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INSIGHT FROM NANOMATERIALS AND NANOTECHNOLOGY TOWARDS COVID-19

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Abstract
There have been concerns expressed about SARS-CoV-2's enhanced capacity to elude the six COVID-19 vaccine candidates that are now under approval, as well as antibodies' decreasing ability to neutralize it. SARS-CoV-2 variants include B.1.1.529 for Omicron, B.1.617.2 for Delta, and B.1.1.7 for UK, B.1.351 for South Africa, P.1 for Brazil, and B.1.6.17 for India. According to this perspective, in order to assess the existing obstacles and pave the way for a more stable and feasible future for the development of vaccines against SARS-CoV-2 and other pandemics, countries should conduct early effectiveness studies prior to initiating broad vaccination campaigns. The role of nanoparticles as vaccine carriers is also covered. In light of the ongoing cases of severe and critical COVID-19, we also go over the recently developed prophylactics and treatments.

Keywords: COVID-19, alterations in strains, upcoming advancements, nanoparticles, nanotechnology, vaccinations.

Introduction

Covid virus/Overview

Chinese authorities declared on December 31, 2019, that a novel corona virus strain that causes severe illness has been found. We had no idea that the covid-19 Middle East respiratory illness (MERS) and severe acute respiratory syndrome (SARS) were members of the same family. The COVID-19 pandemic was declared to be under way by the World Health Organization (WHO) on March 11, 2020. Today, the illness affects every country on the planet, with instances increasing in the majority of them by the second wave. This disease infected over 151,404,330 persons, with 3,183,177 of those cases ending in death. In the early months of 2021, India emerged as one of the most afflicted countries globally, second only to the United States of America (1) (2).

Single-stranded positive RNA is a feature of the beta-coronavirus group, which includes the coronavirus that causes COVID-19 disease (3). This virus is in the Nidovirales order of the family Coronavirides (4). SARS, MERS, fever, and the common cold are only a few of the symptoms that belong to the huge family Coronaviridae. The two subfamilies of the Coronaviridae are Coronavirinae and Torovirinae, for example. Coronavirides (5) cause diseases in birds and mammals. Only betacoronaviruses can cause respiratory illnesses in

humans, however both betacoronaviruses and alphacoronaviruses can infect mammals. Avian and certain animal diseases are caused by other coronavirus types, namely Gammacoronavirus and Deltacoronavirus (6). In comparison to other diseases, the sickness is spreading relatively quickly. When the viral genome is transmitted, the structural projections known as spikes that are formed from the virus's cell surface are crucial (Figure. 1). by effective viral genome transfer into the host cell with the aid of the spike virus, which adheres to the surface of the host cell. All that makes up a spike is a protein that gives an object a crown-like shape. Angiotensin-converting enzyme 2 gene (ACE2) receptor protein is where spike protein binds (7).

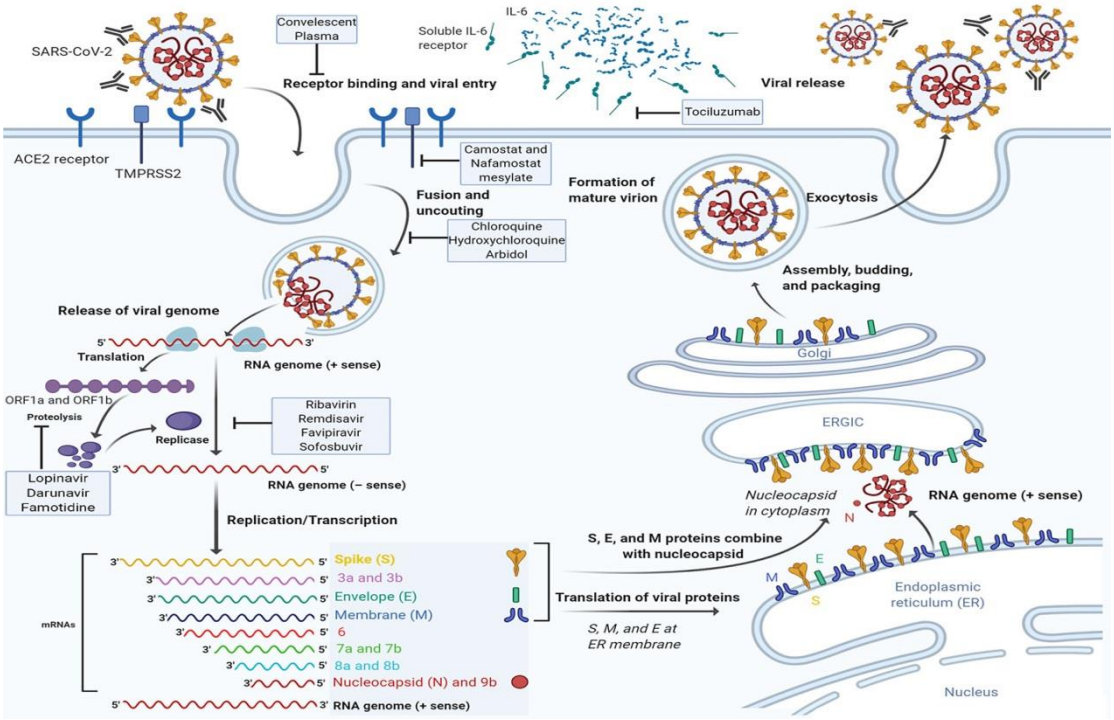

Figure (1): Modified and reposted from Cascella et al., 2020 under the terms of the Creative Commons Attribution 4.0 International License. Possible impact of chloroquine on SARS-CoV-2 representation of the stages of viral infection and anti-body mode of action.

The disease is spread through droplets when someone sneezes or coughs, and the world is currently battling the corona virus epidemic (8). Even with the availability of COVID-19 vaccinations for the general public, social distancing, self-isolation, mask use, and hand sanitizer use are still recommended in order to restrict the spread of the virus (9). Various scientific fields are attempting to create their own methods of combating and healing this fatal illness despite the worst circumstances (10). One further strategy to combat COVID-19 in this area is to employ nanoparticles and nanotechnology. In order to efficiently destroy the virus, antiviral drugs are now being developed, hand sanitizers, disinfectants, masks to lower the viral load, and personal protective equipment are all using nanoparticles.

The human host undergoes fast cell division and reprogramming as soon as SAR-CoV-2 penetrates through the nasal epithelial cells (11). Targeting the ciliated and goblet cells in this host, SARS-CoV-2 would multiply and shed its virus, building up a significant amount of the virus in the upper respiratory tract. Replicating viruses infect the lungs of severe-to-critical COVID-19 patients as the disease worsens, as shown in Figure 2. Neutrophils then attack these viruses, resulting in the death of the afflicted lung cells. Subsequently, the patient will cough up mucus-filled dead virus-infected lung cells, neutrophils, and a high-protein fluid (12).

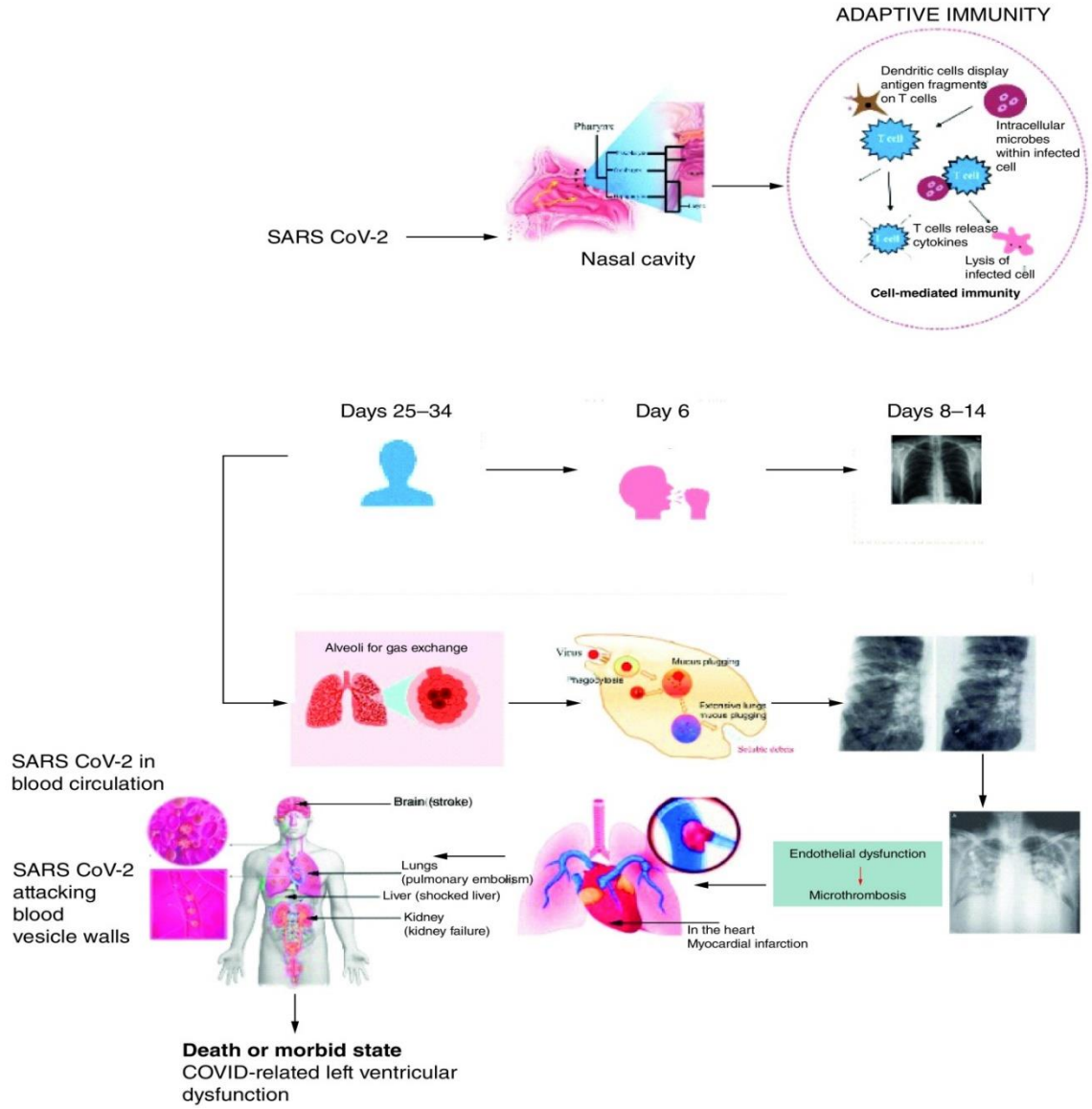

Figure 2:SARS-CoV-2 disease progression.

Additionally, due to direct immune cell-induced destruction to the lung parenchyma linings, dyspnea and bilateral widespread pneumonia of both lungs occur alongside these symptoms. These damages are based on the concept that replicating SARS-CoV-2 causes cell

hyperinflammation, which in turn causes an overreaction of cytokines. A severe-to-critical COVID-19 infection is indicated by this process, which is known as the "cytokine storm" (13).

Current vaccine technologies

Several routes and strategies have been followed in the scientific research and modular production of COVID-19 vaccines. The four most common approaches are the protein approach, the complete pathogen (whole-microbe approach), the viral vector, and (nucleic acid vaccines). Certain approaches are described in Figure 3.

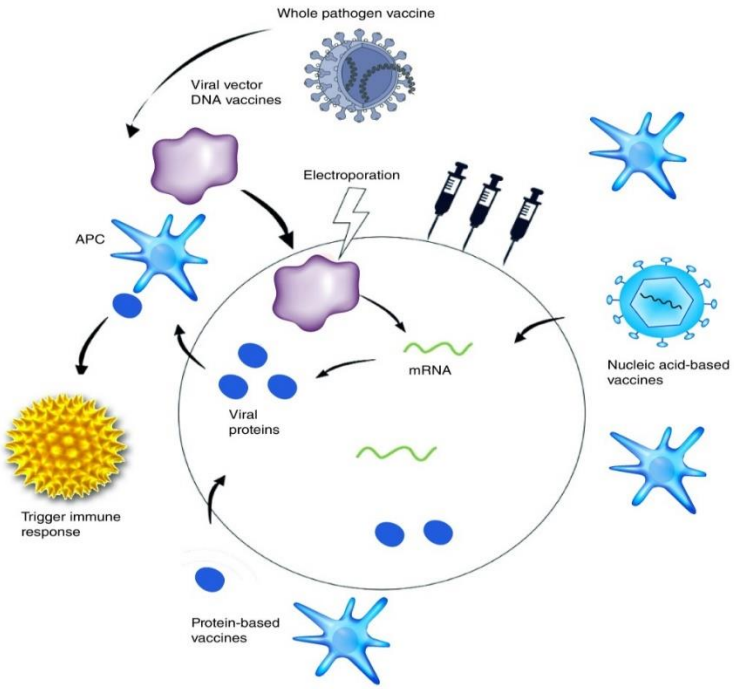

Figure (3):SARS-CoV-2 vaccine approaches.

Whole-microbe approach

The whole-microbe method, which uses modified viral vector vaccines, live attenuated vaccines, and inactivated vaccines, is another term for the whole-pathogen vaccine (14). The most well-known and well-established method of vaccination is the whole-virus vaccine production methodology, because, after vaccination, the full pathogen that causes the disease is used to elicit an immune response. The SARS-CoV-2 virus is completely inactivated within the inactivated vaccination method by heat, radiation, or chemicals.In the past, this method has shown promise in producing vaccines against the flu and polio, whose post-vaccination treatment results against the two disorders are favorable. Several vaccines, notably the Sinovac and Sinopharm vaccines from China and Valneva, Using inactivated vaccine technology, the Scottish SARS-CoV-2 candidate vaccine was created. The weakened virus approach is the

foundation of the live-attenuated vaccine. Live-attenuated vaccines such the rotavirus vaccine, MMR vaccine, nasal flu shot, shingles vaccine, chickenpox vaccine, and BCG vaccine are now part of the UK schedule. Those with significant immunosuppression should not use this technique, which is its principal drawback (15).

Viral vector vaccine approach

Vaccines against viruses that carry specific genetic instructions and are genetically modified to render them incapable of replicating are known as viral vector vaccines. Utilizing the ChAdOx1 vaccination method, the AstraZeneca Oxford COVID-19 vaccine, for example, safely extracted adenovirus type 5 from chimpanzees. To make the vaccine (AZD1222) that is presently being used to prevent SARS-CoV-2, genetic material from the viral vector was incorporated. Due to genetic engineering, the virus produced mRNA specific to SARS-CoV-2 spike proteins that can enter the human cytoplasm through the ribosome. The newly produced protein product has the ability to induce humoral antibody production by B cells and a T cell memory response. which can also initiate an antigen presentation. Zika, MERS, and flu vaccine candidate vaccines are descended from the ChAdOx1 vaccine technology (16).

The genetic approach (nucleic acid vaccine)

Genetic material encoding instructions for producing particular immunogenic proteins is used in the nucleic acid vaccination strategy. Using nucleic acids like DNA, mRNA, or siRNA, these vaccines provide targeted human cells with a predetermined set of instructions that are then translated into targeted proteins inside the cells, inducing humoral antibodies and memory T-cell responses. This strategy gave rise to the Pfizer-BioNTech and Moderna COVID-19 vaccines (17,18).

RNA instability

A critical factor in mRNA vaccines is RNA instability. In the pursuit of developing nucleic acid-based vaccinations, one of the major obstacles facing researchers studying nucleic acid therapies is the problem presented by RNA instability. Due to RNA instability, lipid nanoparticles (LNPs) must properly encapsulate the mRNA and strict cold chain criteria must be followed. The ratio of encapsulation efficiency attained in the development stage serves as the process's ultimate barometer of success. For any nucleic acid-based vaccination to be effective after uptake into cells, a complete, undamaged mRNA molecule is necessary. Defective expression of the target antigen may arise from any little RNA-degradation reaction that occurs along an mRNA strand or along the line, as this can seriously hinder or delay the damaged strand's optimal translation or activity.

Pharmacodynamics and pharmacokinetics

During the BNT162b2 vaccine development, Preclinical investigations were carried out to assess the main in vitro pharmacodynamics and validate the effectiveness of the RNA-based BNT162b2 (V9) product in terms of protein expression, the frequency of BNT162b2

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transfection, and the production of the SARS-CoV-2 P2 S protein antigen on the cell surface. HEK293T cells transfected with BNT162b2 (V9) showed sufficient expression of the SARS-CoV-2 P2 S protein on their surface (19).

Nanomaterials

The term "nanomaterials" describes materials with a single unit tiny size of 1 to 100 nm (20)(21).It is called nanotechnology that this substance with nanoscale properties was used in. A billionth of a meter, or 10-9 meters, is the size of the nanomaterial. Nanomaterials can be thought of as pathogen scales, similar in size to viruses. Their ability to recognize and eradicate unwanted pathogens follows (22). Nanomaterials can arise from natural processes, accidental releases, and manufacturing processes. Manufactured nanomaterials are tailored to specific applications. A variety of nanoparticles known as naturally occurring nanomaterials can be found in our surroundings, including ash emitted by volcanic eruptions, forest fire residue, ocean spray, and radioactive decay of radon gas. Weathering is another mechanism via which it may form. Nanomaterials may be shaped like spheres, needles, platelets, or tubes, and their chemical makeup may include metals, metal oxides, polymers, carbon, semiconductors, and biomolecules (23). Based on the quantity of dimensions, the nanomaterials are separated. Nanofiber, nanoplate, nanoribbon, and nanoparticles are these. When two big dimensions are significantly different from one another, they are called nanoribbons. The external dimensions of nanoparticles are three, nanofiber is two, and nanoplate is one. Once more, based on the components they include, they can be categorized into four groups: nanocomposite, nanofoam, nanoporous, and nanocrystalline. Although a gaseous phase can be present in one phase of a liquid or solid matrix and a dimension in another phase, a nanocomposite is composed of solid particles in a single area and has one dimension on the nanoscale (24). Solid and with nanopores, nanoporous material is different from nanocrystalline material, which has nanoscale crystal grains. Nanomaterials have shown their advantages over other technologies recently and are being used in numerous fields. The sports, cosmetics, and apparel production industries take advantage of them. They are also used as additives, coatings, filters, and insulation in health care goods. Artificial enzymes based on nanotechnology are employed in tumor diagnostics, biosensing, anti-biofouling, and targeted drug delivery. Premium nanofilters are capable of detecting minute dangerous viruses through filtration. the widespread use of nanoparticles in computers and mobile phones as processing capabilities for sensors improve. Cleaner energy, improved energy storage, and water treatment to provide a safe and clean environment for humankind are further potential effects of this technology. They serve a variety of purposes in the fields of horticulture and agriculture, including food processing, storage, packing, and preservation against spoilage. Crop growth screening, soil condition monitoring, and disease detection in plants are among the applications for nanosensors. The technology that has emerged in the last few decades has demonstrated its capacity to change and advance various fields. A new generation has thus been brought in and has completely changed the scientific landscape (25).

Nanoparticles for diagnosis

Because of its exceptional sensitivity, high specificity, and user-friendliness, reverse transcription polymerase chain reaction (RT-PCR) is the preferred method for most viral RNA detection procedures. It is predicated on the RNA produced throughout the process growing exponentially.(26). Although RT-PCR is the most used technique for detecting coronaviruses, it has some drawbacks that need to be fixed, such as low extraction efficiency, the necessity for laborious procedures, and false positives brought on by contamination (27). NPs have been included into RT-PCR and other techniques including reverse transcription loop-mediated isothermal amplification (RT-LAMP) and enzyme-linked immunosorbent test (ELISA) to increase the efficacy of viral detection. This is due to their vast surface area and incredibly small size. Many types of nanoparticles (NPs) have been studied in connection to virus detection, including metal, silica, carbon nanotube, quantum dots (QDs), and polymeric NPs. The application of metal nanoparticles (NPs), magnetic nanoparticles (MNPs), metal nanoislands (NIs), and quantum dots (QDs) to coronavirus detection is described (28). Many diagnostic procedures, including colorimetric, electrochemical, fluorescence, and optical approaches, are based on these methodologies. Viruses are extremely sophisticated in that they may form new strains of themselves that are resistant to the majority of antiviral drugs by mutating inside the host cell and developing an amazing genetic adaptability to withstand the inhibitions of antivirals. Maybe the emergence of this new strain presents a significant challenge for the medical research community. Consequently, it is imperative to conduct multidisciplinary research projects involving clinical trials, pharmacologists, nanotechnology, traditional medicine, bioactive substances, essential oils, and epidemiology in order to tackle COVID-19. With the ability to precisely target the site of infection and inhibit viral replication, nanotechnology has emerged as an intelligent material that may limit the spread of the virus within the host cell (Fig. 4). Metal nanoparticles with virucidal properties, like gold or silver, can kill a wide range of viruses. Metal nanoparticles may inhibit the replication of viral genomes (DNA or RNA) and create antiviral activity through their interaction with viral surface glycoproteins. Adjustments should be made to metal nanoparticles used in different therapeutic or preventive therapies to lower the risk of long-term toxicity (29).

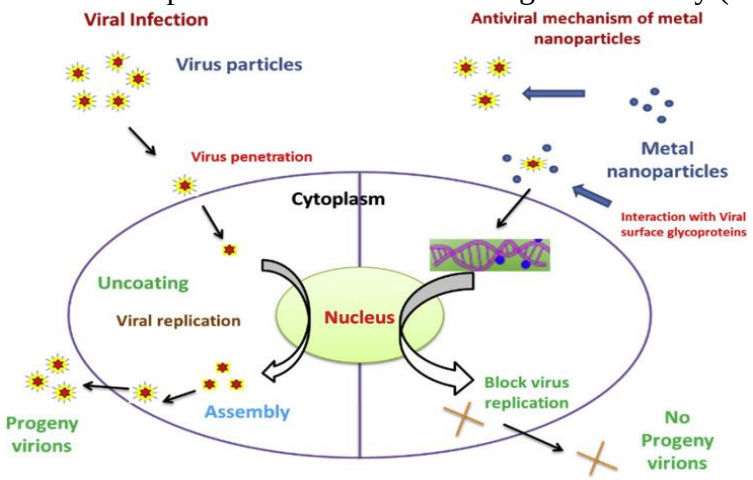

Figure (4): Schematic representation of antiviral mechanisms of Nanoparticle.

Rapid diagnosis, surveillance and monitoring, treatments, and vaccine development are some of the possible areas where nanotechnology involvement can be extremely helpful in the fight against COVID-19 (30). Detecting, treating, and preventing COVID-19 can also be investigated with it. Antiviral nanomaterials can be used to cover personal electronics, remove corona viruses from surfaces, create vaccinations, or modify immune systems.Nanosensors for the quick, easy, and affordable detection of SARS-CoV-2 are being developed for use in diagnostics. For the purpose of treatment, antiviral medications are delivered to the pulmonary system in a targeted and regulated manner using nanoparticles in combination with other medications to prevent viral replication. The amount of virus on the contaminated surface may be lessened by it. The development of point-of-care biosensors as diagnostic tools is utilizing the electrical and optical capabilities of nanomaterials. We are able to identify analytes at low concentrations because the biosensor's sensitivity was enhanced by the use of nanoparticles. This made it easier to isolate the SARS-CoV-2-infected patient and diagnose them quickly. Therefore, nanotechnology offers a wealth of opportunities to combat the ongoing pandemic through diagnosis, vaccine development, medicine delivery, therapy, protective coating for personal equipment, and a reduction in virus load in masks (31).

Silver nanoparticles to fight against covid-19

Silver nanoparticles are tiny particles of silver, ranging in size from 1 to 100 nm. They are distinguished by their low sintering temperatures, optical characteristics, and strong electrical conductivity. They are used by combining them with other items, such as chemical, biological, and photovoltaic sensors. The use of silver nanoparticles in anti-microbial coatings is one of their major uses. It effectively inhibits the growth of bacteria and possesses antibacterial qualities. Gram-positive and gram-negative bacteria were shown to be equally efficient with it (32). Given that compounds based on silver are extremely hazardous to germs, it is used in dentistry, surgery, the treatment of wounds and burns, and biomedical equipment. Its use as a catalyst and in household items are further applications. For biological agents like dyes and chemical agents like benzene, silver nanoparticles exhibit catalytic redox attribute quality. Both synthetically and physiologically, silver-based nanoparticles can be produced. In terms of biology, they are primarily present in bacteria that produce lactic acid and can be produced from the organic bacterial matrix. It has also been shown that even low concentrations of silver do not pose a threat to humankind.Due to the COVID-19 pandemic, which has put the world in its worst predicament, numerous researchers are looking at the possible applications of silver nanoparticles as a viable therapy option for this terrible illness. However, as of right now, the treatment lacks a conclusive analysis. The respiratory system's nasopharynx or bronchial tree region is the site of COVID-19 viral infection. Once inside the lower respiratory tract, the bacterium spreads the infection. If the infection is severe, it will eventually spread and weaken our immune system, maybe leading to death. Treatment of sick individuals early on, when the virus is in the upper respiratory tract, is therefore somewhat beneficial. It has been demonstrated that antivirals can be made using 3–7 nm colloidal nanoparticles (33). Use an aerosol source with an increasing dose three times that of a breath-actuated nebulizer source

for breathing cycle losses. The minimum inhibitory concentration (MIC) for antiviral application is approximately 10μ/ml. The percentage of targeted tissue deposition under oral breathing should be 5μm for aerosol droplets. There are two different kinds of inhaled silver particle suspensions or solutions. Silver ions and silver colloidals are what they are. As an excellent topical or external solution, ionic silver is made of atomic silver ions that dissolve in water. Oxidation produces silver ions, which are toxic to bacteria, yeasts, and other microorganisms. On the other hand, colloidal silver, which is composed of minuscule metallic silver nanoparticles or chunks, is more suited for internal use because it is not damaged by stomach acid. It is included in a wide range of commercially available products at very low particle concentrations, both as injections and as skin-direct applications. Colloidal silver nanoparticles can treat cancer, hepatitis B, HIV/AIDS, and other diseases. They can fight against viruses and bacteria and strengthen immunity. These are its modes of action: i) It binds itself straight to the DNA of the virus, destroying the hydrogen that binds cells together and wiping it out. ii) It acts as a foil to keep the virus from infecting by encasing its cell membrane. iii) It creates a barrier between the virus and the host cell by attaching itself to oxygen molecules and acting as a catalyst. When tested on specific coronavirus strains, silver solution has been shown to have some efficacy by both deactivating and enhancing the immune system, according to naturopathic physician Sherrill Sellman. Thus, it can be said that there is potential for using silver nanoparticles to treat COVID-19, but further study, testing, and encouraging data are needed before using them. In addition to their numerous medicinal uses, such as wound treatment, silver nanoparticles (AgNPs) have antibacterial, antiviral, and anti-influenza capabilities. Prior to subjecting such nanoparticles to direct human testing, their level of toxicity should be taken into account. Silver nanoparticles, however, are frequently inhaled via solutions or suspensions in water. The existence of the molecules differs in both situations because of the size of the particles. While colloidal silver solution has nanoparticle sizes ranging from 1 nm to 100 nm in diameter, ionic silver particles can be large enough to float in water. Antibacterial properties are present in both compounds (34).

Colloidal particles possess antiviral effects ten times more powerful than ionic silver (35). The concentration level in the solution and its nano range particles could be the cause of this. Between 3 and 7 nm-sized colloidal silver particles have the potential to be very efficient against viral infections. However, its potential effect on respiratory infections is not well recognized. Colloids that are treated with the virus have a minimum inhibitory concentration (MIC) of about 10 μg/ml, meaning that they are more effective against the target tissue concentration of 25 μg/ml. These colloidal silver nanoparticle compositions may be helpful in preventing respiratory virus infections and in treating SARS-CoV-2 infections (33).

Chloroquine and nanoparticles interaction

When applied to cell lines and the mononuclear phagocyte mice technique, It is known that chloroquine is a broad-spectrum nanoparticle regulator because it keeps produced nanoparticles of different sizes (14–2600 nm) and forms (spherical and discoidal) from aggregating (36). PICALM, also known as phosphatidylinositol binding clathrin assembly

protein, is one of the three most prevalent proteins in polymer-coated pits.can also be controlled by chloroquine, according to research findings. There is a chance that PICALM will prevent clathrin-mediated endocytosis (CME). One major route for the ingestion of artificial nanoparticles is through this CME. The absence of changes in clathrin and clathrin adaptor protein 2 (AP2) levels in macrophages treated with chloroquine suggests that PICALM-specific effects, rather than a general decline in proteins linked to clathrin-structured endocytosis (37,38).

COVID-19 RT-LAMP-NBS is the name of these brand-new, innovative kits. This technology is beautiful because it combines the LAMP test with reverse transcription and multiplex analysis, using a nanoparticle-based biosensor. A one-step, single-tube reaction facilitates the complete experiment. Unlike other techniques, this assay is straightforward and quick to perform, eliminating the need for complicated procedures like electrophoresis, reagent preparation, and the usage of pricey instruments. Given its excellent specificity, sensitivity, affordability, convenience of use, and low cost for COVID-19 diagnosis, this test is highly intriguing (39).

Clothing masks and surfaces treated with ionic zinc oxide (ZnO; Zn2+–O2−) nanoparticles (40) in a wurtzite form, or maybe PEGylated ZnO nanoparticles (also known as oxozinc), are known to possess potent antibacterial and antiviral properties (41). Materials can be stabilized and given the ability to instantly destroy infections by including ZnO-nanoparticles (42). Based on preliminary data, it appears that 2019-nCoV binds to the enzyme that breaks down angiotensin II after entering pulmonary cells via acetylcholinesterase level 2. Pulmonary hypertension, edema, acute respiratory distress syndrome, and pneumonia-related mortality are caused by the additional local concentration of angiotensin II that results (43). The mRNA-1273 vaccine is currently being administered to the general public following the conclusion of scientific testing. mRNA-1273 is an innovative mRNA-based vaccine encapsulated in lipid nanoparticles (LNPs) that contains the genetic material encoding the stabilized spike (S) protein of SARS-CoV-2. Moderna Therapeutics, a biotech business, has contributed to its evolution by testing and developing vaccines against SARS-CoV-2, MERS-CoV, and SARS-CoV. Cells are instructed to express the S protein by the vaccine's RNA component in order to initiate an immune reaction. The vaccine is released for additional public immunization after demonstrating efficacy in animal trials. Many more mRNA-based vaccinations are being developed for use in the general public, such as CureVac and BNT162 by BioNTech & Prifzer. Moreover, the nucleic acid is encapsulated in 80 nm-sized glycol-lipid nanoparticles in the BioNTech mRNA vaccine (Mainz, Germany) (44).

At this point, it is unknown which antiviral medication has the best chance of treating COVID-19 effectively and efficiently. Nonetheless, there are reports that certain current medications can be somewhat helpful in treating both mild and severe COVID-19 patient conditions by repurposing their intended usage. Anecdotal use of medications such as lopinavir, ritonavir, interferon-1b, RNA polymerase inhibition remdesivir, and chloroquine and its derivatives may be associated with these antiviral drugs (45). Zinc nanoparticles have been demonstrated to have inhibitory effects on the H1N1 virus load; nevertheless, it is unknown and untested what

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effect they have on COVID-19. There are various ways that vitamin C administration can prevent pneumonia and evaluate its impact on COVID-19 cravings (46).

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Conflict of interests.

There are non-conflicts of interest.

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