A Silent Attacker SARS-CoV-2 - A Review

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Abstract— The recent coronavirus (known as COVID-19 or SARS-CoV-2) has created a pandemic of unheard proportions affecting virtually every country and region of the world. As of April 15, 2020, the virus has resulted in over 2 million infections, and over 100,000 deaths and has brought world economic activities to a standstill and has led to social isolation and massive unemployment with possible economic recessions on an unprecedented scale around the corner. Till now, the virus shows no signs of abatement. Also till now, scientists have not been able to come out with an effective drug or vaccine against the virus. This review attempts to give a comprehensive view of the origin of the virus, the mode of its entry and infecting human beings, and further discusses the possibility of new drugs and vaccines against the virus.

Index Terms— COVID-19; SARS-CoV-2; coronavirus; anti-viral drugs; ACE2.

I. INTRODUCTION

The Novel Corona Virus Disease of 2019 or COVID-19 is now counted as the worst pandemic disease after AIDS/HIV, Flu along with Asian-Flu, Cholera and Plague outbreaks. This novel (new) disease originated in Wuhan city of Hubei province of China at the end of 2019 [1]. Though SARS-CoV-2 first appeared in China, it has become the worst nightmare in the world with nations trying every means to bring it under control. The most affected countries with total cases of coronavirus diseased patients are given in Fig. 1. The disease spread swiftly among the people of many countries before any precautions or awareness could be made. COVID-19 virus shares 70% similarity in genetic sequence with SARS (severe acute respiratory syndrome), which became an epidemic before in 2002 [2]. The COVID-19 virus infection starts almost unnoticeably in a person and within 14 days it can cause pneumonia and other complications. Till 15th April 2020, total cases of corona patients in the world was 2,083,326; total death accounted for 134,616 and recovery cases were 510,350 [3]. Till now, number of death cases are lower than recovery cases.

Still there is no cure for any corona virus diseases like SARS, MERS (Middle East Respiratory Syndrome) and COVID-19. Scientists from over the world are trying to discover drugs and vaccines. Many of the scientists are claiming the effectiveness of different drugs, but in any respect, they are effective or not is yet to be seen through appropriate clinical trials.

Fig. 1. COVID cases in some of the worst affected countries of the world. [Adapted from Worldometer. <https://www.worldometers.info/coronavirus/>. Accessed on 21st April 2020.]

II. COVID-19

Corona virus can be defined based on phenotypic methods like culture, electron microscopy and serological studies. These viruses are RNA virus and have the name “corona” because of the presence of spikes on their surface which give them a crown like shape. They are an enveloped virus of 120-160nm in diameter. These spherical particles contain a single stranded RNA, some essential viral proteins such as nucleocapsid protein (N), membrane glycoprotein (M), and spike glycoprotein (S). Two additional features are that they encode an additional glycoprotein, which has acetyl esterase and hemagglutination properties (HE), which make these viruses different from others [4, 5, 6]. The nucleocapsid protein (N) of corona viruses is a structural protein that has an important role in intensifying the efficiency of virus transcription and assembly. This is done by forming complexes with genomic RNA, and during virion assembly they interact with the viral membrane protein. Besides this, coronavirus N protein has several activities such as viral core formation, viral assembly, budding and envelope formation, genomic mRNA replication and genomic RNA synthesis, chaperon activity, cell cycle regulation, cell stress responses-host translational shutoff, viral pathogenesis-immune system interference, and signal transduction [7]. M proteins are possibly responsible for biological properties and their intracellular budding [8]. S proteins are type I membrane glycoproteins which are required for receptor binding and viral entry. These proteins contain the most variable

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sequences in the virus genome and are responsible for the crown like shape of the virus. S proteins have two subunits; S1 subunit binds to the receptor of host cell surface and S2 subunit helps to fuse the viral and host membrane [9].

Corona viruses are of several types which depends on varieties of host (Table I). Mainly seven types are recognized as human corona virus and they are 229E (alpha), NL63 (alpha), OC43 (beta), HKU1 (beta), MERS-CoV or MERS (Middle East Respiratory Syndrome), SARS-CoV or SARS and SARS-CoV-2 (the novel corona virus that causes corona virus disease 2019 or COVID-19) [10]. Some other corona viruses along with their respective hosts are shown in Table I [5].

Table I: Types of corona viruses along with their hosts.

Viruses	Hosts
Alpha coronavirus	
Human corona virus 229E	Humans
Human corona virus NL63	Humans
Transmissible gastroenteritis virus	Pigs
Porcine respiratory coronavirus	Pigs
Porcine epidemic diarrhea virus	Pigs
Feline coronavirus	Cats
Rhinolophus bat coronavirus HKU2	Chinese horseshoe bats
Miniopterus bat coronavirus HKU8	Bent-winged bats
Miniopterus bat coronavirus 1A	Bent-winged bats
Miniopterus bat coronavirus 1B	Bent-winged bats
Scotophilus bat coronavirus 512	Lesser Asiatic yellow house bats
Beta coronavirus Subgroup A	
Human coronavirus OC43	Humans
Human coronavirus HKU1	Humans
Bovine corona virus	Cows
Equine corona virus	Horses
Mouse hepatitis virus	Mice
Porcine hemagglutinating encephalomyelitis virus	Pigs
Subgroup B	
Human SARS related corona virus	Humans
SARS related Rhinolophus bat coronavirus HKU3	Chinese horseshoe bats
Subgroup C	
Tylonycteris bat coronavirus HKU4	Lesser bamboo bats
Pipistrellus bat coronavirus HKU5	Japanese pipistrelle bats
Subgroup D	
Rousettus bat coronavirus HKU9	Leschenault's rosette bats
Gamma coronavirus	
Infectious bronchitis virus	Chickens
Turkey coronavirus	Turkeys
Beluga whale coronavirus	Beluga whales
Delta coronavirus	
Bulbul coronavirus HKU11	Chinese bulbul
Thrush coronavirus HKU12	Gray-backed Thrushes
Munia coronavirus HKU13	White-rumped Munias

People who have a normal immune response (immunocompetent) can suffer from common cold and self-limiting respiratory problems due to OC43, HKU1, 229E, and NL63 human coronavirus. Then again, these coronaviruses attack the lower respiratory tracts of people having an

impaired immune system (immunocompromised) like mostly the elderly [11].

III. SARS-CoV-2

The name of coronavirus SARS-CoV-2 was given by the Coronavirus Study Group (CSG) of the International Committee on Virus Taxonomy. They gave this name based on phylogenetic analysis of related coronaviruses. SARS is a disease and the name SARS-CoV-2 is a natural extension of taxonomic practice of viruses to relate it with SARS species. Viruses of the same species can be named so whether they cause SARS like disease or not. The same applies to MERS-CoV. The name of this human coronavirus SARS-CoV-2 is already being used in the scientific articles; however, people still know it as COVID-19 [12].

IV. HOW SARS-CoV-2 ATTACK HUMANS

Viruses are intracellular parasites and they need host cells to multiply themselves. So, to do so, human SARS-CoV-2 bind to human ACE2 (angiotensin converting enzyme; a membrane protein) and enter the cells. ACE2 receptors bind with ACE2 hormone therefore raising blood pressure by constricting blood vessels. Not only the blood vessels or heart contains these receptors, but they are found all over the body to some extent. They remain abundantly in cells of tongue, esophagus, kidneys, gastrointestinal tract, lungs (mostly in alveoli), and bladder urothelial cells. So, there is a huge way open for invasion of coronavirus in human body. But coronaviruses prefer to invade through airway and attack the lungs as they are rich in ACE2 receptors [13-16].

After invasion in the airway the viruses pass an incubation period for 5-14 days [17]. Then coronaviruses bind with ACE2 receptor and do membrane fusion to invade into the cells by using its spike protein (S). S protein has two regions, S1 does the binding with receptor and S2 helps to fuse with the cell membrane. S1 region of spike protein contains an N-terminal domain (NTD) and three C-terminal domains (CTD1, CTD2, and CTD3). SARS-CoV-2 enter to the human cell by attaching to ACE2 receptor with CTD1 domain as it is the receptor binding domain of these viruses. After entering into the cells, they start to multiply and eventually cause the destruction of the cells and suppress the immunity system [18-21].

So, as coronaviruses attack ACE2 receptors, there normally arises a question if people with overexpression of ACE2 receptor are at higher risk or not. Well, scientists also have found the answer. They indeed are at higher risk [22, 23].

V. TRANSMISSION

The viruses are zoonotic, which means they can transmit between animal and people. Not all coronaviruses can transmit from animal to human except SARS and MERS because they need close contact with infected people. The first SARS-CoV-2 patients were found to have a connection with the Hunan Seafood Market, which suggested that the coronavirus can transmit from animal to person. It is now believed that the initial source of the virus was bats with pangolins or some other animal acting as an intermediary host. Later infections were reported among the medical staffs and other who had a negative history of link with the market. This report indicated human-to-human transmission [25-26].

These viruses spread through air and can travel a distance of meter or possibly tens of meters. Viral particles from infected persons are transmitted through droplets when they sneeze, cough and also by contact and urine [27, 28]. Droplets and aerosols can spread when infected people talk or breathe; these aerosol particles are so small, and the person is called “super-spreader” [29].

The viruses can also be transmitted through maternal-fetal interface to the fetus if the mother is infected. The maternal-fetal interface is the interface which has both fetal and maternal components such as fetus shares placenta and extraplacental membranes and mother shares circulation of blood others. In a study researcher found that ACE2 expression occurs in a rich amount in this interface and some body organs of fetus [30, 31]. Children are found less affected by these viruses and therefore they transmit less [32].

The viruses can remain on surface for days and in favorable atmosphere. So, if a person touches a surface with viral particles and then touches his nose, face or rub his eyes, viruses can easily enter the person’s body. The viruses are found in stool and vaginal fluid as well [33]. It is also possible that the survival of the virus on different surfaces have not completely been elucidated.

VI. CLINICAL FEATURES

Patients positive with coronavirus, show different symptoms. Common symptoms are fever, cough, fatigue, sneezing, runny nose, headache, haemoptysis, diarrhea, dyspnea, and lymphopenia. The rate of these symptoms is different in different patients [34]. In another study of 99 patients were found some more symptoms such as shortness of breath (31%), muscle ache (11%), confusion (9%), sore throat (5%), chest pain (2%), nausea and vomiting (1%). Comorbid conditions were also found as acute renal injury, acute respiratory injury, and septic shock [35]. In imaging of coronavirus patients including adults and children, lungs were found with interlobular thickening, ground glass opacities, adjacent pleura thickening and multifocal lung lesion [36, 37]. Some other symptoms were also found such as sputum production, haemoptysis, loss of appetite, pharyngalgia and abdominal pain [38].

VII. DIAGNOSIS

SARS-CoV-2 remain in oropharyngea and nasopharyngea after entering the human host. Therefore, the first test to diagnose coronavirus disease must be testing the presence of viruses by taking oropharyngeal as well as nasopharyngeal swabs. Presence of viruses can also be determined by testing antibodies like IgM and for certain people, IgG in blood. Soluble CD-163 (sCD-163) that indicates presence of macrophages also can be tested [39, 40]. RT-PCR or real time PCR is now a popular choice to detect SARS-CoV-2 infections [41].

According to World Health Organization (WHO) guidelines for coronavirus disease diagnosis, detection of unique sequences of virus RNA by nucleic acid amplification tests (NAAT) is the base of routine conformation of this disease. In this case real-time reverse (rRT-PCR) polymerase chain reaction should be done. The viral genes that are targeted for tests so far are N, E, S and RdRp genes [42].

Antigen detection tests that can detect respiratory syncytial virus (usually causes mild cold like symptoms) and influenza virus antigen by immunoassay have been also suggested to detect SARS-CoV-2. A new antigen detection test is on the horizon, which can be done by applying monoclonal antibodies against the nucleocapsid protein of SARS-CoV-2 [43, 44]. Some other diagnostic ways can be followed such as computed tomography, checking some biomarkers which increase or decrease in SARS-CoV-2 patients (albumin, C-creative protein, lactate dehydrogenase). Lymphopenia, leukopenia, increased erythrocyte sedimentation rate, elevated bilirubin and creatinine level, increased aspartate aminotransferase, alanine aminotransferase and creatinine kinase levels, and leukocytosis which were found in SARS-CoV-2 patients can also be tested in suspect’s blood to detect coronavirus [45, 46].

VIII. TREATMENT

Treatment of coronavirus patients depends on the symptoms and severity of the disease. World Health Organization (WHO) has published a guideline on treatment of coronavirus which describes about the treatment of mild, severe and critical coronavirus patients. For details following reference number “WHO/2019-nCoV/clinical/2020.4” has been suggested by WHO [47].

Traditional Chinese medicines were practiced on coronavirus patients to some extent. Some traditional Chinese medicines were recommended by the National Health Commission of the People’s Republic of China to treat coronavirus patients at different stages of the disease (Table II) [48]. Clinical trials of some formulations are ongoing such as *Tan Re Qing* injection, *Lian Hua Qing Wen* capsule/granule, *Shuang Huang Lian* oral liquid, *Xue Bi Jing* injection, *Tan Re Qing* capsules [49].

Table II: Traditional Chinese Medicines Recommended by Chinese National Health Commission

Stages of disease	Traditional medicine
Medical observation period (MOP): fatigue with gastrointestinal discomfort	<i>Huo Xiang Zheng Qi Shui</i>
Medical observation period (MOP): fatigue with fever	<i>Lian Hua Qing Wen</i> Capsule, <i>Shu Feng Jie Du</i> Capsule, <i>Jin Hua Qing Gan</i> Capsule
Confirmed patients: Mild case	<i>Qing Fei Pai Du Tang</i>
Confirmed patients: General case	<i>Qing Fei Pai Du Tang</i>
Confirmed patients: Severe case	<i>Xi Yan Ping</i> Injection, <i>Xue Bi Jing</i> Injection, <i>Re Du Ning</i> Injection, <i>Tan Re Qing</i> Injection, <i>Xing Nao Jing</i> Injection, <i>Qing Fei Pai Du Tang</i>
Confirmed patients: Critical case	<i>Xue Bi Jing</i> Injection, <i>Re Du Ning</i> Injection, <i>Tan Re Qing</i> Injection, <i>Shen Fu</i> Injection, <i>Sheng Mai</i> Injection, <i>Shen Mai</i> Injection, <i>Su He Xiang</i> Pill, <i>An Gong Niu Huang</i> Pill

Different antiviral drugs have been studied since the disease appeared. Several of them used to be used for SARS treatment and rest of them for other diseases including viral diseases. Antimalarial drug hydroxychloroquine, antiviral drugs like rifampicin and oseltamivir were such drugs tested for coronavirus disease treatment [50]. A list of such drugs is given in Table III. Though Lopinavir/Ritonavir combination

was used for early SARS-CoV-2 patients, further studies revealed that in severe case no such benefits were found from this combination [63, 64]. Oseltamivir showed exacerbation of psoriasis in SARS-CoV-2-infected patients [65]. It is an open question whether using chloroquine or hydroxychloroquine for the treatment of SARS-CoV-2 is safe or not. Studies showed that use of chloroquine resulted in hemolysis and increases in oxidative injury [66].

Table III: List of therapeutic agents that have been used in SARS-CoV2

Therapeutic agents for SARS-CoV-2	Originally used for	Mechanism	Result in SARS-CoV-2	Ref.
Lopinavir/Ritonavir (LPV/r)	HIV-1, retrovirus, SARS, MERS	Inhibit viral replication by interfering with protease	Decrease body temperature, abnormal amount of WBC, C-reactive protein and lymphocytes	[51]
Baricitinib, Fedratinib, Ruxolitinib	Anti-inflammatory	Inhibition of numb-associated kinases (NAK), JAK-STAT signalling	In tolerated doses reduced viral infectivity	[52]
Myo-Inositol	Respiratory distress syndrome	Inhibition of interleukin 6 (IL-6) by blocking its receptor	Reduced inflammatory cascade by decreasing IL-6 level	[53]
Remdesivir	Ebola	Delayed chain termination, inhibition of viral RNA polymerase	Inhibited viral infection (<i>in vitro</i>)	[54, 55, 56]
Chloroquine	Malaria	Interfere the growth of parasite in RBC	Antiviral activity by increasing endosomal pH required for virus/cell fusion and interfering with the glycosylation of cellular receptors of SARS-CoV	[57, 58, 59]
Hydroxychloroquine and Azithromycin	Malaria, Zika and Ebola virus	Prevent respiratory tract infection	Lowered viral nasopharyngeal carriage	[60]
Oseltamivir with Lopinavir/Ritonavir	Influenza	As neuraminidase inhibitor	Recovery of patients	[61, 62]

Extracorporeal membrane oxygenation or ECMO application to severe coronavirus diseased patients lead to a dramatic recovery [67]. Some interferons (INF) such as INF β 1, INF α , INF α 2b, and INF β 1b were found effective in combination with Lopinavir/Ritonavir [68]. Some other therapeutic agents such as Ribavirin (inhibits viral RNA dependent RNA polymerase), Umifenovir (inhibits membrane fusion of viral envelop by targeting S

protein/ACE2 interaction), corticosteroids, immunomodulatory agents are also in the line for treating SARS-CoV-2 [69].

IX. FUTURE MODES TO TREAT SARS-CoV-2

To defeat coronavirus several ways can be followed: (I) developing a vaccine, (II) designing drugs that target virus/host cell, (III) testing existing drugs, (IV) genetically engineering human T-cell using CRISPR, and (V) stem cell therapy.

Some US scientists and Australian scientists have begun working to invent a vaccine against SARS-CoV-2. Australia's Commonwealth Scientific and Industrial Research Organisation (CSIRO) have already started trials of two potential vaccines on ferrets (by nose or intramuscular injection); level of immunity will be checked. Clinical tests will be started by the end of April. Sarah Gilbert, a Professor of vaccinology along with her team at Oxford University, has developed a vaccine named "ChAdOx1nCoV-19". This vaccine has been made from chimpanzee adenovirus (a weak common cold virus), which when injected into the body, will produce antibody. Human trial is going to be held within a week. Inovio, a Pennsylvania-based pharmaceutical company has developed a DNA vaccine; by using proprietary technology, INO-4800 is injected into the body which will stimulate a particular type of immune cell (T cell) and antibodies against the coronavirus [70, 71, 72]. Mesenchymal stem cells possess immunomodulatory and regenerative properties for which it has become a way for future treatment. After intravenous injection of mesenchymal stem cells to coronavirus patients these cells can give effects by recovering pulmonary microenvironment, protecting alveolar epithelial cells, arresting pulmonary fibrosis, cure lung dysfunction along with SARS-CoV-2-induced pneumonia [73].

Scientific interest is now centering on phytochemicals, in particular flavonoids, which are said to directly inhibit the 3C-like protease of SARS-CoV-2. A recent paper has shown that three compounds, namely herbacetin, rhoifolin, and pectolinarin can efficiently block the activity of the SARS-CoV-2 3C-like protease [74].

X. PREVENTION

SARS-CoV-2 spreads quite easily and swiftly. So, before going through the treatment it is important to know and maintain some preventive measures. To prevent spreading of these viruses the confirmed patients must be isolated and kept under proper treatment. Mouth covering while sneezing, coughing, trying not to touch mouth, nose, and eye before washing specially after exposure in public places, washing hand with disinfectants for several times, keeping distance from one another are the essential preventive measures. Above all boosting immunity should be prioritized first. Taking healthy immune-boosting foods can prevent from being a victim of this deadly disease [75].

XI. CONCLUSION

Coronavirus disease is not a very recent disease. It showed its symptoms in 2002-2003 during SARS outbreak. This virus was then called SARS-coronavirus as well and also invaded

through lungs [23]. There is some controversy about this disease as to whether it is human produced or just an evolution of previous human coronaviruses; however, WHO position is that it is a natural coronavirus. Considering all these confusions, people are attempting to defeat this disease. But it seems the long way is yet to be walked. Still there is a hope for cure as scientists are continuously trying to combat the disease.

AUTHOR CONTRIBUTIONS

MR is guiding the COVID-related work. KJ wrote the manuscript, which was edited and approved by all the authors.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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