

# Distinctive Therapeutic Strategies against Corona Virus-19 (COVID-19): A Pharmacological Review

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## ABSTRACT

Coronaviruses (CoVs) are RNA viruses threatened the global health. The causative microorganism, causing coronavirus disease-2019 (COVID-19), is known as (novel coronavirus) or (severe acute respiratory syndrome coronavirus-2) (SARS-CoV-2). Furthermore, respiratory illnesses such as pneumonia and breathing failure are caused by COVID-19, first reported in Wuhan, China. So far, over 939,968 COVID-19 death cases out of approximately 29,765,666 confirmed cases have been globally reported. However, global research institutions and companies have exerted tremendous effort to develop vaccines and drugs against SARS-CoV-2. Finally, our aim is to comprehensively review epidemiology, etiology, pathophysiology as well as the outlined the several strategies (preclinical/clinical) of COVID-19 treatment at the molecular level.

**Keywords:** SARS-CoV-2, COVID-19, Pathogenesis, Therapeutics, Pharmacology

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## INTRODUCTION

In 1960s, HCoV-229E and HCoV-OC43 have been discovered. They are enveloped positive RNA virus which can be categorized under order Nidovirales, family Coronaviridae and subfamily Coronavirinae<sup>1</sup>. The subfamily Coronavirinae is divided and made up of several principle classes of coronavirus based on their genomic and serological properties ( $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$ -coronavirus). Beta-coronavirus in particular has four lineages (A, B, C, and D)<sup>2</sup>. In 2002, SARS has been arisen as a novel of coronavirus. In 2004 and 2005, HCoV-NL63 and HCoV-HKU1 aroused<sup>3</sup>. In 2012, MERS-CoV was isolated which was discovered to have some commons with SARS-CoV-2 identified nowadays as an acute respiratory syndrome coronavirus. SARS-CoV-2 infects the lower respiratory tract causing severe respiratory infection syndrome<sup>4</sup>. SARS-CoV-2 undergoes under Sarbecovirus of the genus lineage B Beta-coronavirus<sup>5</sup> and characterized to be one of Beta-CoVs[6]. More serious diseases can be caused by these viruses in young, elderly, or immunocompromised individuals. It was first discovered in Wuhan, Hubei Province December 2019<sup>6</sup>. Despite the genetic similarities and the name between MERS-CoV and SARS-CoV-2, SARS-CoV-2, it shows clinical and genetic differences with MERS-CoV. One of the similarities is that all previous cases (SARS-CoV and MERS-CoV) of coronaviruses were recorded to be originated from bats or rodents and transmitted directly

to humans<sup>7</sup>. Bat SARS-like CoVs (Bat-SLCoVs, MG772933 and MG772934) was found to be the nearest in ethnic investigation within the subgenus Sarbecovirus. Moreover, these records were to be believed according the genomic viral sequence, which was explained as follow: spike proteins (S-protein) cover all related coronavirus which contains receptor binding domain (RBD) leading to its binding to angiotensin-converting enzyme-2 (ACE-2) receptor. ACE-2 receptor is found in lungs, heart, kidney and gastrointestinal tract ease the viral inlet into the target cells<sup>8</sup>. Once the virus can easily enter into target cells, RaTG 13 was sampled from bats which was found to be closely related virus to the mutated version of BRD-SARS-CoV-2 which can easily infect other animals<sup>9</sup>. Moreover, (RO) value is defined as the main reproduction number and the expected number of cases where all individuals are susceptible to infection. Indeed, both virus behavior and human behavior are reflection of it. Early epidemiologic studies in case of SARS-CoV-2 states that RO value was (2.2) and this value was similar to the value of SARS-CoV-1 and pandemic influenza<sup>10</sup> suggesting that with proper interventions and controls RO value can be reduced. Unfortunately, after one-month, the mortality rate of SARS-CoV-1 has exceeded MERS-CoV and SARS-CoV-1 with late decisions for quarantine and social distance precautions as shown in Fig. 1.

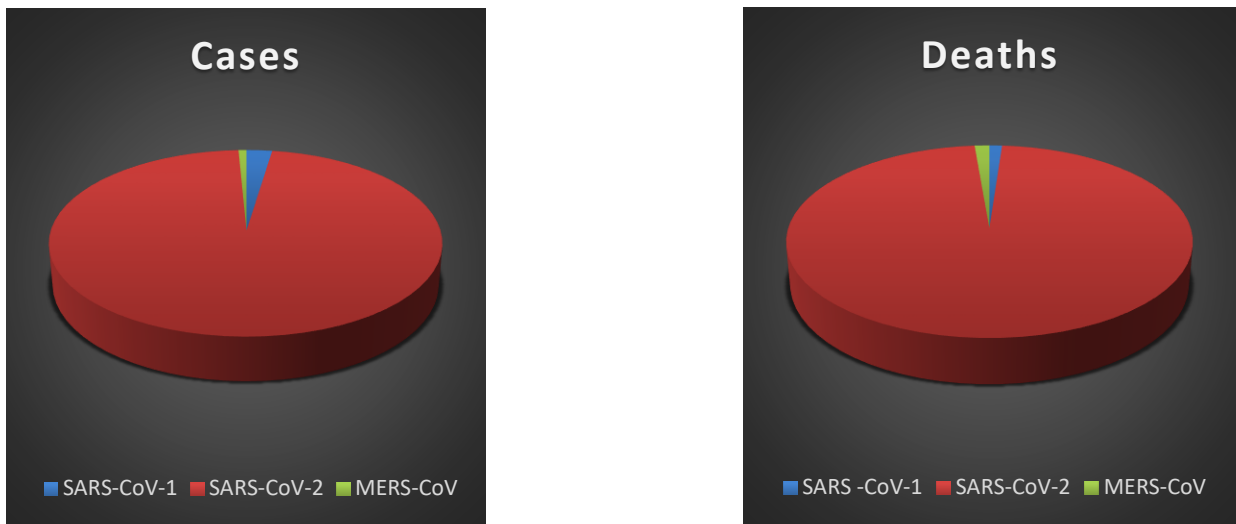


Fig 1: Comparison between infected cases and deaths from SARS-CoV-1, SARS CoV-2 and MERS-CoV.

However, the vision is unclear regarding the original source of the fiction coronavirus. It still needs much experience and knowledge to be learned from the previous outbreaks which will impact on nowadays work recognizing the SARS-CoV-2.

**EPIDEMIOLOGY**

Many suggestions were arisen in the beginning of this epidemic outbreak. Primarily, it was reported that Huanan Seafood Wholesale Market is the main source of infection and coronavirus was contagious was transmitted from one person to another <sup>11</sup>. A retroactive survey on 425 patients showed that basic RO value was 2.2 as mentioned before <sup>12</sup>. However, Chinese government followed stringent rules in prevention, the RO value was gradually decreased <sup>13,14</sup>. There were 169,930 confirmed cases on March 16 and nearly half of them were in China, 18% severe disease, 82 % mild cases and a total 889 tested-positive cases were

asymptomatic <sup>15</sup>. Moreover, SARS-CoV-2 has been spread and detected into 157 countries and one cruise ship. SARS-CoV-2 confirmed cases diverge among 169 countries across all continents except Antarctica. From here, WHO declared that SARS-CoV-2 infection is pandemic. Furthermore, China hospitals reported that the majority of those infected patients were suffering from comorbid conditions such as hypertension, obesity, asthma, diabetes and chronic obstructive pulmonary disease (COPD) <sup>16</sup>. In 15-september-2020, WHO published a report of COVID-19 outbreak situation which was revised by national authorities confirming that total number of cases globally 29,765,666 and deaths 939,968 and totally recovered 21,566,468, as coronavirus COVID-19 is affecting 213 countries and territories around the world and 2 international conveyances <sup>17</sup> as shown in Table 1 and Fig. 2. However, these numbers keep increasing in the last couple of weeks.

Table 1: Total number of cases and deaths globally up to 15 September 2020

Regions	Total number	Deaths
Globally	12 552 765	561 617
Pacific region	241 267	7 578
European region	2 907 654	203 285
South-East-Asia	1 130 247	28 640
Eastern Mediterranean region	70293	3794
Regions of America	6 540 222	283 357
African region	461 296	8 092

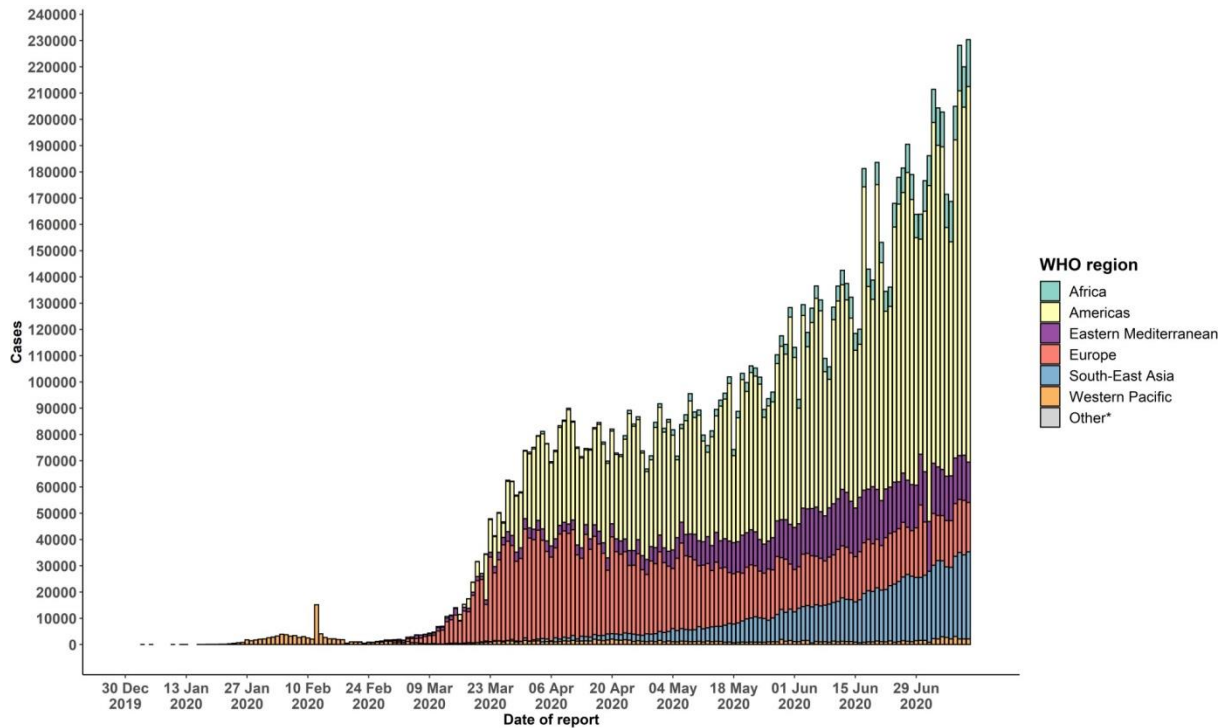


Fig 2: Curve showing epidemic regions with confirmed COVID-19, according to WHO report 30 December through 12 July - 2020<sup>17</sup>.

**Fatality COVID-19 rate by age**<sup>18</sup>

Death Rate (%) by virus differs depending on the age group (number of deaths divided by number of cases).

According to the age group this probability differs, which are shown in Table 2<sup>18</sup>.

Table 2: Total number deaths according to age globally January to July 2020.

Age	Confirmed death cases (%)	All death cases (%)
85+ years old	3.4%	14.8%
65-85 years old	19.4%	8.0%
25-65 years old	64%	3.6%
15-25 years old	9.6%	1.3%
5-15 years old	2.5%	0.4%
0-5 years old	1.2%	0.2%

According to information in Table 2, (0.2%) total death cases were reported in children. However, 3.6% of the total fatalities was over age 40, while, (8%) of the total fatalities was over 65 y. Highest number of fatalities was shown in old ages over 85 years (14.8%) of the total fatalities. China was the mainland with the highest number of confirmed cases. The WHO published, From 24 February through 12 July 2020 (epidemiological weeks 9 to 28), the proportion of cases aged 0-4 years, 5-24 years and 25-64 years have increased by seven-fold, six-fold and three-fold, respectively<sup>17</sup>. It was noticed that acceleration rate of new cases has been slowed down due to their strict quarantine strategies. Now cases in China become nine times lower than the other parts of the world. In 2002,

SARS showed 8096 infected people and 774 deaths; while, in 2012 MERS showed 2494 infected people and 858 deaths. Therefore, SARS-CoV-2 showing higher mortality rate raising epidemiologic red flags<sup>15</sup>. To estimate the extent of the risk present by the SARS-CoV-2, we consider several boundaries that we trust: the incubation period, the rate of transmission, the detection of asymptomatic transmission which can take place, and the case fatality rate (CFR).

**Sources of infection**

The first reports about CoVs infected cases were identified in animals<sup>19,20</sup>. Veterinary species related to CoV are shown in Table 3.

Table 3: Different animal species contributed to CoVs infections.

Host	Virus	Genus	Affected organs
Bovine	Bovine coronavirus	Beta-coronavirus	-GIT -Respiratory tract
Porcine	-Porcine respiratory coronavirus -Porcine epidemic diarrhea virus -Porcine hemagglutinating encephalomyelitis virus	-Alpha-coronavirus -Beta-coronavirus	-GIT -Respiratory tract -CNS
Feline	-Feline enteric coronavirus -Feline infectious peritonitis virus	-Delta-coronavirus Alpha-coronavirus	-Respiratory tract -GIT tract -CNS
Canine	Canine coronavirus Canine Respiratory coronavirus	-Alpha-coronavirus -Beta-coronavirus	-GIT -Respiratory tract
Equine	Equine coronavirus	Beta-coronavirus	-GIT -Respiratory tract
Camel	MERS respiratory syndrome	Beta-coronavirus	-GIT -Respiratory tract
Chicken	Avian infectious bronchitis virus	Gamma-coronavirus	-Trachea -Kidney -Reproductive tract

In SARS-CoV-2, it is claimed that bats were contributed to the source of infection <sup>21</sup>. Furthermore, in MERS-CoV, camels were contributed to the transmission of the virus <sup>22</sup>. All of these pathogenic MERS, SARS and CoVs show severe danger over the world for their risky of human-to-human transmission and fetal results. The overview of coronavirus with high spreading all over the world creates evolutionary reports based on genome analysis with respect to the therapeutics in advance and recent research on vaccines.

**Modes of transmission**

The spread starts through respiratory droplets followed by anal swabs. In the later stage of infection, some studies suggest the availability of oral fecal route transmission <sup>23</sup>. In China, 75,456 cases were respiratory infections referred to air droplets less than 5-10µm and can be transmitted through contact routes <sup>24,12</sup>. Droplet

transmission can be also available when one person in close contact with another person (1m) who is suffering from respiratory syndrome, especially if their mucosa, conjunctiva or sneezing were at risk of infection. In addition, transmission could be through fomites in the surrounding environment of infected person or objects they are using <sup>14</sup>. Moreover, airborne transmission, which belongs to the existence of the microbes within droplet nuclei, might be possible during treatments such as endotracheal intubation, bronchoscopy, open suction, manual ventilation, tracheostomy and cardiopulmonary resuscitation <sup>25</sup>. There are some evidences of intestinal infection in feces, but only one study of stool specimen cultured COVID-19 virus with no confirmed reports <sup>25</sup>. COVID-19 virus can be transmitted in different routes of transmission explained in details Table 4.

Table 4: Showing different animal species contributed to CoVs infections.

Fomites	-Environment around infected person with surfaces or instruments used on infected person such as stethoscope or thermometer.
Airborne	-Specific surrounding and protocols in which procedures or aid treatments that give rise to aerosols, droplet particles < 5µm in diameter remains longer in air and transmitted longer distance.
Fecal transmission	-Up to date, no record of fecal-oral transmission of the COVID-19 virus and only one study was reported

**Implications during the discovery of COVID-19 virus from air sampling**

Initial evidences reported that COVID-19 virus could be find in air where there were some suggestions that airborne transmission could be there. New England Journal of Medicine has evaluated the existence of COVID-19 virus in air. The study depends on using a three-jet collision nebulizer generating aerosols and fed into goldberg drum under laboratory conditions. But this machine does not reflect normal human cough conditions. Furthermore, COVID-19 virus findings in aerosols particles up to three hrs does not give the full picture same like a clinical setting using aerosols <sup>26</sup>. In some studies, WHO reported COVID-19 in air samples but not published yet<sup>27</sup>. Further studies to determine whether it is possible to detect COVID-19 virus in air samples in patient

rooms, where support treatment is not available which produce aerosols.

**Challenges and prospects in development**

Developing vaccines against human coronavirus infection passed through several trials. But such vaccines are limited due to their limited cross protection and widespread in antigenic variants with the strains of ethnic sub-cluster <sup>28</sup>. Up to now, there is no approved particular antiviral treatment for MERS and SARS; although, few efforts were made to develop vaccines and remedial for SARS-CoV and MERS-CoV. Since we are waiting for developing new vaccines and therapeutics which would end coronavirus and on the same time would take long time, we need to take advantage of existence of some antiviral agents and insist on highly effective control prevention measures to minimize mortality and

transmission rates<sup>27</sup>. Vaccines for coronavirus can be developed by targeting the viral spike glycoprotein (S-protein)<sup>28</sup>, which most vaccines and antiviral agents are targeted, and inducing neutralizing antibodies. S-protein based vaccine includes, S-protein based and recombinant RBD protein-based vaccines, DNA based vaccine, and viral vector-based vaccine recombinant<sup>29</sup>. Furthermore, S-protein based antiviral therapies include, S-cleavage inhibitors, RBD-ACE-2 blockers, protease inhibitors, S-protein inhibitors and small interfering RNAs<sup>30</sup>. All these agents are effective *in-vitro* studies but undergo limited human trials, which will not give them the opportunity to be effective in our present COVID-19. Recently, many attempts are carried out to recognize and develop monoclonal antibodies which are identified and been successful against SARS-CoV-2.

#### PATHOPHYSIOLOGY OF COVID-19

COVID-19 is caused by SARS-CoV-2, a Beta-coronavirus consists of a single-stranded ribonucleic acid (RNA) belonging to the Coronaviridae family. Its genome is analogous to a previously identified coronavirus strain SARS in 2003<sup>31</sup>. In structure, the coronavirus (SARS-CoV) has fourteen binding residues that directly interrelate with human angiotensin-converting enzyme-2 (ACE-2). The exact pathophysiological mechanisms are unknown until a thorough research in these aspect take place<sup>32</sup>.

The Beta-coronavirus particle is a single-stranded RNA virus, measuring 29.9 kb. The Fig. 3 depicts the structure of the virus. The virion comprises a nucleocapsid consisting of (N-protein) genomic RNA and phosphorylated nucleocapsid. It also has spike protein (S-protein), membrane protein (M-protein), hemagglutinin-esterase (HE), and protein envelope (E-protein).

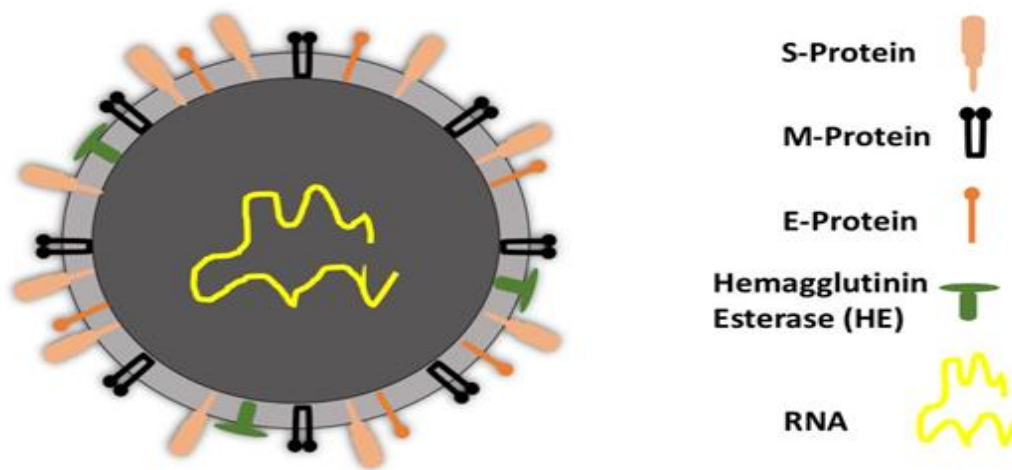


Fig 3. Structure of Beta-coronavirus particle<sup>33</sup>.

#### Disparity in genes

It is clear that the initial ten SARS-CoV-2 genomic sequences were nearly the same, allowing more than 99.98% sequence similarity without much difference<sup>34,35</sup>. According to Tang et al., SARS-CoV-2 has two major forms (L and S) types based on 103 genomes analysis. The L-type could be more violent and spread faster; while, the S-type could remain milder<sup>36</sup>. SARS-CoV-2 is predominantly spreading through respiratory droplet, contact, and also in fecal and oral routes as described above<sup>37</sup>. Main viral replication occurs in nasal cavity and pharynx mucosal epithelium, with further proliferation in the lower respiratory tract and gastrointestinal mucosa<sup>38</sup>. Some patients have also exhibited non-respiratory symptoms such as acute heart and liver damage, kidney failure, and diarrhea have also been noted in a few patients<sup>39,40</sup>. ACE-2 is widely expressed in the body and all ACE-2-expressing organs are also prone to SARS-CoV-2<sup>41</sup>.

#### Pathological observations

Few reports were emphasized on pathological observations of COVID-19 and in one of the reports<sup>44,2</sup> the morbid detections of a severe COVID-19 case showed diffuse of alveolar damage with cellular fibromyxoid exudates. Pulmonary edema with hyaline membrane formation has been found in the tissue of left lung indicated initial-stage acute respiratory distress syndrome (ARDS). It also showed inflammatory interstitial

mononuclear infiltrates and presence of lymphocytes in both lungs. In addition, it showed multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, amphophilic granular cytoplasm, and prominent nuclei. These findings are similar to those seen in SARS<sup>43</sup> and MERS<sup>44</sup>. One of the features, which differs from both SARS and MERS, is presence of excessive mucus secretion in lungs<sup>45</sup>.

#### Cytokine storm

In respiratory infections caused by influenza or SARS-CoV-2 viruses, A "cytokine storm" involves a robust immune response resulting in the production of high levels of inflammatory mediators: cytokines and chemokines. These molecules enrol inflammatory cells to the site of the virus infection in COVID-19 patients leading to pulmonary inflammation. SARS-CoV-2 causes a swift viral replication and cellular damage, virus-induced ACE-2 down regulation and shedding. An antibody dependent enhancement (ADE) is accountable for vigorous inflammation<sup>46</sup>. In SARS-CoV-2, there is an entry of receptor ACE-2, the same cells being targeted and infected<sup>45,47</sup>. This viral replication can cause huge death and vascular leakage of epithelial and endothelial cells, prompting the development of ebullient pro-inflammatory cytokines and chemokines. Losing of ACE-2 pulmonary activity causes acute damage to the lungs<sup>48</sup> because of down regulation and discharge of ACE-2, which ultimately

can lead to inappropriate working of renin-angiotensin system (RAS), causing edema. In antibody-dependent enhancement (ADE), there is a viral cellular uptake of infectious virus-antibody complexes following their interaction with Fc receptors (FcR), FcγR, or other receptors, resulting in enhanced infection of target cells<sup>48</sup>. There was a significant increase of cytokines and chemokines in patients with COVID-19 infection which include a group of interleukins such as IL-1β, IL-1RA, IL-10 and many more. Also, basic FGF-2, GCSF, GMCSF, IFNγ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGFB, TNFα, and VEGFA

were predominantly high. In few severe cases, there were an increase of pro-inflammatory cytokines which indicate the severity of the disease<sup>49</sup>.

**Impaired immune system**

There was a remarkable reduction in the peripheral CD-4 and CD-8 T cells. High concentrations of proinflammatory CD-4 T cells and CD-8 T cells were observed antiviral immunereaction and over activation of T cells<sup>42</sup>. In addition, lymphopenia is a prominent trait of COVID-19, responsible key factor for severity and mortality.

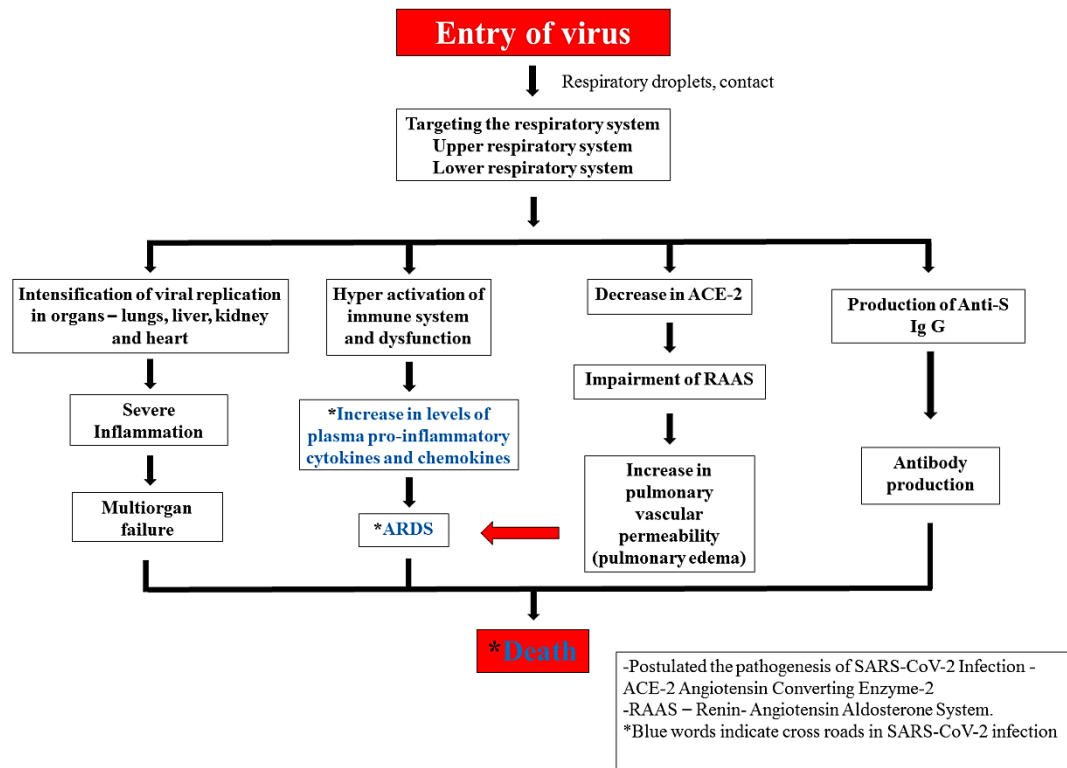


Fig 4. Summary of the SARS-CoV-2 pathogenesis.

**POTENTIAL TREATMENT OF COVID-19**

**Anti-viral treatment**

Currently, there is no available treatment for COVID-19. As there is an urgent necessity for successful treatments, there evolved a keen interest in developing the drugs which are available for immediate use. In the meantime, in humans, up to now COVID-19 infection has no specific antiviral drugs or vaccine against<sup>50</sup>. Broad-spectrum antiviral drugs like nucleoside analogues and also HIV-protease inhibitors are the only options available. Additionally, HIV-protease inhibitors could be used, with use of two times a day oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0.25 g ganciclovir for 3-14 d. Another study reveals the use of remdesivir and chloroquine in the control of CoV infection *in-vitro*<sup>51</sup>. Keeping in view of the safety records, these antiviral drugs can be used. Moreover, there are several compounds under development. These include EIDD-2801 which has shown high therapeutic value as compared to seasonal and pandemic influenza virus infections and considered one of the potential drugs for the treatment of COVID-19 infection<sup>52</sup>. Also, it is mandatory to boost up the research in these lines to identify new chemotherapeutic drugs for treating COVID-19 infections. Hence, it is advised to perform an animal model to evaluate newer agents and

understand the virus-host interactions so that a potential and favorable therapeutic outcome ensue faster<sup>53</sup>.

**Ribavirin**

Ribavirin is a purine nucleoside and acts by inhibiting the enzyme inosine monophosphate dehydrogenase preventing replication of both RNA and DNA viruses<sup>54</sup>. Ribavirin is given orally (with an absolute bioavailability of 40% to 50%), intravenously or as an aerosol. In adults, an oral dose of 600 mg yields peak plasma level of 1.3 μg/mL and an intravenous dose of 1000 mg results in 24 μg/mL. In children, aerosols are preferred considering the risk factors like chronic lung disease, immunodeficiency, or severity of the disease<sup>55</sup>. In SARS patients, with high doses adverse effects like hypocalcemia and hypomagnesemia (electrolytic disturbances) were observed. Adding on, hyperammonemia and pancreatitis have also been reported. This drug is contraindicated in pregnant women, renal insufficiency, hypersensitivity subjects and also with few cardiac disorders<sup>56</sup>.

**Lopinavir/Ritonavir (LPVr)**

Lopinavir/ritonavir is strongly advised for COVID-19 clinical treatment. Lopinavir is an anti-retroviral drug which is a protease inhibitor used for the treatment of COVID-19 and also HIV. LPVr is a protease inhibitor which may inhibit the action of 3CL<sup>pro</sup>, an enzyme 3-chymotrypsin-like protease required for processing the

viral RNA<sup>57</sup>. Finally, LPVr disrupts the viral replication cycle and secretion into the host cells. Few adverse effects have been reported such as GIT disturbances, diabetes, dyslipidemia, pancreatitis and hepatic disorders. It is contraindicated in patients with cardiovascular disorders and hemophilia. Very few reports proved that it has been used efficiently in the treatment of COVID-19<sup>58</sup>. Nowadays, there is not enough evidenceto suggest the use of LPVr for COVID-19 apart from the research studies. Hence, more research is essential in order to prove the efficacy and safety of drug usage.

#### **Remdesivir(RDV)**

An *in-vivo* study revealed thatremdesivir was previously used to restrain SARS-CoV<sup>59</sup>. Remdesivir is a nucleoside analog which acts by inhibiting the action of RNA polymerase. It gets incorporated into RNA, terminating RNA transcription and haltingviral replication. In a case report, remdisivirforCOVID-19 patients was started in the seventh day of treatment by intravenous route<sup>60,61</sup>. It is CoV infections can be maintained by giving remdesivirtwice daily. However, a dose of 200 mg once daily on the first day, followed by 100 mg once daily were used in clinical trials<sup>61</sup>.

#### **Nelfinavir**

Nelfinavir is a potent and orally bioavailable HIV-1 protease inhibitor, which was approved by FDA in 1997 for the treatment of HIV infection. Nelfinavir in a clinical trial showed remarkably high peak and trough concentrations at a dose of 1875 mg BID against SARS-CoV-2. Nelfinavir was detectable in broncho-alveolar lavage (BAL) fluid in 100% patients treated at four weeks<sup>62</sup>. Nelfinavir in the lung epithelial lining fluid was found to be same found in plasma, enabling the high penetration capability of nelfinavir into the alveolar compartment. Nelfinavir was reported to be effective and inhibits inflammatory cytokines in pediatric HIV patients<sup>63</sup>. Ahigh potency against SARS-CoV-2 in Vero E6 cells, a higher exposure in lung than in plasma and a good safety profile, nelfinavir deserves further exploration as potential treatment of COVID-19.

#### **Ribonucleoside analog β-D-N4-Hydroxycytidine**

This group of treatment possesses abroad-spectrum antiviral activity against SARS-CoV-2, MERS-CoV, and SARS-CoV. A study revealed human airway epithelial (HAE) cellstreated with this agent induce a reduction depending on the dose in SARS-CoV-2. It also determined that β-D-N4-hydroxycytidine-5'-isopropylester (NHC) would elevate the mutation frequency during MERS-CoV infection in HAE<sup>64</sup>. This drug was evaluated for *in-vivo* efficacy using EIDD-2801, an orally bioavailable prodrug of NHC, designed to improvepharmacokinetics as well as oral bioavailability in humans and non-human primates. In this study, an oral EIDD-2801 was a strong antiviral and has the ability to inhibit SARS-CoV replication and disease. EIDD-2801 likely provides benefit to the patient who is severelyinfected and also in those individuals with extended virus replication<sup>65</sup>.

#### **Antimalarial**

##### **Chloroquine (CQ) and Hydroxychloroquine (HCQ)**

Quinine is another existing drug candidate possibly used to treat COVID-19. Chloroquine (CQ) is an amine acid tropic type of quinine. Hydroxychloroquine (HCQ) shares the same structure with CQ; however, a hydroxy group is attached to the side chain of the molecule. Over 70 y ago, CQ and HCQ have been widely known as antimalarial agents and given as (prophylaxis and treatment)<sup>15,66,67</sup>. They are known to be small, affordable and safe approved antimalarial drugs<sup>68</sup>. Moreover, previous reports proved

that CQ/HCQ are wide spectrum antiviral activities against human immunodeficiency virus (HIV)<sup>69</sup>, Marburg virus, Zika virus, dengue virus, Ebola virus<sup>70</sup> influenza (A/B)<sup>71</sup>, SARS-CoV-1 and possibly SARS-CoV-2<sup>66,68,72</sup>. In more details, the IC50 of CQ against SARS-CoV-2 Vero E6 cells pre-infected cells was (1.13 μM)<sup>73</sup>. In terms of mechanism of action, actually both CQ/HCQ show the same mechanism action; however, the safety profile of HCQ is much better than CQ<sup>67</sup>. Therefore, HCQ is more preferable than CQ. First of all, SARS-CoV-2, in particular, binds to angiotensin converting enzyme-2 (ACE-2) receptor permitting its entrance to the human cells<sup>67</sup>. Glycosylation of ACE-2 cellular receptors is one of the potential mechanisms by which CQ and HCQ disrupt SARS-CoVviral cycle<sup>15,66,73</sup>. Second, the pH-dependent endosome and lysosome-mediated SARS-CoV entry is another mechanism by which viral cycle is disrupted<sup>74</sup>. In more details, proteases mediated spike viral glycoprotein (S-protein) cleavage is essential for cell entry of SARS-CoV. This process depends on the specific pH value<sup>75,76</sup>. On the other hand, accumulation of CQ in the organelles such as endosomes and lysosomes (acidic organelles) leads to pH neutralization of these organelles believed to inhibit the protease roles in cleavage of S-protein. CQ and HCQ-pH neutralization also impairs the post-translational modification or maturation of the viral proteins. Consequently, the viral entry into the cells will be blocked<sup>75,77</sup>. Furthermore, a study revealed that CQ is able to inhibit SARS-CoV-2 not only at entry level but also after the infection which leads to inhibition the virus transmission<sup>67,73,75,78</sup>. Due to these promising effects of quinine molecules, clinical trials for CQ and HCQ are in urgent demand. Therefore, Chinese research group was the first group who conducted CQ clinical trials against COVID-19. Actually, 100 patients were included in study and found that CQ superiorly reduces their symptoms duration, exacerbation of pneumonia, radiological improvements which lead to virus-negative seroconversion<sup>67,79</sup>. However, French investigators group studied HCQ in combination with azithromycin (antibiotic). They include 36 patients in this study. HCQ (600 mg daily) in addition to azithromycin were administered by 20 of them. After six d of the treatment, a substantial reduction of viral burden and much lower average time carrying the virus were found in comparisons to the control group<sup>67,80</sup>. Currently, several clinical trials are going on to use CQ and HCQ as antiviral agents. Moreover, regarding their safety profile, CQ and HCQ showed adverse reactions ranging from mild rash to mild headache which can be managed by slight regimen adjustment<sup>75</sup>. Based on these results, it is been suggested by the government authorities and clinical trials organizers that CQ and HCQ are promising antiviral agents targeting COVID-19.

#### **Anti-parasitic**

Ivermectin, which is a broad spectrum antiparasitic agent, is FDA-approved drug. In the last 27 y, several research groups have shown that ivermectin induced antiviral effects against wide variety of viruses including RNA types of viruses<sup>81,82,83,84</sup>. In terms of ivermectin molecular mechanism, it inhibits the heterodimeric complex between the human immunodeficiency virus-1 (HIV-1) integraseprotein(IN) and the importin (IMP) α/β1 accountable for IN nuclear import. This led to impair HIV-1 replication as a result of IN transportation to the nucleus<sup>85,86,87,88,89,90</sup>. However, this is not the only reported mechanism of action<sup>87</sup>. Furthermore, a study has shown that one-time treatment of ivermectin had an inhibitory effect against the COVID-19 causative virus (SARS-CoV-2),

previously two h infected Vero-hSLAM cells. Treatment with ivermectin induced IC50 of around (2 µM) which is accountable for approximately 5000-fold reduction in viral RNA (48 h treatment) <sup>90</sup>. Moreover, ivermectin has not shown any toxicity signs at any points of the study <sup>90</sup>. Collectively, a single dose ivermectin for 48 h treatment has an *in-vitro* antiviral action against the SARS-CoV-2 pre-infected cells by regulating viral replication. This effect is hypothesized to be possible as seen by inhibiting IMP α/β1-mediated nuclear import of viral genomic material and proteins, as revealed for other many types of viruses <sup>84,89,91,92</sup>. However, further research in the case of SARS-CoV-2 is needed. Ivermectin, therefore, requires additional research for its potential clinical effects to treat COVID-19.

#### **Anti-Protozoal agents**

The Antiviral effects of antiprotozoal agents, examples of which are nitazoxanide and nafamostat, were proposed and evaluated *in-vitro* <sup>91</sup>. In terms of mechanism of action, nitazoxanide was able to modulate the growth, survival and proliferation of several microorganisms including viruses (coronaviruses) <sup>61,93,94</sup>. However, nafamostat induced its antiviral effects by preventing viral getting into the host. In more details, the viruses including coronaviruses and Ebola viruses utilized cathepsin B, protease inhibitor, to activate their glycoprotein envelopes. Activation of viral membrane leads to its fusion with cellular endosomal membrane helping viral entrance into the cell. Membrane fusion protects the virus from the endosome. Taken together, cathepsin B is an important factor in viral life cycle <sup>95,96,97,98,99,100,101</sup>. However, more than 90% of viral infection were reduced when cathepsin B is blocked <sup>95</sup>. Studies have shown that nafamostat inhibit the membrane integration by decrease the release of cathepsin B in case of influenza, Middle East respiratory syndrome-related coronavirus (MERS) and Ebola infections <sup>102,103</sup>. Therefore, nitazoxanide and nafamostat have high potential to treat COVID-19 and their mode of action against SARS-CoV-2 need to be further studied.

#### **Immunotherapy**

RNA viruses tend to be highly liable causative agents of newly-emerging infections. One such emerging infection is severe acute respiratory coronavirus-2 (SARS-CoV-2). SARS-CoV-2 has gained the capability to rapidly be contagious resulting in a global outbreak. Therefore, therapeutic approaches against this infection which potentially threatens our life are necessary to be created. SARS-CoV-2 causes an acute infection which makes targeted passive immunotherapy an attractive strategy for treatment <sup>104</sup>.

#### **Interleukin-6 inhibitors**

These area human monoclonal antibody that binds and blocks IL-6 receptors as result they inhibits the interleukin-6 (IL-6) pathway. In patients who are suffering from COVID-19, IL-6 may have a role in monitoring the overactive inflammatory response in the lungs of patients. In 21 patients suffering from severe respiratory symptoms related to COVID-19. Non-peer reviewed study was performed in China. All had a SARS-CoV-2 confirmatory diagnosis. The patients in the study were 56.8 y of median age (18 of 21 were males). While all patients who were admitted of requirements of (1) respiratory rate of 30 breaths/min or more, (2) 93% or less of SpO<sub>2</sub>, and (3) 300 mm Hg or less of PaO<sub>2</sub>/FiO<sub>2</sub>, only two of the patients needed invasive ventilation. The remaining 19 patients received different types of oxygen delivery including nasal cannula, mask, high-flow oxygen, and non-invasive ventilation. All patients were treated with common medications including lopinavir and methylprednisolone.

Patients were given a single 400 mg dose of tocilizumab via intravenous infusion. Patients situation has improved with lower oxygen requirements, lymphocyte numbers have been restored to normal, and 19 patients have been discharged with 15.5 d in average after treatment with tocilizumab. The authors mentioned that tocilizumab is effective in severely COVID-19 patients <sup>105</sup>. However, those findings should be viewed with extreme cautions. This study did not use any controls and only one patient provided invasive mechanical ventilation. Additionally, all patients received common therapy at least one w before tocilizumab began.

#### **Convalescent plasma therapy**

Convalescent is the plasma from patients who has recovered from an infectious disease and they became rich in antibodies against the infectious agent of the disease. Convalescent plasma or immunoglobulins were used, improve the survival rate of SARS patients, who are continued to suffer even after taking methylprednisolone treatment. In addition, decreased mortality rates and shorter hospital stay was showing in patients treated with convalescent plasma showed a than those not given convalescent plasma <sup>106</sup>. In 2014, WHO recommended the use of convalescent plasma as an empirical treatment during outbreaks as it was collected before from patients recovered from Ebola virus disease <sup>107</sup>. In 2015, a protocol was established for convalescent plasma in the treatment of Middle East respiratory coronavirus syndrome (MERS) <sup>108</sup>. For patients with 2009 pandemic influenza A H1N1 (H1N1pdm09) virus infection, a cohort study by Hung and colleagues showed a significant reduction in mortality rates (odds ratio 0.20) (95% CI 0.06-0.69) (p = 0.01) for patients with convalescent plasma treatment <sup>109</sup>. In addition, viral load after convalescent plasma treatment was significantly decreased in a sub-group analysis on d 3, 5 and 7 following admission to ICU. Moreover, in most viral infections, viremia comes to the top during the first w of infection. A primary immune response occurs usually by d 10 to 14, followed by viral clearance <sup>106</sup>. Theoretically, the administration of convalescent plasma in earlier stages should therefore become more effective <sup>106</sup>. However, other therapies which comprises antiviral medications, steroids, antibiotics, and intravenous immunoglobulin, may have an influence on the relationship between convalescent plasma and antibody levels <sup>110</sup>. According to WHO <sup>111</sup>, COVID-19 management has concentrated primarily on prevention of infections, case detection and monitoring, and supporting care. However, because of lack of evidence, no specific anti-SARS-CoV-2 therapy is endorsed. More importantly, the current recommendations, particularly the comment published in the Lancet, emphasize this treatment approach against COVID-19 <sup>112</sup>. Systemic corticosteroids should not be routinely given. Studies showed that convalescent plasma from patients who have recovered from viral infections can be used as a therapy with no side effects. Therefore, checking the welfare and efficacy of convalescent plasma transfusion in patients infected with SARS-CoV-2 may be worthwhile <sup>113</sup>.

#### **Anti-bodies**

Biological therapies have a beneficial effect on the treatment of infections with coronavirus and include a many available options, including bioengineered and vector-based antibodies, cytokines and viral nucleic acid therapies and vaccines. Ninety-nine patents have been established for MERS and SARS with curative as well as diagnostic possibilities including information on antibodies. Of these, 61 are: SARS-specific patent-claimed



preparations (23), MERS-specified antibodies (17), or diagnostic-applicable antibodies (21). As in SARS-CoV, the SARS-CoV-2 S-protein receptor-binding domain (RBD) is linked to the human ACE-2 receptor to enter host cells<sup>30</sup>. Viral S-protein in SARS-CoV, stimulates a responding defense system<sup>114</sup>. Liu *et al.*, developed a patents table related to SARS therapy antibodies production<sup>115</sup>. About 90% of these antibodies target for the S and RBD proteins. The information shows that S-protein is a supposed focus of antibody production in SARS-CoV-2. A further 38 patents covered descriptions of other antiviral antibodies for SARS and MERS treatment. This involved the neutralization of protein-based antibodies examples of which include: ITAM (immunoreceptor tyrosine-based activation motif), IL-6/IL-6R, CD16, TLR3 (toll-like receptor 3), DC-SIGN (dendritic cell-specific intercellular adhesion molecule-grabbing non-integrin), IP-10/CXCL10 (interferon  $\gamma$ -inducible protein-10) or ICAM-3 (intercellular adhesion molecule-3)<sup>115</sup>.

#### **Vaccines**

The production of safe and efficient vaccines is essential for controlling the COVID-19 pandemic, minimizing its distribution and potentially preventing its possible recrudescence. Due to the strong sequence similarity of the SARS-CoV-2 virus with two other lethal coronaviruses, SARS and MERS, the SARS and MERS-related vaccines listed in those patents may potentially controlling the protocol of anti-SARS-CoV-2 vaccines. The following are types of antiviral vaccination typically present as live attenuated or inactive viruses, viral vectors, virus-like particles (VLPs), DNA-related vaccines, protein-related vaccines, as well as mRNA vaccines. Viral S-protein subunit vaccines were reported to have better, more titers, and safer DNA-based neutralizing antibodies in compare to live-attenuated SARS-CoV, full-length S-proteins, and S-proteins (DNA based)<sup>116</sup>. As predicted, most patents are focused on protein vaccines that contain the S-protein subunit vaccine, and on vaccines that specifically target the S1 subunit of the viral S-protein receptor binding domain (RBD). S-protein/gene is collectively the target site selected to improve the MERS and SARS vaccine and the exact method would be possibly successful for creating vaccines against SARS-CoV-2<sup>115</sup>.

#### **Attenuated virus vaccines**

US20060039926 coronavirus or torovirus vaccines are stated in the patent application which is live attenuated. The introduction in the polyprotein Orf1 $\alpha/\beta$  of a mutation (Y6398H) (p59/nsp14/Exon) showed that mouse coronavirus virulence (MHV-A59) is totally attenuated. On the fifth d after intracerebral inoculation, replication reduction in mice was showed in the attenuated MHV virus<sup>115</sup>.

#### **DNA-based vaccines**

WO2005081716 patent application reveals compositions and procedures for the induction/enhancement of immune responses against SARS coronavirus antigens, mostly antigen-specific CD-8 T cell-mediated responses. Fanciful nucleic acids encoding an endoplasmic reticulum chaperone polypeptide (e.g., calreticulin) linked with at any rate one SARS-CoV antigenic polypeptide or *in-vivo* peptide induce an increased immune reaction including particularly cytotoxic T cell immune reaction. T-cell-mediated immune reaction as well as humoral nucleocapsid-specific was developed as a result of mice vaccination against calreticulin-nucleocapsid fusion protein using DNA-coated gold particle delivery from gene guns. Vaccinated animals have been able to minimize

substantially the titer of a vector vaccine that expresses the SARS N-protein<sup>115</sup>.

#### **Protein-based vaccines**

GlaxoSmithKline (GSK) WO2010063685 patent application reveals a vaccine that can evoke a defensive immune reaction against SARS. It consists of an immunogenic S-protein as well as an adjuvant of o/w emulsion. Along with the emulsion adjuvant, GSK2, an engineered immunogenic ectodomain (dissolved S-protein) induced elevated antibody response levels of anti-SARS-CoV IgG2a, IgG2b, and neutralized antibody reaction of animal-model. GSK recently partnered with Chinese company Clover Biopharmaceuticals in February 2020 to find a candidate for a coronavirus (COVID-19) vaccine. The partnership will include the use of Clover's protein-based candidate for coronavirus vaccine (COVID-19 S-Trimer) adjuvant system by GSK<sup>115</sup>.

#### **Virus-like particle vaccines**

In 2015, an immunogenic composition consisting of MERS-CoV nanoparticle VLPs comprising at minimum one S-protein trimmer developed by baculovirus overexpression in Sf 9 cells was revealed in Novavax's patent application WO2015042373. This VLP formulation, caused a neutralizing antibody reaction in mice and genetically modified bovine if given together with their patented adjuvant Matrix M (RN 1235341-17-9). Additionally, vaccinated bovine sera preparations (SAB-300 or SAB-301) have been inserted with Ad5-hDPP4 converted into BALB/C mice previous to MERS-CoV challenge. Through a single prophylactic injection, the mice were able to defend MERS-CoV contamination with both SAB-300 and SAB-301. Novavax announced in 26<sup>th</sup> February, 2020 that it will be conducting animal research on possible candidates for the COVID-19 vaccine based on its prior success in treating different coronaviruses, both SARS and MERS. The COVID-19 candidate vaccines that target SARS-CoV-2's S-protein were established by their recombinant nanoparticle vaccine technology and their patented Matrix-M adjuvants<sup>115</sup>.

#### **mRNA-based vaccines**

The probable benefits of a prophylactic mRNA vaccine strategy are the capability to imitate natural infection in order to cause much more efficient immune reaction, and also the capability to incorporate several mRNAs under one single vaccine. mRNA vaccines made up of mRNAs encoding full-length antigenic S, S1, and S2-proteins from SARS-CoV along with MERS-CoV viruses, formed in cationic lipid nanoparticles were revealed by WO2017070626 Moderna's patent application. It was demonstrated that mice vaccinated with a full-length coronavirus S-protein encoding mRNA created significantly higher neutralizing antibody titers in comparison to the S2 subunit protein encoding mRNA. There was a decrease in viral load in the rabbit's lungs by more than 90% and caused a large amount of MERS-CoV neutralizing antibody in New Zealand white rabbits vaccinated with MERS-CoV mRNA vaccine encoding the full-length S-protein. In February 24<sup>th</sup>, 2020. Moderna revealed that it has launched mRNA-1273 for human use in the first batch against SARS-CoV-2. Vials of mRNA-1273 were sent to the National Institute of Allergy and Infectious Diseases (NIAID), the National Institutes of Health (NIH) branch, to be included in the proposed Phase 1 research. Moderna reports that mRNA-1273 is an mRNA vaccine targeting a prefusion-stabilized version of the S-protein associated with SARS-CoV-2, selected by Moderna in collaboration with researchers at the NIAID Vaccine Research Center<sup>115</sup>.

**RNA silencing (SiRNA) oligonucleotide: a potential defense mechanism against CoV-2019 genome**

Coronaviruses (CoVs) are RNA viruses that range in size (60-140 nm) in diameter<sup>117</sup>. Targeting this type of RNA virus is one of the potential mechanisms that has been discovered recently. Basically, an oligonucleotide or RNA silencing (SiRNA) ranging 21-25 nucleotides (nt) in size is a structure used to target the pathogenic RNA by different molecular mechanisms leading to the post-transcriptional termination of gene expression indicated by fragmentation of the interested mRNA<sup>118</sup>. The process starts when the host cell is infected by the virus and empties its cargo in the host cell. Recently, the genome sequence of CoV-2019 was published (Gen-Bank: MN908947.3)<sup>119,120</sup>. However, research is still going on to find the optimum SiRNA targeting viral sequence and going beyond in terms of clinical studies. Using oligonucleotide approach as a potential treatment for CoV-2019 seems promising but it has several pitfalls:

**Gene delivery challenges**

The major questions that you encounter when you have your SiRNA synthesized are how would you deliver it into the lung<sup>119,121</sup>. If you were able to deliver it to the lung, would be effectively stopped the infection or made a difference clinically<sup>119</sup>. Actually, tremendous efforts were made to answer these questions. For example, lipid nanoparticles vehicles were used as a delivery system showing partial success in terms of oligonucleotide doses and activity<sup>121</sup>. This explanation answered why oligonucleotide designed against Ebola has achieve a great success in preclinical studies and failed in the clinical trials<sup>91,119,122,123,124</sup>.

**Manufacturing and timing issues**

Another point that we have to put in mind is that if we discovered a clinically active SiRNA, the production of SiRNA drugs in a large scale of huge pathogen-infected people would be very limited. Additionally, we are in lack of resources to produce this treatment in a quick time. This explain why SiRNA based treatment is currently manufactured only for rare diseases<sup>119</sup>.

**Traditional Chinese Medicine (TCM) for COVID-19**

The new outbreak of COVID-19 is progressing rapidly, and no particular drug has been discovered yet as we mentioned before. A few results from clinical experience have indicated that TCM plays a major role in COVID-19, providing prevention and controlling way for COVID-19. TCM has an extended experience in preventing as well as treating serious infectious diseases. TCM intervention also achieved impressive therapeutic success during the 2003 SARS epidemic. Throughout the COVID-19 period, around 3100 TCM medical staff were sent to the province of Hubei, and TCM was involved in the COVID-19 diagnosis and cure guidelines and TCM experts were actively involved in the entire saving process. TCM decoction, Chinese patent medicine, acupuncture, and other traditional ways of treatment were widely practiced, primarily focused on differentiation of syndrome. Many cases with mild symptoms were treated by TCM in which the disappearance time of the clinical symptoms was shortened by two days, the recuperation period of body temperature decreased by 1.7 days. In the TCM treatment of critical patients, the average length of hospital stays and the time of the nucleic acid turning negative became less by more than two d. TCM has recommended that patients with COVID-19 symptoms of pneumonia to get prescriptions which are likely to be effective, such as qingfeipaidu decoction (QPD), Gancaoga njiang decoction, Sheganmahuang decoction, Qingfeitouxiefuzheng recipe,

etc. QPD consisting of: Ephedra herba, Glycyrrhizae radix, Rhizomapræprata cummelle, Gypsum fibrosum, Cinnamon miramulus, Citroreticulata epericarpium and Pogo stemonisherba were recommended in China in the COVID-19 diagnosis and treatment program as a general prescription. Of the 701 reported patients treated with QPD, 130 patients were healed and released, 51 cases of severe symptoms disappeared, 268 condition cases enhanced, and 212 non-aggravated cases with stable symptoms. QPD successful cure rate against COVID-19 exceeds 90%. COVID-19's target organ location is the lung according to TCM theory and the causative agents is "damp and plague of toxins". Its pharmacology review showed that QPD has a regulatory impact through many components and targets. The lungs are the main site of pharmacological action, which suggests that the decoction is specifically applicable to lung disease. It has also the function of dehumidification through the spleen and stomach rise and fall, and exhibit heart, kidney, and other organs protection<sup>125</sup>. In the period of ten years, researchers have exerted substantial efforts to detect many botanical formulae in TCM with action against SARS-CoV. Detection of the substances found in TCM herbs, accountable for anti-SARS-CoV action, has been attempted. Numerous TCM alleged to have anti-SARS-CoV effect by several mechanism of actions: chymotrypsin-like protease (3CLpro) is crucial for virus duplication and therefore represents a promising target for the development of SARS-CoV-1 therapeutic agents and other human coronaviruses like SARS-CoV-2. It has been stated that the upcoming list of TCM herbal extracts have the ability to prevent SARS 3CLpro enzymatic activity: Chinese rhubarb extracts<sup>126</sup>, houttuyniacordata water extract<sup>123,124</sup>, litchi seed flavonoid<sup>127</sup> and Beta-sitosterol isolated from *isatisindigotica* root extract<sup>100</sup>. In addition, the preceding naturally occurring herb-derived compounds including sinigrin, indigo, aloe-emodin, hesperetin<sup>100</sup>, quercetin, epigallocatechingallate, galloocatechingallate<sup>127</sup>, herbacetin, rhoifolin and pectolarin<sup>128</sup> could inhibit the activity of SARS 3CLpro. In addition, flavonoids such as, isobavachalcone, 3 -  $\beta$  - D glucoside quercetin, herbacetin and helichrysetine could block MERS-CoV 3CL protease enzymatic activity. The helicase protein is also claimed to be a possible target for anti-human coronavirus (HCoV) drugs production. Yu *et al.*, stated that by affecting ATPase activity *in-vitro* scutellarein and myricetin inhibited nsp13 (SARS-CoV helicase protein)<sup>125</sup>. Emodin of the genus *rheumandpolygonum*<sup>129</sup>, baicaline of *scutellariabaicalensis*<sup>130,131</sup>, tetra-O-galloyl- $\beta$ -D-glucose (TGG) of *gallachinensis* and luteoline of *veronicalinariifolia*<sup>132</sup> significantly suppressed the association between SARS-CoV S-protein and ACE-2. Generally, these compounds must be evaluated for their anti-SARS-CoV activity. In addition, emodin suppression of the 3a ion channel<sup>133</sup>, or kaempferol derivatives-juglanin<sup>134</sup> in which the viral release of infected cells may be prevented. Saikosaponins<sup>135</sup>, glycyrrhizin<sup>127,136</sup>, TSL1as well as quercetin isolated from *toonasinensisroem*<sup>137</sup> allegedly had strong anti-SARS-CoV activity by inhibiting the entry, adsorption as well as penetration of viral cells<sup>138</sup>. Because there is similarity between SARS-CoV-1 and SARS-CoV-2, the previous studies highlighted the natural compounds with potential for inhibition of SARS-CoV-2. Chymotrypsin-like protease (3CLpro) is essential for multiplication of the virus and therefore it is a potential target for the SARS-CoV-1 therapeutic agents' production as well as SARS-CoV-2. The following TCM herbal compounds have been reported to

have the ability to suppress enzymatic activity of SARS 3CLpro.

Taken all these mechanisms together, Fig. 5 an overview of the potential targets that in the future could be one of the drugs of choices in the treatment of COVID-19.

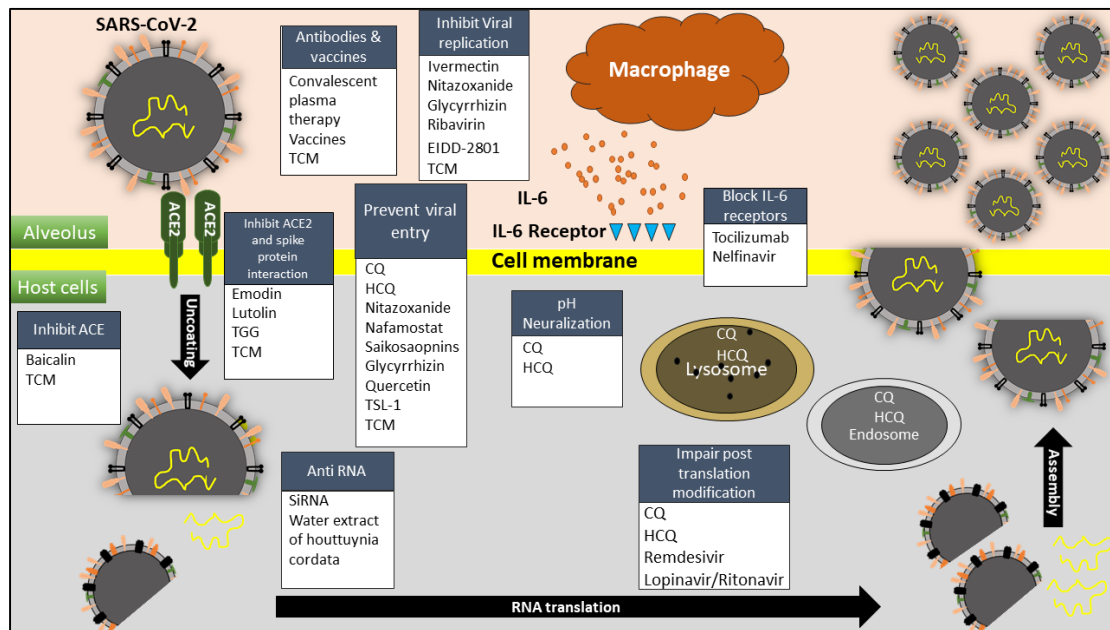


Fig 5. Summary of the potential agents that can target SARS-CoV-2 at several points of the viral life cycle.

**SOLIDARITY TRIAL WORKS AND CLINICAL DRUG TRIALS**

Adults with COVID-19 admitted to participant hospitals that can join this study. Conditions were recorded and treatment started according to each patient condition. Study plan is not a choice of patients or physicians but computers randomly make this allocation. Critical cases with critical anonymized information for the trial were collected at the randomization stage, and when the patient

is discharged or dies, a detailed study about which drugs were taken, for how long, whether ventilation or intensive care was received, cause of death and date of discharge. Global Data and Safety Monitoring Committee monitor all trials <sup>5</sup>. A research studies of COVID-19 and of the treatment trials effects in different countries explained in details Table 5 according to WHO Global research on COVID-19 last update April 20, 2020.

Table 5. Clinical trials showing the effect of several interventions globally.

Country	Primary sponsor	Interventional study	Interventions	Primary outcomes	Result
<b>Iran</b>	Tehran University of Medical Sciences	Effect of Sobosbuvir, Ledipasvir on COVID-19	Hydroxychloroquine 400 mg single dose + Cap Osetamivir 75 mg twice daily +Tab Lopinavir /Ritonavir 200/150 mg two tablets twice daily at least fived, and will take one tablet of Sobosbuvir/Ledipasvir 400/100 mg daily for 10 d.	Improvement of patients complaining from paraclinic and radiologic findings	In Progress
<b>China</b>	Hospital, College of Medicine, Zhejiang University	Triple combination antiviral therapy plus interferon alpha 2b On Novel COVID-19 Pneumonia	Lopinavir /Ritonavir plus interferon alpha-2b	Lymphocytopenia Creatinine CRP	In Progress
<b>China</b>	Guangdong Provincial Hospital of	Study for Xinguan-2 formula in treatment of	Xinguan-2-formula+standard treatment	Body temperature return to normal after 24 h, relief	In progress

	Chinese Medicine	COVID-19 Pneumonia		main symptoms disappear (fever, cough and shortness of breath)	
<b>China</b>	Tongji Medical College, Huazhong University of Science and Technology	Clinical research on blood cortisol and adrenal morphology changes in Novel COVID-19 (10 patients)	Basic symptomatic therapy with Glucocorticoid therapy	Cortisol, ACTH, Form of adrenal tissue	In progress
<b>China</b>	Shenzhen Third People Hospital	Clinical study for the effect of Chimeric COVID-19 Epitope Dc Vaccine in Novel COVID-19	Immunotherapy with recombinant Chimeric DC Vaccine	Shorten the duration of the disease, negative rate of viral nucleic acid Blood gas analysis WBCS-Lymphocyte subtype analysis IL-17	In progress
<b>China</b>	Shenzhen National Medicine Inheritance Medical Research institute Co.Ltd	Clinical study for HUO-Shen particles in the treatment of COVID-19	Traditional Chinese medicine soup	Chest CT scan, Nucleic acid of novel COVID-19, Routine blood test Routine urine and stool test	In progress
<b>China</b>	Shanghai 10 <sup>th</sup> people Hospital Tongji University	Clinical study of Probiotics in the regulation of intestinal function and micro flora structure of COVID-19 Pneumonia	Probiotics	Gut micro biome Fecal metabolism Blood routine, albumin serum CRP, ALT, AST, Urea, hepatitis b antigen, IFN, TNF-β, IL-10, IL-12, Chest CT, abdominal CT	In progress
<b>China</b>	Shanghai Changzheng Hospital	Clinical study for the effect and safety of Adalimumab injection on severe COVID-19 patients	Conventional treatment and Adalimumab	Time to Clinical Improvement	In progress
<b>Norway</b>	Oslo University Hospital	Clinical study to evaluate the efficacy of antiviral drugs in COVID-19 patients	-Trade name: Plaquenil -Product name: Plaquenil film coated tablet	-Investigate the effect of Remdesivir and Hydroxychloroquine in relation to primary and secondary endpoints -Compare effect of early and late intervention with Remdesivir and Hydroxychloroquine -Establish the safety of the study drugs -Analyze markers giving information about mechanisms of COVID-19 with	In progress

				ICU patients and treated patients at hospital yard	
<b>China</b>	Shanghai Changzheng Hospital	Clinical trials on Ulinastatin injection for severe Novel COVID-19 patients	Conventional treatment and Ulinastatin	-Blood gas -SOFA score	In progress
<b>Pakistan</b>	Aga Khan University	Clinical trials on Gargling agents in reducing Intraoral Viral Load in COVID-19	Gargle mouth wash	Intraoral viral blood	In progress
<b>United States</b>	Washington University School of Medicine	Double Blind Placebo Controlled Clinical trials of Fluvoxamine for symptomatic individuals with COVID-19	Fluvoxamine and Placebo	Time to clinical worsening	In progress
<b>China</b>	Wuhan Third Hospital	Medical Analysis for death factors of COVID-19 patients in Wuhan Hospital	Traditional Chinese medicine	Mortality rate	In progress
<b>China</b>	Department of Emergency, Tongji Hospital, Medical College	Medical Assessment of invasive fungal infection in COVID-19 pneumonia	Prophylactic antifungal therapy	Mortality rate	In progress
<b>China</b>	Wuhan Women and children Health care center	Medical Study for correlation between Angiotensin II Type 1 receptor and COVID-19	ARBs treatment	Incidence of ARDS	In progress
<b>China</b>	Guangzhou Eighth People Hospital	Medical records study on Tou-Jie-Qu-Wen Granules in treatment of COVID-19	Tou-jie-Wem Granules treatment	Syndrome of nucleic acid of n CoV-2019	In progress
<b>China</b>	Hospital of Zhejiang University School of Medicine	Study on the efficacy of Suramin Sodium in COVID-19 patients	Suramin Sodium IV	-Cure rate -Mortality rate by 28 d -ICU admission by 28 d	In progress
<b>China</b>	Hospital of University of Science and Technology of China	Trials for efficacy and safety of Tocilizumab in COVID-19 patients	Conventional therapy + Tocilizumab	Cure rate	In progress

**CONCLUSION**

Declaring coronavirus as a pandemic and a global serious health issue represent one of the major threats that we have ever been encountered. The virus has an inclination to infect huge number of individuals, and the outbreak had negative impacts on several aspects of life such as health, economy and society. Moreover, there are several factors involved in increasing the number of infected areas around the world such as people movement and trading

goods. However, effective management of the novel coronavirus requires huge effort in terms of people inspection along with the robust response of governmental agencies, health professionals, and scientists. Identifying and well understanding about the virus origin and its reservoir, pathogenesis, transmission, and patients' signs and symptoms are in urgent need to established research models, diagnostic tools and therapeutic strategies.

Unfortunately, there is no approved vaccine or definitetherapy for COVID-19. However, understanding the molecular pathology of the COVID-19 may provide valuable information helping to come up with new strategies which may lead to rapidly discover the vaccines, new drugs and even improve the prevention and control procedures. Repurposing of previously approved drugs such as antiviral, antimalarial, antiparasitic and antiprotozoal is one approach that showed promising effects against COVID-19 clinically or in the preclinical studies. In addition, immunotherapy and gene therapy are two choices that seem to be applicable in the treatment of this disease. Scientist in China also showed that several Traditional Chinese Medicines (TCM) as another treatment choice against COVID-19. Nonetheless, all these likely treatment approaches need to be further clinically validated to be approved. In record time, a great work has been accomplished in terms of complete genome sequencing of SARS-CoV-2 even though COVID-19's treatment development is still in early phases.

In this article, we gave a brief review of epidemiological, etiological information about COVID-19 and a deep explanation the pathology of the disease and an introduction of the latest advancement in the treatment in terms of molecular mechanisms were emphasized. This comprehensive review provides a solid background to researchers about the potential approaches of COVID-19 treatment, which may help to fasten appraise up to date information about several fact on CoV-2019 treatment targets. In conclusion, the battle against this deadly novel coronavirus continues and the discovery journey of the treatment seems to be long and challenging. However, there is no choice except stopping the outbreak and bring our life back to normal as early as possible.

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#### CONFLICT OF INTEREST

No conflict of interest.

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