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A REVIEW ARTICLE ON CORONA VIRUS (SARS-CoV-2)

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ABSTRACT

Despite advances in drug discovery, viral infections remain a major challenge for scientists across the globe. The recent pandemic of COVID-19 (coronavirus disease 2019), caused by a viral infection with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), has created a disastrous situation all over the world. As no drugs are available to treat this life-threatening disease and the mortality rate due to COVID-19 is high, there is an utmost need to attempt to treat the infection using drug repurposing. Patient shows various symptoms like as fever, cough, sore throat, breathlessness, fatigue etc. The disease is being cured by general treatment, symptomatic treatment by using oxygen therapy and by the immune system. This article emphasizes possible drug candidates in the treatment of COVID-19. Most of these drugs were found to be effective in in vitro studies. There is a need to re-assess in vitro data and to carry out randomised clinical trials. Further investigations of these drugs are recommended on a priority basis.

KEYWORDS: COVID-19, SARS-CoV-2, Drug repurposing, Coronavirus.

ABBRIVIATIONS

CoV, coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV, severe acute respiratory syndrome coronavirus.

1. INTRODUCTION

COVID-19 (coronavirus disease 2019) is a respiratory tract infection caused by a novel coronavirus that was first identified in the city of Wuhan, Hubei Province, China, at the end of 2019. Corona is the Latin word, means 'the crown'. As the virus has crown like protein structure on its surface it is named as corona. Corona virus is the zoonotic virus. Certain

drugs are showing good results for treatment of corona disease 2019(COVID 19) infection. Several industries are trying for the development of vaccine but till now, there is no Food and Drug Administration (FDA) approved drug for the treatment of COVID 19 infection. As prevention is better than cure, preventive measures should be followed.

It has spread across the globe to more than 190 counties within a short period, i.e. within 45–90 days of its initial recognition. To date, there is no specific treatment available to treat infection with SARS-CoV-2 and the disease COVID-19.

ORIGIN

Since 12 December 2019, the epidemic of unknown acute respiratory tract infection broke out first in Wuhan, China, which is possibly related to a seafood market. From the several studies it is predicted that bats are possible potential reservoir of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The SARS-CoV-2 is a zoonotic virus. α–/ β–/γ–/δ-CoV are the four genera of coronavirus. α- and β-CoV can infect mammals, while γ- and δ-CoV able to infect birds. SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) are known β-CoV, which can cause severe and potentially fatal respiratory tract infections. From the studies it was found that the genome sequence of a bat CoV RaTG13 has 96.2% similarity to SARS-CoV-2, whereas SARS-CoV is 79.5% identical. Based on this evolutionary analysis and genome sequencing results, bat has been suspected as natural host of virus origin. From bats, SARS CoV -2 infects human, via unknown intermediate hosts. SARS-CoV-2 and SARS- CoV could use same receptor i.e. Angiotensinconverting enzyme 2 (ACE2), for causing infection to humans. However, human SARS-CoV-2 and bat CoV might share the same ancestor; bats are not available for sale in this seafood market. So, there is more possibility of alternative of intermediate hosts like snacks, turtles and pangolin.

In India, most of the drugs and antibiotics used to treat COVID-19 have been repurposed (off-label/investigational use) and have been found to be very effective in affected individuals. This might be one of the reasons for the low mortality rate in India (0.02 deaths per million persons) compared with Italy (178 deaths per million persons). Chloroquine and its hydroxyl analogue hydroxychloroquine have been reported for their use as an antiviral agent in various studies.

The major stages of the coronavirus replication cycle and the probable sites of action of different drugs are shown in Fig. 1.

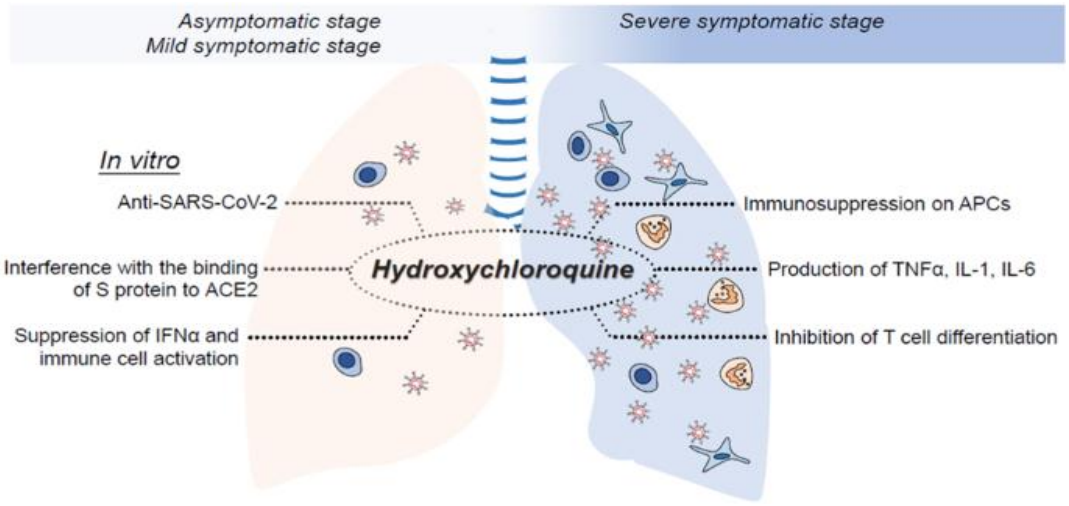

Fig.1: Major Stages Of Saras-Cov-2 (Severe Acute Respiratory Syndrome Coronavirus 2) Life Cycle In Host Cells And Probable Site Of Action Of Hydroxychloroquine.

TRASMISSION

Transmission: Huainan seafood market have been tracked for the primary cases of COVID 19, but as secondary cases occurring at hospitals among nurses and physicians who had extensive contact with COVID-19 patients. Through the respiratory droplets from cough and sneeze of COVID 19 infected patient confirmed to be human to human transmission pathway. The incubation period is average 5 – 14 days. During the incubation period patient may be pre symptomatic but contagious. Furthermore, several individuals who did not have direct contact with the Huainan seafood market were diagnosed. The predominant modes of transmission is respiratory droplets or secretions of infected individuals from human to human. The spread of infection is more rapid for the current outbreak than SARS epidemic. Between family members, including relatives and friends who intimately contacted with patients or incubation carriers are mainly showing human to human transmission of SARS-CoV-2.

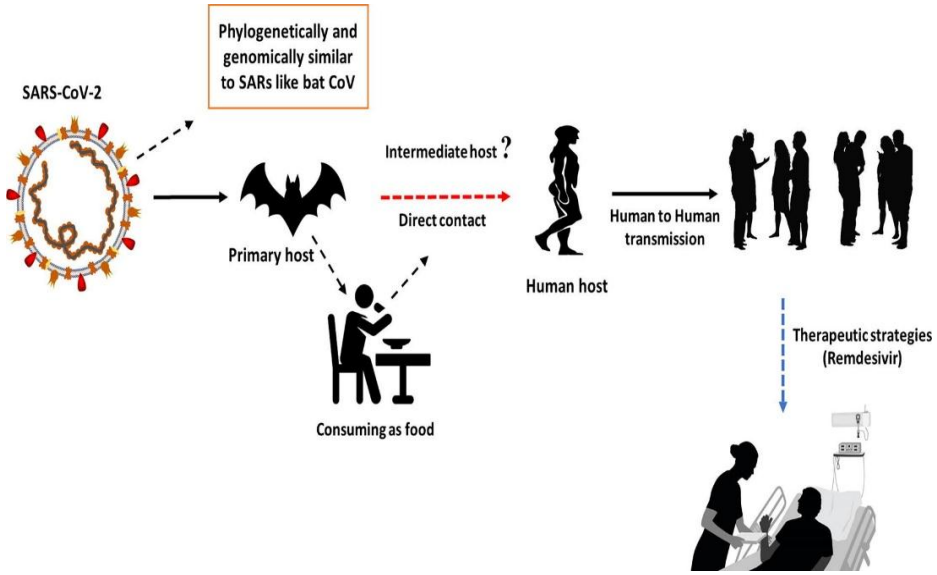

Fig 2: Transmission of Saras-Cov-2 (Severe Acute Respiratory Syndrome Corona Virus 2).

MEDICATIONS

Few researchers are against the use of antibacterial agents and antibiotics to treat viral infections, but drugs such as teicoplanin can inhibit the growth of viruses in human cells.[5] Staphylococci infections can be treated with teicoplanin and it was also shown to be efficacious in the first stage of the Middle East respiratory syndrome coronavirus (MERS-CoV) viral cycle. Teicoplanin mainly inhibits the low-pH cleavage of the spike (S) protein by cathepsin L in the late endosomes, hence preventing viral RNA release and replication of virus.

Remdesivir, an antiviral agent initially developed for Ebola virus infection, revealed more effective results against SARS-CoV-2 in vitro.[11] It is an adenosine analogue that incorporates into nascent viral RNA chains and results in premature termination. Further investigations of remdesivir are anticipated in human COVID-19 patients on an urgent basis.

Nitazoxanide is used to treat parasitic infections and has also been found to be effective in treating a wide range of viruses, including human coronaviruses, in vitro at very low concentrations. It selectively blocks haemagglutinin intracellular trafficking and insertion of this protein into the host plasma membrane, a key step for correct assembly and exit of the virus from the host cell.

Padmanabhan reported a combination therapy approach using hydroxychloroquine and nitazoxanide.[12] A synergistic effect can be produced by using both drugs, as hydroxychloroquine inhibits viral entry and fusion whilst nitazoxanide upregulates the innate immune response to prevent ongoing viral replication.In India, hydroxychloroquine plus the antiviral combination lopinavir/ritonavir have been used to treat COVID-19 patients. Lopinavir/ritonavir affects the viral protease 3CLpro responsible for proteolysis in the coronavirus replication cycle.[18]

The Japanese antiviral drug favipiravir used to treat influenza, developed by FUJIFILM Toyama Chemical Co., Ltd., showed considerable success in clinical trials of more than 340 patients[19] where it was found to be safe and effective in the treatment of COVID-19 patients. Further investigations are recommended in this context.

Ascorbic acid (vitamin C) possesses antioxidant properties. It does not have a direct lethal effect on viruses, but it has been reported that viral respiratory infections in humans are affected by vitamin C levels.[20] When viral infection occurs, the subsequent cytokine surge is activated and neutrophils accumulate in the lungs, destroying alveolar capillaries. Early clinical studies have shown that vitamin C has the potential to inhibit these processes.[21] Combining ascorbic acid with other drugs like zinc and vit.d3 will definitely be helpful for affected COVID-19 individuals.

2. Recommended drugs (off-label) for treatment of COVID-19

Recommended drugs for the treatment (off-label/investigational use) of COVID-19 are shown in Table 1

Table No.1: Recommended Drugs For Covid-19 Treatment.

Drug	Dosage
Hydroxychloroquine	400 mg b.i.d. × two doses, then 200 mg b.i.d. for 5 days
Remdesivir	200 mg i.v. loading dose, then 100 mg i.v. for up to 10 days
Oseltamivir	150 mg b.i.d. for 5 days
Lopinavir	400 mg b.i.d. for 10 days
Ritonavir	100 mg b.i.d. for 10 days
Ribavirin	2 g loading dose, then 600 mg t.i.d.

PATHOPHISIOLOGY

The SARS-CoV-2 shares similarities with severe acute respiratory syndrome coronavirus (SARS-CoV) in genome, sequence, biological behavior, clinical manifestations.

Structure of corona virus

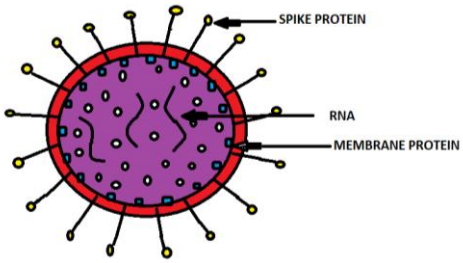

Fig 3: Structure Of Corona Virus.

Four major structural proteins are found in the 2019nCoV, 1. Spike surface glycoprotein (S): It attaches to host receptor Angiotensin Converting Enzyme 2 (ACE2), including two subunit S1 and S2. S1 determines the virus host range and cellular tropism by Receptor Binding Domain (RBD). S2 medicates virus cell membrane fusion by Heptad Repeats 1 (HR1) and Heptad Repeats 2 (HR2). 2. Matrix protein (M): It is responsible for the transmembrane transport of nutrients, the bud release and the formation of envelope. 3. Small envelope protein (E): It is responsible for production and maturation. 4. Nucleocapsidprotein (N): Primarily to bind to the CoV RNA genome, making up the nucleocapsid.

TARGET PROTEIN (RECEPTOR) & BINDING

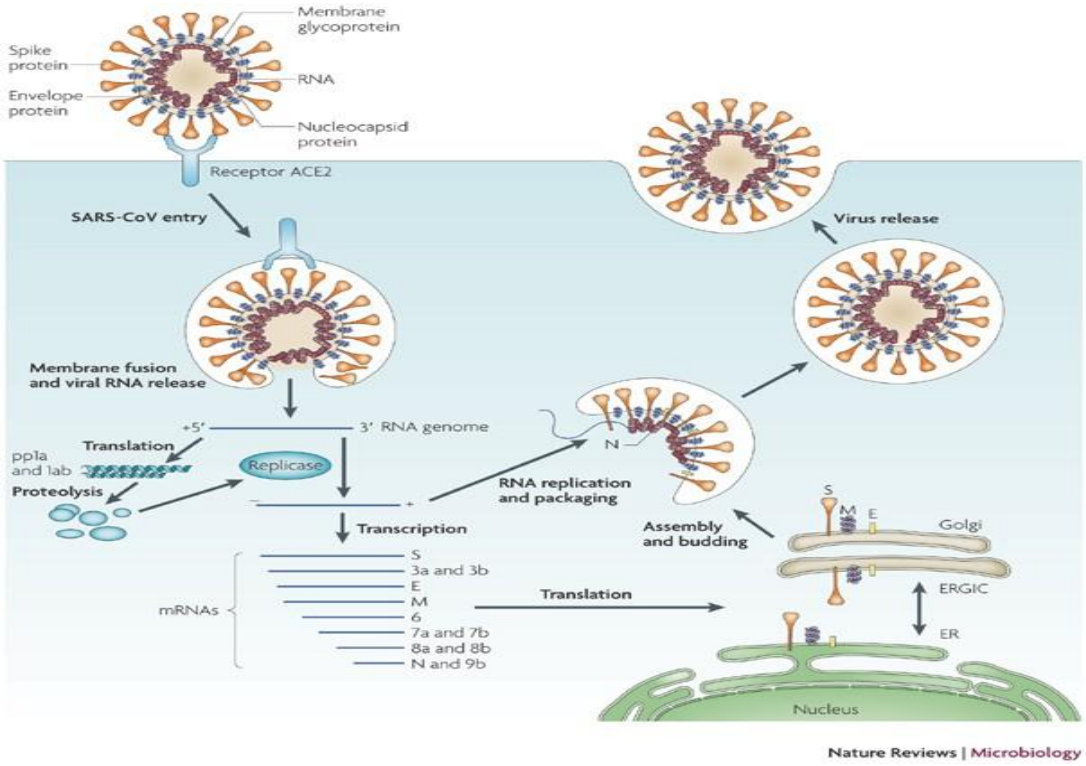

Fig 4: Sars Cov Interaction With Receptor-Binding Domain, Specific Cell Receptors (Ace2), And Host Cellular Transmembrane Serine Protease (Tmprss).

3. Concluding remarks

About 73% binding affinity of 2019-nCoV in comparison with the SARS-CoV. Transmission and pathogenesis of COVID 19 infection from coronaviruses to humans mainly depend on the interactions, from virus attachment, receptor recognition, protease cleaving and membrane fusion, of its transmembrane spike glycoprotein (Proteins) receptor-binding domain, specific cell receptors (ACE2), and host cellular transmembrane serine protease (TMPRSS). In the same host cell TMPRSS2 are co-localized which latter exerts hydrolytic effects responsible for S-protein priming and viral entry into target cells. ACE2 based strategies against COVID-19 such as ACE2 fusion proteins and TMPRSS2 inhibitors should be accelerated into clinical research and development for diagnosis, prophylaxis, or treatment.

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