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ROLE OF NANOMEDICINE TO COMBAT COVID-19- A REVIEW

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ABSTRACT: COVID-19 has been proved to create a pandemic over the world within a few years. All scientists and health workers are trying to develop an effective treatment with collaboration. Various strategies such as antiviral, antibacterial, and antimalarial drugs have been employed to treat COVID- 19, but they were found to relieve the symptoms only. The formation of various variants of the virus in various global parts made the treatment of COVID-19 more difficult. Developing an effective vaccine is the main goal of clinicians and scientists, which is under clinical trials, and some vaccines which have been approved for the treatment such as COVAXIN, COVISHIELD, ASTRA Zenaca, and SPUTNIK V vaccines are being used to develop antibodies against COVID-19, but due to spread of variants of virus these vaccines are not supposed to be 100 percent protective against the virus. With the help of nanotechnology, the treatment of SARS-CoV-2 can be made efficient due to its direct target on viral cells and modifying its genetic material functionings. In this review, we summarized the role of nanomedicine in the treatment of SARS-CoV-2.

INTRODUCTION: During the last century, various subtypes of the influenza virus caused five pandemic respiratory diseases, and pigs were found to be a major reservoir of such viruses. About 50 million population were killed over the world by 1918 H1N1 (Spanish flu), around 4 million people were killed worldwide by Asian flu (1957 H2n2) initiated in China, 2005 H5N1 (Bird flu) caused deaths of 1 million population over the world, as well as birds and 2009H1N1 (Swine flu), caused the death of 18000 people. From the family of the coronavirus, the pandemics severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) was originated in 2001 and 2012 respectively [1].

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Recently in December 2019, a new outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China. Due to its rapid rise of confirmed cases, it was announced as a pandemic by the world health organization and was named 'COVID 19' [2]. In 2020 various countries faced the 2nd and wave of the coronavirus. India is currently facing this deadly wave nowadays, which is affecting young people more. Experts assumed the peak of the 2nd wave will be approximately the 30th of May 2021 in India, and a third wave can be originated in India nearly in October 2021, which can be more fatal to children. According to WHO, it should be located in the early stages so that its spread can be controlled out.

Coronaviruses are a large group of viruses that belongs to the family Coronaviridae that caused disorders, for example, sickness of respiration or gastrointestinal tract illnesses. With respiratory disorders, coronavirus can cause more serious

infections such as the Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV) [2, 3]. These viruses can affect humans as well as some animals. The crown-like spikes on their surface make their structure unique [4]. The RNA genome of SARS-CoV-2 consists of four proteins and 30000 nucleotides. According to studies, there are three types of structural proteins present on the surface, involving small envelope protein (E), spike surface glycoprotein (S), and matrix protein (M). The S protein is responsible for interacting with the cellular membrane (80%) **Fig. 1** [5].

Alpha, beta, gamma, and delta are the four subgroups of coronavirus, which are the largest known spherical RNA viruses. These viruses are enveloped with a positive sense single-strand RNA genome [1, 6, 7]. They have low stability but high mutation potential [4, 7, 8]. These are very smart viruses as they exhibit reactions and symptoms differently in the host system. They can optimize these reactions and symptoms with the increase in genetic material proliferation for its survival [7, 9, 10]. These viruses are assumed to be zoonotic, which implies that the viruses can spread among creatures and humans [11].

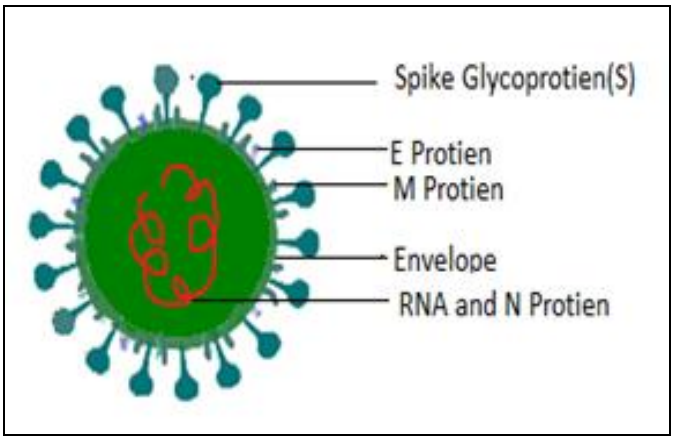

FIG. 1: STRUCTURE OF CORONAVIRUS

Challenges of COVID 19 Therapy: So far, no treatment for COVID-19 has been considered effective and several strategies are being tested [12].

All viruses – including SARS-CoV-2, the virus that causes COVID-19 – evolve. The Virus sometimes changes itself due to its replications which are termed as "mutation". If a virus shows one or more mutations it is said to be a "variant" of the original virus.

If a virus is widely spread in any population, causing various infections, the likelihood of the virus mutating increases. The virus has more opportunities to spread as the more it replicates – and the more it changes. Most viral mutations have little to no impact on the virus's ability to cause infections and disease. Depending on where the changes are located in the genetics of viral material, they may affect the properties of the virus, such as transmission or severity (for example, it may cause more or less severe disease).

The vaccines developed for COVID-19, which have been approved, are expected to provide some protection against any viral variant, as these vaccines elicit a broad immune response involving a range of antibodies and cells. Therefore, changes or mutations in the virus should not make vaccines completely ineffective. If any of these vaccines prove to be less effective against one or more variants, it will be possible to change the composition of the vaccines to protect against these variants [13].

To date, the adopted treatment is the application of broad-spectrum antiviral drugs. Among the tested antiviral drugs used is interferon, which is effective against COVID-19 [14, 15] and has been recommended by The National Health Commission of the People's Republic of China in addition to lopinavir and ritonavir protease inhibitors [16]. Ribavirin, a nucleoside analog, was used to treat SARS-CoV in Hong Kong, representing another option [17] combined with protease inhibitors [18]. The National Medical Products Administration of China approved favilavir for marketing at the beginning of the COVID-19 outbreak [19]. Another drug under test is Arbidol, which reduces the reproduction of SARS *in-vitro* [20].

Remdesivir, a nucleotide analog developed for the Ebola virus, was reported as a potential treatment for COVID-19 since it demonstrated the blocking of SARS-CoV-2 replication when combined with interferon or chloroquine, as well as alone [21]. Other antiviral drugs under test are nafamostat, nitazoxanide, penciclovir, oseltamivir, and baricitinib [22, 23]. The number of registered clinical trials using antiviral drugs for the treatment of patients with COVID-19 is 195, up to 3 June 2020.

The antimalarial drugs chloroquine and hydroxy-chloroquine were considered by recent publications worldwide [24] and are included in the recommendations for the prevention and treatment of COVID-19 pneumonia in several countries. These drugs alter the endosomal and lysosomal pH, preventing viral fusion and inhibit the endocytosis mediated cell uptake of SARS-CoV-2 [25].

However, the lack of results from well-performed randomized trials makes it difficult to support the use of these drugs, especially considering their well-known cardiac toxicity.

Besides antiviral drugs, other approaches have been investigated to treat COVID-19. Antiviral antibodies produced in recovered patients, for example, were isolated from their blood plasma, exhibiting positive results [26]. Besides, umbilical cord blood, rich in natural killer cells and mesenchymal stem cells, represent the body's defense activity against SARS [26]. Regarding antibiotic therapy, a broad spectrum of antibiotics is indicated, only in case, the patients develop bacterial or fungal infections during advanced stages of COVID-19 [27]. In the same way, the administration of corticosteroids must be avoided, except in cases of urgency due to adverse effects [28]. Hence, a review study revealed that more than 85.5% of patients were treated with antiviral agents, while empirical antibiotics were prescribed in 90.0% of cases [29]. To test different mechanisms to combat SARS-CoV-2, the WHO has announced a clinical trial design to be joined by doctors from around the world [30].

Replication in Corona Virus: Coronavirus rapidly forms new copies of a virus with the help of structural proteins. The viral envelope is structured by M and E proteins, while the helical ribo-nucleocapsid complex, along with positive-stranded genomic RNA, is framed by N proteins [31]. The attachment and host cell entry of SARs-CoV-2 is facilitated by S proteins. When there is a viral infection, the S proteins are cleaved to S1 and S2 subunits. During the transition to post-fusion confirmation, the S1 subunit is released along with the receptor-binding domain (RBD), whereas the fusion machinery is contained in the S2 subunit. The SARS-CoV-2 entry to humans is facilitated by the enzyme Angiotensin I converting enzyme which is released by type two alveolar epithelial cells **Fig. 2** [32, 33, 34].

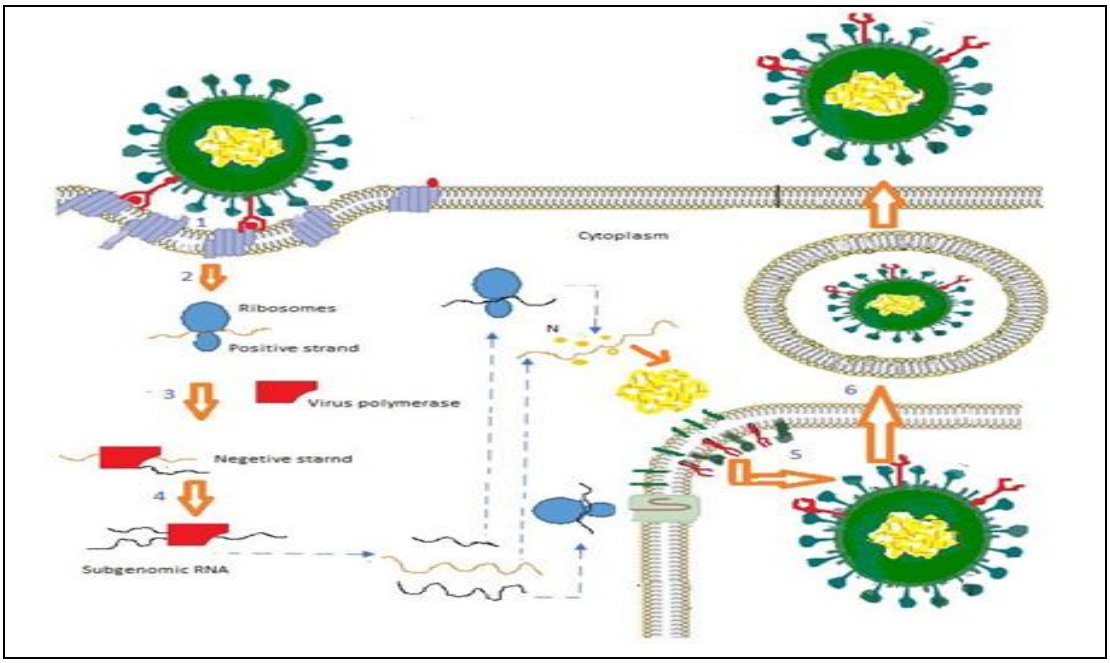

FIG. 2: REPLICATION PROCESS IN CORONA VIRUS

1. Binding of coronaviruses with cell surface molecules by S proteins. 2. Endocytosis. 3. Synthesis of RNA polymerase that only recognizes and produces viral RNAs (RNA polymerase synthesize the negative strand by using the positive strand as a template). 4. Replication of new positive-stranded RNA genome by the negative strand which serves as the template. 5. Binding of protein N to genomic RNA and integration of M protein into the membrane of endoplasmic reticulum (ER) with the engagement of assembled nucleocapsids with helically twisted RNA Budd in the ER membrane. 6.Viral progeny transported by Golgi vesicles to the cell membrane and exocytosis takes place.

SARS-CoV-2 binds to ACE2 present on the surface of host cells through the S1 subunit and then with the help of the S2 subunit it fuses with the host membrane 35. Various studies show that SARS-CoV-2 binds to ACE2 with an affinity more than SARS-CoV-2 [36-37]. For the entrance of SARS-Cov-2 to the host cell, the cellular proteases cleave the S proteins at 2 sites. This process is known as S protein promising, which confuses cellular and viral membranes. TMPRSS2 (transmembrane protease serine 2, which is a serine protease, causes the entrance of SARS-CoV-2 in human lung cells with the help of S protein promising. The camostat-mesylate a TMPRSS2 inhibitor, is found to be able to block the entry of SARS-CoV-2 to the cells [38]. The 2 typical furin cleavage sites may cause the invasion of virus and replication [39]. The cleavage of S proteins may be caused after leaving the epithelial cells as furin is abundantly found in the respiratory tract. It can cause the infection to spread through other cells. TMPRSS2 and furine interactions determine the degree of protein priming [40].

The Role of Nanomedicine to Combat COVID-19: Nanomedicine is ruling all fields of medical sciences, and it has been considered an important technology for novel diagnostics, medical imaging, nanotherapeutics, vaccines, and to develop of bio-materials for regenerative medicine [41]. Nanomaterials that are obtained from polymers (polymeric nano-particles), lipids (lipid-solid nanoparticles, nano-structured lipid carriers, liposomes), surfactants (microemulsion, nanoemulsions, liquid crystals), and proteins (protein nanoparticles) are applicable in nanomedicine, especially to deliver the drugs. Their various medical applications are based on the degree of interaction between nanomedicines and tissues/biological molecules [41, 42]. Drug-based nanoparticles have been developed for decades, and several are under clinical trials for cancer, neurodegenerative, inflammatory, cardiovascular, and infectious diseases, although only a few of them are approved for human use [43]. The improvement of biopharmaceutical, pharmaco-kinetic, and pharmacodynamic aspects of drug loading are the main tool of soft nanomaterials. Also, nanoparticles can promote specific drug targeting (passive or active targeting) and controlled drug-release rate, thereby affecting the efficacy and safety of the treatment. Besides, soft and metal nanoparticles have been applied in nanomedicine, mainly due to their various antimicrobial activities (antibacterial, antifungal, antiparasitic, and antiviral) [45, 46].

Due to the emergence of pathogenic bacteria resistant to antimicrobials, several studies have reported the efficacy of nanotechnology-based antimicrobial therapy. Innovative therapies are required due to emerging new pathogens and their heterogenicity. Nanotechnology is known for its specific targeting, which can be applied for the therapeutics of viral diseases [47]. The involvement of nanotechnology to combat SARS-CoV-2 is based on the mechanism that the nanoparticles can affect the entry of the virus to the host cells until their inactivation. Specifically targeting the viral surface protein and blocking it can lead to the inactivation of a virus as well as its internalization [48, 49]. The commonly used antiviral therapies show non-specific targeting, which can cause the host cell cytotoxicity. With the help of nanotechnology, the drug can be delivered to the targeted site of action. For COVID-19 antimicrobial drugs have been clinically tested, such as chloroquine, lopinavir, ritonavir, ribavirin, and remdesivir, and have demonstrated promising results against SARS-CoV-2 [50].

Metal nanoparticles have shown the ability to block viral attachment to the cell surface, leading to the inhibition of viral internalization and thereby impairing viral replication during viral entry [51]. Nanoparticles composed of titanium (Ti), silver (Ag), gold (Au), and zinc (Zn) have already shown results against HIV, influenza virus, herpes simplex virus, respiratory syncytial virus, transmissible gastroenteritis virus, monkeypox virus, and zika virus [52]. The mechanism of action is based on the nanoparticles binding onto the viral envelope or its protein, impairing the interaction with the host cell. The efficacy of the treatment is related to the size, shape, and surface charge of the nanoparticles; however, safety measures must be taken regarding the concentration to avoid cytotoxicity of host cells [53]. Organic nanoparticles have been applied for the delivery of antiviral drugs such as acyclovir, zidovudine, dapivirine, *etc*., to improve the drug bioavailability and for specific targeted delivery [53, 54]. Nanoencapsulation of antimicrobial drugs may contribute to the development of timid treatments

for COVID-19 and other viral diseases. Although it is well-established that nanotech-based drug-delivery systems improve existing therapeutics in medicine, its application in viral diseases is underexplored and underused, as observed in the SARS-CoV-2 pandemic. Nanostructured systems can impact diagnosis since they can improve the detection, sensitivity and increase the signal amplification specificity in polymerase chain reaction analysis; and prophylaxis as adjuvants for vaccines, as well as therapeutics for COVID-19 through the targeting of antiviral drugs [54, 55].

In summary, nanoparticles may play a key role at different stages of COVID-19 infections, as during the initial attachment of the virus, their fusion to the membrane and fusion of infected cells can be inhibited by nanoparticles. Furthermore, nano encapsulated medicines can be more effective for the activation of intracellular mechanisms that cause damage to viruses irreversibly and inhibit viral transcription, translation as well as replication.

CONCLUSION: To date, we lack in treating SARS-CoV-2, and the vaccines are going through clinical trials. To combat the Covid-19, all efforts are welcome, and nanotechnology-based treatments could bring a new viewpoint to conventional drug delivery systems to inhibit viral internalization and its treatment. For the understanding of nanoparticles and SARS-CoV-2 interactions, more studies are required so that a coherent fabrication of targeted therapeutics can meet. Nanotechnology could represent a convenient strategy along with other approaches to achieve the treatment of COVID-19 as it is considered a pandemic that involves whole health organizations and as the pathogenesis of SARS-CoV-2 is not well understood.

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