

Review

COVID-19: morphology and mechanism of the SARS-CoV-2, global outbreak, medication, vaccines and future of the virus

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1. Abstract

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a lethal virus that was detected back on 31st December 2019 in Wuhan, Hubei province in China, and since then this virus has been spreading across the globe causing a global outbreak and has left the world fighting against the virus. The disease caused by the SARS-CoV-2 was named COVID-19 and this was declared a pandemic disease by the World Health Organization on 11th March 2020. Several nations are trying to develop a vaccine that can save millions of lives. This review outlines the morphological features of the virus describing the outer and inner structures of the virus along with the entry mechanism of the virus into the host body and the infection process. Detailed reports of global outbreak along with preventive measures have also been included, with special emphasis on China, the United States of America, India, Italy, and South Korea. Broad-spectrum antiviral drugs being used at vari-

ous health care centres around the world, namely Remdesivir, Camostat & Nafamostat, Famotidine, Chloroquine & Hydroxychloroquine, Lopinavir/ritonavir, Ivermectin, and Tocilizumab & Sarilumab have also been included. World Health Organization guidelines on preventive measures and use of soaps, alcohol-based hand-rubs and wearing face masks have also been described. The vaccines that are in one of the phases of human trials, namely Oxford University's vaccine, the United States-based Moderna's vaccine, India's Covaxin and the Russian vaccine, have also been incorporated in the review article.

2. Introduction

The Coronavirus disease 19 (COVID-19), considered a highly transmittable disease was first reported during mid-January, 2020 in Wuhan, Hubei province in China. The SARS-CoV-2 is phylogenetically related to the previously known SARS-CoV virus. During the outbreak of the

novel Coronavirus (SARS-CoV-2), the world has seen what a virus can do to mankind. Coronavirus is placed in the family Coronaviridae in the Nidovirales order. COVID-19 is caused by an RNA virus (ssRNA) 50–200 nm in diameter consisting of four structural proteins, namely spike protein, envelope protein, membrane protein, and nucleocapsid protein [1]. The virus has crown-like spikes on its outer surface, i.e., corona thus the virus came to be known as coronavirus due to the resemblance [2]. SARS-CoV-2 also has the common structure of coronaviruses with spike protein on its outer surface (Fig. 1). It consists of different polyproteins, nucleoproteins, and membrane proteins, for example—RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins [2]. In a host, membrane-derived lipid bilayer that envelops the helical nucleocapsid which contains the RNA virus, the coronavirus surface viral protein spike, membrane and envelope are inserted [3]. The genome of coronavirus is between 26 and 32 kb in size and consists of 6–11 open reading frames and 9680 amino acid polyproteins are encoded. About 67% of the genome is present in the first ORF which encodes 16 non-structural proteins, while the rest of ORFs encode for structural and accessory proteins. There is an insufficiency of the hemagglutinin-esterase gene in the genome of SARS-CoV-2. Two untranslated flanking regions are found at the 5' end of 265 and 3' end of 358 nucleotides. There are no notable dissimilarities between open reading frames and non-structural proteins for sequence variation among SARS-CoV and SARS-CoV-2. Two viral cysteine proteases namely papain-like protease, chymotrypsin-like, 3-chymotrypsin-like or main protease, helicase, and others are found in the non-structural proteins, perhaps took part in the transcription and replication of SARS-CoV-2. The spike glycoprotein structure of SARS-CoV-2 is similar to the spike protein of SARS-CoV with a root-mean-square deviation of 3.8 Å [3].

There have been various natural and artificial drugs that have been used in the treatment of COVID-19. Various potential antimalarial drugs namely, hydroxychloroquine and azithromycin, antifilarial drug ivermectin and certain antiviral drugs have been put to test against the COVID-19. There was a probability that certain probability that the use of hydroxychloroquine, ivermectin, azithromycin, remdesivir, and a few more drugs as single agents or in combinations with immunomodulators would work against COVID-19 [4].

Mesenchymal stem cells and their derived exosomes are considered to have potential effects as immunomodulatory agents for COVID-19 patients. It has been earlier observed that stem cell research and treatment exhibited encouraging results for various diseases such as diabetes, cancer and neurodegeneration. Lately, mesenchymal stem cells (MSCs) have been applied as possible therapeutic agents for treating SARS-CoV-2. They release certain cytokines to inhibit viral infections, which are usually

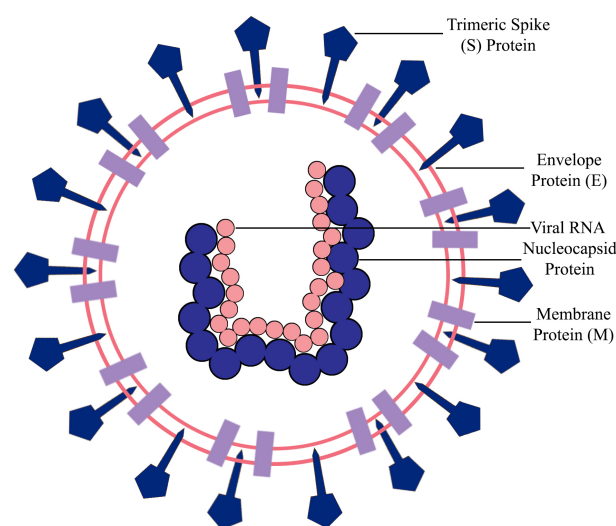


Fig. 1. Morphological structure of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

present naturally; however, the mesenchymal stem cells exist in their niche before being quarantined from the source tissue. Thus, mesenchymal stem cells and their exosomes (MSCs-Exo) are anticipated to survive even after transplantation into the body of a COVID-19 patient. Since the treatment with the help of mesenchymal stem cells is still uncertain, various trials and researches are being performed to measure its effectiveness [1].

Ilimaquinone (marine sponge metabolite) exhibited inhibitory prospects against SARS-CoV-2. It was assessed in comparison with hydroxychloroquine, azithromycin, favipiravir, ivermectin and remdesivir at the active binding pockets of 9 different vital SARS-CoV-2 target proteins, following an *in silico* molecular interaction centred approach [5, 6].

Medications that have been used against COVID-19, along with precautionary measures, and also a detailed list of COVID-19 vaccines have been listed further in this review.

3. Global outbreak

3.1 Americas

In the United States, the first COVID-19 was reported and confirmed on 20th January 2020 [7]. The United States and South Korea encountered their first COVID-19 cases around similar timeframes [8]. A 35-year-old man with a 4-day record of mild fever and cough was put on record by an urgent care clinic in Snohomish County, Washington on 19th January 2020. After investigation, it was discovered that he was on a family visit to Wuhan, China, and he returned to Washington State on 15th January 2020. The patient was concerned about his symptoms when he saw a health alert from the United States Centers for Disease Con-

trol and Prevention about the outbreak of the COVID-19 in China, so he decided to get himself checked at a health care centre. He was a healthy non-smoker with only a history of hypertriglyceridemia. Various tests were performed on him, and the initial results were normal for all the tests, but later on, he was diagnosed with COVID-19 [7].

The United States was slow to start large-scale coronavirus testing. As of 27th February 2020, less than 4000 tests were being performed in the United States [9–11]. On 5th March 2020, the Vice President of the United States, also the leader of the coronavirus response team, acknowledged that the United States was not performing enough tests to meet the future demand. Lesser than 10,000 tests had been performed in the United States as of 11th March 2020 [12, 13]. The United States was testing approximately 125 people per million of their population by mid of March 2020. That was substantially lower than various other nations [14]. By the end of March 2020, the United States had tested over a million suspected people who showed symptoms [15]. Inaccuracies were encountered because of shortage of testing, the rate of growth in cases and the total number of confirmed cases was reasonably inaccurate [16]. The general recommendation was to test 500,000 people per day before the termination of social distancing, while the United States was testing around 150,000 people per day [17]. The United States approximately started testing 240,000 to 260,000 people per day as of the first week of May 2020, which was still not sufficient to suppress the outbreak of COVID-19 [18–20].

In mid-March 2020, the United States government issued orders for people to stay at home, avoid public gatherings, and made it obligatory for entertainment cum recreation venues shut down for the time being. Dine-in restaurants and other non-essential businesses were also ordered to remain closed so that the spread of the virus could be suppressed. Several pharmacies, financial institutions, grocery stores, mass media and critical infrastructure were usually allowed to keep functioning. Police checkpoints were also set up at state borders [21]. About nine-tenths of the United States population was under restriction as of 2nd April 2020 [22]. 42,034,347 total cases in the United States were reported on 22nd September 2021, with approximately 671,728 deaths [23].

3.2 Europe

On January 31st, 2020, Italy reported its first COVID-19 cases, two Chinese tourists were tested positive in Rome [24]. The Chinese couple arrived in Italy on 23rd January 2020 via Milan Malpensa Airport. Then they reached Rome via Verona and Parma on 28th January 2020. On 29th January 2020, they developed some symptoms and were assisted to the Lazzaro Spallanzani National Institute for Infectious Diseases, and after performing tests, they were reported COVID-19 positive [25]. A week later, an Italian citizen was deported back to Italy from Wuhan,

China. He was then hospitalized and later tested positive for COVID-19. On 21st February 2020, 16 COVID-19 positive cases were reported in Lombardy, Italy [26]. 22nd February 2020, saw Italy's first COVID-19 death and an addition of 60 more cases [27]. By the first week of March 2020, the outbreak was seen all over Italy [28].

On 31st January 2020, the Italian government professed a state of emergency and also deferred all flights that were destined to and from China. The two main clusters of COVID-19 positive cases were identified to be a part of the eleven municipalities in northern Italy, most of the cases traced back to these two primary clusters [29]. Lockdown was imposed on these areas, and violating the lockdown would result in a penalty of €206 and possibly imprisonment for 3 months [30]. The Italian army along with the law enforcement departments was instructed to manage the lockdown [31]. Quarantine was imposed in Lombardy and 14 other northern and central provinces in Piedmont, Emilia-Romagna, Veneto, and Marche, were put under lockdown on 8th March 2020. The next day, quarantine was imposed all over Italy, putting over 60 million people under quarantine [32, 33]. The Italian government prohibited people from going out on the streets and shut down all non-essential businesses and organizations [34]. Italy tested over 3,923,000 people as of 26th July 2020. The genuine number of infected people in Italy was projected to be much greater than the official count as Italy did not implement an adequate amount of tests. Internationally lost COVID-19 cases [35, 36]. During mid-March, 2020, an increase in the number of deaths along with a slowdown in the number of new cases per day was seen [37]. The president of the Italian National Institute of Health on 31st March 2020, declared that the outbreak had reached its peak in Italy [38].

The effects of the lockdown were evident, Italy reported a decline in the number of new cases and deaths per day. An increased discharge rate was also observed and in turn, the intensive care units were starting to be less occupied [39]. Educational institutions were shut down in ten municipalities in Lombardy, one in Emilia Romagna, and one in Veneto. Various public events were also cancelled during this lockdown period [40]. All religious services were cancelled [41]. Regional trains were also shut down in the severely affected areas, with trains skipping Codogno, Casalpusterlengo and Maleo stations [42, 43]. Basilica Di San Marco in Venice, along with La Scala, Duomo di Milano and Piccolo Teatro in Milan were closed until further notice [44–46]. 4,641,890 total cases in Italy were reported on 22nd September 2021, with approximately 130,421 deaths [23].

3.3 South East Asia

3.3.1 China

A group of 59 people were reported on 31st December 2019 to be infected with pneumonia who were allied to the Hunan Seafood Wholesale Market in Wuhan, Hubei Province in China [7]. The 59 alleged patients with symptoms such as fever and dry cough were relocated to a hospital shortly. On the very same day, the native health authority issued an epidemiological alert, and on the following day, the market ceased activity. After the alert was issued, the establishment of a group of experts was initiated, which included physicians, virologists, epidemiologists and government officials [47].

The cause of commencement of these infections is unknown, the diagnosis of the people infected with pneumonia was being done based on clinical features, which included chest imaging, and blacklisting of the regular bacterial and viral pathogens which caused pneumonia. In Jinyintan Hospital, Wuhan, China, the infected patients were isolated using airborne precautions for aerosol-generating procedures, and N95 masks were also being provided to them. The National Health Commission of China and the Ethics Commission of Jinyintan Hospital permitted this study [47]. Chinese health authorities validated that a novel coronavirus, 2019-nCoV is allied to the group of pneumonia patients who had been suspected on 31st December 2019 [7]. An outbreak of a novel coronavirus was encountered by China, where approximately 1800 patients died and over 70,000 patients were infected within the first 50 days of the epidemic. This novel virus belonged to the β group of coronaviruses. The Chinese researchers named this novel virus the Wuhan coronavirus or the 2019 novel coronavirus. Later, the virus was termed SARS-CoV-2 and the disease as COVID-19 by the International Committee on Taxonomy of Viruses [2]. The 2019-nCoV was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since the first one (SARS-CoV-1) which is also known as the Chinese bat coronavirus, originated and caused an epidemic of severe human respiratory disease, 17 years ago in China [48].

In China, it was assumed in the beginning that patients infected with Wuhan coronavirus were originally suffering from pneumonia, who may have visited the seafood market and probably consumed infected animals or birds. Further studies reported that few of the patients who were declared COVID-19 positive did not even have a travel history to the seafood market. This study confirmed human to human transmission of the virus, which was further reported in approximately more than 100 countries worldwide [2]. To curb the epidemic, the Chinese authorities quarantined 17 cities and over 50 million people were a part of this procedure [49].

During the initial phase of the COVID-19 pandemic, blood count, coagulation profile and serum bio-

chemical test were being performed. Respiratory specimens were collected which included nasal and pharyngeal swabs, bronchoalveolar lavage fluid and a few others, which were tested for various typical viruses including influenza, respiratory syncytial virus, adenovirus, SARS-CoV and MERS-CoV using instantaneous reverse transcription-polymerase chain reaction evaluations approved by the Chinese National Medical Products Administration. Frequent fungal and bacterial check-ups were also executed. Oseltamivir and other antibiotics were administered to the COVID-19 patients orally or intravenously. For acute community developed pneumonia patients, methyl prednisolone corticosteroid therapy was provided, and oxygen support to those suffering from severe hypoxemia. Thorough check-ups were performed for the COVID-19 positive patients to confirm the viral clearance before being discharged from the hospital [47]. 124,232 total cases in China were reported on 22nd September 2021, with approximately 5689 deaths [23].

3.3.2 India

On 30th January 2020, India reported its first COVID-19 case [50]. The Epidemic Disease Act of 1897 was invoked, educational institutions and various commercial foundations had been shut down from mid-March, 2020. As most of the positive cases were linked to people visiting from other countries, the Indian Government decided to suspend all tourist visas. Lockdown was imposed in over 75 districts across the country where COVID-19 cases had been confirmed. On 22nd March 2020, the Janta Curfew was declared by the Indian Prime Minister. The people of India were requested to stay at home for a few weeks and also work from home in possible cases [51]. The first positive case in India was reported to be a student in Kerala who was a student of The Wuhan University and had returned to India after the pandemic alert was declared. As of 7th February 2020, 3 positive cases were reported in Kerala, all of whom had a travel record to Wuhan, China. 33 positive cases were reported by the first week of March, 2020, 16 of the 33 cases were Italian tourists. 114 COVID-19 cases were confirmed as of 16th March 2020. The numbers rose to 17,264 by 19th April 2020 [52].

On 18th January 2020, the Indian Government issued orders, instructing 3 major airports in India, namely, Delhi, Kolkata and Mumbai to perform screening of travellers from China. All international sea ports also performed screening. Screening of all flights from Singapore, Hong Kong, Thailand, Japan, South Korea, Vietnam, Nepal, Indonesia, Malaysia and China were made compulsory from 23rd February 2020. Soon the list was discontinued, all international and domestic flights were made subject to compulsory screening. It was made essential that every passenger filled up a self-declaration form which was then transferred to health and immigration officials, it was also necessary that the passenger was quarantined for at

least a week [53]. As of 30th March 2020, 1,524,266 passenger screenings were performed at airports. Quarantine centres were set up, along with a few hospitals and stadiums being turned into quarantine facilities too. Containment zones were set up where a group of positive cases were reported, which was followed by a buffer zone [52].

A total number of 830,201 tests had been performed in India as of 30th April 2020. Guidelines were issued by the Indian Council of Medical Research on the usage of Truenat™ beta CoV (Molbio Diagnostics Private Limited, Kolkata, India) while screening [54]. As of April 26, 2020, the production capacity of indigenous N-95 masks and personal protective equipment kits was approximately 100,000 per day. 2033 COVID-19 facilities with over 190,000 isolation beds, approximately 24,000 ICU beds and more than 12,000 ventilators were made available as of 23rd April 2020. Two high-risk groups, first the people over 65 years of age, and the second being children under 10 years of age, were advised to avoid public gatherings and stay at home. A 21-day nationwide lockdown was imposed on 24th March 2020. People were banned from stepping out of their homes. A 19-day extension was declared on 14th April 2020 [52]. 33,531,498 total cases in India were reported on 22nd September 2021, with approximately 445,768 deaths [23].

3.3.3 South Korea

South Korea has shown well-organized methods for restraining the COVID-19 disease. On 20th January 2020, South Korea reported their very first COVID-19 case [55]. The early outbreak at about 30 cases showed that most of the cases were foreign or from family members. The 31st case caused a lot of trouble for declining the tests and continuing to attend Shincheonji Sunday services which is a religious movement in the Daegu district of South Korea, which is also known as a cult to many and it undergoes missionary activities in Wuhan where the pandemic had its beginning. About 3 weeks later sporadic cluster outbreaks were spreading reportedly in large crowded places like churches or long-term-care facilities [56]. South Korea reported its highest number of cases from 20th February 2020, to 9th March 2020, mainly in Daegu all of which originated from Shincheonji [55]. 876 cases were reported from 30th March 2020 to 13th April 2020, where 81.5% of the cases were from people living outside of South Korea and about 27.5% of people were related to long-term-care hospitals [56]. After resolving the cases linked to the religious group South Korea successfully sustained the number of new cases from the middle of April 2020, from 100 cases to less than 50 cases every day. After the 2015 MERS outbreak, South Korea was already prepared to cope with COVID-19 because of their experience in overcoming the difficulties. To combat the difficult times, several health-care personnel went to Daegu where the initial outbreak occurred. The citizens or ordinary people also started helping

by working at mask production factories to prevent shortage of masks [56]. The government also provided masks satisfactorily to the citizens who showed their IDs [55]. In Daegu, due to the swift spread of COVID-19, the number of critically ill patients increased and the health care system could not treat everyone; as a result, some patients died fighting the disease. Intensive care units with airborne infection isolation rooms are extremely necessary for the treatment of critically ill patients and to overcome these, temporary airborne infection isolation rooms were set up with negative air machines in intensive care units, which was also done in the past to fight the breakout of MERS [57]. South Korea's death toll increased with the rapid increase of the disease which led to social distancing for the prevention of the disease. Due to globalization, one country can influence others, so Korea's anti-COVID-19 initiatives could be helpful to other countries pursuing successful steps to tackle this disease. Compared to the United States and Europe, South Korea reported a lower number of cases each day because the government worked efficiently to knock down the rise of the pandemic [55].

Since COVID-19 has spread rapidly, diagnostic testing was an important strategy in South Korea, systematic COVID-19 monitoring, effective tracking of infected people, and proper care of infected people were the most important features of the government's policies [55]. In Seoul, the Korean government quickly approved private-sector testing and developed several makeshift testing kiosks or walk through examination institutions to avoid interaction between medical staff and patients so patients were also diagnosed inside their cars. Screening clinics in public health centres were set up for testing people reckoned to show symptoms like fever or cough to keep the hospitals and healthcare institutions safe and free from the virus. Such measures varied operating models to adapt to the growing demand for diagnostic tests in a more beneficial way. An infected person after being detected receives a real-time text message on their phone via the local government near the patient's area and disinfecting is done at the screening facilities they went to. Tracking of the affected patient can be done in the same way by knowing about the movement locations using credit cards, mobile phone GPS and security camera recordings and the government also make the general public aware of the affected person by providing necessary information. Daily the emergency alert system warns the public via their mobile phones and makes them aware of the newly reported cases [56].

To keep COVID-19 contained within a group of people contact tracing is necessary. A well-developed system has been developed through which epidemiological investigations were done in health care institutions and the isolation of the probable patients was approved thus stopping the further spread. The people who came in close contact with the patient were put in self-quarantine for 2 weeks and were connected to one-on-one government employees

via a mobile phone-based 'self-quarantine protection app', which the Korean government launched as a tool to monitor symptoms of the disease. When the self-quarantine rules were violated, this software warned the public health staff and helped them tracking the symptoms of the person two times each day. The health staff conducted this tracing system primarily and monitoring took a few days. Several central agencies worked together to establish a swift tracking program at the beginning of April 2020, and through this system, the agencies shared real-time information. These brand new apps also focused on geo-locating and identifying affected people. Across the city, wide-ranged data analysis tools were used to check the real-time environment, transportation and well-being. The said system is Infectious Disease Control and Prevention Act based which allows personal information to be used for proper epidemiological investigations during the outbreak of any contagious diseases. However, a robust security framework assured the Korean people of no false use of the information by being anonymous [55].

In South Korea, the government treated COVID-19 patients based on the seriousness of the illness and made room for them correspondingly to hospital or other health care centres. Confirmed COVID-19 patients were first detected by health specialists at public health care centres and then they were categorized according to the severity of symptoms, which included asymptomatic, mild, moderate, severe and extremely severe. Every group based on the severity of illness was treated differently and were admitted to separate hospitals. Patients with moderate, severe and extremely severe symptoms were treated at National infectious disease hospitals and various other government-designated institutions, whereas patients with mild symptoms were examined at their retrospective homes and health care centres. Healthcare specialists examined them twice a day to make sure that they are ready to be transferred to other healthcare centres if symptoms worsen or are ready to be discharged if their symptoms diminish [56]. The central and the local governments of South Korea appointed numerous hospitals as infectious disease hospitals. AI was another technology used by them for better detection efficiency and patient categorization. Chest X-Ray AI is an example of such technology, used to identify unusual detections on chest X-rays, categorizing intensive care patients and find lung abnormalities within a few seconds. Treatment of COVID-19 patients in South Korea concentrated on identifying and prioritizing patients with high risk, especially those over 60 years of age or those with any other comorbidities and transferring them immediately to hospitals, however patients with low-risk were instructed to stay at home quarantine. Few of the possibly efficacious drugs ritonavir/lopinavir, ribavirin, hydroxychloroquine and interferon were advised for severe patients. At a certain point due to the high demand for masks, there was a shortage of mask supply. The South Korean government also executed

a rule for the 5-day rotational distribution of masks from 9th March 2020 to treat every citizen equally [55].

One of the major factors that helped South Korea to rapidly lower the outbreak of COVID-19 was wearing face masks in public and only a few cases were reported in May and June 2020. Citizens were instructed to avoid gatherings and congested places and to follow quarantine formalities which included washing hands, wearing face masks and maintaining social distancing [55, 58]. It was reported from a current survey that about 63.2% of Koreans wear a mask whenever they go outside. Whereas, another international study reported that in the case of the COVID-19 pandemic the rate of wearing face masks was even higher, approximately 94% and that was the highest rate amongst 28 countries. Another reason was in 2015, an outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection caused 38 deaths with 186 total cases. Another instance was witnessed by South Korea in 2015; an outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infection caused 38 deaths with 186 total cases. This led to the gradual acceptance of the use of face masks in public, and thus during the COVID-19 pandemic, the people were well aware of the situation and accepted the use of face masks very quickly [58]. Amongst the Organization for Economic Cooperation and Development Countries, South Korea is known to have the highest particulate matter level. Medical specialists of South Korea also warned about the health problems which can originate due to this problem, ranging from infant health abnormalities to increased adult deaths, thus wearing face masks was highly recommended. Over the recent years, due to the high alerts imposed by the South Korean government from April 2014, the people also became well aware of this increasing particulate matter level and thus practised wearing masks whenever outside. Korean pop singers made wearing face masks fashionable which also influenced the common people. Thus, it can be concluded that in South Korea, wearing face masks and following self-quarantine principles played a major role in lowering the spread of SARS-CoV-2 [58, 59].

It was around 27th January 2020, members of the Korea Centers for Disease Control and Prevention instructed the infectious disease specialists from the Korean Society for Laboratory Medicine and 20 other pharmaceutical companies to quickly start the production of detection test kits [55]. On January 31st, 2020, the latest one-step real-time polymerase chain reaction test kit, giving results within just 6 hours was ratified and made available in 18 Research Institute of Public Health and Environment locations. Around mid-March, 2020, a hospital in South Korea invented a walk-in diagnosis booth that implemented the principle of a negative pressure glove box. As of 10th April 2020, a total of 580 healthcare centres and public health centres were able to perform detection tests. And around 23 March 2020, the number of daily tests was about 100,000

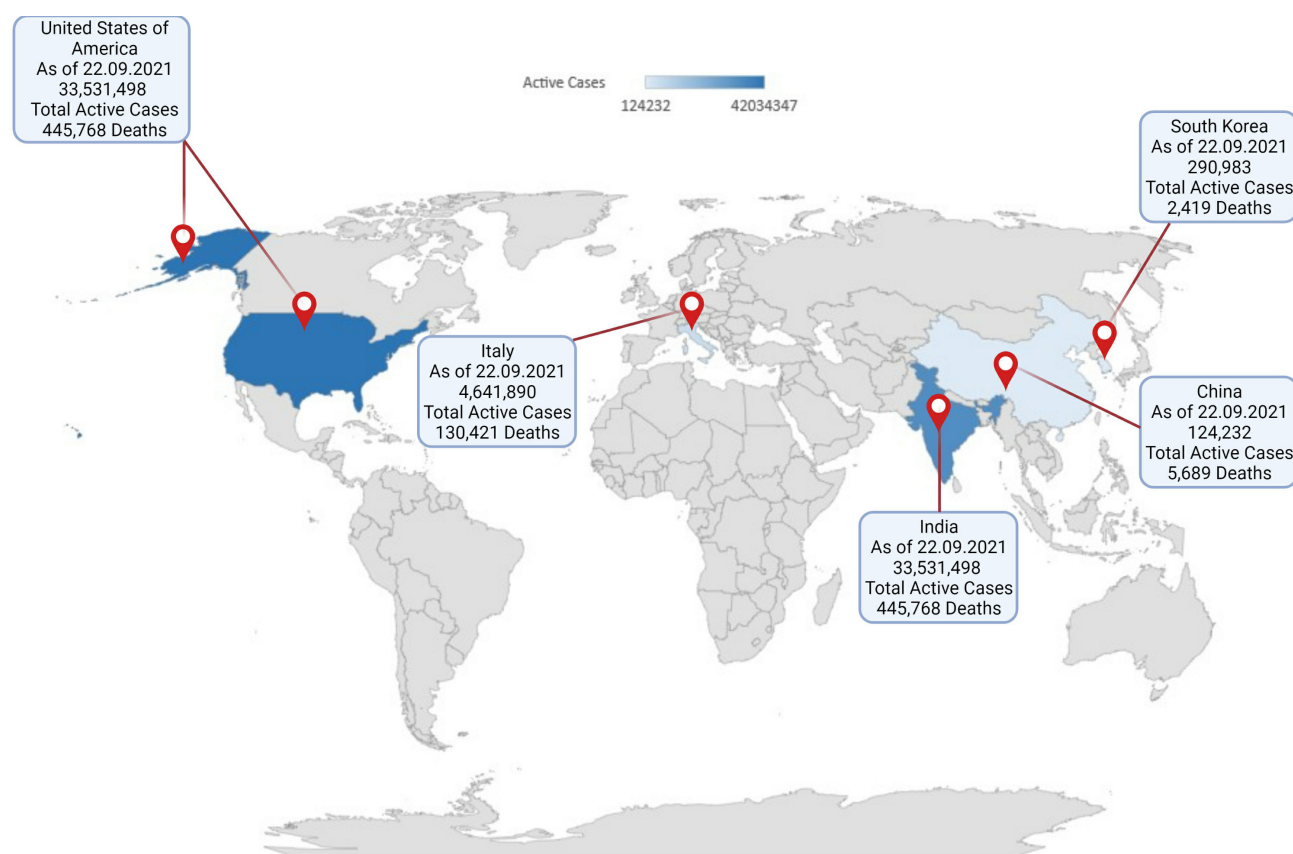


Fig. 2. World map depicting the total number of cases and deaths in China, United States of America, India, Italy, and South Korea, as of 22nd September 2021 (Created with [BioRender.com](#)).

and a total of 518,743 tests were performed till 23rd April 2020 [56]. 290,983 total cases in South Korea were reported on 22nd September 2021, with approximately 2419 deaths (Fig. 2) [23].

4. Symptoms

Coronaviruses including SARS-CoV, SARS-CoV-2, HCoV-NL63 have been proven to be present in tears through RT-PCR techniques. Conjunctivitis is also being considered as another symptom of COVID-19, especially after taking into account the increasing number of case reports of COVID-19 patients infected with conjunctivitis. Various researchers are considering another probability of a different viral mechanism by which the coronavirus can enter the host body through epithelial cells of the eyes [60].

Various oral diseases like mouth ulcers, necrotising gingivitis, blisters, salivary gland alterations, gustatory dysfunction were mainly reported in the clinical reports which examined the oral health of COVID-19 patients. Moreover, the lesions were proven associated with loss of taste and smell. SAR-CoV-2 showed tropism for endothelial cells and COVID-19 facilitated endotheliitis was proven capable of stimulating inflammation of oral tissues and thereby enabling the further spread of the virus. Tis-

sue homeostasis and delayed disease recovery are also some of the critical symptoms caused due to higher level of pro-inflammatory mediators in patients infected with COVID-19 [61].

5. Mechanisms

The most significant factor for the initiation of COVID-19 host-pathogen interaction is the host body where the evolution of the viral cell takes place. Human RNA virus SARS-CoV-2 caused the viral disease COVID-19. The virus undergoes several genetic manipulations to get to its mutated characters for the initiation of the infection and the struggle for existence inside the host body [62].

The virus has glycoprotein spikes on its outer surface which result in the attachment and entry of the virus into the host cells [63]. The process of entry of the virus is reliant on cellular proteases which helps to split the spike proteins for example—Human Airway Trypsin, cathepsins and transmembrane protease serine 2. The most important receptor of SARS-CoV-2 is angiotensin-converting enzyme 2. The critical lysine 31 residue present on the angiotensin-converting enzyme 2 human receptor identifies the 394 glutamine residue of the SARS-CoV-2 in the receptor-binding domain region. The life cycle of SARS-CoV-2 begins when

the Spike protein binds to the cellular receptor angiotensin-converting enzyme 2 [2, 64, 65].

Employing the endosomal pathway, the viral envelope fusion with the cell membrane is assisted by the conformation change in the S protein after receptor binding. The RNA is then released in the host cell by SARS-CoV-2. Viral replicase polyproteins pp1a and 1ab are translated from the Genome RNA which is then broken down by viral proteinases into small products. Discontinuous transcription of the polymerase generates a series of sub-genomic mRNAs which are translated into appropriate viral proteins. The virion's viral proteins and genome RNA is accumulated eventually in the Golgi body and endoplasmic reticulum. Then through vesicles, it is transported and let out of the cell. An effectual environment for external stability and survival of SARS-CoV-2 functions as an intermediate from one host to another [2].

Its host body is feasible and more conveyable than any other coronavirus. Temperature changes and relative humidity increases the rate of exposure of the host to some pathogen and also penetration and persistence of the pathogen within the host body [62]. SARS-CoV-2 through numerous clinical outputs is received by the environment, mainly in the form of droplets or aerosol that is predominantly the respiratory secretions from an infected individual that can be either a susceptible host or a carrier. It can survive in this form in various inanimate objects that can carry these pathogens. These droplets or aerosol can protect the virus on its own after it is accepted in the external environment and helps in sustaining it for a long time; in aerosol media the virus can stay in a stable form for three hours and on steel surface, the stability of the virus is about 2–3 days [66]. It acts as a maintaining media of the virus outside the host body. This is one of the reasons for the firmness of SARS-CoV-2 in the external environment [62]. The following flowchart describes the mechanism of infection of the SARS-CoV-2 (Fig. 3).

Rapid replication of SAR-CoV-2 takes place after the initiation of infection and acute inflammatory outcomes were also observed due to cytokine storms. This consequent inflammatory outcome causes severe damage in capillary endothelial cells, alveolar epithelia, which in turn results in interstitial and alveolar edema and also disrupts pulmonary activities. These losses lead to acute hypoxic respiratory failure and result in acute respiratory distress syndrome (ARDS) [4].

6. Preventive measures

Currently, the world is facing a threatening health crisis with the emergence and spread of coronavirus disease (COVID-19). This disease is usually transmitted by contact with an infected droplet or by inhalation, and its incubation period ranges from 2 to 14 days. The symptoms of this disease include fever, dry cough, tiredness, sore throat along

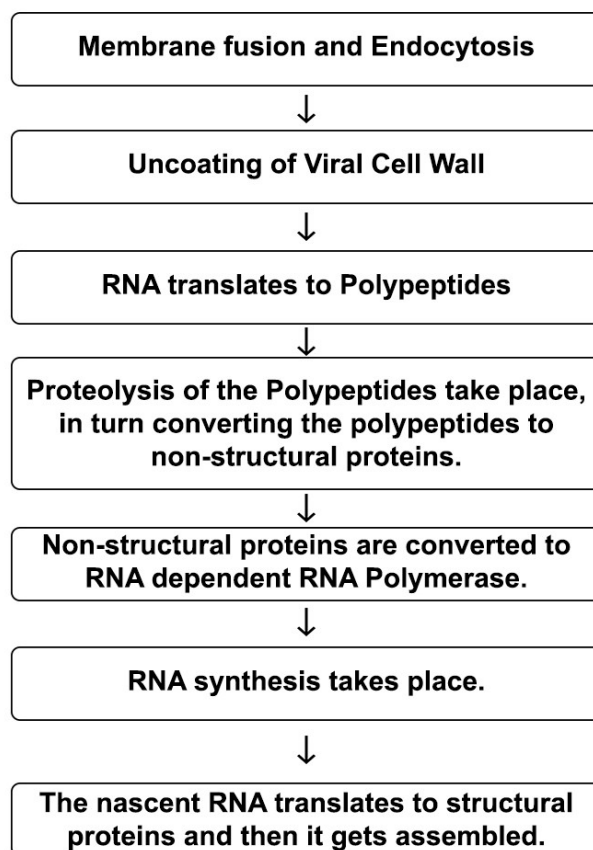


Fig. 3. Mechanism of infection of SARS-CoV-2 in humans.

with few others. The majority of infected people are experiencing mild to moderate respiratory sickness and are recovering without any such special treatment. Elderly people and those with any other existing disease like diabetes, cardiovascular disease, chronic respiratory disease, and cancer are more prone to severe illness [67, 68]. Due to the lack of a therapeutic vaccine or any other antiviral treatment, the only possible way to prevent the spread of COVID-19 is to obey the following preventive measures [69]. These include isolation, social distancing, quarantine, maintaining personal hygiene.

6.1 Isolation

Isolation is when an infected person is separated from an uninfected person and which can be done in a hospital or at home for mild infections. The period for isolation should be at least 13 days since the initiation of COVID-19 symptoms. To make the isolation process work the detection of infected people should be done early, i.e., before the commencement of shedding of the virus [70].

6.2 Quarantine

Quarantine is needed for asymptomatic or healthy people, who may or may not have been exposed to an infected person but was not showing any such symptoms. Such a person should stay in quarantine for 14 days to make

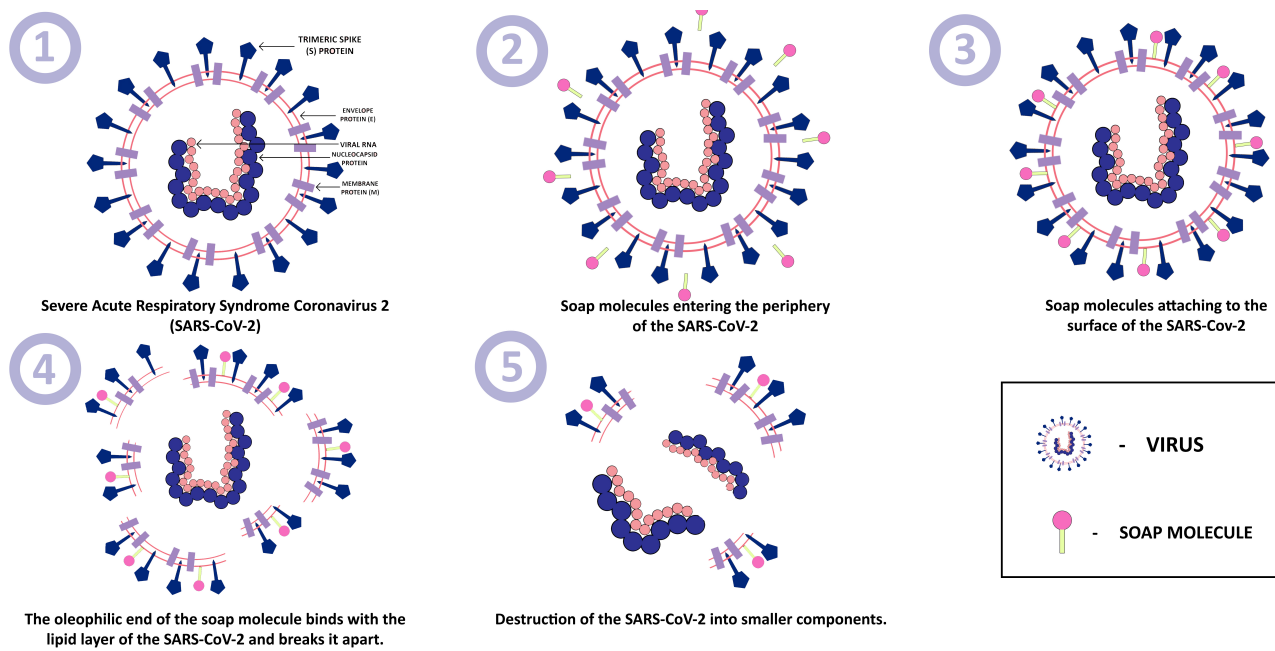


Fig. 4. The action of soap on Severe Acute Respiratory Syndrome Coronavirus-2.

sure whether that person is infected or not. Ideally, quarantine involves movement limitations, along with medical assistance and observation during the period of the quarantine. Quarantine usually can be done in the home or selected hotels and can be done at an individual level or community level. If symptoms were developed in people in the quarantine they were further investigated at the chosen health care centre. The main objective of quarantine is to stop the spread of this disease by efficiently reducing the R_0 or the reproduction number of the disease to less than one [70].

6.3 Containment measures

When it is no longer possible to individually select infected persons and those who were in contact with them, a next method should be applied which is to implement containment measures throughout the whole community. This is meant for a whole community, region or a city instructed to lower interactions within them and to encourage people to maintain social distancing, avoid gathering, increasing awareness to slow down community transmission. Communitywide containment measures are a lot more complex process than isolation and quarantine since a larger number of people is concerned [70].

6.4 Personal hygiene

Maintaining personal hygiene is a very basic yet important step in preventing the spread of the COVID-19. Some vital guidelines given by WHO are as follows:

(1) Maintaining a distance of about 1metre from others whenever one goes out [71].

(2) Going to crowded places should be avoided since their people are more likely to come in contact with

each other and that way risk of virus spreading is more [71].

(3) While going outside one should always wear a mask and avoid touching the face, nose or eyes since contaminated hands can also spread this virus [71].

(4) If one is having a mild cough, cold, headache, sore throat they should stay at home and undergo self-isolation [71].

(5) Staying physically active and eating healthy foods is another imperative way to boost the body's natural immunity [71].

(6) One of the World Health Organization's important recommendations towards every individual is to wash hands frequently with any kind of soap available for at least 20seconds. World Health Organization also stated that alcohol-based hand rubs having at least 60% alcohol content can be used as a replacement for soap [48, 71].

6.5 The effect of soap and alcohol-based hand rubs on coronavirus

Most of the viruses including coronavirus have their genetic material enclosed by a layer of fat which is known as a lipid envelope. Soap molecules have two ends one is hydrophilic and the other one is oleophilic. The oleophilic end tends to attract the lipid layer of the virus and thus the fat layer gets pulled when soap interacts with the virus. The oleophilic end also interacts with the bond which binds the RNA and the lipid envelope and thus destroys the virus into smaller components which later gets removed by water (Fig. 4). But this whole mechanism takes about 20 seconds. Just like soap alcohol-based hand rubs also destroy the lipid envelope and thereby inactivates the virus. The alcohol-based hand rubs also denature the spike pro-

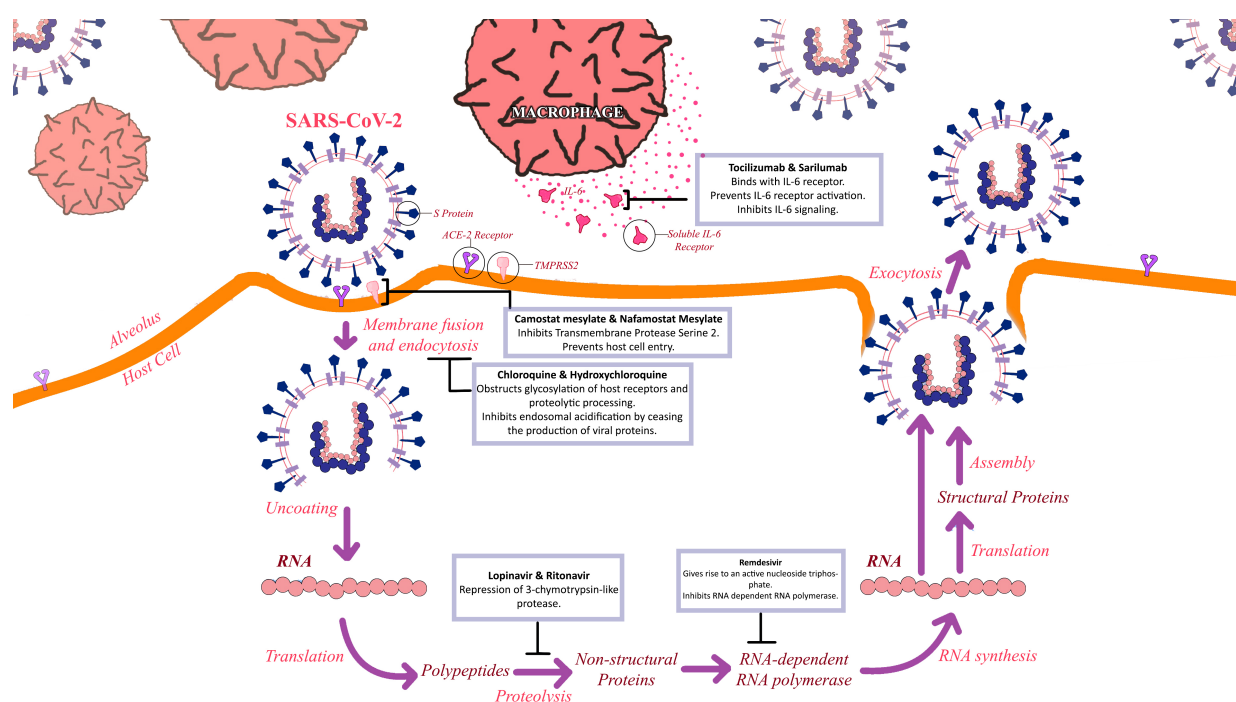


Fig. 5. The mechanism of Severe Acute Respiratory Syndrome Coronavirus-2 entry into the host body and the actions of the discussed medications. ACE2, Angiotensin-Converting Enzyme 2; S protein, Spike Protein; and TMPRSS2, Transmembrane protease, serine 2.

teins present at the outer surface of the virus, which helps the virus to enter the host body. The hand rubs should contain 60% alcohol content for this mechanism to be effective [72].

7. Possible medications

Since the inception of the breakout, various medications that affected COVID-19 have been offered. Numerous antiviral compounds were made a part of the latest guidelines from the National Health Commission, including interferon, chloroquine phosphate, ribavirin, arbidol, lopinavir/ritonavir. Angiotensin receptor blockers, such as losartan have also been recommended for the treatment of COVID-19. The COVID-19 treatment guidelines are varied between countries. The guidelines presented by World Health Organization are very general, suggesting administration of symptoms, and handling pediatric patients, pregnant women and patients with underlying comorbidities with great awareness. As of now, no approved treatment for COVID-19 has been proposed [73].

7.1 Medicinal plants

Medicinal plants along with their bioactive molecules have certain antiviral properties which are being considered to have potential inhibiting capabilities against SARS-CoV-2 infection (Table 1, Ref. [5]). These plants are recognized to have established antiviral properties which can inhibit viral replication and can cure certain viral infections. Some of these plants were exclusively chosen based

Table 1. A list of the medicinal plants acting against specific target proteins and receptors are tabulated below [5].

Specific target proteins and receptors	Name of the plants
Angiotensin-converting enzyme-2 (ACE-2)	1. <i>Rheum palmatum</i> L.
	2. <i>Citrus aurantium</i> L.
	3. <i>Rubia tinctorum</i> L.
	4. <i>Allium sativum</i> L.
3 Chymotrypsin-like protease (3CLpro)	1. <i>Torreya nucifera</i> L.
	2. <i>Houttuynia cordata</i> Thunb
	3. <i>Artemisia annua</i> L.
	4. <i>Angelica keiskei</i> (Miq.) Koidz.
RNA-dependent RNA polymerase (RdRp)	1. <i>Salvia miltiorrhiza</i> Bunge.
	2. <i>Houttuynia cordata</i> Thunb.

on the mode of action and potency, along with specific ethnobotanical evidence against coronaviruses. These plants have proven effects against specific target proteins and receptors like ACE-2 (Angiotensin-converting enzyme-2) receptor, 3CLpro (3 Chymotrypsin-like proteases), and RdRp (RNA-dependent RNA polymerase) which are mostly used by coronaviruses, and in turn, inhibits the replication of RNA [5].

The advice is to furnish supportive administration according to each patient's requirements, like antipyretics for fever, oxygen therapy for respiratory distress. World Health Organization's recommendations suggest that severe cases should be treated with observational antimicrobial therapy, with mechanical ventilation

used depending on the patient's condition. The treatment protocols across countries are pretty alike and include hydroxychloroquine, chloroquine phosphate, remdesivir, lopinavir/ritonavir (Fig. 5) [73]. The drugs which are being tested for possible treatment against COVID-19 covers two perspectives: those drugs which aim for the replication cycle of the virus and those which aim to manage the symptoms of this disease [74]. Some of the capable repurposed drugs to fight against this virus are listed below.

7.2 Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are some known polymerase inhibitors previously used as medications for malaria. In the case of COVID-19, the virus is thought to obstruct glycosylation of host receptors, proteolytic processing and inhibits endosomal acidification by ceasing the production of viral proteins. Chloroquine in initial in vitro studies was successful in blocking COVID-19 infection at a less-micromolar concentration [74].

A succession of more than 100 COVID-19 cases was reported to be successfully treated in China by the use of chloroquine/hydroxychloroquine, which resulted in developed radiologic results, reduced disease advancement, and superior viral clearance. These reports could not be validated because of the lack of published data. A different arbitrary investigation of 30 COVID-19 patients in China was reported, it was found that they furnished no benefit over standard treatment. Another study in France presented the reports of 36 patients, of which 20 were treated with hydroxychloroquine, and the other 16 were given standard treatment. This report included improved virologic clearance with hydroxychloroquine compared to the patients receiving standard treatment. The patients in the French study who were treated with hydroxychloroquine further showed critical illness or intolerance of the medications. In addition to these limitations, concerns of additive cardiotoxicity with combination therapy were not supportive to the adoption of this medication without additional studies [75].

At a renowned medical centre in New York City, the involvement of hydroxychloroquine concerning patient's deaths was recorded. The patients who were treated with hydroxychloroquine were critically ill compared to the patients who were not treated with hydroxychloroquine. The study concluded that there was no significant involvement of hydroxychloroquine in a patient's death [76].

An international clinical trial known as The Solidarity Trial was supervised by The World Health Organization and its associates to help determine an effective treatment for COVID-19. Lopinavir/ritonavir, Remdesivir and Lopinavir/ritonavir with Interferon β -1a were the proposed treatment choices for the trial. By investigating numerous pieces of evidence from laboratory, clinical and animal studies, these treatment options were initially preferred. As of 17th June 2020, the hydroxychloroquine arm which was initially integrated into the study, was terminated; this was

due to the negative results that hydroxychloroquine portrayed as it did not reduce the mortality of the hospitalized COVID-19 patients as compared to standard care [75].

Records from The Solidarity Trial, The French discovery trial along with The UK's Recovery Trial were reported recently and showed that the use of hydroxychloroquine does not reduce the mortality of the hospitalized COVID-19 patients as compared to standard care [77].

7.3 Lopinavir/ritonavir

United States Food and Drug Administration [FDA] permitted oral drug—lopinavir/ritonavir was previously used for treating HIV and also exhibited action against other novel coronaviruses in an in vitro study employing repression of 3-chymotrypsin-like protease. The clinical studies that were associated with SARS concluded in reduced mortality and intubation rates, but their retrospective, experimental character prevents decisive outcomes. The initial peak viral replication phase which is about 7–10 days is very crucial for the administration of the drug since delayed treatment commencement with lopinavir/ritonavir would have no positive clinical outcomes [74].

Lopinavir/ritonavir is generally used in a medicating schedule for COVID-19 treatment as 400 mg/100 mg twice daily for a maximum of 14 days. Gastrointestinal distress such as hepatotoxicity, nausea and diarrhoea are a few of the side effects that lopinavir/ritonavir have on COVID-19 patients. In a recent randomized clinical trial, roughly 50% of the patients who were treated with lopinavir/ritonavir underwent adverse effects and 14% of the patients terminated its use due to gastrointestinal problems [75].

According to the solidarity trial published by the World Health Organization on 15th October 2020, lopinavir/ritonavir had little or no consequence on overall mortality, the commencement of ventilation and the total period of hospital stay in hospitalized patients [78].

7.4 Nafamostat and camostat

The camostat mesylate (NI-03) is a serine protease inhibitor that is effective against transmembrane protease serine 2 which inhibits SARS-CoV-2 infection in human lung cells. It was also previously used in Japan for the treatment of pancreatitis. As a medicament of COVID-19, the suitability of camostat mesylate is under evaluation in a clinical trial. Though, it is not known if sufficient compound concentrations in the lung can be attained to inhibit the viral spread [74, 75].

Due to the lack of this data, other serine protease inhibitors for obstruction of SARS-CoV-2 access being tested are very significant. Gabexate mesylate and nafamostat mesylate were tested along with camostat mesylate for suppression of SARS-CoV-2 infection in lung cells. All these drugs are permitted for human use in Japan.

The transmembrane protease serine 2-dependent host cell entry of MERS-CoV is suppressed by nafamostat mesylate. According to the results, gabexate mesylate suppressed spike protein directed host cell entry of SARS-CoV-2 minutely, whereas camostat mesylate suppressed the host entry efficiently. United States Food and Drug Administration (FDA) accepted drug, nafamostat mesylate inhibited SARS-CoV-2 spike protein operated host cell entry with much higher efficiency than camostat mesylate, with an effective concentration of 50% in the low-nanomolar range [79]. Nafamostat mesylate worked better than camostat mesylate in blocking SARS-CoV-2 infection in human lungs with greater efficiency [79].

7.5 Famotidine

Famotidine, the H₂ receptor competitor heartburn drug is being analyzed as a possible treatment for COVID-19. It was reported in Wuhan, China that patients were consuming heartburn medication after being infected by COVID-19; this reduced the likelihood of the patients' death [80]. A papain-like protease which is encoded by the genome of SARS-CoV-2 is very essential in the entry of SARS-CoV into the host body, which is restricted by famotidine [74].

7.6 Ivermectin

A broad-spectrum anti-parasitic drug, ivermectin is also effective against few invertebrates, is a lipophilic macrolide. In the case of COVID-19, it binds and weakens the cell-transport proteins which allow them entry into the nucleus. Observations obtained from a randomized clinical trial showed that the administration of ivermectin resulted in a reduced death rate, 7% compared to 21% in the case of patients kept under normal treatment. As for intubated patients, the death rate reduced from 21% to 7% [74, 81, 82]. In an in vitro study, it was reported that ivermectin treatment promisingly killed approximately all viral particles in 48 hours. This study was the first to approve the antiviral effect of ivermectin against COVID-19, and it concluded that it inhibited the importin α/β receptor which is in charge of the transportation of viral proteins into the nucleus of the host cell. The authors anticipated human trials to be performed so that the possible advantages of ivermectin in the treatment of COVID-19 can be confirmed [83].

7.7 Tocilizumab and sarilumab

Approximately 200 patients with COVID-19 in a retrospective study, experienced major types of ailments and had greater inflammatory cytokine Interleukin-6 levels. It was assumed that cytokine-release syndrome is involved in worsening the reactions caused by the virus and resulted in acute respiratory distress syndrome even when the viral load seemed to reduce [84]. Clinical trials are being performed to test a variety of drugs that can block various cytokines. Tocilizumab and sarilumab are two of the drugs being tested out, both of which are monoclonal-

antibody competitors of Interleukin-6 receptors that are usually used as a treatment of rheumatoid arthritis and cytokine release syndrome by chimeric antigen receptor T-cell therapy. Tocilizumab, a United States Food and Drug Administration (FDA) approved medicine showed encouraging results in a randomized controlled study. A phase 2 analysis of sarilumab used in a group of patients in critical condition portrayed positive results, but a negative result was seen in a group of severely ill patients (patients requiring oxygen supplementation but not intubation). A higher dosage of sarilumab was being administered in the severe group during the third phase of the trial, while there was no change in the dosage in the case of critically ill patients [74]. A report comprising of COVID-19 positive patients showed that tocilizumab was used as a regimen of 400 mg, where 91% of patients portrayed enhanced respiratory function, faster decrease in body temperature and successful discharge, most of the patients receiving only one dose [75]. Administration of intravenous and subcutaneous tocilizumab was capable of lowering the risk of intubation or death in patients suffering from acute COVID-19 pneumonia [85].

7.8 Remdesivir

Remdesivir (GS-5734), a monophosphate prodrug of parent adenosine analogue which when metabolized gives rise to an active nucleoside triphosphate. In the case of COVID-19, remdesivir inhibits RNA dependent RNA polymerase. Remdesivir is a broad-spectrum antiviral drug that has confirmed effects against RNA viruses, including Coronaviridae, Flaviviridae and Filoviridae. Remdesivir was formerly developed to treat Ebola virus infection and was also effective to prevent lung bleeding, lower viral lung titers in case of murine lung infections caused by MERS-CoV [75, 86].

In Japan, the use of remdesivir in patients undergoing treatment against COVID-19 has been approved. The United States Food and Drug Administration (FDA) also permitted the use of remdesivir as an Emergency Authorization for the treatment of severely ill COVID-19 patients [87]. Successful use of remdesivir against COVID-19 has been reported in several case reports [75].

In a study, the hospitalized patients who had been infected by SARS-CoV-2 were randomized into 3 groups of patients, two of the groups were put under 5 days and 10 days of remdesivir treatment, and the third group was put under standard treatment. The study was based on results from an 11 day-long examination of the patients, which ranged from an increase in oxygen level to hospital discharge and ventilatory support to death. Another objective of this study was to determine the antagonistic effects of remdesivir administered patients compared to standard care.

On the 11th day, the results showed that patients of the 5-days treatment group gained improvement in clini-

cal status as compared to the group receiving standard care. Also, a non-statistical increase in the degradation of a patient's health in the standard care group was observed compared to the groups receiving remdesivir treatment. Remdesivir use should be prohibited for those who are hypersensitive to any of the ingredients of remdesivir. If any clinical side effects are observed, the administration of the drug should be immediately ceased and significant treatment should be initiated. When patients with moderate COVID-19 infection were treated with remdesivir, a 5-days course showed higher rates of improvement compared to those treated with standard care, ultimately annexing more evidence in favour of the use of remdesivir [87].

8. Vaccines designed against SARS-CoV-2

During the global outbreak of the novel Coronavirus, the scientific world is facing a major crisis due to the lack of any therapeutic vaccine. As of July 2020, over 160 vaccines for the novel Coronavirus are under development all around the globe. 25 candidate vaccines have progressed to one of the three phases of trials on humans, according to the World Health Organization. Among the 25 candidate vaccines, two Indian vaccines, namely the vaccines from Zydus and Bharat Biotech make it to the list. As of 28th July 2020, pre-clinical trials were in progress in 139 other vaccine candidates. The United States-based Moderna Therapeutics had a lead in the production of the vaccine as it had completed its phase I and II trials and already entered the phase III trials with over 30,000 volunteers being tested with the vaccine [88].

8.1 United States-based Moderna vaccine and Pfizer vaccine

Two 30,000-subject trials of COVID-19 vaccines were made operational by Moderna Incorporated and Pfizer Incorporated. Both the vaccines were based on the latest technology that allowed for faster development and manufacturing than normal vaccine production. The United States government made a \$1 billion investment in Moderna, which never actually brought a vaccine to the market. Pfizer also had an agreement in which the company agreed to sell the vaccines to 50 million United States citizens for approximately \$2 billion. During the announcement for Moderna's giant phase III trial, the director of the United States National Institutes of Health reportedly said that the goal of having an effective vaccine by the end of 2020 was a pretty tough one, but it was the right goal for the Americans. Pfizer vowed to produce over 1.3 billion doses of the vaccine by the end of 2021 [89].

The potential side effects of the Moderna vaccine after injecting the jab in the arm, include pain, redness, and swelling. On the other hand, tiredness, headache, muscle pain, chills, fever and nausea can be the few side effects that can be felt throughout the body. According to the results

from clinical trials, the efficacy rate of the Moderna vaccine was noted to be 94.1% after two doses of the vaccine, in patients with no prior COVID-19 infection history [90].

The possible side effects of the Pfizer vaccine after injecting the jab in the arm, include pain, redness, and swelling. Also, tiredness, headache, muscle pain, chills, fever and nausea can be the few side effects that can be felt throughout the body. According to the results from clinical trials, the efficacy rate of the Pfizer vaccine was noted to be 95%, in patients with no prior COVID-19 infection history [91].

8.2 Oxford University's COVID-19 vaccine (AstraZeneca)

A perfect vaccine against SARS-CoV-2 would be the one that protects the elderly people, immunosuppressed patients and people with comorbidities, would grant defence for at least 6 months; and would prevent further transmission of this virus. In the case of immunosuppressed patients, viral vectored vaccines lacking replication were used, taking into account the safety of those patients. ChAdOx1 was also able to produce immune responses in elderly people and this vaccine can be produced at a large scale, making it an encouraging contender to develop the vaccine against COVID-19. In the case of primates other than humans, this vaccine was able to develop an immune response to protect the lower respiratory tract against infection, after high dosage application of this vaccine. It can be concluded that ChAdOx1 nCoV-19 was secure, endurable and was able to produce an immune response, while paracetamol was used to reduce the expected side effects. Only a single dose triggered both humoral and cellular responses against SARS-CoV-2, with a booster immunization enhancing neutralizing antibody titers [92].

The initial findings of the first-in-human medical trial upheld clinical advancements into progressing to the phase 2 and phase 3 tests. Elderly people with comorbidities, those who are involved in healthcare works and people with more chances of vulnerability towards SARS-CoV-2 are being recruited and tested for the effectiveness, welfare and immunogenicity of ChAdOx1 nCoV-19 as single dosage or two dosage administration courses for more tests in the United Kingdom and abroad [92].

The possible side effects of the AstraZeneca vaccine after injecting the jab in the arm, include pain, redness, swelling, tenderness, itch, warmth, and swollen armpit glands. Also, fatigue, headache, muscle pain, diarrhoea, arthralgia, myalgia, fever, nausea, chills and shiver can be the few side effects that can be felt throughout the body. According to the results from AstraZeneca's primary analysis of phase 3 trial data, the efficacy rate of the vaccine was noted to be 76% after two doses of the vaccine [93–95].

Table 2. A list of available approved vaccines in the market active against COVID-19 [90, 91, 93–95, 98, 100–106].

Name	Vaccine type	Primary developers	Country of origin	Efficacy rate	Side effects
Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech, Fosun Pharma	Multinational	95%	In the arm: Pain, redness, swelling. Rest of the body: Tiredness, headache, muscle pain, chills, fever, nausea.
Moderna COVID-19 Vaccine (mRNA-1273) (AZD1222)	mRNA-based vaccine	Moderna, BARDA, NIAID	United States	94.10%	In the arm: Pain, redness, swelling. Rest of the body: Tiredness, headache, muscle pain, chills, fever, nausea.
COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Non-replicating viral vector	Janssen Vaccines (Johnson & Johnson)	The Netherlands, United States	66.30%	In the arm: Pain, redness, swelling. Rest of the body: Tiredness, headache, muscle pain, chills, fever, nausea.
COVID-19 Vaccine AstraZeneca also known as Covishield	Adenovirus vaccine	BARDA, OWS	United Kingdom	76%	In the arm: Pain, redness, swelling, tenderness, itch, warmth, and swollen armpit glands. Rest of the body: Fatigue, headache, muscle pain, diarrhoea, arthralgia, myalgia, fever, nausea, chills and shiver.
CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	50.38% to 91.25%	In the arm: Pain. Rest of the body: Elevated blood pressure, headache, dizziness, and rash.
BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products, China National Pharmaceutical Group (Sinopharm)	China	86%	In the arm: Swelling, scleroma, rash, and itching. Rest of the body: Headache, fever, fatigue, muscle ache, joint pain, cough, difficulty breathing, nausea, diarrhoea, and itchy skin.
Sputnik V	Recombinant adenovirus vaccine (rAd26 and rAd5)	Gamaleya Research Institute, Acellena	Russia	91.60%	In the arm: Pain. Rest of the body: Weakness, and fatigue, with mild flu-like symptoms.
Covaxin	Inactivated vaccine	Contract Drug Research and Development Bharat Biotech, ICMR	India	81%	In the arm: Pain, redness, swelling, itch. Rest of the body: Malaise, headache, fever, nausea, vomiting and rashes.

8.3 Russia based Sputnik V

The first country to finish clinical trials of the COVID-19 vaccine on humans was Russia, as per media reports the outcomes demonstrated the vaccine's effectiveness. In a report, Elena Smolyarchuk stated that the research was completed and it proved that the vaccine was safe for humans, and the volunteers would be discharged on 15th and 20th July 2020. Two potential COVID-19 vaccines were approved for clinical trials by Russia. Gamaleya National Research Center for Epidemiology and Microbiology was in charge of the development of the Sputnik V vaccine. A liquid vaccine for intramuscular administration was carried at Burdenko Military Hospital. While another vaccine named EpiVacCorona, which is a peptide vaccine was tested under the Vektor State Research Center of Virology and Biotechnology. Immunity boost against the coronavirus was seen in the case of the volunteers on whom the vaccine was tested. According to the Russian defence ministry, the data analysis by the Gamaleya National Research Center for Epidemiology and Microbiology showed that volunteers of the first and second groups formed an immune response after they got injected with the vaccine [96, 97].

The possible side effects of the Sputnik V vaccine after injecting the jab in the arm, include pain, weakness, and fatigue, with mild flu-like symptoms. According to the reports of COVID-19 patients from 21 days after the first dose of the vaccine, the efficacy rate of the Sputnik V vaccine was noted to be 91.6% [98].

8.4 India based Covaxin

Bharat Biotech is an Indian biotech company that has obtained consent from the Drug Controller General of India (DCGI) to propel its COVID-19 vaccine prospect Covaxin on humans in a controlled human trial. This is the very first time an Indian domestic vaccine was approved to be tested. Approval by DCGI would allow the company to initiate Phase I and Phase II studies. In association with the Indian Council of Medical Research's National Institute of Virology, Covaxin is created. Bharat Biotech's facility in Genome Valley, Hyderabad was responsible for the development of the immobilized vaccine [99].

The possible side effects of the Covaxin vaccine after injecting the jab in the arm, include pain, redness, swelling, and itch. Also, malaise, headache, fever, nausea, vomiting and rashes can be the few side effects that can be felt throughout the body. An extreme allergic reaction may very hardly occur after getting a dose of Covaxin. According to the results from phase 3 trial data, the efficacy rate of the Covaxin vaccine was noted to be 81% after two doses of the vaccine [100].

A list of available vaccines along with their type, nature, name of developers, country of origin, efficacy rate and all the possible side effects has been well documented in the Table 2 (Ref. [90, 91, 93–95, 98, 100–106]).

9. Conclusions

The worldwide spread of this pandemic has shaken the world in a way that recovery seems far-fetched. But the hopes and the future possibilities are helping everyone to keep going. As of 27th July 2020, the total number of cases worldwide was noted to be 16,114,449 along with 646,641 deaths. The most number of cases being accounted in Americas (8,610,134), Europe is second (3,234,043), and South-East Asia with the third most confirmed cases (1,786,145). During such tough times, with no possible cure for the virus, implementing preventive measures would possibly be the best strategy to fight against COVID-19. To decrease the spread of the virus, widespread testing measures should be executed, with an increase in the testing rate. Newly developed and improved tracking systems along with testing kits would help the world flatten the curve. Global vaccine trials are being performed in different countries, which is the only hope for a few countries where the virus has vastly spread. The distress this pandemic has caused will take some time to fade away even after overcoming this in the future. The daily lifestyle will differ in the post-COVID-19 situations. In the future, scientists would be more prepared for the upcoming viruses and other microbial organisms that could cause such devastating losses to human life. Many aspects of COVID-19 that the scientists have observed or discovered will help them to overcome other viruses or microbial organisms that are close to SARS-CoV-2. Even with the arrival of any vaccine against COVID-19, the end of this disease will still be uncertain so people should be aware. They should maintain proper hygiene and should follow basic preventive measures such as wearing masks and maintaining social distancing. The social and economic losses several countries have suffered from this pandemic will impact the future of the people. But people should remain optimistic and learn from this adversity and be more prepared in the upcoming years.

10. Author contributions

Conceptualization—PB, SD, SA; Methodology—PB, SD, SA; Formal analysis and investigation—PB, SD, SA; Writing—original draft preparation—PB, SD, SA; Writing—review and editing—JS; Supervision—JS.

11. Ethics approval and consent to participate

Not applicable.

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14. Conflict of interest

The authors declare no conflict of interest.

15. Availability of data and material

Not applicable.

16. Code availability

Not applicable.

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