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CLINICAL FEATURES, TREATMENT APPROACHES AND PROMISING CONTRIBUTIONS OF NANOMEDICINES TOWARDS COVID-19

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ABSTRACT: The World Health Organization (WHO) declared COVID -19 a pandemic on March 11 2020. As of today, there have been 122 million COVID -19-update cases worldwide, and the counting goes on. Unfortunately, strategic measures such as total lockdown, social and self-isolation, and gradual lifting of some of these restrictions both pose economic, social, and psychological distress and are thought to have affected people more than the virus itself. There is no specific antiviral drug available at this time. However, there are currently five main vaccines on the market that aim to protect the population from contracting the coronavirus. Moderna, Pfizer/BioNTech, Oxford/AstraZeneca, Sputnil V, and Sinopharm vaccines are among those included. Furthermore, developing an effective medication that is reliable for the treatment may be more effective, but it is more difficult. To accomplish this, molecular bio-interaction, virulence, clinical, and pathological features of COVID -19 viruses must be clearly understood. Additionally, the designation of potential antiviral drugs in the form of nanomedicines will optimize the therapeutic outcome and improve the quality of life. This study expanded on the clinical, pathological, and virulence features of COVID-19 and highlighted the need to investigate nanomedicines as a gold option that could potentiate the world to win the fight against COVID-19 infection.

INTRODUCTION: Coronavirus is a single-stranded RNA virus, zoonotic and pleomorphic, having a diameter range of 100-160 nm. The virus named "corona" due to the resemblance of its spikes with the crown (monarch's ornamental cap), as illustrated in **Fig. 1**.

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However, coronavirus (COVID-19) out-broke in December 2019 at Wuhan Seafood Wholesale Market in China. The disease spreads rapidly, it transformed from epidemic to pandemic in a short period.

It was initially considered as "pneumonia of unknown etiology" because its clinical manifestations resemble pneumonia. Until January 2020, the genetic sequence of the virus discovered to have mimic that of SARS-CoV, a virus that causes severe acute respiratory syndrome, in 2003. This is why it was named SARS-CoV 2/COVID – 19 [1]. SARS-CoV 2 is a highly contagious virus

transmits that spreads easily via orofacial routes through aerosol inhalation, physical contact, respiratory droplets, coughing, and sneezing from an infected person. It has a half-life of 1.1 hours in aerosols, 4 hours on copper, and 72 hours on plastic and stainless steel. However, you can only survive for less than 24 hours on cardboard [2]. The current exponential escalation pandemic COVID-19 might only be the tip of the iceberg due to underreporting and inadequate testing equipment, and shortage of the available vaccines. Besides, developing effective antiviral and vaccine against COVID-19 remains a substantial challenge [4]. The review focused on the elucidation of molecular bio-interactions, pathological and clinical presentations of the virus and emphasized the need to explore nanomedicines as a gold possibility against COVID-19.

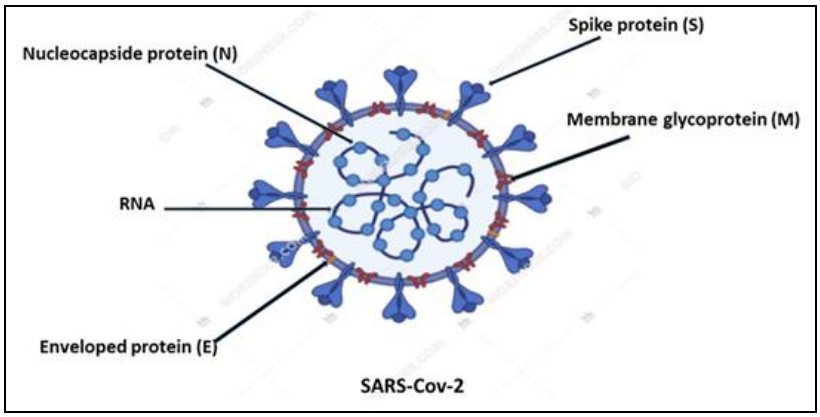

FIG. 1: STRUCTURE OF COVID-19

Molecular Bio-Interaction:

Life Cycle of SARS-Cov-2 in A host Cell: The cycle begins when the spike protein (S protein) binds to the angiotensin-converting enzyme (ACE 2) cellular receptor. The conformation changes in the S protein facilitates the viral envelope fusion with the cell membrane through the endosomal pathway. Then SARS-CoV-2 releases RNA into the host cell. Genome RNA is translated into viral replicase polyproteins PPa 1a and PPa 1b, which are then cleaved into small products by viral proteinases. The polymerase produces a series of subgenomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins; viral proteins and genome RNA are subsequently assembled into virions in the ER and Golgi and then transported *via* vesicles and released out of the cell. shows that, upon As illustrated in **Fig. 2.**

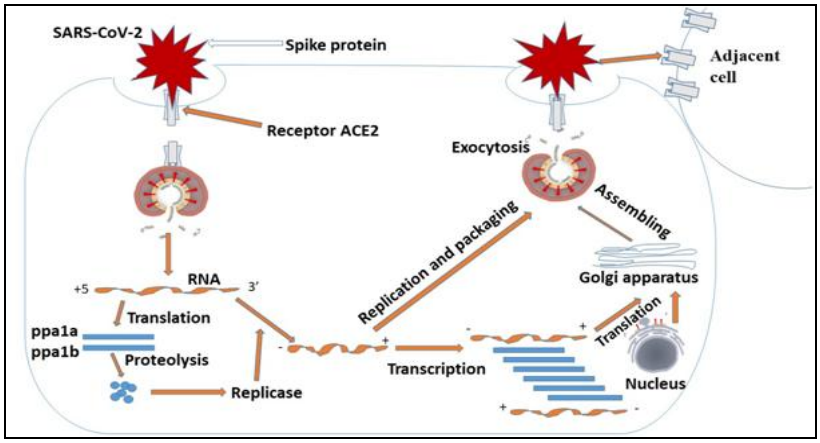

FIG. 2: THE LIFE CYCLE OF SARS-COV-2 IN HOST CELLS

Pathogenesis and Virulence: Available literature shows that after COVID-19 had infected the cell, it produces many viral proteins *via* different signalling pathways pathways and suppress the innate immune responses. Some of these inhibit the production of interferon (IFN), leading to the uncontrolled stimulation of potent proinflammatory cytokines, which acerbate the process of patho-genesis ranging from cellular and tissue damage, organ failure, and death [6]. The spike surface

glycoprotein of coronavirus plays an essential role in binding to receptors on host cells and determines phototropism. Spike protein (S-protein) of 2019 - nCoV is reported to bind with angiotensin-converting enzyme 2 (ACE2), the same receptor of SARS- CoV, to invade host cells, whereas MERS-CoV uses dipeptidyl peptidase 4 (DPP4) as the primary receptor [7]. The amino acid sequence of S-protein in 2019-nCoV is 76.47% identical to that of SARS-CoV, with the same structural confirmation and electrostatic properties in the interaction interface.

The residues at positions 442, 472, 479, 487, and 491 in S-protein were reported to be at the receptor complex interface with ACE2. However, four of the five critical residues in the 2019- nCoV S-protein were not preserved except for Tyr491. The binding free energy for 2019-nCoV S-protein to bind with human ACE2 increases by 28 kcal mol–1 compared to SARS-CoV S-protein (50.6 kcal mol–1 *vs.* 78.6 kcal mol–1), due to the loss of hydrogen bond interactions by replacing Arg 426 with Asn 426 [8]. The furin-like cleavage site was supposed to be cleaved by proprotein convertase furin at special viral envelope glycoproteins, thereby enhancing viral fusion with host cell membranes [9]. Overall, the binding affinity between 2019-nCoV S-protein and ACE2 is comparable or even stronger than that of SARS-CoV's S- protein and ACE2 respectively.

This may explain the rapid development and strong ability of human-to-human transmission in COVID-19. After infection, envelope (E) protein (small protein) induce viral morphogenesis, influence "SARS-CoV – host" interaction and trigger a pathogenic inflammatory response that leads to the severity of illness and death. Fortunately, it could understand that anti-COVID-19 vaccines and novel drugs could be developed by targeting and modification of the (E) protein [7].

Clinical Presentation: Clinical presentation of COVID-19 greatly resembled viral pneumonia such as SARS and MERS. About 81% of COVID-19 reported cases are mild with the high rate of recovery that happens in two weeks [10].

Severe patients progressed rapidly with acute respiratory distress syndrome (ARDS) and septic shock and eventually ended in multiple organ failure. The elderly people suffering from comorbidities are more prompt to SARS-CoV-2 infection, as men are more susceptible than women are. A similar result has seen in the case of SARS-CoV and MERS-CoV infections [11], due to X chromosome and sex hormones' role on innate and adaptive immunity [12]. Many chronic diseases such as hypertension, cardio-cerebrovascular and developed to 87.9% following hospitalization 13 compared to as high as 99% and 98%diseases, and diabetes may increase the risk of 2019-nCoV infection [13], which is similar to MERS-CoV infection [11]. Smoking may be a negative prognostic indicator for COVID-19 [13, 14]. The onset of symptoms was usually mild and nonspecific, presenting with fever, dry cough, and shortness of breath.

Very few COVID-19 patients had prominent upper respiratory tract and gastrointestinal symptoms (*e.g.,* diarrhoea) [13, 15] compared to 20–25% of patients with MERS-CoV or SARS-CoV infection who developed diarrhea [16]. However, only 43.8% of COVID-19 patients had an initial presentation of fever and rises to 87.9% following hospitalization when compared to 99% and 89% of SARS-CoV and MERS-CoV infections respectively. Besides, if the surveillance methods of evaluating the infected patients heavily focused on fever, asymptomatic patients could be left undetected and non-quarantined as a silent infection source if the surveillance methods focused heavily on fever detection. Moreover, the onset of symptoms may help physicians in identifying patients with poor prognosis. Patients admitted to the ICU were more likely to report pharyngeal pain, dyspnea, dizziness, abdominal pain, and anorexia [17].

In terms of laboratory findings, a substantial decrease in the total number of lymphocytes could be used as an index in the diagnosis of 2019-nCoV infection, indicating consumption of immune cells and impairment to cellular immune function [18]. Non-survivors developed more severe lymphopenia over time. Initially, pro-inflammatory plasma cytokines concentration was higher in COVID-19 patients than in healthy adults. ICU patients had even higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα compared to non-ICU patients [15]. There were numerous differrences in between the patientsadmitted to the ICU and

non-admitted patients. The differences include the detection of the high level of white blood cells, neutrophil, D-dimer, creatine kinase, and creatine counts among the ICU patients [18]. Typical chest CT manifestations of COVID-19 pneumonia were initially small subpleural ground-glass opacities that grew larger with crazy-paving patterns and consolidation. After two weeks of growth, the lesions were gradually absorbed, leaving extensive opacities and subpleural parenchymal bands in recovery patients. It was demonstrated that patients with normal radiologic findings on initial presentation consisted of 23.9% and 5.2% of severe and non-severe cases respectively.

Epidemiology: Even though, COVID-19 was reported to originate from Wuhan market of China. Nevertheless, phyloepidemiological analyses revealed that the Wuhan market was not the origin of 2019-nCoV. The virus was imported from elsewhere and boosted in the crowded market [19]. Some pieces of evidence indicated the virus spread silently through droplets or contact transmission between people in Wuhan before the cluster of cases from the Wuhan market was discovered in late December 2019. More so, the transmissibility of a virus is measured by repro-ductive number (R0) that indicates the average number of new infections generated by an infectious person in a naïve population. For R0>1, the number of new infections is likely to increase, while the R0 <1, means the transmission rate is likely to decline and die out [20].

The preliminary R0 of 2019-nCoV was reported as 2.24–3.58. Several research groups reported an estimated R0 of the outbreak depending on distinct estimation methods and the validity of underlying assumptions [21]. The global healthcare agencies including the Centre for Disease Control and Prevention (CDC) recommended the 14 days as quarantine period for COVID – 19 exposed individual. Nonetheless, 19 May 2020 considered the pandemic threshold because about 1, 12,637 new cases were recorded, which was the highest in the global history of COVID-19 cases. Presently, the United States of America had overtaken China and became the largest COVID-19 hotspot having the highest morbidity and mortality rates. Followed by, Brazil, Russia and the United Kingdom. Whereas, some countries like Saint Barthelemy, Anguilla, Saint Pierre, and Miquelon recorded the lower cases of 6, 3, 1, and 0 respectively [22]. Moreover, the decline in the rate of daily new cases in China was discovered on February 26, 2020 [23].

Proposed Conventional Treatment Approaches: For the time being, there is no specific antiviral therapy that is effective against COVID-19 in general. Conversely, there are currently five main vaccines on the market that aim to protect the population from contracting the coronavirus. The vaccine includes Moderna, Pfizer/BioNTech, Oxford/AstraZeneca, Sputnil V, and Sinopharm vaccine. Despite the fact that researchers are currently investigating to understand clearly the features, pathogenesis, and treatment options of COVID-19, it is deemed necessary to concentrate on competitive therapeutic options and drug cross-resistance.Thus, there is an urgent need for global surveillance of COVID-19 patients. New therapeutic drugs are emerging one after another. However, double-blinded randomized controlled trials with larger sample sizes are needed to determine the safety and efficacy of these new drugs and guide the clinical decision. Currently, Medical interventions can be divided into four major categories: general treatment, coronavirus specific treatments, antiviral treatments, and vaccinations.

General Treatments: Generally, the treatment approach included nutritional interventions, immune enhancers, and Chinese medicine, Interferon, intravenous gamma globulin and thymosin were believed to boost the immune system to fight SARS-CoV and MERS-CoV as well as 2019-nCoV. Besides, chloroquine, an old Chinese medicine for the treatment of malaria and autoimmune disease, had demonstrated remarkable inhibition in the spread of SARS-CoV by interfering with ACE2 in Vero E6 cell lines [24, 25]. It was demonstrated that chloroquine functioned at both entry and post-entry stages of the 2019-nCoV infection in Vero E6 cells, as well as an immune-modulating activity that enhanced the antiviral effect *in-vivo* [26].

Due to the indispensable role of the S-protein in coronavirus, therapies and vaccine exploration targeting S-protein-ACE2 interaction may be very promising. Previous therapies targeting SARS-CoV

and MERS-CoV may accelerate the development of treatment of COVID-19 because of their structural resemblance and genome similarities. The human monoclonal antibody could efficiently neutralize SARS-CoV and inhibit syncytia formation between S-protein and ACE2 expressing cells [27]. The appropriate modification of the monoclonal antibody may be effective for the treatment of COVID-19. Furthermore, potential therapies targeting the renin-angiotensin system to increase ACE2 expression and inhibit ACE, may be developed to treat COVID-19 in the future [28].

The American College of Cardiology (ACC) reported; "Covid-19 patients that have the comorbidity of cardiovascular diseases have the higher mortality rate of 10.5 and fatality rate than the average population, but the cardiac patients had the highest fatality rate among all categories [29]. However, some reports suggested that ACE-I and ARB drugs might have increases the mortality rate of Covid-19 patients [30]. In contrast, the European Society of Cardiology recommends doctors and patients to continue with usual anti-hypertensive therapy due to a lack of clinical or scientific evidence to prove the harmful effect of ACEI or ARBs in the Covid-19 infection [31].

SARS-CoV-2 Specific Treatments: Currently, there are no effective antiviral treatments for the treatment of COVID-19 infection; even strong candidates such as *lopinavir/ritonavir* and *abidol* exhibited no remarkable effect on clinical improvement, day 28 mortality, or virus clearance. Expectation and attention were shifted to *"remdesivir"*, which may be the wide-spectrum drug for antiviral treatment of 2019-nCoV with the most potential. *Remdesivir* is an adenosine analogue, which incorporates into novel viral RNA chains and results in premature termination [32]. It is currently under clinical development for the treatment of Ebola virus infection. It was revealed that *remdesivir* was highly effective and safe in the control of 2019-nCoV infection in Vero E6 cells and Huh- 7 cells. A successful application of *remdesivir* on the first 2019- nCoV infected case in the United States when his clinical status was worsening was recently released [33]. Animal experiments also showed the superiority of *remdesivir* over *lopinavir/ritonavir* combined with interferon-β by reducing MERS-CoV titers of infected mice and improving the lung tissue damage.

The effectiveness and safety of *remdesivir* can be expected by the clinical trial lead by Dr. Bin Cao. The 2019-nCoV infection is associated with a cytokine storm triggered by the over-activated immune system similar to SARS and MERS. The aberrant and excessive immune responses lead to long-term lung function and structure damage in inpatients released from ICU. Ongoing trials of the IL-6 antagonist tocilizumab, which has been shown effective against cytokine release syndrome resulting from CAR-T cell infusion against B cell acute lymphoblastic leukaemia, may be expanded to restore T cell counts and treat a severe 2019-nCoV infection [35].

Antiviral Treatments and Others: The available observational studies and Meta-analysis of corticosteroid treatment suggested impaired antibody response, increased mortality and secondary infection rates in influenza, increased viremia, and impaired virus clearance of SARS-CoV and MERS-CoV and complications of corticosteroid therapy in survivors [36]. Therefore, corticosteroids should not be recommended for treatment of 2019-nCoV or used on severe patients with special caution.

A review on convalescent plasma for treatment of SARS-CoV and severe influenza infection suggested a reduction in hospital stay and mortality rate, especially when administered early after symptom onset [37]. However, another study demonstrated no significant improvement of convalescent plasma transfusion on the survival of Ebola virus-infected patients. Possible reasons may be the unknown levels of neutralizing antibodies in convalescent plasma and transfusion timing [38]. In terms of vaccine, if any cross-reactive epitopes were identified between 2019-nCoV and SARS-CoV, the previous vaccine for SARS-CoV might be re-utilized to facilitate 2019-nCoV vaccine development. We recommend influenza and *Streptococcus pneumonia* vaccination for pro-phylaxis, especially in elderly adults [39]. Both pandemic viruses result in similar respiratory symptoms and are hard to distinguish. The 2019-nCoV pandemic began in flu season when it is easy to develop a combination infection of 2019-nCoV

and influenza or Streptococcus infection. Vaccination against influenza and Streptococcus pneumonia in vulnerable elderly people with comorbidities is highly cost-effective and is demonstrated to be associated with reductions in the risk of hospitalization and death from all causes during influenza seasons [40].

The Promising Contributions of Nanomedicines: The concept of nanomedicine can be exploited to potentiate the efficiency of both novel and repurpose anti COVID - 19 drugs [41]. The available literature indicated that metallic nanoparticles (NPs), metallic oxides NPs and some Quaternary ammonium cations NPs possess promising potentiality to inactivate the viruses [42]. According to the recent finding of the Chinese scientist, nanomaterial can absorb and deactivate virus with 96.5% to 99.9% efficacy [43]. Vishnu *et al.* recommended that, since the COVID-19 is a novel virus with no specific approved medication, the treatment approach for curing the SARS CoV (2003) can be applied because of their genetic similarities, in which he described the employment of nanomedicines will contribute significantly in the fight against SARS-CoV 2. Fortunately, the diameter of SARS-CoV-2 is around 125 nm, which is desirable to detect and neutralized by biocompatible theranostic NPs as previously employed to neutralize SARS (2003) or MERS coronaviruses [34].

According to the study findings of Dung N Tran et al. 2020, SNPs possesses an excellent antiviral affinity against African Swim Fever Virus ASFV with a promising affinity to disinfect its transmission process silver-based nanomedicine, in particular, has a significant role to play [45]. However, Oron Zachar *et al.,* synthesized nano-silver colloids (NAgC) and proved that the formulation is can effectively arrest the early stages of respiratory bacterial and viral infections including; hospital ventilator-associated pneumonia (VAP) and SARS-CoV-2 (COVID-19) [46]. More so, AgNP-based nanomaterials could be an alternative to aid the mitigation of COVID-19 spread as a result of surface contamination. Theranostic nanoparticles like Carbon Quantum Dots (CQDs) and gold NPs do not only limited to the killing or inhibition of viruses but also reported to have hindered the transfection process of coronaviruses entry into cells, due to their privilege of owing high ability to bind to several antigens or compounds in their large surface area.

Hence, these promising features could aid the development of safe and effective antiviral drugs that can overcome the obstacle faces in targeting specific viral strain [47].

Previously, Alnylam pharmaceutical company manufacture first approved lipid NPs -formulated RNA in 2018 and the clinical safety of the drug has been proved [48]. Recently, Faul F. *et al.* demonstrate an *in-vivo* experiment on mice, where they immunized the mice with a vaccine made from "self-amplifying RNA encoding the SARS-CoV-2 spike protein encapsulated within a lipid nanoparticle" and compared the antibody titers with that of recovered COVID – 19 patients. The study concluded that the "saRNA LNP vaccine" has efficiently produced robust antibodies and shows similar immunogenicity with the recovered COVID – 19 patient [49]. Perhaps, it was not yet clear how coronavirus manifested as a severe life-threatening illness, mild to some, and even asymptomatic to certain patients. The severity of the illness is associated with serious inflammatory responses (cytokines storm), which are bound to cause cellular, multiple organ damages, and death. Unfortunately, corticosteroid anti-inflammatory drugs were found to be unsafe due to their harmful side effect on cellular repair.

However, in an attempt to resolve the said problems, a French Scientist Dr. Couvreur and co-researcher employed a nanotechnology approach developed "multi-drug nanoparticles" by encapsulating adenosine and squalene in the alpha-tocopherol/ vitamin E (a powerful antioxidant). The result of this *in-vivo* experiment conducted on hyper-inflammatory mice indicated a significant decrease in tissue cytokines storm (tumour necrosis factor) along with an increase in the level of interleukin-10 (Human anti-inflammatory cytokines) [50].

CONCLUSION: The study of SARS CoV 2 virulence, pathogenesis, epidemiology, and other clinical features will assist scientists in identifying the most important targets for COVID-19 drug and vaccine development, as well as disease prevention

measures. However, there is no doubt that nanoparticles improve drug efficacy and reduce side effects by delivering drugs to specific sites of action. As a result, nanoparticles have been discovered to effectively deliver a drug *in-vivo*. An ideal nanoparticle discovery pipeline would allow scientists to create new or repurposed drugs and vaccines that are effective against contagious coronavirus and other pathogenic diseases. For instance, Moderna's vaccine was designed by encapsulating mRNA of COVID-19 in lipid nanoparticles. Likewise the Pfizer and many other vaccines in the trial.

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