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ARTICLE

Nanomedicine for SARS-CoV-2: Therapeutic and Prophylactic Approach in Immunocompromised Individuals

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ABSTRACT

SARS-CoV-2 is a novel coronavirus that first appeared in Wuhan, China in December 2019 and then spread all over the world, causing a global respiratory epidemic COVID-19 illness. Certain health conditions can increase your exposure to COVID-19, such as chronic obstructive lung disease, high blood pressure, cardiovascular disease, and diabetes. The immune system of the host is severely compromised in the event of a respiratory viral infection. Immunocompromised patients have a more difficult time avoiding respiratory viral infections, making them more vulnerable to COVID-19 pneumonia and increasing the death rate to 19%. The ability of SARS-CoV-2 to damage the host cell by modifying its own DNA or RNA and proliferating inside the host cell, with antiviral treatments and prophylactic vaccinations being tested. In recent years, numerous innovative technologies have been examined to diagnose, prevent and treat viral infections. Nano technology opens the way to distinguish the living cell mechanisms and develop new technologies that make it possible to diagnose and cure various viral infections in the early stage. The therapeutic and preventative approaches of nanomedicine are essential factors for curing SARS-CoV-2. The delivery of antiviral drugs based on nanocarrier, changes in pharmacokinetic/pharmacodynamic properties, leading in dose reduction, reductions in toxicity, increased bioavailability, and the prevention of the virus. The overall efficiency and safety of vaccinated adjuvant vaccine nanoparticles (VANs) helps enhance the immune response of older, immunocompromised persons with the greatest death rate of SARS-CoV-2. The review focuses on recent advancements in nanomedicine treatments and prevention strategies for SARS-CoV-2.

1. Introduction

The world has advanced in many areas, but there are still viral diseases that contribute to human death and their social and economic manifestations. Corona virus, nipa virus, Ebola virus, Zika virus, Dengue virus, Chikungunya virus, and various influenza virus strains - H5N1 (Avian influenza), H1N1 and H3N2 (Swine flu) causes numerous viral infections [1]. Environmental hazards, as well as water supply, sanitation facilities, climate, lifestyle smoking, alcoholism, a specific geological area, and various medical procedures such as body fluid transfusion, surgery, and vector broadcast, have all been identified as risk factors for viral infection [2]. While some of these factors can be predicted and precautions taken to avoid them, others can be targeted for a positive response [3].

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A severe pandemic caused by the new corona virus (nCoV) recently killed nearly 2.1 thousand people [4]. It originally surfaced in China, then spread rapidly to other countries around the globe as a new Coronavirus-2019 (COVID-19) [5]. The virus's emergence and rapid spread of infection has resulted in a worldwide respiratory epidemic disease Covid-19 [6]. The major symptoms are fever, muscle suffering, weariness, headache, and bleeding [7]. While 5% of infected persons are in critical condition and 14% are in severe condition, most infected people have relatively minor symptoms like mild pneumonia [8]. The elderly and those with comorbidities such as anorexia, pharyngeal soreness, diabetes, and hypertension are the most likely to require the intensive care unit (ICU) [9]. COVID-19 susceptibility can be increased by certain health problems such as pulmonary obstruction, hypertension, cardiovascular and diabetes health difficulties [10].

Immunocompromised patients have a more difficult time avoiding respiratory viruses, rendering them more receptive to nCoV. In immunocompromised patients, 19% of deaths were caused by viral lung infection [8]. Pneumonia caused by the Coronavirus was responsible for 24% of deaths, with the viruses spread more commonly in cancer patients than in non-cancer individuals (3%) [11]. Conventional corona viruses have been linked to a high degree of oxygen use and mortality in individuals with malignant hematomas [12]. COVID-19 hospitalized patients have severed lymphopenia with time [9], which, in turn, causes pneumonia in patients with malignant hematomas who also have respiratory virus infections [13]. Up until now, Coronavirus infection had no vaccinations or antivirals [5]. In the case of viral infection, the host's immune system is greatly compromised, and relapses are common. The ability of a virus to destroy a host cell by editing its own DNA or RNA and multiply within the host cell presents difficulties in developing antiviral therapies [14]. Because of prior exposure, viral antibodies may be triggered in the host, making symptomatic infection harder to detect [15].

2. SARS-CoV-2

The new coronavirus has been named severe acute respiratory syndrome-2 (SARS-CoV-2) by the International Committee on Virus Taxonomy [16]. On February 11, 2020, the World Health Organization designated the nCoV as COVID-19, and the outbreak quickly grew in scale [15]. "COVID- 19" was the name of the new virus. The ICRC Virus Classification (ICTV) has updated this to "SARS-CoV-2," indicating an 80 percent similarity to the sequence of SARS-like coronaviruses (SARS-CoV) and a 50 percent similarity to the sequence of Coronavirus-like virus (MERS-CoV) [17]. Corona viruses have caused three epidemic diseases in the last two decades: COVID-19, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS) [18]. Coronaviruses (CoVs) are enveloped viruses from the family Coronaviridae (Coronavirinae subfamily), with a single-tagged RNA genome (26-32 kb) and positive viruses that infect the host widely, multiply in the affected cytoplasm, and cause diseases ranging from the common cold to death [19]. COVID-19 cases have been discovered in several nations throughout the world, and the World Health Organization (WHO) has declared COVID-19 a Public Health Emergency of International Concern (PHEIC) [20]. A large range of possible vaccine candidates, including live-attenuated, inactivated, viral-vectored based, sub-unit vaccines, DNA, mRNA, peptide, adjuvant, plant, and nanoparticle-based vaccines, are undergoing several clinical trials to treat COVID-19 disease [21]. Antiviral drug development requires an understanding of the pathogenesis of molecular immune dysfunction and the identification of COVID-19 [16].

3. Genome and Proteins of SARS-CoV-2

Human coronaviruses (HCoVs) have a positive RNA genome that is single-stranded encased within them (26-32 kb) [22]. SARS-CoV-2 has a genome like that of other CoVs, with up to ten open frames for reading (ORFs). Almost two-thirds of the viral RNA are translated into two large proteins by the first ORFs (ORF1a/b). In SARS-CoV-2 and MERS-CoV, two multiple proteins, pp1a and pp1ab, were converted into 16 non-structural proteins (nsp1-nsp16)., which make up the viral replication complex [23].

Viral replication and transcription are carried out in double-membrane vesicles from the rough endoplasmic reticulum (RER) [24]. Other SARS-CoV-2 ORFs found inside the genome's four primary structural proteins are spike (S), envelope (E), nucleocapsid (N), and membrane (M), as well as several unknown functionally complementary auxiliary proteins that aren't involved in viral replication [16]. To enter cells, SARS-CoV-2 requires angiotensin converting enzyme 2 (ACE2) as a receptor [25]. Because it crossed species to infect humans, the SARS virus ACE2 most likely evolved in bats [26] and adapted to species other than bats [27].

4. Mechanisms SARS-CoV-2 Pathogenesis

COVID-19 patients demonstrate clinical symptoms, such as fever, non-productive cough, respiratory shortness, muscle discomfort, exhaustion, normal or low white cell numbers, and radiological pneumonia [28], that are like symptoms of SARS and MERS infection [29]. Different

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stages of pathogenesis are followed: (1) viral attachment at the entry point, (2) host cell infiltration, (3) the removal of the virus cover, (4) transcriptive replication and translation leading to virus-specific protein synthesis, (5) nude capsid accumulation through nucleocapsid, and (6) viral release that causes infection spread [30]. Many factors affect pathogenic pathways such as tissue access to causative viruses, vulnerability of virus cells, and virus host protection. The affinity of the virus to specific tissues is determined by multiple elements, amongst them, the existence of cell transcriptions for virus-specific receiver, the cell's cell transcription factors, the local pH, temperature, and the presence of viral enzymes, which can hinder activity [31]. The host's defenses may interact with the virus by inhibiting its growth or by stimulating the immune response in infected tissues [32].

5. Viral Entry and Replication

The essential component of SARS-CoV-2 input into host cells has been identified as the spike protein (protein S) [18]. SARS-CoV-2 entrance into cells was originally considered to occur by means of direct membrane fusion between the S protein virus and the receptor Angiotensin-Converting Enzyme 2 (ACE2) [33]. SARS-CoV-2 is similarly mediated through membrane fusion, clathrin-dependent and clathrin-dependent endocytoses [34]. After entering the virus, the virus RNA genome is released into the cytoplasm and converted to two numerous proteins and structural proteins, which lead to the virus multiplication of the genome [35]. The newly created glycoprotein envelopes are introduced into the reticulum membrane or Golgi and a mixture of genomic RNA and nucleoside proteins is formed from the nuclear plug. In the endoplasmic reticulum - Golgi medium chamber, the viral particles germinate. Finally, the plasma membrane fuses with the virus-containing vesicles, which releases it [18].

6. Immune Response to the SARS-CoV-2

After the virus enters the cells, its antigenic peptides are presented by antigen-presenting cells (APC), major histocompatibility complex (MHC), or human leukocyte antigen (HLA), and are then recognized by the virus's cytotoxic T lymphocytes (CTLs). SARS-CoV-2 antigen presentation depends mostly on the MHC I molecules, but MHC II plays a role as well [36]. Previous research has linked several types of HLA to SARS-CoV-2 exposure, including HLA-B 4601, HLA-B 0703, HLA-DR B1 1202, and HLA-Cw 0801 [37], while alleles for HLA-DR0301, HLA-Cw1502, and HLA-A 0201 are linked to protection against SARS infection [9]. MHC II molecules, such as HLA-DRB1 11:01 and HLA-DQB1 02: 0 in MERS-CoV infection, are associated with MERS-CoV infection [38]. In addition, several genotypes of antigen presentation are related to a higher risk of SARS infection [39].

The antibody form against SARS-CoV-2 is immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, as with common acute viral infections. The IgM antibody for SARS disappears by the end of week 12, however the IgG antibody can last for months, indicating that the IgG antibody may be the primary protective factor [40]. SARS IgG antibodies are made up predominantly with S and N specific antibodies [18]. The number of $CD4^+$ and $CD8^+$ T cells in the peripheral blood of patients infected with SARS-CoV-2 was significantly reduced, indicating hyperactivation, as indicated by high levels of HLA-DR (CD4 3.47%). And double positive fractions of CD38 (CD8 39.4 %) [43]. CD4+ and CD8+ memory cells can survive for four years in a subset of SARS-CoV-2 patients if no antigen is present and perform T cell proliferation and interferon (IFN) production if no antigen is present [11].

During SARS virus infection, a cytokine storm is induced by uncontrolled systemic synthesis of pro-inflammatory cytokines, and other chemokines and cytokines are produced by immune cells. Individuals with SARS-CoV-2 and MERS-CoV had higher levels of IL-6, IFN-, CCL5, CXCL8, and CXCL-10 in their serum than those with mild to moderate disease [41]. In severe cases of emerging coronavirus infection, a cytokine storm will cause a violent immune system attack, acute respiratory distress syndrome, and organ failure, ultimately leading to death [40].

7. SARS-CoV-2 Therapeutics Approach

Many viral infections remain dormant for long periods of time, posing diagnostic and treatment challenges [42]. Antiviral selectivity toward the virus on the host cell and the identification of a unique target for the virus's life cycle are two other challenges in the virus's evolution [43]. It's difficult to develop a broad-spectrum antiviral agent because each virus has its own structure and function [44]. Many antivirals have a short half-life, resulting in increased treatment frequency and poor patient compliance [45]. Reduced bioavailability due to restricted solubility or permeability could result in greater doses and consequently in hazardous effects [46]. The development of medication resistance is probably owing to extended drug exposure, especially to immunocompromised patients [47].

8. Nanomedicine Approach for SARS-CoV-2 Therapeutics

The cellular mechanics of living cells are being devel-

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oped by nanotechnology and similar technologies which help to diagnose and treat diverse viral diseases in the early stages [50]. Nanotechnology Some of its uses include medicinal products and genes. Use of biological fluorescent labels and protein, pathogens, and tumor screening; biological molecules and cells separation and purification; fabric engineering; increased RMI contrast and Pharmacokinetic study [49]. It has since opened the door to a wide range of research and application with the ability to effectively treat viral disorders while also dealing with traditional anti-viral medications [50].

The nanomedicine method is an effective tool for improving COVID-19 treatment and renovating antiviral medicines [51]. Current antiviral therapies' limitations, such as impaired aqueous solubility and reduced bioavailability of antiviral drug sub-concentrations at reserve sites, can be overcome by nano transmitter-based antiviral drug delivery, resulting in dose reduction and reduced toxicity [52]. Specific organ, cell, and intra-cellular vectors engaged in pathophysiology of SARS-CoV-2 may also be targeted by targeting nanoscale vectors and reaching therapeutic concentrations in protective virus reservoirs, likely ACE2-expressing cells, and cathepsin-binding sites [53]. The supply of nanometer-based pharmaceuticals (including primary biological medications) ensures better biological half-life by preventing early dropping and degradation and avoiding renal or hepatic clearance [54].

Several nanoparticle strategies for co-encapsulating hydrophobic and hydrophobic drugs [55] have been described. To overcome lymph node drug deficiency in the oral synthesis of these drugs, lipid nanoparticles (LNPs) loaded with three antiretroviral drugs (ARVs) (two hydrophobic: lopinavir and ritonavir and one hydrophilic: tenofovir) were formulated, which demonstrated a long-term effect of plasma drug profiles and levels. In an in vivo model, a lymph node drug performs better in macaques [56]. This multifunctional nano therapy can be used to target SARS-CoV-2 in the central nervous system [57].

9. Nanomedicine Approach for SARS-CoV-2 Prophylactic

Most preventive techniques are designed to cause a strong neutralizing impact of the surface-exposed S protein, which produces specific T-cell response and neutralizes antibodies [58]. The fundamental achievement for protection against viral infection is the neutralization of antiviral antibodies. In US vaccine trials the nanoparticles of lipid-coated mRNA that cover the encoding of spike protein and recombinant adenovirus are used. Most coronavirus neutral antibodies are directed at RBD [59]. As a result, preventing viral attachment to ACE2 is the key immunological mechanism for avoiding infection, and most vaccine candidates adopt the technique of developing vaccine-inducing antibodies against RBD [60]. Nanoparticle delivery techniques can deliver antigens and adjuvants in the same particle carrier [61]. Reduced particle size, high loading efficiency, surface charge, increased bio-penetration across the mucosal barrier, and appropriate protection from intestinal fluids are all features of nanoparticles that promote their immunity [62].

Adjuvants that promote safety convey a counter-regulatory signal to the immune system, telling it to develop tolerance to incoming antigens. Vaccine auxiliary nanoparticles (VANs) are required to reduce the required antigen dose (dose sparing), allowing more units to be produced, made available to a larger population, and they improve the overall efficacy and safety of the generated immune response, particularly in the case of the COVID-19 pandemic [60]. Antigen and cyclic dinucleotide (adjuvant; agonist of interferon gene stimulator that produces type I interferon when cells are infected with intracellular viruses to protect the infected cells and nearby cells from local infection) co-loaded liposomal nanoparticles showed a dose-sparing effect, resulting in safe and uncompromised immune responses [63]. VANs designed to improve potency (by acting as immune booster signals, also known as "risk signals") work by informing certain immune cells to mount a protective immune response against a specific antigen [64]. VANs can operate as molecular adjuvant nanocarriers or have a physio-chemical property that stimulates or inhibits the immunological or anti-immunomodulatory pathway [65].

VANs have been used to improve vaccine efficacy and antibody responses in the elderly, who have the highest SARS-CoV-2 fatality rate [8]. Aging is linked to chronic subclinical systemic inflammation (inflammatory ageing) and acquired immune system impairment, also known as immune ageing [66]. Immune ageing is characterized by a significant decrease in immunoglobulin M, interferon levels, T cell number, rate of cell division and proliferation, neutrophil chemical concentration, and phagocytosis [67]. Many adjuvant technologies have been developed to improve influenza vaccination in the elderly, including cationic and anionic liposomes, viruses, and fine particles [68]. Adjuvant drugs have been shown in clinical trials to reduce the risk of developing pneumonia and influenza, and they play an important role in stimulating the immune system [69].

10. Conclusions

A Novel nanotechnology is one of the most imperative fields of science, that proposition incomes from the use

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of nano systems, like metallic nanoparticles, polymeric, liposomes, micelles, and lipid nanoparticles for drug encapsulation, improvement of its pharmacological properties, and drug delivery for effective target drug release. Nanomedicine and its components exert an imperative role in different stages of diagnosis, prevention, treatment, vaccination, and scientific research related to SARS-CoV-2 disease. Nanoparticles possess antiviral effects, as it can target the binding, entry, replication, and budding of SARS-CoV-2. As a result, nanomedicine-based therapeutic and preventive strategies are key assets for the curative management of SARS-CoV-2 disease, particularly in elderly immunocompromised patients, who have the highest SARS-CoV-2 fatality rate.

Consent for Publication

Not applicable.

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Abbreviations

ACE2	Angiotensin converting enzyme 2
ARDS	Acute respiratory disease syndrome
ARVS	Anti-retroviral drugs
APC	Antigen-presenting cell
COVID-19	Coronavirus-2019
CTLs	cytotoxic T lymphocytes
E	Envelop protein
HCoVs	Human coronaviruses
HLA	Human leukocyte antigen
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LNPs	Liposomal nanoparticles
MHC	Major histocompatibility complex
nCoV	Novel corona virus
N	Nucleocapsid
PHEIC	Public health emergency international concern
RBD	Receptor binding domain
S	Spike protein
SARS-CoV	SARS- Like corona virus
VANs	Vaccine adjuvant nanoparticles
VLP	Virus like particles
WHO	World health organization

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