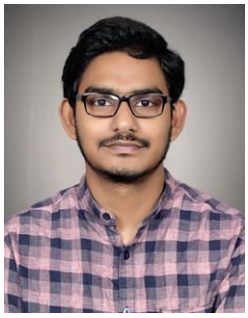
CHAPTER 3

AUTHOR'S INFORMATION



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CHAPTER-3

AN OVERVIEW OF SARS-COV-2: FEATURES, REPLICATION, PATHOPHYSIOLOGY AND THERAPEUTIC APPROACHES

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ABSTRACT

This chapter summarized the basic features, pathophysiology, and treatment approaches of the novel coronavirus (COVID-19) that originated from Wuhan, China and since then declared pandemic worldwide by the World Health Organization. It covers an overview of the structural composition of the SARS-CoV-2 virus where the features of the surface proteins are thoroughly explained. The genomic organization of the single-stranded RNA virus is also elucidated in this chapter taking special note on the open reading frames and the associated peptide products. This chapter presents the viral life cycle and replication machinery inside a human host taking an account on the spike protein and receptor binding mechanisms. It also accentuates on the pathophysiological changes in the alveolar tissues of the SARS-CoV-2 infected patient. Proposed therapeutic approaches targeting viral entry mechanism and viral replication to treat COVID-19 and mechanisms of actions of two of the most heavily discussed potential drug candidates, namely Remdesivir and Hydroxychloroquine, are mentioned briefly in this chapter. An overview of the general approaches made to prepare viral vaccines and the progress regarding the research and development of SARS-CoV-19 vaccine till date is provided.

1. Introduction

Over the past few months, we have been getting acquainted with new terminologies, starting with the novel Coronavirus or Covid-19 to the words like quarantine, lockdown or social distancing. The coronaviruses are nothing new to the biological science community as they were responsible for the 2003-SARS and the 2012-MERS outbreaks [1,2]. Moreover, the coronavirus is also capable of causing respiratory diseases in mammals and birds [3]. In December 2019, an outbreak of an unknown type of pneumonia occurred in China's Wuhan province, causing severe damage to the nation [4]. It soon became a global scourge, and today there are almost 12 million people in the world with the disease, of which about 550,000 are dead as on 11 July 2020 [5]. The Chinese Center for Disease Control and Prevention (CCDC) was the first to identify a new beta coronavirus, 2019 n-COV belonging to the β-coronavirus family, as the causative agent behind this disease [6].On 11 February 2020, the International Committee on Taxonomy of Viruses (ICTV) named the novel virus as 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2) due to its significant resemblance to the SARS coronavirus outbreak of 2003 [7].

The World Health Organization (WHO) named the disease caused by the virus as Coronavirus disease-19 or COVID-19 and later declared the outbreak as a pandemic on 11 March 2020 [8,9]. The novel COVID-19 is the third coronavirus to provoke such a large-scale epidemic in the past twenty years after the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003 (began in China) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 (began in Saudi Arabia) [10]. In the case of SARS and MERS infections, the viruses were transmitted from bats to human via an intermediate mammalian host [11]. Currently, two animals, bats and pangolins, are thought to be potentially responsible for originating the disease [12]. As scientists discover that the coronavirus found in these animals show more than 90% resemblance to the SARS-CoV-2 at the genomic level, but no accurate and conclusive information has been found yet regarding its origin [12]. The virus can spread from person to person through droplets, and its transmission rate is much higher than the previous two coronaviruses [13]. This article reviews the key features of SARS-CoV-2 thoroughly, mechanism of its

replication, pathophysiological changes occur in the human host and the potential therapeutic approaches for the development of drugs and vaccines against the disease.

2. Features

The Coronaviruses are classified under family Coronaviridiae (order: Nidovirales) and possess enveloped positive-sense RNA virus with club-like spike proteins on its surface[14]. These spike proteins on the viral membrane make the virus resemble a crown, hence named as 'corona' [15]. The genome size of the coronavirus is quite large for an RNA virus; it ranges between 26 kb to 32 kb nucleotides long [16]. As observed under the cryo-electron microscope, the size of a SARS-CoV-2 virus is about 60-140 nm [6]. Its genome has 14 open reading frames (ORF), which encode a total of 27 proteins[16]. The virus RNA genome encodes for both structural and few non-structural proteins (NSPs) within the 3' end of the genome. Meanwhile, 5' two-third of the viral genome is coded by several non-structural proteins (NSPs)(such as papain-like protease, 3-chymotrypsin-like protease, helicase and RNA-dependent RNA Polymerase) (Figure 2) and are involved in viral replication through RNA-dependent RNA polymerase (RdRP) [17]. In addition to the spike (S) proteins, three other structural proteins are also found on its surface; membrane (M) protein, nucleocapsid (N) protein, and envelope (E) protein [18] (figure 1). The S proteins are distributed across the surface, which allows the virus to bind to the receptor and enter the host cell [19]. M protein is the most abundant protein and is thought to help in the reconstruction of the virus [20]. The N proteins remain attached to the viral genome to form the nucleocapsid [21], and they are commonly involved in the replication, transcription and packaging of the viral genome inside the host [22].The E-protein is a small membrane protein composed 76 to 109 amino-acid residues, and it contributes significantly in membrane permeability of the host cell, virus assembly and virus-host cell interaction [18,23]. They all remain embedded on the capsid of the virus. The two-third of the genome encodes several non-structural proteins (NSPs) [24]. The coronavirus also has six additional proteins that are encoded by ORF3a, ORF6, ORF7a, ORF7b, and ORF8 [25]. However, as there is a lack of scientific information available at the moment for expressions of ORFs, it is hard to say which proteins are encoded by them (Figure 2). Scientists have identified two novel features in SARS-CoV-2,

which was absent in previously known coronaviruses. Firstly, the spike protein being optimized for binding to the human receptor ACE2, and it has a functional polybasic (furin) cleavage site at the boundary of S1 and S2 [12].Spike proteins are type I transmembrane glycoproteins that form a homotrimer to help the virus survive in the host's body [26]. A unique feature of this protein is that it has 22 N-linked glycan sites [26,27]. Spike protein has two subunits, S1 and S2[26]. S1 helps in binding of the virus to the host receptor as it contains the receptor-binding domain (RBD) while S2 is responsible for fusion of viral membrane to the host cell membrane [28,29]. With the help of these two subunits, the SARS-CoV-2 spike protein can enter the human respiratory epithelial cells by forming a complex with the human ACE 2 (angiotensin-converting enzyme 2) receptor [30,31].

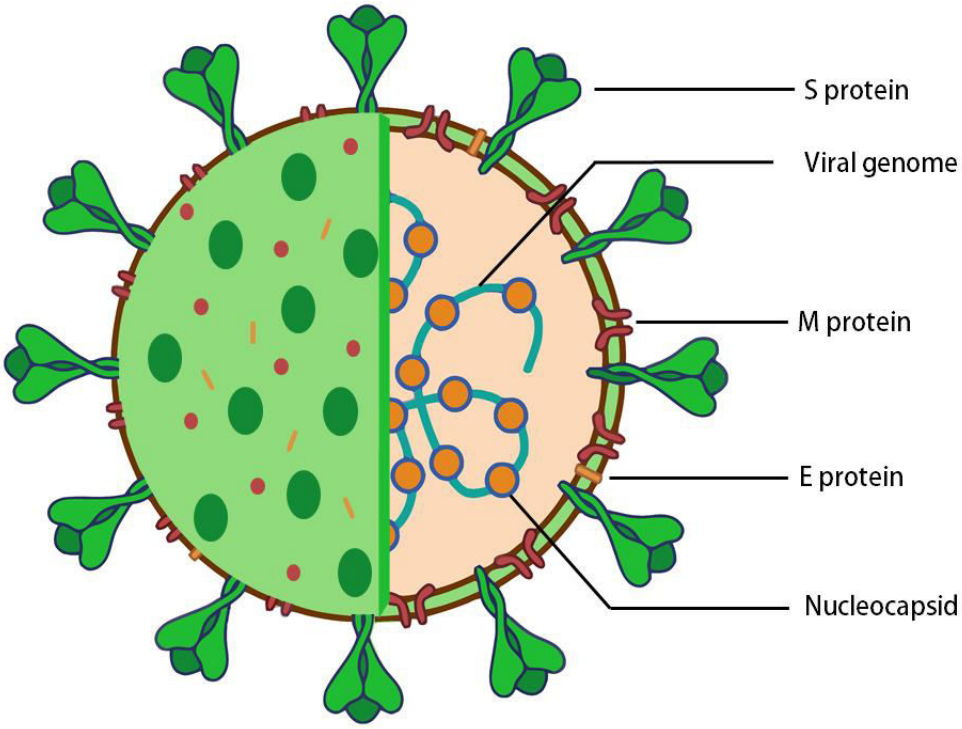

Figure 1: Structure of SARS-CoV-2.

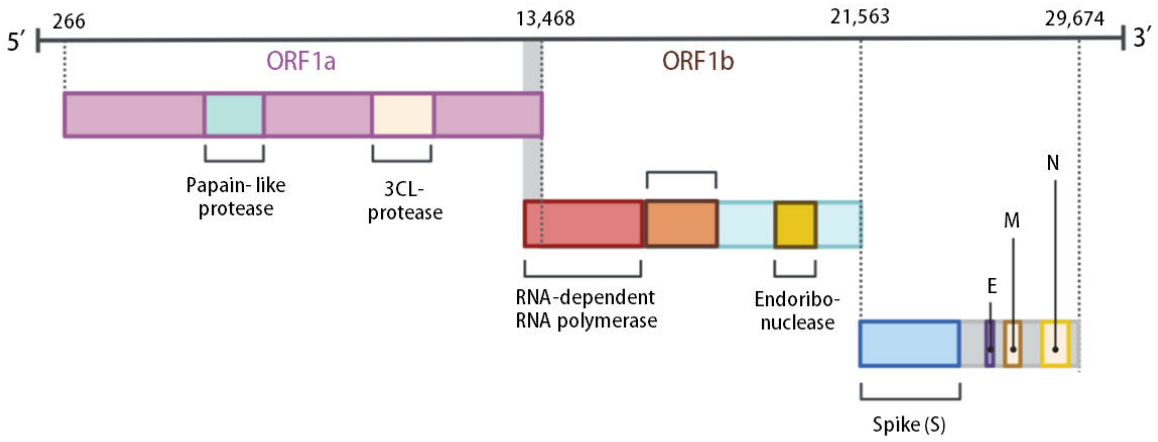

Figure 2: Genomic organization of SARS-CoV-2.

The S1 subunit has two subdomains N terminal and C terminal, and both of them can act as RBD [31](figure 3). Spike proteins are class I viral fusion proteins as the S2 subunit contain two repetitive heptapeptides [32]. Generally, in all coronaviruses, the cleavage site is located at the boundary of S1 and S2 [33]. However, surprisingly in case of SARS-CoV-2 spike proteins, there is a furin cleavage site at the S1- S2 boundary[26,34]. This feature has a moderate effect on the entry of the virus, but it may help in expanding the virus tropism [26]. Recent studies have shown that SARS-CoV-2 binds with ACE2 with 10-20 fold higher binding affinity as compared to previous SARS-CoV. These results show the highly infectious capability of SARS-CoV-2 in humans. Considering the higher binding efficiency of SARS-CoV-2 with ACE2 receptor, soluble ACE2 could be a potential candidate for therapeutic approach [35,36].

3. Replication

The SARS-CoV 2 virus transmits human to human when a person becomes exposed to respiratory droplets from an infected person via coughing, sneezing or by touching any contaminated surface [37]. Those viruses within the droplets can easily travel inside the human body when the person touches his/her mouth, nose or eyes [38]. Asymptomatic carriers can also transmit the virus, therefore, play a crucial role in the spread of COVID-19 [39].

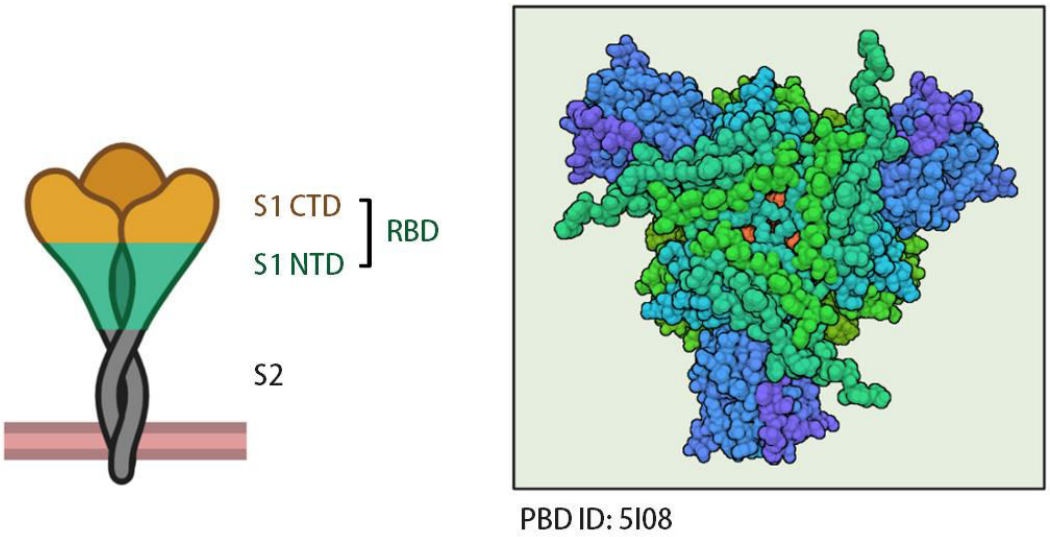

Figure 3: Structure of spike protein

Besides, some researchers have reported SARS-CoV-2 presence in a sample of stool, urine and saliva. This indicates that the virus can replicate in the digestive tract, also [40]. However, vertical transmission from a pregnant woman to newborn baby has yet to be confirmed [41].The SARS-CoV-2 virus enters the host cell through its binding to ACE2 receptor, which is abundant on surfaces of many cells such as heart, kidneys, gastrointestinal tract, and especially in type II pneumocytes of lung alveoli [42]. This binding is strong enough as there are 394 glutamine residues present in the RBD of the spike protein is recognized by the 31 lysine residues present on the ACE2 receptor[30]. Following the binding with the receptor, a conformation change occurs in the S protein structure, and the virus can enter the cell either by fusion of virus and host cell membrane or by endocytosis where virus bounded with the receptors got internalized within the cell [26,43]. The membrane fusion occurs due to the proteolytic cleavage of S protein by host proteases which in turn release the fusion peptide that triggers the activation of the membrane fusion process [44]. After entering the cytoplasm, the virus membrane fuses with the endosome through cathepsin L proteolysis by intercellular proteases [45,46]. The hydrolyzing enzymes within the endosome destroy the viral capsid, and subsequently, the single-stranded RNA comes out in the cytosol [47]. In another suggested mechanism of virus entry, the fusion of viral and host membrane occurs at low ph and the genetic

material directly released in the cytosol [32,46]. After that, the RNA strand translates to produce replicase proteins coded by the ORF1a/b [48,49]. The replicase then mediates the production of negative-stranded genomic RNA as well as positive-stranded subgenomic RNA [50]. Formation of a replication-transcription complex occurs which comprises of non-structural proteins mainly [35,51]. While the genomic RNA continues to replicate, the subgenomic RNA aids the transcription of structural proteins [35,46]. Theses structural viral proteins translocate into the endoplasmic reticulum and eventually get transferred to the endoplasmic reticulum-golgi intermediate compartment (ERGIC) [17]. Concurrently the nucleocapsids formation happens in the cytoplasm, and they get transported to ERGIC for the virion assembly [52]. The newly assembled viruses then translocate to the plasma membrane by vesicular transport and ultimately secrete outside via exocytosis. These newly released viruses then attack nearby cells, and the cycle continues [14,17] (figure 4).

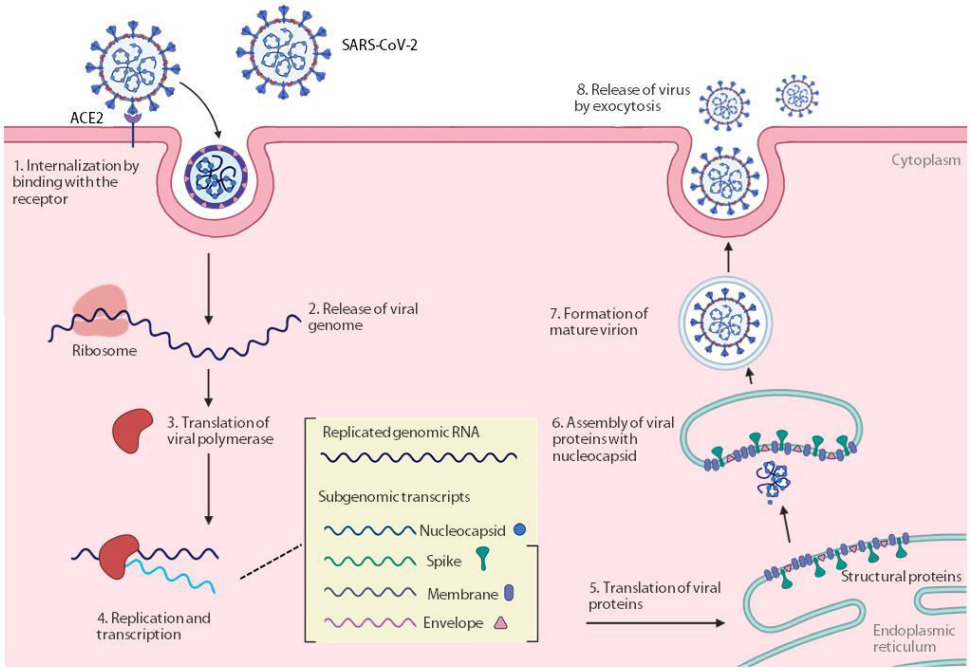

Figure 4: The life cycle of SARS-CoV-2 in a human host.

4. Clinical manifestations and Pathophysiology

The period from the onset of COVID-19 symptoms ranged from 6 to 41 days, with a median of 14 days [53]. However, this period mainly depends on the patient's age and health status. This disease is more vulnerable among patients having age >70 as compared to those who are under 70. Also, the severity of this illness has been found in patients showing comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease (COPD) and obesity but the still valid scientific explanation is needed [54–56]. According to reports, the typical clinical spectrum of COVID-19 varies from asymptomatic to severe multi-organ failure and sometimes even death [57]. The main symptoms include fever, dry cough, fatigue, dyspnea, rhinorrhoea, sneezing and sore throat [58]. The rare symptoms manifested by some COVID-19 patients are gastrointestinal symptoms, diarrhoea and vomiting [59]. The pathophysiological changes occur in a patient affected with SARS-CoV-2 can be several. The viral infection in patients can be asymptomatic to severe multi-organ failure and death[57]. The organ being most affected in this disease is the lung [58,60]. CT scan reports show pulmonary ground-glass opacification even in asymptomatic patients, probably because of the damaged and destroyed ACE2 receptors on the apical side of lung epithelial cells [61,62]. The dendritic cells and macrophages located in the lung epithelium fight against the virus until the commencement of the adaptive immune response [63,64]. Following the antigen presentation by antigen-presenting cells, the T cell responses initiate [65,66]. Helper and cytotoxic T cells play a highly crucial role here. Helper T cells activate B cells to produce specific antibody against the viral proteins while cytotoxic T cells directly kill the virus-infected cells [67].

The increased level of interleukin 6 (IL6), IL10, granulocyte-colony stimulating factor (G-CSF), monocyte chemo attractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1α, and tumour necrosis factor (TNF)-α were reported in severely infected patients [68]. IL6 sometimes produces in excess, and the condition is called a cytokine storm [69]. Exhausted T cells were also detected in critical cases [70]. The lung epithelial cells produce both IL8 and IL6. IL8 is a chemo attractant which can attract T cells and neutrophils [71]. An abundance of inflammatory cells was noticed in the lungs of the

patients [72]. Amongst the innate immune cells that were reported to be found in clinical samples, the majority were neutrophils [73]; which can damage the lung epithelium itself [74]. Whereas in the case of adaptive immune cells, the preponderant were T cells as a decline in the number of circulating T cells was noted in many cases [63,70]. In some patients, CD4+ pathological cytotoxic T cells sometimes can destroy the virus, but they can contribute to lung injury too [75,76]. ACE2 Receptors were also observed to increase significantly in lymphoid cells ILC2 and ILC3s [76]. All the above-mentioned inflammatory responses can induce severe tissue damage if there is a severe infection. Along with the respiratory symptoms, in some cases, thrombosis and pulmonary embolism were also observed [76–78]. The endothelium plays a very vital role in regulating thrombosis [79,80], and ACE2 receptors are also expressed on it [81,82]. The injury in endothelial cells may result in microvascular permeability which might help the virus to propagate further [76,83] (figure 5).

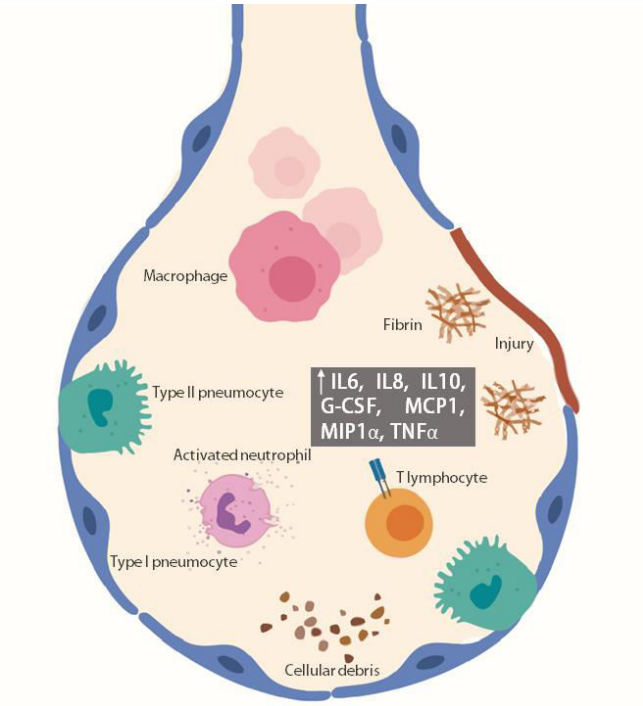

Figure 5: Pathophysiological changes in the alveolar tissues due to COVID-19 infection

5. Therapeutic approaches

Currently, three types of therapeutic strategies are being taken to treat or prevent COVID-19. The first one being the application of repurposed drugs and the development of new drugs. Several existing antiviral drugs are being applied in patients with COVID-19 [84]. Along with antiviral drugs, other drugs and antibiotics are also being practised in combinations [85]. Among them, two drugs exhibited promising effect against the SARS-CoV-2 infection, remdesivir and hydroxychloroquine [86,87]. Remdesivir is a broad-spectrum antiviral medicine [88] whereas hydroxychloroquine is a derived form of chloroquine which is generally used to treat autoimmune diseases like rheumatoid arthritis and lupuserythematosus [89]. It is proposed that the active molecules from remdesivir named GS – 441524 and GS-5734 can prevent viral replication by blocking the viral polymerase protein (RdRp) [88,90,91]. The potential mechanism involved in the protective action of hydroxychloroquine against SARS-CoV-2 is not well understood. It may prevent the formation of endosome during virus entry, it may restrict the viral genome release by interfering with the endosome acidification [89], or it may block the viral transcription by altering the map kinase signalling [92]. Scientists also suggested that it can affect the post-transcriptional modifications of viral proteins and can also interfere with the vacuole formation during viral release from an infected cell [89,93].

Currently, there are 249 drug candidates aimed to treat COVID-19; amongst them, 161 are in various phases of the human trial [37]. Drugs are mainly based on the strategy of preventing virus entry mechanisms [94]. In one approach compounds resemble the structure of RBD of spike proteins are used as drugs, they might eventually outcompete the SARS-CoV-2 viruses to bind with the ACE2 receptor [95]. Another approach is developing drug compounds which can bind to the RBD of spike protein before it enters the cell, and this will block the binding [95]. Secondly, the most crucial type of therapeutic strategy is to develop a vaccine. Currently, there are 139 vaccine candidates proposed, among which 18 are currently in the human trial [96]. Some of the vaccines showed promising results. There are several approaches to viral vaccine development. In some vaccine live attenuated virus, or whole inactive viruses are used, in some circumstances, the genetic material is used as a vaccine, and in some cases, parts of

virus-like proteins are used to develop a vaccine. Currently, each of the following approaches is taken to produce a vaccine as early as possible [97,98] (figure 6). The third therapeutic strategy is convalescent plasma therapy, where the plasma from recovered patients are collected and injected into infected patients. The plasma containing antibodies against the virus act immediately on the patient; this approach is quite successful in many patients in all parts of the world [99].

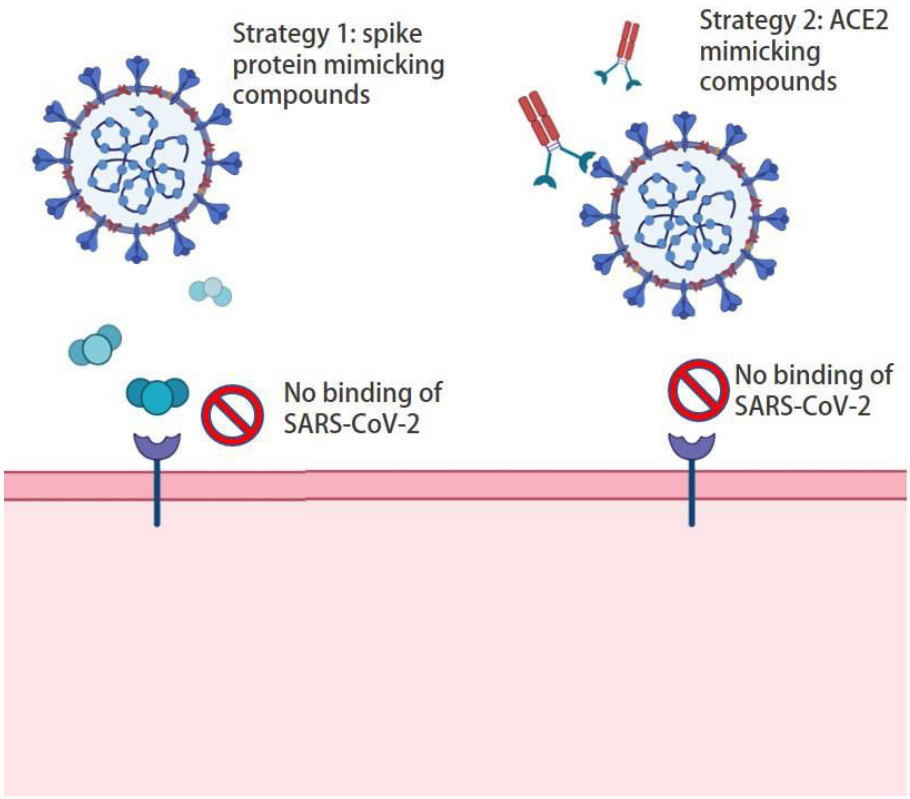

Figure 6: Strategies for developing a drug against COVID-19

6. Future Directions

The SARS-CoV-2 virus has become a significant threat through worldwide. Extensive measures are required to combat person-to-person transmission of SARS-CoV-2 infection and to control the outbreak as soon as possible. Drug testing always requires an established and stable animal model before their clinical use in humans. However, in the current scenario, no promising model has been found to study the pathogenesis and potential treatment for the deadly virus. The development of drugs against COVID-19 is

very challenging due to the repeated emergence of SARS-CoV-2 virus with distinct features. Repurposing the drugs that have been considered as effective drugs against COVID-19 should be screened invitro in order to confirm their activity against this virus. The drugs which will show activity in in-vitro condition should then be investigated in animals and clinical trials. Although many commercial companies are working for the development of effective coronavirus vaccines, still there is a dire need of human and animal-based trials because potential vaccines may take almost 3-10 months for proper commercialization. Along with that, the strategy for accurate and rapid diagnostic kit for COVID-19 detection in the suspected patient is also needed, because no doubt PCR testing kit is not only expensive but also time-consuming.

7. Concluding Remarks

In summary, this review gives insight into the current pandemic situation of COVID-19 and provide a clear-cut picture in terms of epidemiology, key features, transmission, clinical manifestations, pathophysiology and some potential therapeutic approaches. As our current knowledge regarding SARS-CoV-2 virus is limited, hence there is rapidly ongoing research on this topic, and hopefully, this will aid in finding clinical treatment in controlling the outbreak. Therefore, till then, preventive measures should be encouraged, such as social distancing, staying at home and avoiding mass gatherings to prevent the virus spread. Moreover, the research should be focused more on understanding the pathogenicity of SARS-CoV-2 virus as it may help in developing a potential vaccine and effective drugs.

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Declaration of competing interest

The writers claim no conflicting interests.

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