IJPSR (2021), Volume 12, Issue 6 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 09 May 2021; received in revised form, 15 May 2021; accepted, 16 May 2021; published 01 June 2021

THE POTENTIAL ROLE OF NANOTECHNOLOGY TO COMBAT SARS-CoV2 -2019: DIAGNOSIS, TREATMENT OPTIONS, APPROACHES – A SCOPIOUS REVIEW

Subashini Rajaram *, Anjuna Prakashan, B. Pragathi, K. Saieswari, A. R. V. Sree and Yashoda Mariappa Hedge

Department of Pharmaceutics, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode, Namakkal - 637205, Tamil Nadu, India.
The TN Dr. M.G.R, Medical University, Chennai - 600032, Tamil Nadu, India.

Keywords:

Nanotechnology, SARS-CoV2 -2019, Antiviral treatment, Nano vaccines, Post COVID-19, Viral therapeutics

Correspondence to Author:
Dr. R. Subashini

Associate Professor,
Department of Pharmaceutics,
Swamy Vivekanandha College of Pharmacy, Elayampalayam,
Tiruchengode, Namakkal - 637205,
Tamil Nadu, India.

E-mail: subababu.r@gmail.com

ABSTRACT: Coronavirus disease (COVID-19), an infectious disease caused by a novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The infection began in bats and was communicated to people through yet obscure go-between creatures in Wuhan, Hubei territory, China, in December 2019. Its outbreak threatened the lives of many people throughout the world. There is no distinct treatment available yet, and is an urgent need to treat, prevent and eradicate this virus. Recently, numerous new technologies have been explored for the diagnosis, prevention, and treatment of viral infections. Among these, nanotechnology has emerged as a promising antiviral treatment, and currently, the development of COVID-19 drug delivery involving nanotechnology is under investigation. This review aimed towards the prospective treatment options integrating the ever-expanding field of nanotechnology against COVID-19. We focused on the current scenario in the developments of nanotechnology-based approaches because of the ongoing pandemic of COVID-19, the effectiveness of nanomaterials as vaccines, nanosensors as diagnostic or antiviral tools against coronaviruses, and post COVID-19 era has been discussed in this review.

INTRODUCTION: In December 2019, the World Health Organization (WHO) was notified about the pneumonia case of an obscure cause detected in the seafood market of Wuhan city in Hubei province, China. The cause was identified as a novel coronavirus (n-CoV) based on the laboratory findings of Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS).

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(6).2966-81

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(6).2966-81

Following, on 30 January 2020, WHO declared the 2019-nCoV outbreak a Public Health Emergency of global health concern, accentuating the need for worldwide action, international cooperation, solidarity, and collaboration to control the outbreak. On 11 February 2020, WHO announced a name for the new coronavirus disease: COVID-19, later 11 March 2020, assessed that COVID-19 can be marked as a pandemic.

The journey status of the swiftly progressing COVID-19 outbreak can be globally categorized into four stages. The first stage is when cases of infection are imported from one infectious country to another. The second stage of an outburst occurs when there are cases of local transmission from infected patients.

Community transmission is the third stage of an outbreak, and the fourth stage is when an infection becomes endemic with no clear terminus. The world has seen three coronaviruses in the last twenty years, SARS, MERS, and now COVID-19. SARS-CoV was recognized at the end of February 2003 in Guangdong, China, and expanded to many countries, including European Union (EU), Southeast Asia, South Africa, and North America [1].

The transmission was primarily occurred through infectious droplets from person to person during coughing or sneezing, through personal contact (shaking hands), or by touching infected surfaces. SARS-CoV-2, SARS, and MERS coronaviruses are deemed to have originated from bats and transmitted to humans from an intermediate host, civets, and dromedary camels, respectively. For SARS-CoV-2, the zoonotic source and intermediate host is not confirmed yet, and research is going on [2]. The mean incubation period is about 5 days, ranging from 1 to 14 days, and 95% of patients are expected to experience symptoms within 12.5 days of contact. Nevertheless, asymptomatic carriers have been reported, and the incubation period is 19 days, addressing it even more cumbersome to screen the infection [3]. The concern advice is to give fluid management, oxygen support to patients [4, 5], and antibiotics in subsequent infection if any reported [6]. Based on indications from the laboratory, animal, and clinical studies, the following treatment options were selected according to WHO: Remdesivir; Lopinavir/ritonavir; Lopinavir/ritonavir with interferon β-1a [7]. There is solely one way the world can end this pandemic and which is through science. We need a diagnostic detection kit to identify and prevent the spread of the virus, vaccines for long-term protection, treatments to rescue lives in the shorter term, and social science to understand the behavioral and societal involvements. It's crucial that the global research endeavor is rapid, sturdy, and is conducted in order and coordinated across multiple countries. The WHO solidarity trial will implement this by testing existing and new drug molecules to treat COVID19 and guarantee equitable access to any drugs that prove effective. Global powers must now rise to ensure the WHO has all the assistance needed [7].

The major hurdle that remains in the development of effective antiviral agents is the ability of the virus to reproduce in the host cell by liberating its DNA or RNA. The host's immune system is extremely compromised in case of viral infections, and recurrences are very common. Also, due to the complexities linked with viruses, treatment is frequently symptomatic, and comprehensive eradication of the virus may not be possible. Recognizing and diagnosing the exact type of viral disease is considerably challenging. At times, due to prior exposure, viral immunoglobulins present in the host may get stimulated, rendering it challenging to detect incidental infections [8].

Although the number of infected cases is dramatically increasing, there aren't any officially established medications or vaccination for COVID-19 available yet. The contemporary treatments are mainly for symptomatic relief and respiratory support in severely ill patients. Attempts to develop effectively, targeted and competent drugs and vaccines to manage this virus are currently under research. Some researchers have been studying the similarity of transmission between the novel SARS-CoV-2 and SARS-CoV to develop drugs targeted towards profoundly conserved key proteins, such as those involved in viral replication and proliferation. Examples of these proteins are spike, viral, and envelope proteins, and RNA proteases, which are distinct viral targets. Entertainer receptors and proteases, which are liable for virus entry and endocytosis, are also inherent targets for drug development [9].

The currently available drugs for the treatment of viral infections mostly fall in one of the followings classes: antiviral therapies, immune therapy, anti-inflammatory therapy, and other treatments that include traditional medicines based on natural products. The effectiveness of conventional treatments for viral infections progressively fades away due to viral mutations and the emergence of new viral strains. Recently, the development of broad-spectrum antiviral drugs has caught the attention of numerous researchers, as these drugs are less predisposed to resistance and could be used against several types of viruses, including new strains. However, the development of new drugs is lagging because of the long process necessary to prove their efficacy and safety. To overcome these limitations and to improve antiviral treatments, multidisciplinary research efforts are required

toward the development of alternative antiviral therapies, targeting different phases in the viral replication cycle. In this regard, nanotechnology has attracted increasing attention and has already been investigated for potential use in the prevention and/or treatment of viral infections [9].

Nanotechnology can be broadly characterized as the design, development, and utilization of several materials and devices where at least one dimension is less than 100 nanometers. In the pharmaceutical field, the employment of nanotechnology involves the application of nanomaterials for diagnosis, treatment, control, and prevention of diseases is known as nanomedicine. Over the decades, nanoparticles are broadly used and investigated due to their novel properties, such as small size, enhanced solubility, surface versatility, and multifunctionality, leading to the development of more reliable and safer drugs, personalized and tissue-targeted methods, advanced diagnosis, and inhibition of diseases are also probable using nanomedicines. Thus, it appears that nano-based strategies will be the first choice for the expansion of the most effective treatments for an extensive range of diseases soon. Nanotechnology likely endures huge potential in the diagnosis, treatment, and prevention of COVID-19 [9].

Nanotechnology could expedite the fight against COVID-19 through different approaches, like avoiding viral contamination and spread through the: (a) design of infection-safe personal protective equipment (PPE) to strengthen the safety of healthcare workers and development of active antiviral disinfectants and surface coverings that can inactivate the virus and hinder its spread; (b) design of extremely specific and perceptive nano-based sensors to quickly recognize the infection or immunological response; (c) development of innovative drugs, with intensified activity, reduced toxicity and sustained release, as well as tissue targeting, markedly to the lungs; and (d) development of a nano-based vaccination to shove up both humoral and cellular immune responses [9].

Several nano-based formulations have been bestowed to improve both targeted drug delivery and the therapeutic efficacy of antiviral drugs. In addition, due to the inadequacy of therapeutic alternatives for numerous viral infections, several trials are done to explore the antiviral activity of natural compounds, like plant metabolites. However, most of the compounds obtained from plants have inadequate water solubility and low availability, ending in a lack of therapeutic effect. To heighten the therapeutic effect, plant compounds are coupled with various nano-based carriers. Besides, nano-based biosensors could be used as a diagnostic tool for the detection of viral infection with huge specificity and sensitivity. Another quite promising proposal is the new generation of vaccines based on varied kinds of nanomaterials, with improved antigen stability, target delivery, and controlled release. Finally, the use of nanoparticle-based markers can further enable the investigation of the mechanism by which viruses infect host cells [9].

Infected surfaces in public places, like hospitals, parks, public transportation, and schools, are a well-recognized popular source for outbreaks of copious infections. Investigations have also shown the potential of nano-based surface coatings for the restriction of infections. Also, the security of healthcare workers is really important in an exceedingly viral outburst. This is where nanotechnology-based antimicrobial technologies can be included in personal protective equipment for increased protection of healthcare workers [9].

An extensive number of promising anti-viral treatments are currently under research to assist in the advancement of COVID-19 drug delivery. The current review centers on the plausible particulate nanotechnology-based drug delivery approaches and the research agendas to combat COVID-19. The current state of knowledge, research priorities regarding the pandemic and post-COVID-19 have been discussed. We also summarized the possible prospective treatments integrating the ever-expanding field of nanoparticulate delivery systems that have proven to achieve success against other viruses, intending to show that these can potentially be developed for COVID-19 treatment also. The focus is on how nanotechnology can help fight viral infections and take account of any challenges in this regard [9].

Epidemiology: A cluster of pneumonia cases of undiscovered origin occurred in Hubei province, China, which caused concern among health

officials in late December 2019. On December 31, a warning was issued by the Wuhan Municipal Health Commission, then a rapid response team was assigned to Wuhan by the Chinese Center for Disease Control and Prevention (China CDC), and a notification was sent to the WHO. Potential causes, including which are anticipated to happen, such as influenza, avian influenza, adenovirus, SARS-CoV, and MERS-CoV, were ruled out. The epidemiological investigation implicated the corona outbreak likely commenced in Wuhan's Huanan Seafood Wholesale Market, which was later locked down and disinfected, and active case finding was inducted and vigorously pursued. On January 7, 2020, the causative pathogen was recognized as a novel Coronavirus or nCoV, and genomic characterization and detecting methods have ensued. Presently named 2019nCoV, the virus is distinct from both SARS-CoV and MERS-CoV, but nearly related. Early cases recommended that the severity of COVID19may be less than SARS and MERS. However, the incipience of illness among people is rising rapidly, and mounting evidence of human to human transmission infers that 2019 nCoV is more contagious than both SARS-CoV and MERSCoV [10].

The first deadly incident was reported on January 11, 2020. The huge migration of Chinese during the Chinese New Year kindled the epidemic. Cases in other provinces of China and those in other countries (Thailand, Japan, and South Korean quick succession) were reported in people who were coming back from Wuhan. Transmission to healthcare workers from nCoV infected patients was declared on January 20, 2020. By January 23, 11 million population of Wuhan was put under lockdown with restrictions of entry and exit from the region. Soon, this lockdown was prolonged to other parts of Hubei province. Cases of COVID19 in countries outside China were reported in those with no history of travel to China, implying that local human-to-human transmission was be falling in these countries. Airports in several countries, including India, put in screening mechanisms to identify symptomatic people returning from China and placed them in isolation after testing them for COVID19. Shortly, it was evident that the infection could be transmitted from asymptomatic people before the onset of symptoms. Therefore, countries including India that abandoned citizens from Wuhan through special flights or other Indian passengers returning from China placed all people symptomatic or otherwise in isolation for 14 days and examined them for the nCoV virus. Cases proceeded to extend exponentially, and modeling studies proclaimed an epidemic is doubling time of 1.8 days [10].

As of March 22, 2020, around 300,000 cases of COVID19 and approximately 13,000 deaths have been reported globally. India has reported around 394 cases with 7 mortalities to date. These figures are possibly an underestimate of the infected and dead due to the constraints in surveillance and testing. Though the SARSCoV2 originated from bats, the intermediary animal through which it crossed over to humans' is uncertain [10].

Pathophysiology: The specific replication mechanism is still unclear for SARS-CoV-2. It had been described that replication of coronavirus, SARS-CoV-2 is similar to that of other viruses of the coronavirus family, such as SARS-CoV and MERS-CoV. It may involve a two-step reaction of the SARS-CoV-2 virus to enter the body to spread the infection. Firstly, binding to angiotensin-converting enzyme-2 (ACE-2) or CD-147 or dipeptidyl peptidase 4 (DPP-4) or transmembrane protease serine 2(TMPRSS2), and the second is the cleavage of the spike protein by the TMPRSS2 [11].

ACE-2 protein is hugely detected in alveolar epithelial cells of the lungs and enterocytes of the small intestine. It was observed that the primary virus binds to the target site on lung epithelial cells. However, patients with SARS-CoV-2 infection primarily display lesions within the lungs, despite the ACE-2 receptor being broadly distributed in various organs of the human body, so this link needs to be investigated further [11].

After the entry of the virus into the cell, IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. Levels of tumor necrosis factor α (TNF-α), IL-1β, IL-8, IL-12, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1A (MIP1A), and interferon-gamma inducible protein (IP10) are also increased in SARS CoV-2 infected patients. The overview of COVID-19 with special emphasis on structure, induction, immune response, and complications is shown in **Fig. 1** [11].

Infection with MERS coronavirus can induce increased concentration of pro-inflammatory cytokines (tumor 616 necrosis factor α, IL15, and IL17, and interferon-γ,). Excessive tissue damage is occurred owing to the excessive release of cytokines. In some cases, a reaction takes place, which is labeled as a 'cytokine storm' [11].

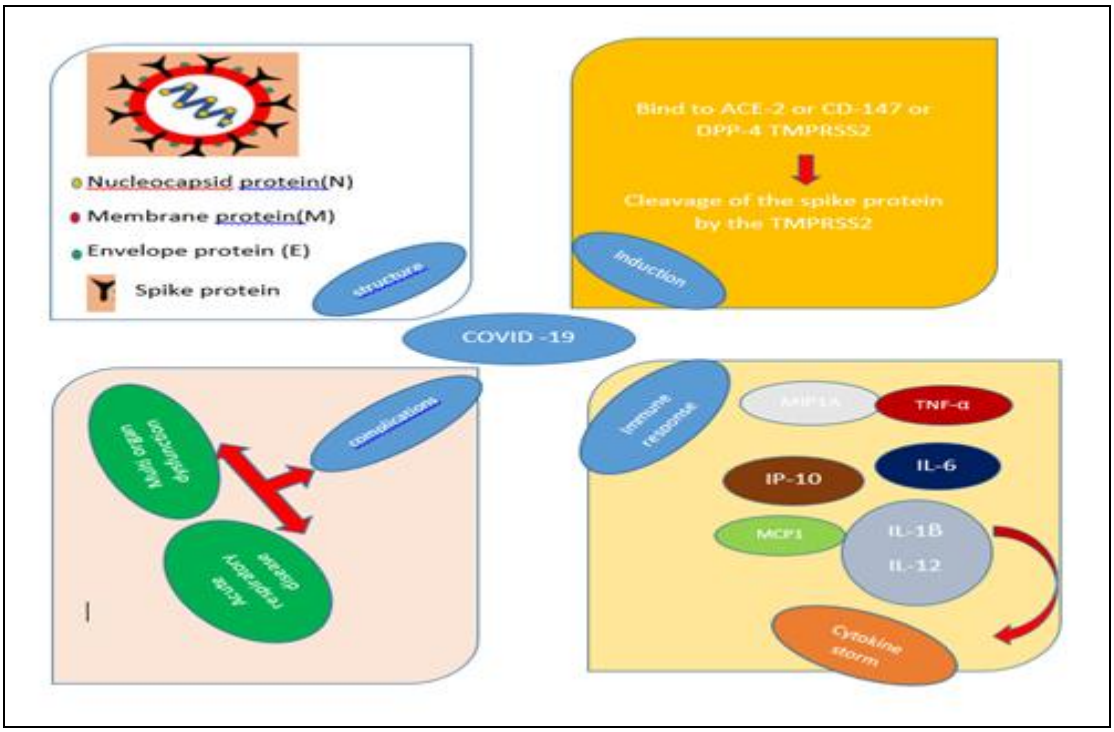

FIG. 1: OVERVIEW OF COVID-19 WITH SPECIAL EMPHASIS ON STRUCTURE, INDUCTION, IMMUNE RESPONSE, AND COMPLICATIONS

Transmission: WHO stated the initial cases of COVID-19 were from the Hunan Seafood market and observed that SARS-CoV-2 was transmitted from animal to human. However, a genomic study has confirmed that the virus was introduced from another source, yet exotic location into the market where it spread more swiftly, although human-to-human transmission is also reported beforehand. Person-to-person transmission is thought to occur through near contacts, chiefly through respiratory droplets produced during coughing or sneezing by an infected person [11].

Fomites may be a huge source of transmission, as SARS-CoV has been found to persist on surfaces up to 96 h and other coronaviruses for up to 9 days. The basic reproductive number (R0) measures the transmissibility of a virus, representing the average number of new infections generated by an infectious person in a fully susceptible population. Therefore, R0can be used to understand the transmissibility of SARS-CoV for predicting transmission. The number infected is likely to increase with stronger transmission potential if R0 > 1, and transmission is likely to die out eventually if R0 < 1. The study by Ying Liu et al. estimated that R0 was 3.28 with a 2.79 median value for COVID-19, which surpasses WHO estimates from 1.4 to 2.5. Studies from previous outbreaks found R0 to be 2.7 for SARS and 2.4 for 2009 pandemic H1N1 influenza. Because R0 denotes an average value, it is also vital to consider the role of super spreaders, who may be hugely reliable for outbreaks within large clusters but who would not considerably influence the value of R0. R0 remains unstable during the initial stages of a pandemic due to short onset time and insufficient data availability [11].

Virology of Covid-19: Most viral infections are subclinical, where the body's defense mechanism halts the course of infection before the clinical symptoms become evident. Various stages of the pathogenesis of viral disease include the following: (i) attachment of virus at the point of entry, (ii) penetration into the host cell, (iii) uncoating of the virus, (iv) replication through transcription and translation resulting in the synthesis of virus-

specific proteins, (v) assembly of naked capsids through nucleocapsid, and (vi) release of virions leading to further spread of infections [12].

Various factors affecting pathogenesis mechanisms include accessibility of tissue to the causative virus, susceptivity of the cell to viral replication, and the resistance of the virus to the host defense mechanisms. The affinity of the virus to infect specific tissue depends on numerous factors like the presence of various virus-specific receptors on the cell, cell transcription factors, local pH, temperature, and presence of enzymes that can inactivate the virus [12].

Mechanisms embraced by the virus to destroy the host cell involve the blockade of cellular synthesis of macromolecules compromising cellular energy. Integration of the viral genome with the host genome causing mutations within the host genome is the indirect route to cell damage. The infection process is scrutinized based on virulence, virus-dependent factors, virulence genes, speed of replication, and the degree to which the viral infection spreads. The key issue linked with the study of viral diseases is that it is difficult to estimate how the host defenses would interact with the virus. It may act by preventing the growth of the virus or it may arouse an immunological response in the affected tissue [12].

Virus Detection and Disease Diagnosis – Nanotechnology Strategies: An extended variety of technologies is available as diagnostic tools in the battle against SARS-CoV-2, including nucleic acid tests principally based on polymerase chain reaction (PCR), and serological assays that can detect the presence of antibodies generated during the respiratory infection. Diagnosis in the initial stages of the disease mainly centers on viral genome detection by real-time (RT)-PCR, while the determination of immunoglobulin IgG and IgM antibody levels commences after 5–7 days or more than 10 days, respectively, utilizing serological tests such as enzyme-linked immunosorbent assay, chemiluminescence assay, immunofluorescence assay, or immune chromatographic test (ICT), among others. Nanomaterials are a very significant component in some of these technologies, being a key factor in the detection or transduction of the biochemical interactions as specified below. Recently, a rapid and substantial colorimetric bio-assay has been developed by modifying plasmonic gold nanoparticles (AuNP) with designed antisense oligonucleotides specific for two of the N-gene regions of SARS-CoV-2. The nanoparticles agglomerate in the presence of the target viral RNA, allowing a naked-eye detection in about 10 min [13].

Typically, nanoparticles are also used as detection components in ICT, also known as lateral flow immunoassays (LFIA), which are mainly applied for the detection of antigens or antibodies. These rapid point-of-care tests can be very valuable for diagnosis when laboratory facilities are not available, as they are easy to use, do not require trained staff, operate with small amounts of sample (around 10–20 µL), and provide a result in typically less than 20 min [13].

Since the commencement of the pandemic, an outsized number of rapid tests have been developed by research groups and *in-vitro* diagnostics companies for the detection of IgM and IgG antibodies in patients with COVID-19. Intense research recapitulates aiming at increasing the sensitivity and specificity of these diagnostic tools. As schematized in **Fig. 2**, a typical ICT configuration for detection of IgG and IgM antibodies against SARS-CoV-2 consists of: i) a sample pad, where the sample and buffer are added; ii) the conjugate pad containing the antibodies or antigens labeled with colloidal AuNP (diameter around 20-40 nm); iii) the chromatographic strip, which is a porous polymer membrane, where the captured biomolecules are immobilized within the test line and an appropriate antibody in the control line; and iv) the liquid adsorbent pad. The Au-labeled molecules bind to the antibodies present in the sample, and by capillary action they are dragged through the chromatographic strip, reaching the test and control lines, where they are concentrating on developing a color that can be seen with the naked eye.

The non -appearance of color in the test line shows the absence of the target antibodies in the blood sample. Synthetic antigens of the S, M, and N proteins of SARS-CoV-2 are immobilized in the test line to detect IgM and IgG specific to this coronavirus [13].

Li and co-workers proclaimed a new ICT configuration with two test lines that can determine simultaneously IgM and IgG antibodies in the same test within 15 min, with a sensitivity of 88.7% and specificity of 90.6% assessed in blood samples from both PCR-confirmed COVID-19 patients and negative patients [13].

Compared to the huge amount of ICT developed for serological assays, a smaller number of ICT are designed for direct viral antigen detection. A current work reports the development of a half strip LFIA for detection of SARS-CoV-2 antigen. This is a simple configuration that comprises only the chromatographic strip. In this method, red latex beads (400 nm) conjugated to polyclonal antibodies and blue latex beads (400 nm) conjugated to an antibody are used for the test and control lines, respectively. After 20 min, the display of color is observed with the naked eye or with an optical reader for semi-quantitative determination. The benefit of this kind of ICT is that detection of the SARS-CoV-2 antigen can provide information in the early stages of the disease, but the specificity and sensitivity of these tests, however need to be improved to become a suitable alternative to RT-PCR [13].

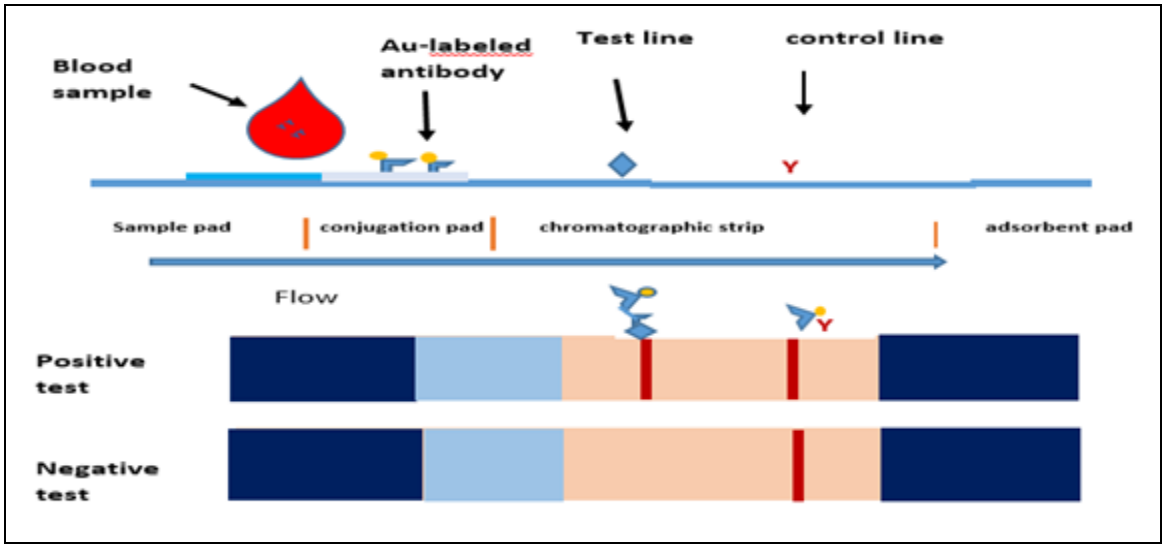

FIG. 2: SCHEMATIC REPRESENTATION OF AN IMMUNOCHROMATOGRAPHIC TEST FOR DETECTION OF ANTIBODIES IN BLOOD OR SERUM SAMPLES, USING AuNP AS A LABEL FOR DIRECT VISUALIZATION

Immunochromatographic tests can also be configured to detect nucleic acids. Broughton and co-workers stated the detection of viral RNA extracts from nasopharyngeal swabs using a highly specific Cas12 protein in CRISPR, a potent gene-editing tool, combined with lateral flow assay using AuNP as a label. The specificity for SARS-CoV-2 detection with this system is very high, with no cross-reactivity for related coronavirus strains. Similarly, a portable integrated microdevice combining RT-PCR and ICT was reported some years ago for the genetic analysis of influenza A H1N1 virus by colorimetric detection and such technology could also be useful at present for SARS-CoV-2 detection. Intensive research is being carried out to promote the reliability and sensitivity of these rapid tests for SARS-CoV-2. Fluorescence-based ICT is being developed for quantitative or semi-quantitative detection, using fluorescent labels rather than AuNP. A recent work makes use of lanthanide-doped polystyrene nano-particles, and detection of fluorescence is carried out in a portable fluorescence reader with good agreement with results obtained by RT-PCR [13].

An anti-SARS-CoV-2 IgG standard is available; this rapid test could be optimized to provide reliable quantification instead of the current semi-quantitative detection. Several biosensor platforms have been reported to date as diagnostic tools for SARS-CoV-2. Biosensors are devices that make use of distinct biochemical reactions and their conversion into a measurable readout in the form of electrical, thermal, or optical signals using a transducer [13].

Seo and co-workers have recently reported a field-effect transistor (FET)-based biosensor platform that provides rapid detection of SARS-CoV-2. This

biosensor consists of graphene nanomaterial as the transducer or sensing material and a SARS-CoV2 spike antibody that was adopted as the receptor biomolecule immobilized on the graphene layer. The biosensor performance was appraised in clinical samples of COVID-19 patients using antigen protein, cultured virus, and nasopharyngeal swab specimens, allowing a rapid and highly responsive detection of SARS-CoV-2. It also conferred high specificity, distinguishing the SARS-CoV-2 antigen protein from those of MERS-CoV [13].

Surface plasmon resonance (SPR)-based biosensor platforms make use of this highly sensitive optical technique, which detects the changes in refractive index occurring at the metal interface, enabling monitoring the biochemical interactions in real-time. Based on the successful performance of SPR-based biosensors developed for SARS-CoV detection, an improved device has been recently reported for SARS-CoV-2. This is a dual functional plasmonic photothermal (PPT) biosensor that consolidates the PPT effect and localized surface plasmon resonance. It consists of 2D gold nano islands functionalized with complementary DNA receptors that can hybridize selected sequences from SARS-CoV-2. The hybridization temperature is increased in situ with the thermoplasmonic heat created by illumination of the gold nanoislands at their plasmonic resonance frequency, which helps to discriminate similar gene sequences and to increase the specificity of the biosensor [13].

Together with FET- and SPR-based devices, other biosensor designs, including nanomaterials were reported for detection of other coronaviruses, for instance, electrochemical immunosensors based on an array of AuNP-modified carbon electrodes for detection of MERS-CoV or an optical biosensor chip modified with QD-conjugated RNA aptamer for detection of SARS-CoV-2. Other alternatives for future biosensors developments for detection of SARS-CoV-2 could be based on the development of biomimetic nanoarchitectures as Wicklein and co-workers developed for the detection of influenza A virus. In this case, sialic acid-galactose receptor molecules imitating those found on the membrane of target cells of the virus act as the sensing entity, which can be transduced by the impedimetric gold detector. The above-mentioned designs can uncover ways to the development of new biosensor platforms for rapid, sensitive, and specific detection of SARS-CoV-2 [13].

Drug Treatment Option Strategies to Combat Covid-19:

Treatment: Avoidance is the principal method of deterrence. Numerous collaborative attempts to discover and decide the effectiveness of antiviral, immune-therapies, monoclonal antibodies, and vaccines have rapidly emerged. These all treatments are based on symptoms, but oxygen therapy using a ventilator plays a major role in the treatment of COVID-19, and the latest available treatment options for COVID-19 is given in **Fig. 3**.

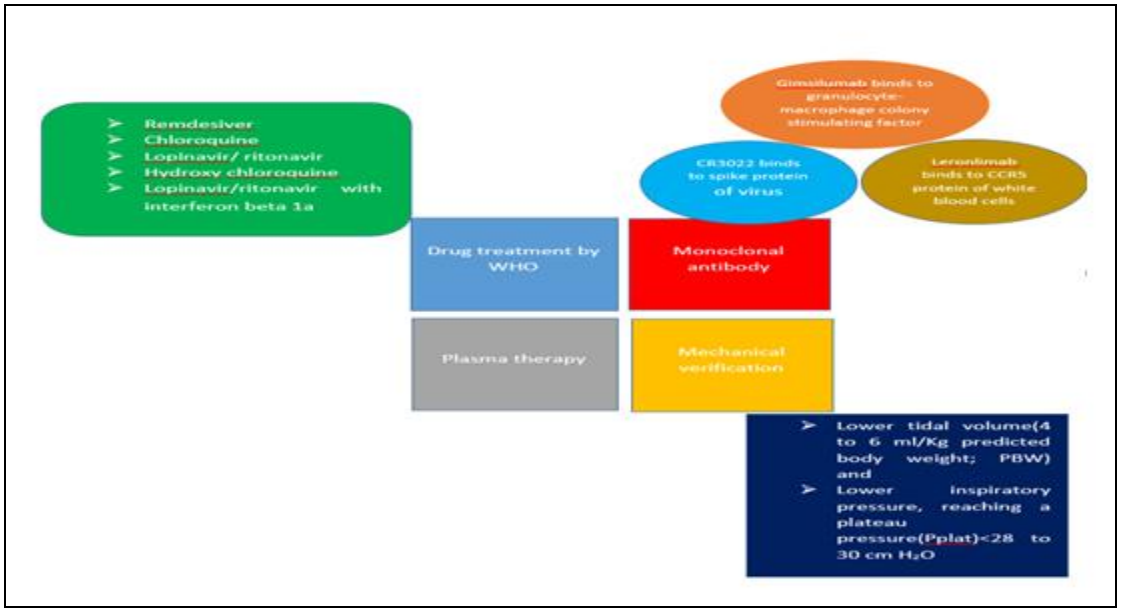

FIG. 3: LATEST AVAILABLE TREATMENT OPTIONS FOR COVID-19

Mechanical Ventilation: When respiratory failure has occurred in COVID-19 patients, mechanical ventilation becomes the mandatory treatment. Mechanical ventilation should always be with lower tidal volumes (4 to 6 ml/kg predicted body weight; PBW) and lower inspiratory pressures, reaching a plateau pressure (Pplat) < 28 to 30 cm H_2O. Positive end-expiratory pressure (PEEP) must be as high as possible to maintain the driving pressure and as low as possible (< 14cmH_2O). Furthermore, one must always remember that avoiding disconnections from the ventilator for preventing loss of PEEP and a telectasis. Finally, the utilization of paralytics is not endorsed unless PaO_2/FiO_2 (partial oxygen pressure/fraction of inspired oxygen) <150 mmHg. The prone ventilation for >12 h per day, and also the use of a conservative fluid management strategy for ARDS patients without tissue hypoperfusion (strong recommendation) are emphasized [11].

As earlier discussed, no effective drug treatment is available for fighting this COVID-19. But several drugs, including anti-viral, anti malarial, anti-microbial, and several anti-bacterial drugs, have been available and used in the treatment against COVID-19. Mostly a combination of drugs serves as an effective treatment against COVID-19 [11].

Systemic corticosteroids (Hydrocortisone, methyl prednisolone, dexamethasone, and prednisolone) are not recommended in the treatment of viral pneumonia or ARDS due to the increased mortality and secondary infection rates in influenza, impaired clearance of SARS-Co and MERS-CoV, and complications of corticosteroid therapy in survivors [11].

Further, COVID-19 is a viral disease, not a bacterial infection. Therefore, one should avoid the inappropriate administration of antibiotics. Several approaches have been introduced, such as lopinavir/ ritonavir (400/100 mg every 12 h), chloroquine (500 mg every 12 h), and hydroxyl-chloroquine(200 mg every 12 h), Alpha-interferon (*e.g.,* 5 million units by aerosol inhalation twice per day) is also used [11].

Mostly Remdesivir, an inhibitor of RNA polymerase with *in-vitro* activity against multiple RNA viruses, including Ebola- could be effective for both prophylaxis and therapy of CoVs infections. *In-vitro* studies revealed that Remdesivir inhibits all human and animal coronaviruses tested to date, including SARS-CoV-2, and have also shown antiviral and clinical effects in animal models of SARS-CoV-1 and MERS-CoV infections. Remdesivir was observed to be superior as a therapeutic regimen as compared to combination therapy of interferon β and lopinavir-ritonavir in a lethal murine model of MERS. In SARS-CoV-2 replication, Remdesivir is identified as a potent inhibitor in bronchial airway epithelial and human nasal cells. Administration of early Remdesivir was shown to exert extensive antiviral and clinical effects in a non-lethal rhesus macaque model of SARS-CoV-2 infection. Authors reported that patient's received Remdesivir had a 31% times quicker recovery in comparison to placebo (p < 0.001). Specifically, the median time to recovery was 11 days for patients treated with Remdesivir compared to15 days for people who received a placebo. Results additionally steered a survival benefit, with a mortality rate of 8.0% for the group receiving Remdesivir versus 11.6% for the placebo group (p = 0.059) [11].

Although many studies have been hinting Remdesivir gives no proper results against COVID-19. Wang *et al.* applied a randomized, double-blind, placebo-controlled, multicentre trial of Remdesivir on 237 COVID-19 patients. The 158 patients got Remdesivir out of 237 patients, and 79 patients were given placebo formulation. It was found that clinical improvement within the Remdesivir group was not considerably different from that of the control group.

Favipiravir (FPV) is the first drug approved by the national medical products administration of China for the treatment of COVID-19. Cai *et al.,* carried out an open-Label Control Study of FPV on COVID-19 patients. In this, 35 patients were given the treatment of Favipiravir and 45 patients were treated with combination therapy of Lopinavir and Ritonavir (LPV/RTV). It was found that those treated with FPV found to have faster viral clearance and better chest imaging change than patients treated with LPV/RTV [11].

Chang *et al.,* also carried out studies on 240 COVID-19 patients by giving Favipiravir versus Arbidol. Among them, 120 patients were given

Favipiravir, and 120 patients were given Arbidol. It was found that no distinction was determined in both treatments after 7 days. Favipiravir showed considerable relief in cough and pyrexia after 7 days of treatments [11].

Clinical trials in the primary stages failed, and no significant changes were observed in COVID-19 patients. In addition to remdesivir, researchers tend to evaluate all of the data related to the other antiviral drugs, which called the attention, such as ribavirin, favipiravir, oseltamivir, and umifenovir. Ribavirin (Tribavirin) is a broad-spectrum guanosine analog effective against RNA and DNA viruses such as hepatitis C and E. Ribavirin in conjunction with interferon displayed synergistic activity *in-vitro* antiviral study. Therefore, combination therapy of interferon and ribavirin was widely used due to the synergistic effect. Concomitant use of three or more antiviral drugs is not suggested and patient symptoms will recover after drug withdrawal. Antiviral drugs ought to be stopped if nucleic acid test results from sputum specimens stay negative for more than three times [11].

Chloroquine and hydroxychloroquine (HC) had received great attention across the globe owing to their viral enzymes or process inhibition, particularly in Iran, U.K, and France. However, FDA revoked the emergency use of these drugs due to severe cardiac adverse events and other potential side effects. HC is superior to chloroquine and reported positive results in some pre-clinical data *in-vitro* and protocols. Both of these anti-malarial drugs might domore harm than good due to many side effects and should be prescribed not more than 7 days. The major concerns in rare cases are cardiac arrest, retinal damage, and ocular toxicity, particularly, people with heart conditions are at higher risk of severity [11].

Philippe Gautret *et al.,* conducted a study on hydroxychloroquine (HC) and azithromycin as a treatment for COVID-19. It was observed that patients treated with hydroxychloroquine showed a significant reduction in viral infection as compared to the control. Combination of Hydroxychloroquine with azithromycin was more effective in the elimination of the virus. Magagnoli et al. conducted a study to showcase the outcomes of hydroxyl-chloroquine in COVID-19 patients. This study was carried out on total 368 patients, and it was divided into three groups, namely HC treatments, without HC treatments, and combination treatments of HC and azithromycin [11].

The primary outcome of this study was an investigation of the mortality rate and required ventilation facility on these groups. It was observed that 27.8, 22.1 and 11.4 mortality rate was found in HC group, combination group and without HC group, respectively. From the studies, it was also found that mechanical ventilation occurred in 13.3% of the HC group, 6.9% of the combination group, and 14.1% of the without HC group. Therefore, it was investigated that no effect was found in mortality rate after HC treatment and combination treatments but, a significant reduction of mechanical ventilation was observed after combinational treatments when compared to the other two groups [11].

The management of venous thromboembolism (VTE) and antithrombotic therapy for acute coronary syndromes (ACS) is very relevant in COVID 19 pandemic. Anticoagulants like Vitamin K antagonists, dabigatran, apixaban, edoxaban, rivaroxaban and antiplatelets like clopidogrel, prasugrelticagrelor, cilostazol may have inter-actions with COVID−19 investigational drug. Therefore, drug interactions should be kept in mind to mitigate the thrombotic and hemorrhagic events in high-risk patients [11].

Monoclonal Antibody: Numerous monoclonal antibodies have been explored in the treatment of COVID-19. Mainly, gimsilumab and leronlimab have been employed in the treatment of COVID-19. Gimsilumab targets a pro-inflammatory cytokine known as a granulocyte-macrophage colony-stimulating factor (GM-CSF). By this mechanism reduces the cytokine storm within the airway pathways and gives symptomatic relief to patients from COVID-19. In a recent study, it was identified that monoclonal antibody namely CR3022, bind and cover the spike RBD of the virus. Therefore, the ACE-2 receptor cannot bind with the epitopes of the monoclonal antibody, which covers the RBD of the virus. However, the entry of the virus into the body cannot be replicated because of the unavailability of the binding site for

the host virus. CR3022 has the potential to be promoted as a therapeutic candidate, alone or together with other neutralizing antibodies for the prevention and treatment of COVID-19 infection. CCR5 is a protein on the surface of white blood cells that plays a vital role in the way HIV develops in the human body. Leronlimab is a monoclonal antibody being studied as a potential treatment for HIV. It binds to the CCR5 receptor, which inhibits the release of inflammatory cytokine [11].

Plasma Therapy and its Advancement: Convalescent plasma (CP) may be a promising plasma antibody treatment that would help patients whose bodies cannot generate enough antibodies fighting against COVID-19 to cure the disease. With the help from UK National Institute for Health Research (NIHR), the trial is led by NHS Blood and Transplant and University of Cambridge experts. The UK Government approved a national clinical trial to assess the efficiency of plasma therapy for the treatment of COVID-19 patients. This trial will decide that these treatments should be used or not within the COVID-19patients in the future. If the treatment becomes effective, a total of 10,000 units of convalescent plasma are going to be provided to the patients during as called-up national program that enabling the treatment of 5000patients per week. Duan et al. also examined the effectiveness of convalescent plasma therapy for COVID-19 patients. It was observed that anti-bodies levels were suddenly increased and reduced the concentration of reactive proteins in COVID-19 patients. The clinical symptoms were significantly improved along with the increase of oxyhemoglobin saturation within 3 days without any antagonistic effects [11].

Researchers will use plasma from recovered patients for at least 28 days to increase antibody levels. The main findings were as follows: (a) in critically ill patients, mortality may be reduced by plasma therapy (b) neutralizing antibodies are increased, and disappearance of SARS-CoV-2 RNA after CP therapy was observed, and (c) beneficial effect on clinical symptoms after administration of convalescent plasma [11].

Based on the limited scientific data, Plasma therapy in COVID-19 patients is safe, clinically effective, and reduces mortality. In this method, doctors isolate antibodies from the plasma of recovered patients' blood and administer them to currently exposed and infected patients. Antibodies aid in the identification of the pathogens and reject the pathogen in the patients. However, large multicenter clinical trials are urgently needed to conclude the optimal doses and treatment time point for the CP therapy to tackle COVID-19 pandemic [11].

Nano-Based Vaccine Candidates & Treatments for Coronaviruses: Vaccination has been referred to as one of the most effective medical interventions used to stimulate an immune response against infectious disease [14]. Meanwhile, as nanoparticles have been proven to possess immunostimulatory effects [15], a great deal of attention has been given to the development of nano-based therapeutic agents or vaccines against different types of coronaviruses.

For example, in 2011, Staroverov *et al*., studied the protective immune response stimulated by the administration of gold nanoparticles (Au NPs) conjugated with a type of coronavirus known as swine transmissible gastroenteritis virus (TGEV) in immunized mice and rabbits [16]. TGEV-conjugated colloidal gold NPs was found to produce higher concentrations of IFN-γ and neutralizing antibody in vaccinated animals. Immunization with the antigen-colloidal gold nanoparticles increased propagation of T cells tenfold as compared to the response to free antigen, and the researchers of the study also reported that administration of this complex resulted in subsequent activation of macrophage respiratory activity and higher immunity against TGEV. Therefore, a virus conjugated to AuNPs could be considered as a potential antiviral candidate for vaccine application.

Kim *et al.,* introduced a ferritin-based NP assembly mediated by RNA as a novel molecular chaperone and demonstrated that using the NP-based vaccine against MERS-CoV can induce CD4+ T cells, which in turn lead to the generation of IFN-γ and TNF-α upon antigen stimulation [17]. Additionally, Jung *et al*., endeavored to develop an immunogenic vaccine against MERS-CoV employing a heterologous prime-boost strategy involving a recombinant adenovirus serotype 5 encoding the

MERS-CoV spike gene (Ad5/MERS) and spike protein nanoparticles [18]. Groups of female BALB/c mice were immunized three times with the prime-boost vaccination. It was observed that the homologous spike protein NPs successfully induced higher antibody titers compared with the Ad5/MERS-only group. However, a Th1 immune response was not observed to be provided by spike protein NPs themselves, and only a Th2 immune response involving induction of neutralizing antibodies was elicited. Therefore, to provide much more durable immunogenicity and an acceptable balance of Th1/Th2 responses, a heterologous one-stage Ad5/MERS prime and two-stage spike protein NPs boost is perceived to be more effective than the homologous prime-boost regimen with either Ad5/MERS or spike protein nanoparticles alone.

In 2019 Lin *et al.*, developed a unique viromimetic nanoparticle-based vaccine coupled with an immunologic stimulator of interferon genes agonist adjuvant against MERS-CoV [19]. Hollow polymeric nanocarriers coated with receptor-binding domain (RBD) antigens followed by cyclic diguanylate monophosphate loading. C57BL/6 mice were then immunized with this developed vaccine. Lin et al. reported that the virus-like NPs induced increased cellular and humoralimmune responses. A constant humoral and CD4+ T-cell response was also detected within the studied mice immunized with the virus-like NP vaccine compared with free RBD antigen admixed with either free cyclic diguanylate monophosphate or MF59 (AddaVax), an adjuvant for influenza vaccines that have been utilized clinically. Compared to MF59, this viromimetic NP vaccine induced higher levels of humoral responses. Furthermore, mice immunized with the proposed NP vaccine produced high levels of RBD-specific IgG2a antibodies without induction of lung eosinophilic immunopathology after the infection. Sekimukai *et al*., recently conducted a study to find the efficacy of two kinds of adjuvants (AuNPs and Toll-like receptor agonists) with recombinant S protein and it was evaluated against SARS-CoV infected mice [20]. Results indicated that vaccination with AuNP-adjuvanted protein elicited a strong IgG response but, in comparison to a Toll-like receptor agonist-adjuvanted vaccine, did not result in induction of protective antibodies and decreasing eosinophilic infiltration.

Thus, owing to their immunogenic properties, various types of NPs, including gold NPs, spike protein NPs, and hollow polymeric NPs have all been reported to possess considerable potency to induce an immune response against coronaviruses in animal models and *in-vitro.*

Nano-based Antiviral Activity: Nanomaterials have continually been applied as antiviral agents [21, 22], or as delivery platforms for antiviral compounds [23]. This section focuses on the application of nanomaterials as antiviral agents against coronaviruses.

In a patent invented in 2014 by Cho *et al.*, a mixture comprising of silver colloid, titanium dioxide (TiO2) NPs, a dispersion stabilizer, a binder, and water showcased its antibacterial, antifungal, and antiviral activities (US 8,673,331 B2) [24] Results of antiviral tests showed that at 100-fold dilution of the composition concentration showed antiviral activity against porcine epidemic diarrhea virus (PEDV) and TGEV at a pace of 99.99% or more. On the other hand, when the concentration of composition was 1000-fold diluted, virus growth inhibition was at a rate of 99.9% for PEDV and 93.0% inhibition for TGEV. The antiviral activity of the nanomaterial introduced by Cho et al. was therefore dependent on composition concentration, meaning dosage should be adjusted to possess desired inhibition[24].

In 2014, Lv *et al*., compared the strength of immune responses induced by four different silver nanomaterials, including silver NPs, silver nano-wires of 60 and 400 nm, and silver colloids, on TGEV infected swine testicle cells [25]. At a concentration of between 3.125–12.5 μg/ml, the percentage inhibition in virus titer was evaluated in different silver nanomaterials. It was observed that from the different types of silver nanomaterials, only Ag NPs and the two types of Ag nanowires induced protection against TGEV. The silver colloids were not reported to restrain the cellular entry of the virus. The Ag NPs and silver nanowires, both were capable of diminishing the number of apoptotic cells elicited by TGEV.

In the year 2017, Hu *et al.*, developed a promising treatment approach based on the diphyllin nanoformulation for the treatment of feline

infectious peritonitis (FIP), which is caused by feline coronavirus [26]. Diphyllin is a vacuolar ATPase that has been illustrated to inhibit endosomal acidification, a necessary process for virus uncoating and cellular entry. It was shown that poly (ethylene glycol)-poly (lactide-coglycolide), which was used as the diphyllin nanocarrier, enhanced the inhibitory activity of diphyllin against FIP and also improved the safety profile. The antiviral activity of diphyllin nanoparticles was also investigated. It was observed that administration of high doses of the nanoparticles was found to be tolerable in mice. Therefore, diphyllin nano-particles proved to occupy a prominent antiviral effect against FIP. Though its potential as a vaccine candidate was not studied as this study still manifests that nanoformulations can be effective against coronaviruses, and this specific example could be a promising candidate for treatment.

In 2018 by Du *et al.*, first founded a therapeutic strategy based on Ag nanomaterials against the alpha coronavirus PEDV [27]. They demonstrated that Ag_2S nanoclusters (NCs) could restrain PEDV proliferation in treated Vero cells. As suggested by authors, this might be attributed to the fact that treatment with Ag_2S NCs inhibited the viral budding and the synthesis of viral negative-strand RNA. Further, the Ag_2S NCs were found to positively regulate the proliferation of IFN-stimulating genes and also the expression of pro-inflammation cytokines, resulting in protection against PEDV infection, making them a good choice to be employed in further studies as a treatment tool.

Chen *et al.*, in 2016, stated the antiviral activity of graphene oxide–silver (GO–Ag) nanocomposites against non-enveloped and enveloped viruses by [28]. To evaluate the antiviral activity of GO-Ag, different dilutions of GO–Ag solutions were incubated serially with a diluted solution of feline coronavirus. After removing the composite particles, the supernatant was evaluated using a virus inhibition assay. They displayed that 0.1 mg/ml of GO–Ag can inhibit 24.8% of feline coronavirus infection. GO–Ag showed higher efficacies in comparison with treatment with GO alone. During the method of restraining viral infection, negatively charged GO sheets interact with the positively charged lipid membranes, and silver particles bind to the sulfur groups of the viral proteins. As a result, it has been found that GO could only have an inhibitory effect on enveloped viruses at noncytotoxic concentrations, while GO sheets containing AgNPs are capable of impeding the infection caused by both non-enveloped and enveloped viruses [28].

To tackle human coronavirus NL63, Cejka *et al*., developed a biopolymeric material to develop nano/microspheres (NS/MS) to tackle human coronavirus NL63 which had good potential for adsorbing coronaviruses [28]. The investigation demonstrated that after the addition of N-(2-hydroxypropyl)-3-trimethyl chitosan (H-HTCC)-NS/MS to viral suspensions, there was a decrease in the number of copies of viral RNA; this showed a good correlation with the amount of added H-HTCC-NS/MS. Their study demonstrated that 2.5 mg/500 µl H-HTCC-NS/MS could cause a decrease of 99.60%. On the other side when 10 mg/500 µl of HHTCC-NS/MS was added, there was a decrease of 99.92%.

Therefore, nanomaterials can have excellent antiviral applications against a range of coronaviruses. However, more focus needs to be placed on investigating the antiviral activity of nanomedicines against SARS-CoV, MERS-CoV [28].

Post-Covid-19 Era: The disastrous COVID −19 led to the social crisis and an economic system failure globally. Post COVID-19 involves complications; lessons learned, immunity, financial loss, and preparedness. The sole complication of COVID-19 is a type of pneumonia called 2019 novel corona virus-infected pneumonia (NCIP) in conjunction with ARDS, anemia, acute cardiac injury, and secondary infection associated with other types of coronavirus [11].

Sekowski *et al*., reported the high chances of Post-Traumatic Stress Disorder (PTSD) in COVID-19 survivors based on previous research on PTSD in epidemic survivors (*e.g.*, SARS). PTSD is a serious mental disorder that negatively affects functioning and social life by reliving the traumatic event, emotional numbness. A preliminary report by Bo *et al.* indicated that nearly all clinically stable patients with COVID-19 in China experienced significant severity of post-traumatic stress symptoms.

Both the studies suggest regularly screen for PTSD and pay attention to individuals at high risk of complications, appropriate crisis psychological interventions, and long-term follow-up assessments should be started immediately for COVID-19 survivors. The issue of the negative detrimental impact of significant post-traumatic stress prevalence of PTSD in individuals posts COVID-19 remains a matter of future research as symptoms may develop up to 6 months after the traumatic event [11].

Immunity remains the cornerstone for post-COVID-19 survival. The strength and duration of immunological response in COVID−19 survivors remain the major knowledge gap. According to WHO, there is no evidence at this point that people can't be infected with the virus again or not, and the development of an antibody response will be protective from secondary infection. Some countries suggested detection of antibodies to COVID−19 could serve as the basis for an 'immunity passport' or certificate of immunity, assuming that they are protected against re-infection. But WHO announced that issuing such a certificate increases the severity of the disease. HERD immunity would be able to play a vital role in addressing the devastating COVID-19, which is indirect protection conferred to the susceptible ones by immune individuals against a specific pathogenic infestation in a given population. It is possible only through vaccination.

Vaccine approval may take up to a decade or more to win approval based on their ability to stop the disease in the population. Typically, HERD immunity isn't achieved in a short time, like a year or two, and would take several years to confer sufficient 'HERD immunity' to fight COVID-19 [11].

The lessons from unprecedented COVID−19 teach one about the importance of readiness, preparedness, and response actions to combat sudden epidemics globally. In the battle of COVID-19, it is very crucial to maintain close watch of recovered patients, understand the long-term complications associated with the risk of relapse, and post-discharge surveillance of COVID-19 survivors. Emergency response mechanisms, risk communication, and public engagement case finding, contact tracing and management, surveillance, public health measures, laboratory testing are the various priority areas of work in the transmission of COVID as per the interim guidance document by WHO [11].

Conclusion and Future Perspective: The entire world is functioning from basic research to advanced technology to mitigate the effects of the COVID-19. Recently the applications of nanoscience and nanotechnology concepts are information about the interaction of nanomaterials with diverse viral particles, especially focusing on SARS-CoV-2, highlighting as much as possible on prevention, diagnosis, and treatment of the COVID-19 disease under the nanotechnology umbrella.

Advancements in diagnostics and treatment of COVID-19 are progressing more and more in a very agile manner, but this disease is much more complex and aggressive than typical seasonal flu infections. The effect of the initially promising drugs, such as chloroquine and hydroxy-chloroquine, is still not clear for COVID19 therapeutics. At present, treatments could include cocktails of antiviral drugs addressed to patients with mild-to-moderate COVID-19 symptoms to inhibit the amplification of the virus. However, the final objective is to develop a new generation of drugs that specifically could target SARS-CoV-2.

Probably, the utilization of recently reported nanocarriers facilitating the transport of those drugs, and most likely their administration via the nasal route, could contribute to finding a cure for COVID-19 or at least saving as many lives as possible. Also, strides in detection systems based on nanotechnology are at this moment under rapid development, antigen and antibody test kits allowing self-diagnosis using blood or exudates like mucus and saliva will exhibit an easy way to enable fast identification of asymptomatic patients and patients with mild symptoms and, hence, quickening their isolation in quarantine.

As indicated above, there are currently numerous attempts in progress to develop COVID-19 vaccines, including clinical trials. Here also nanotechnology approaches could be of help in building innovative nanoarchitectonics-based vaccines to prevent the disease. Just as an example in this context, there are vaccines based on spike

protein nanoparticles or on virus-like particles mimicking nanovesicles recently developed for MERS-CoV, which could be potentially extrapolated to COVID-19 vaccine development. In short, nanotechnology is a powerful multi-disciplinary tool that offers various approaches and strategies that could contribute strongly to promoting research projects around the world against this lethal infectious coronavirus disease.

ACKNOWLEDGEMENT: The authors are thankful to the management of Swamy Vivekanadha College of Pharmacy for providing the facilities and access to online resources for the literature survey to complete this review successfully.

CONFLICTS OF INTEREST: All authors declared that there are no conflicts of interest.

REFERENCES:

1. Guarner J: Three emerging coronaviruses in two decades: the story of SARS, MERS, and now COVID-19.Am. J. Clin. Pathol 2020; 153: 420-21.
2. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY and Yan Y: The origin, transmission, and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Military Medical Research 2020; 7(1): 1-0.
3. He F, Deng Y and Li. W: Coronavirus disease 2019: what we know. J Med Virol 2020; 92(7): 719-25.
4. Nicola M, O'Neill N, Sohrabi C, Khan M, Agha M and Agha R: Evidence-based management guideline for the COVID-19 pandemic-Review article. International Journal of Surgery 2020; 77: 206-16.
5. World Health Organization. Clinical management of COVID-19.2021 https://www.who.int/publications/i/item/clinical-management-of-covid-19.
6. Tobaiqy M, Qashqary M, Al-Dahery S, Mujallad A, Hershan AA, Kamal MA and Helmi N: Therapeutic management of COVID-19 patients: a systematic review. Infection Prevention in Practice 2020: 100061.
7. World Health Organization. Solidarity" clinical trial for COVID-19 treatments 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.
8. Zhu JD and Meng W: Broad-spectrum antiviral agents. Front Microbiol 2015; 6.
9. Campos EV, Pereira AE, De Oliveira JL, Carvalho LB, Guilger-Casagrande M, De Lima R and Fraceto LF: How can nanotechnology help to combat COVID-19? Opportunities and urgent need. Journal of Nanobiotechnology 2020; 18(1): 1-23.
10. Jain N, Choudhury A, Sharma J, Kumar V, De D and Tiwari R: A review of novel coronavirus infection (Coronavirus Disease-19). Global Journal of Transfusion Medicine 2020; 5(1): 22.
11. Bhavana V, Thakor P, Singh SB and Mehra NK: COVID-19: Pathophysiology, treatment options, nanotechnology approaches, and research agenda to combating the SARS-CoV2 pandemic. Life Sciences 2020: 118336.
12. Chakravarty M and Vora A: Nanotechnology-based antiviral therapeutics. Drug Delivery and Translational Research 2020: 1-40.
13. Ruiz-Hitzky E, Darder M, Wicklein B, Ruiz-Garcia C, Martín-Sampedro R, Del Real G and Aranda P: Nanotechnology responses to COVID-19. Advanced Healthcare Materials 2020; 9(19): 2000979.
14. Afrough B, Dowall S, Hewson R. Emerging viruses and current strategies for vaccine intervention. Clin. Exp. Immunol 2019; 196(2): 157-66.
15. Zaman M, Good MF, Toth I. Nanovaccines and their mode of action. Methods, 2013; 60(3): 226-23.
16. Staroverov SA, Vidyasheva IV, Gabalov KP, Vasilenko OA, Laskavyi VN and Dykman LA: Immunostimulatory effect of gold nanoparticles conjugated with transmissible gastroenteritis virus. Bulletin of Experimental Biology and Medicine 2011; 151(4): 436.
17. Kim YS, Son A, Kim J, Kwon SB, Kim MH, Kim P, Kim J, Byun YH, Sung J, Lee J and Yu JE: Chaperna-mediated assembly of ferritin-based Middle East respiratory syndrome-coronavirus nanoparticles. Frontiers in Immunology 2018; 9:1093.
18. Jung SY, Kang KW, Lee EY, Seo DW, Kim HL, Kim H, Kwon T, Park HL, Kim H, Lee SM and Nam JH: Heterologous prime–boost vaccination with adenoviral vector and protein nanoparticles induces both Th1 and Th2 responses against Middle East respiratory syndrome coronavirus. Vaccine 2018; 36(24): 3468-76.
19. Lin LC, Huang CY, Yao BY, Lin JC, Agrawal A, Algaissi A, Peng BH, Liu YH, Huang PH, Juang RH and Chang YC: Viromimetic STING agonist-loaded hollow polymeric nanoparticles for safe and effective vaccination against Middle East respiratory syndrome coronavirus. Advanced Functional Materials 2019; 29(28): 1807616.
20. Sekimukai H, Iwata-Yoshikawa N, Fukushi S, Tani H, Kataoka M, Suzuki T, Hasegawa H, Niikura K, Arai K and Nagata N: Gold nanoparticle-adjuvanted S protein induces a strong antigen-specific IgG response against severe acute respiratory syndrome-related coronavirus infection, but fails to induce protective antibodies and limit eosinophilic infiltration in lungs. Microbiology and Immunology 2020; 64(1): 33-51.
21. Poon WL, Alenius H, Ndika J, Fortino V, Kolhinen V, Meščeriakovas A, Wang M, Greco D, Lähde A, Jokiniemi J and Lee JC: Nano-sized zinc oxide and silver, but not titanium dioxide, induce innate and adaptive immunity and antiviral response in differentiated THP-1 cells. Nanotoxicology 2017; 11(7): 936-51.
22. Miyako E, Nagata H, Hirano K, Sakamoto K, Makita Y, Nakayama KI, Hirotsu T. Photoinduced antiviral carbon nanohorns. Nanotechnology 2008; 19(7): 075106.
23. Calderón L, Harris R, Cordoba-Diaz M, Elorza M, Elorza B, Lenoir J, Adriaens E, Remon JP, Heras A and Cordoba-Diaz D: Nano and microparticulate chitosan-based systems for antiviral topical delivery. European Journal of Pharmaceutical Sciences 2013; 48(1-2): 216-22.
24. Cho IH, Lee DG and Yang YY: inventors; GP&E, assignee. Composition with sterilizing activity against bacteria, fungus, and viruses, application thereof, and method for preparation thereof. United States patent US 8,673,331. 2014.
25. Lv X, Wang P, Bai R, Cong Y, Suo S, Ren X and Chen C: Inhibitory effect of silver nanomaterials on transmissible virus-induced host cell infections. Biomaterials 2014; 35(13): 4195-203.
26. Hu CM, Chang WS, Fang ZS, Chen YT, Wang WL, Tsai HH, Chueh LL, Takano T, Hohdatsu T and Chen HW:

Nanoparticulate vacuolar ATPase blocker exhibits potent host-targeted antiviral activity against feline coronavirus. Scientific Reports 2017; 7(1): 1-1.

27. Du T, Liang J and Dong N: Glutathione-capped Ag2S nanoclusters inhibit coronavirus proliferation through blockage of viral RNA synthesis and budding. ACS Appl. Mater. Interfaces 2018; 10(5): 4369-78.
28. Chen YN, Hsueh YH, Hsieh CT, Tzou DY and Chang PL: Antiviral activity of graphene–silver nanocomposites against non-enveloped and enveloped viruses. International Journal of Environmental Research and Public Health 2016; 13(4): 430.

How to cite this article:
Rajaram S, Prakashan A, Pragathi B, Saieswari K, Sree ARV and Hedge YM: The potential role of nanotechnology to combat Sars-Cov2 - 2019: diagnosis, treatment options, approaches – a scopious review. Int J Pharm Sci & Res 2021; 12(6): 2966-81. doi: 10.13040/IJPSR. 0975-8232.12(6).2966-81.