tavakol *et al*., 2021).

Coronaviruses are enclosed and spherical viruses with a single-stranded RNA genome that belong to the Coronavirinae subfamily (order: Nidovirales, family: Coronaviridae). The recent outbreak of COVID-19-causing new beta-coronavirus in Wuhan, China, is most likely linked to a seafood market. According to WHO Situation Report 148, by the 16th of June 2020, there had been 7,941,791 confirmed cases of COVID-19 worldwide, resulting in 434,796 deaths (Campos *et al*., 2020). The genome sequence of the novel virus responsible for COVID-19 (denominated SARS-CoV-2) is 96.2 percent identical to the genome of bat coronavirus RaTG13, whereas it shares 79.5 percent similarity with SARS-CoV, according to Zhou *et al*., in the publication of Campos *et al*. (2020). SARS-CoV-2, on the other hand, has a far faster human-to-human transmission than SARS-CoV, which has already resulted in its spread over the world, prompting the WHO to designate the epidemic worldwide pandemic on March 11, 2020. However, by 2020, when the pandemic was at its peak and countries were under lockdown, the number of infected individuals was steadily rising, and no officially recognized medicines or vaccines for COVID-19 were available. In very unwell patients, current treatments were mostly focused on symptomatic alleviation and respiratory assistance (Jin *et al*., 2020; Zumala *et al*., 2020). Efforts are presently underway to create effectively, tailored, and safe medicines and vaccines to combat this virus. Antiviral therapies, immunological therapy, anti-inflammatory therapy, and other treatments that include traditional medications based on natural materials make up the majority of currently available drugs for the treatment of viral infections (Kang *et al.*, 2020). Because of viral modifications and the advent of new viral strains, the effectiveness of traditional treatments for viral infections is gradually fading (Strasfeld and Chou, 2010). Researchers have recently become interested in the creation of broad-spectrum antiviral medications, which are less prone to resistance and may be employed against a variety of viruses, including novel strains (Jackman *et al*., 2016). However, due to the lengthy procedure required to verify efficacy and safety, the creation of new pharmaceuticals lags behind the demand for them (Chen *et al*., 2020). Multidisciplinary research efforts are needed to develop alternative antiviral medications that target distinct phases of the virus replication cycle to overcome the limits and improve antiviral treatments (Revuelta Herrero *et al*., 2018; Mohammadi *et al*., 2019). Nanotechnology has gotten a lot of attention in this area, and it's already being studied for its possible utility in the prevention and/or treatment of viral infections (Campos *et al*., 2020).

1.1 Brief history about Covid-19

Virus outbreaks such as Ebola, Influenza a (H1N1), Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Zika have plagued the world for nearly two decades. All of these diseases had a significant economic and public health impact on the world (Boopathi *et al*., 2020). SARS was the first epidemic of the twenty-first century, first reported in November 2002 in Guangdong, China, and then ten years later in June 2012 in Jeddah, Saudi Arabia (Lau and Chan, 2015; Zheng et al., 2019). The World Health Organization (WHO) announced 2,494 confirmed cases of MERS-CoV infection in November 2019, with 858 deaths recorded across 27 countries. 26 nations were affected by the SARS-CoV outbreak, which resulted in 8,096 confirmed cases and 744 deaths (Hassan *et al*., 2020; Hua *et al*., 2020; Wang *et al*., 2020a). A novel coronavirus (CoV) that causes usual pneumonia was discovered in Wuhan, China, in December 2019. (Du *et al*., 2020). The virus was identified and classified as Severe Acute Respiratory Syndrome CoV-2 (SARS-CoV-2) by the Chinese Center for Disease Control and Prevention (Anastasopoulou and Athanasia, 2020; Lai *et al*., 2020; Wang *et al*., 2020).

SARS-CoV-2 infection has expanded dramatically since then, quickly transforming an epidemic into a pandemic. On March 11, 2020, the WHO classified the CoV disease 2019 (COVID-19) a public health emergency of worldwide significance (Cardoso *et al*., 2020). SARS-CoV-2 has infected about 21.8 million people in 216 countries, resulting in over 772 thousand deaths (numbers that are continually rising) (World Health Organization, 2020d). COVID-19 is regarded as one of the world's most serious humanitarian disasters, and because to the gravity of the situation, enormous efforts have been made to combat the disease (Cardoso *et al*., 2020). Cough (68.7%), fever (85.6%), weariness (39.4%), and loss of taste and smell are the most prevalent COVID-19 symptoms among infected people. Other problems such as pneumonia, difficulty breathing, and ground-glass opacity in the lung have been described in more severe cases. These symptoms have been used to screen suspected cases who are then submitted to chest radiological tests such as computed tomography and X-Rays (Cardoso *et al*., 2020). According to studies, SARS-CoV-2 is transmitted mostly through contaminated droplets exhaled by sick patients, such as through coughing or sneezing. Individuals can be infected either directly or indirectly by fomites. Direct contact transmission occurs when infected people come into touch with saliva, respiratory secretions, or droplets that are expelled through coughing, sneezing, or speaking. Indirect contact transmission occurs when a susceptible host comes into contact with a contaminated object or surface (fomite transmission).

2.0 Nanotechnology: an overview

Nanotechnology, according to Singh *et al.* (2021), is the creation and implementation of materials with dimensions of less than 100 nanometers. Many fields of study, including materials science, physics, chemistry, biology, engineering, and computer science, have benefited greatly from it. Nanotechnology has seen a surge in biomedical sciences in recent years, where it has been successfully used for illness detection, diagnosis, and therapy. Nanotechnology's widespread use in medicine is due to its unique properties such as small size, large surface area, multifunctionality, surface adaptability, and enhanced solubility, which aid in the development of safer and more efficient drug candidates, tissue-targeted therapies, personalized medicines, and early diagnostic devices. The potential of nanotechnology is undeniable in the current COVID-19 pandemic predicament. It can be utilized in a variety of ways to combat COVID-19, including prevention, diagnosis, and treatment (Singh *et al*., 2021).

It can be used to build effective disinfectants and surface coatings, as well as self-sterilizing personal protective equipment (PPE) for healthcare workers and infection-safe masks, to stop the virus from spreading. COVID-19 is a highly infectious disease, thus developing specific and sensitive sensors that can swiftly detect infection or immune response for rapid point-of-care (POC) diagnostics, surveillance, and disease monitoring are critical. Nanotechnology can be utilized to construct tests to monitor the presence of SARS-CoV-2 and similar biomarkers, as it has the potential to produce simple, rapid, and cost-effective assays employing gold-based nanoparticles and other inorganic nanoparticles (Singh *et al*., 2021).

2.1. Surface disinfection strategy employing Nanotechnology

There's little doubt that coronavirus spreads faster than it can be detected, but the mechanism of transmission is unknown and still being investigated.

Physical separation was used throughout the pandemic's breakout, but it did not affect the propagation of this new coronavirus until 2020. According to recent research, SARS-CoV-2 spreads by micro-droplets released mostly from person to person or through contact with contaminated surfaces (Campos *et al*., 2020). Many scientists, on the other hand, are working around the clock to develop new and effective materials to help slow the spread of the disease. Nanotechnology, which is defined as the creation and application of materials with a diameter of fewer than 100 nanometers, presents several intriguing options for the development of disinfectants using these nanoparticles. Some metallic nanoparticles are also known to have a broad spectrum of action against viruses and other microorganisms, and according to Rai *et al.* (2020), "metallic nanoparticles, particularly silver nanoparticles, could be used as a potent and broad-spectrum antiviral agent either with or without surface modification." The antiviral action of these nanoparticles, on the other hand, is still largely unknown." As previously said, a nano-disinfectant based on engineered water nanostructures (EWNS) created using electrospray and aqueous suspension ionization of various active components is still in his report. This product's results revealed a considerable reduction in pathogen concentrations (including H1N1 influenza). Furthermore, the concentrations of the active ingredient (hydrogen peroxide) required for inactivation were substantially lower (nanogram level), suggesting the platform's feasibility. As a result, nanotechnology has a crucial role to play in the fight against coronavirus illness. Researchers should take advantage of this opportunity to develop an effective substance that would result in a large reduction in the global pandemic while having fewer adverse effects.

2.2. Nanotechnologies in the Diagnosis of COVID-19

Many nanomaterials have been used in POC devices because they have features that are advantageous for sensings, such as chemical stability, excellent electrical conductivity, and the LSPR effect (Localized Surface Plasmon Resonance) (Syedmoradi *et al*., 2017; Kumar *et al*., 2019). The introduction of nanoparticles in analytical equipment could improve detection systems' sensitivity and specificity (Zhang *et al.*, 2020). Gold NPs (AuNPs) is one of the most appealing nanomaterials because they exhibit optical electronic properties that may be explored by various types of biosensors, including those based on colorimetric, electrochemical, and plasmonic detection.

AuNPs have been widely employed to label the target molecule in lateral flow assays (LFAs), resulting in a color shift in the test zone that may be read by the naked eye for qualitative results or evaluated by a smartphone that can determine the concentration of the target from a taken image (Cardoso *et al*., 2020). In POC analysis, LFAs are often employed to detect antibodies and proteins in complex samples like urine, blood, and saliva. They are inexpensive, produce quick results (5–30 minutes), and can be stored at room temperature without impairing biomolecule performance. Although alternative labels are used by some LFAs, several studies have demonstrated that AuNPs boost the biosensor's signal and sensitivity, allowing analyte detection at lower concentrations (Cardoso *et al*., 2020). In a report by Cardoso *et al.* (2020), Udugama *et al*. reported that LFAs biosensors were used in the diagnosis of Covid-19 by detecting only immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies that recognize the SARS-CoV-2 proteins, indicating that the patient had been infected. It is easier to detect this unique virus and isolate affected people with nanomaterials because it is a simple-to-use technology that is more accurate and sensitive than going through the difficult laboratory processes of doing preliminary testing.

2.3. Nanotechnologies in the Treatment of COVID-19

Nanotechnology has a wide range of applications in COVID-19 therapy, with the ability to disrupt virus-cell interaction, membrane fusion, cell internalization, transcription, translation, and viral reproduction, as well as activate intracellular mechanisms that cause irreversible virus damage (Mainardes and Diedrich, 2020). Because of their characteristics, nanoparticles (organic and inorganic) have gotten a lot of attention. Luminescence, variable size, shape, composition, huge surface-volume ratio, and the capacity to reveal many interaction sites on the surface are all properties of inorganic NPs (INPs). Mesoporous silica NPs, iron oxide NPs, and metallic NPs are the most frequent forms of inorganic NPs (gold, silver). Organic NPs also have the advantages of site-specific drug targeting, controlled drug release, biodegradability, biocompatibility, and non-toxicity. Polymeric and lipid-based NPs, dendrimers, extracellular vesicles (or exosomes), liposomes, and nanomicelles are among the most commonly employed organic NPs (Kerry *et al*., 2019).

Because of their lipid characteristics, lipid nanoparticles (LNs) are biocompatible and can be used selectively in sectors such as biomedical science. Liposomes in the shape of spherical capsules, which are hydrophilic on the inside and have a phospholipid bilayer on the outside, are the most appropriate for intranasal delivery among the various LNs (Yang, 2021). Antiviral chemical ML336, which is unstable and highly hydrophilic against Venezuelan equine encephalitis virus (VEEV), has been administered into VEEV-infected mice using lipid-coated mesoporous silica nanoparticles, a kind of LNs. It has been demonstrated that suitability, cycle time, and virus titer all improve. Drug candidates in the form of nucleic acids, such as siRNA, have the drawback of being unstable in the systemic circulation. Transporting siRNA with LNs, on the other hand, can target specific organs and has the added benefit of avoiding degradation during systemic circulation (Yang, 2021).

The ability of gold nanoparticles (GNs) to quickly elicit an immunological response from antigen-presenting cells makes them a promising candidate for vaccine development. The advantage of GNs is that they may be easily modified for distribution through the nasal cavity. By spreading to the lymph nodes, it also has the advantage of stimulating the immunological response associated with CD8+ (cytotoxic) T cells (Yang, 2021). NPs are effective against coronavirus in some investigations. Fortunately, airborne nanoparticles are well adapted to penetrate alveolar epithelial type II cells (AECII) in the deep lung due to their tiny size and tunable physicochemical features. The nanomaterial could be a viable option for delivering therapeutic medicines to COVID-19 patients (Weiss *et al*., 2020). The most crucial aspect concerns the discovery of some similar properties in viruses that might be used to repurpose pharmaceuticals, such as the attachment of virus attachment ligand (VAL) to heparan sulphate proteoglycans (HSPG) or sialic acids (SA) on the surface of host cells. The viral attachment will be reduced as ligand sites on cell surfaces are occupied (Weiss *et al*., 2020). However, it is necessary to consider the clearance and dilution of nanomaterials during virus propagation. Carbon dots of various sorts have recently been studied for the treatment of human coronavirus HCoV-229E infection. Ethylenediamine/citric acid and modified boronic acid ligands were used to create these nanoscale materials. In a concentration-dependent manner, carbon nanomaterials block and inactivate the HCoV-229E entrance (Tavakol *et al.*, 2021). Carbon quantum dots have functional groups that interact with HCoV-229E entrance receptors and limit viral multiplication. In the meantime, gold nanorods (AuNRs) have been used to boost MERS-CoV inactivation. Conjugation of AuNRs with an HR1 peptide inhibitor, pregnancy-induced hypertension (PIH), inhibits membrane fusion in MERSCoV infections and effectively stops it. This stable PIH-AuNRs combination was identified as a potential novel antiviral drug. These biocompatible PIH-AuNRs could allow rapid clinical translation for MERS and, eventually, COVID-19 treatment (Tavakol *et al*., 2021). Furthermore, molecular docking research found that Fe_2O_3 NPs had a strong interaction with the SARS-CoV-2 S1-RBD protein, which increases antiviral efficacy by changing the viral protein shape (Tavakol *et al*., 2021). Another option is to use nano-sponges to capture the virus. They created nanosponges from the cell membranes of human macrophages and lung epithelial type II cells, which were then coated with SARS-CoV-2 host receptors. Viruses are captured and neutralized by nanosponges (Tavakol *et al*., 2021).

3.0 Barriers to Overcome

Due to the urgency of combating the global virus pandemic, the effectiveness of a new drug is now being declared every day, which is understandable, but it should be reviewed more carefully. Nanomedicines, on the other hand, are a double-edged sword. On the one hand, there are concerns about their toxicity, but on the other hand, they have the potential to improve drug efficacy or act as a nano drug to inhibit virus attachment, fusion, replication, and infection, as well as restrain the inflammatory and damaging cascade that occurs after virus infection in patients. Mutagenicity, tumorgenicity, production of free radicals, penetration into the brain, and other properties of NPs, particularly metallic NPs, have been reported in various studies. The toxicity and size of dose dependency, the mode of administration, biodistribution, and biodegradability of NPs should all be taken into account (Tavakol *et al*., 2017). Another important consideration is the cell death mechanisms induced by NPs and how they interact with the efficacy of antiviral medicines, such as autophagy and ferroptosis (Tavakol *et al*., 2019). In vitro experiments that were not followed up with definitive research that looked into the biocompatibility of NPs resulted in irreversible harm.

3.1. Future Perspective

In the identification and therapy of viruses, such as COVID-19, medical nanotechnology has ushered in a new and powerful era. However, nanoparticles' safety, dose-response, and size-efficacy are all issues that need to be addressed before they may be used in therapeutic settings. It is important to develop nanoplatforms to identify and treat COVID-19, as well as to minimize the initiation of a tissue damage cascade in human cells. To achieve this goal, a thorough understanding of NPs' deadly death mechanisms in cells and viruses, NPs' occupancy of virus receptor binding sites in human cells, and ways for manipulating virus structures and enzymes by NPs (Virus-NP interaction) are required. Meanwhile, researchers are interested in developing NPs with increased circulation time, drug entrapment efficacy, and biodistribution that limit drug metabolization and release in undesirable tissue and organs. It's worth noting that NPs can be functionalized with specific antibodies and ligands for active targeting to improve the efficacy of antiviral medication delivery. NPs, on the other hand, have passive targeting potential due to their small size. Advanced methods for predicting the involvement of viruses' structures with NPs and Virus-NPs interaction, such as molecular dynamic and molecular docking, stochastic, and microfluidic, would be useful in achieving this goal. Therefore, it appears that NPs themselves and also as a combination therapy system or carriers for the aim of drug repurposing and development will be promising in designing rapid test diagnosis methods and therapeutic agents.

CONCLUSION

The SARS-CoV-2 outbreak has claimed numerous lives and put governments all around the world on high alert since December 2019. The seriousness of the COVID-19 pandemic underscores the significance of new technical proposals for containing and arresting the disease's spread. As of 200, novel therapeutic options against COVID-19 are required due to the lack of licensed antiviral medicines or vaccines, as well as low efficacy and the prevalence of side responses. Antiviral medicines and adjuvant compounds, which have been utilized in other viral disorders and can decrease virus uptake in tissues and block protease activity in infected cells, were formerly used as standard therapy techniques. This method, on the other hand, only reduces virus multiplication and symptoms.

Nanomedicine is a valuable tool in the fight against new coronaviruses, but it still faces substantial obstacles in clinical practice, particularly in terms of in vivo behavior, nanocarrier toxicity, and industrial-scale production. Other significant challenges include a lack of knowledge about the specific characteristics and components of disease physiopathology, the processes involved in the nano-biointerface, and biocompatibility, safety, and regulatory concerns. COVID-19 specific features and nanosystem physicochemical properties can be investigated and used to design personalized nanostructures for specific therapeutic purposes, reduce the current threat to global public health, and develop more sustainable nanotechnology-based approaches. These variables, while not fully understood, are critical for the safe and effective application of nanotechnologies to combat SARS-CoV-2 infection. This review looked at how nanotechnology could be used to prevent viral spread, improve the efficiency of protective equipment, increase personal and social safety, and improve the accuracy of COVID-19 diagnosis by detecting infectious pathogens in a small volume of biological fluids quickly and precisely. Furthermore, because nanocarriers may be tailored to deliver antiviral compounds directly to sick cells while also activating a host immune response against the virus, nanosystems augment conventional medicines and help overcome their therapeutic barriers. As a result, nanomedicine offers considerable potential for COVID-19 prevention, diagnosis, and treatment, but it must be further investigated and comprehended. In many aspects, the lack of antiviral medicines for COVID-19 presents an opportunity to increase the use of nanotechnological methods in virology.

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