INSIGHTIA JOURNAL OF RESEARCH AND INNOVATION
OPEN-ACCESS JOURNAL | ISSN (ONLINE): [XXXX]

Review

Volume 1, Issue 1 (May-June) 2026
Article No. 02, Pages 01-45
https://doi.org/10.33/IJRI11.02

COVID-19: Current Perspectives on Epidemiology, Pathogenesis, Diagnosis, Therapeutic Strategies, and Vaccine Development

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Received: 21 April 2026 | Accepted: 15 June 2026 | Published online: 14 July 2026

Abstract: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a major global public health challenge. The virus is primarily transmitted through respiratory droplets and can spread via asymptomatic, pre-symptomatic, and symptomatic individuals. The incubation period averages approximately five days, with most symptomatic cases developing within 11.5 days of exposure. Common clinical manifestations include fever, dry cough, fatigue, and shortness of breath, while laboratory findings such as lymphopenia and elevated lactate dehydrogenase are frequently observed. Reverse transcription polymerase chain reaction (RT-PCR) remains the gold standard for diagnosis; however, false-negative results may occur due to variations in specimen quality and testing timing. Consequently, chest computed tomography (CT) has been widely employed as a complementary diagnostic tool, demonstrating characteristic findings such as ground-glass opacities and pulmonary consolidations. Despite extensive research on antiviral agents, immunotherapies, and repurposed drugs, no universally curative treatment has been established. Vaccination remains the most effective strategy for reducing disease transmission, severity, and mortality. This review summarizes current knowledge regarding the epidemiology, transmission, pathophysiology, clinical presentation, diagnostic approaches, therapeutic interventions, and vaccine development related to COVID-19, highlighting ongoing challenges and future directions in disease management.

Keywords: COVID-19; SARS-CoV-2; Pathogenesis; Molecular Diagnosis; Antiviral Therapy; Vaccine Development

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1. Introduction

A broad range of creatures, including humans, birds, rodents, carnivores, chiropters, and other mammals, can become infected by coronaviruses (CoVs), a vast group of enclosed, single-stranded, positive-sense RNA viruses [1,2]. Although seven coronaviruses can infect people worldwide, the four human coronaviruses that infect humans most frequently are 229E, NL63, OC43, and HKU1. The most recently identified coronavirus, COVID-19, causes infectious diseases, and they typically cause respiratory infections, from the ordinary cold to more serious conditions like Middle East Respiratory Syndrome (MERS) and Severe Acute-Respiratory Syndrome (SARS)[3]**.** Two coronavirus outbreaks in the past, SARS in 2002–2003 and MERS in 2012, caused worry on a global scale. Over 200,000 people have already died

from the new virus, which is extremely contagious and has an estimated sCFR (symptomatic case fatality risk) of 1.4% (0.9-2.1%). [4]. In contrast, MERS was one of the deadliest human diseases, with a fatality rate of up to 35% compared to about 10% for SARS.[5].

Nevertheless, it has been demonstrated that SARS-CoV-2 has a significantly higher human-to-human transmissibility.[6]. This novel coronavirus resembled SARS-CoV, which caused the SARS outbreak in 2002–2003.[7]. It was thought that a zoonotic transmission linked to the seafood market in Wuhan, China, was the initial cause of the SARS-CoV-2 outbreak. Human-to-human transmission was later found to be a significant contributing factor to the outbreak that followed[8]. It was thought that a zoonotic transmission linked to the seafood market in Wuhan, China, was the initial cause of the SARS-CoV-2 outbreak. Human-to-human transmission was later found to be a significant contributing factor to the outbreak that followed.[9].

Initially known as Novel Coronavirus-Infected Pneumonia (NCIP) by the WHO, the virus is now known as 2019 novel coronavirus (2019-nCoV). The WHO formally renamed the clinical disease COVID-19, which is an acronym for Corona Virus Disease-19, on February 11, 2020. The announcement was made via Twitter. The current COVID-19 outbreak, which is considered a pandemic, started in December 2019 in Wuhan, Hubei Province, China, and was brought on by the 2019 new coronavirus (SARS-CoV-2).[10]. Readers are encouraged to stay up to date on this virus because understanding about it is changing quickly.[11]. Usually, the virus spreads quickly from person to person through respiratory droplets released while sneezing and coughing. [12]

Investigations are being conducted into the potential for virus transmission through environmental factors like airborne dust and wastewater tainted by the virus. The best course of action in this case is to control transmission by preventing and screening for COVID-19. It is necessary to build powerful and automated virus monitoring methods. [13–17]. Few patients were found to be asymptomatic when the clinical spectrum of COVID-2019 was examined, and other patients exhibited mild to severe symptoms, such as fever, cough, flu, and severe respiratory discomforts.[18–20]. The symptoms of SARS-CoV-2, which first affects the respiratory system, include fever, vomiting, headache, disorientation, general weakness, and diarrhea, among others. [21,22].

These symptoms get more varied as the days go by, leading to the onset of ARDS, which may cause death given the increasing number of people who pass away worldwide. It is anticipated that these mortality rates will be greater among the elderly than among young people.[23–25]. Because of the high case fatality and symptomatic infection rates, elderly patients are said to have a higher mortality rate.[26,27].

According to Hu et al. (2020), age also influences viral clearance and the length of time between hospitalization and death.[28]. Although transmission may occur before patients exhibit symptoms, it is thought to be most contagious when people are exhibiting symptoms. The average time between exposure and the beginning of symptoms is five days, but it can range from two to fourteen days.[29]. Reverse transcription polymerase chain reaction (rRT-PCR) from a throat or nasopharyngeal swab is the standard diagnostic method. Additionally, a combination of symptoms, risk factors, and a chest CT scan displaying pneumonia-like characteristics can be used to diagnose the infection.[30].

There isn't a specific antiviral medication or vaccine available at the moment; supportive care and symptom eradication are the only options. Washing your hands with soap, covering your mouth when coughing, keeping a 1-meter distance from other people, and

monitoring and isolating yourself for 14 days are all advised preventive measures.[31]. Without an effective COVID-19 treatment or vaccination, we are currently facing a global crisis that is impacting every society and has put billions of people under lockdown. Desperate attempts are being made worldwide to stop this pandemic, which has caused health systems to collapse and brought about long-lasting geopolitical and economic consequences. Since there is currently no recognized medical therapy, social separation is the only effective way to prevent the virus from spreading [32].

Future CoV outbreaks are believed to be inevitable due to ecological and climatic changes as well as increased human-animal contact. Consequently, the development of efficient treatments and vaccinations against CoVs is necessary.[33]. Researchers worldwide are still working around the clock to develop a vaccine or medication that can both prevent and treat COVID-19. Although treatment has been provided with already-developed medications, no special medication has been recommended for the cure of COVID-19 despite these enormous efforts to contain the infectious disease.[34,35]. To stop the virus from spreading further, many nations have imposed lockdowns and social separation. Here, we will summarize what we now know about COVID-19 and examine the underlying mechanism that explains the diverse symptomatology, paying special attention to the differences between patients in childhood and adults.

The history, phylogeny, genomes, epidemiology, mechanism of action, symptoms, diagnosis, and potential treatment options of COVID-19, as well as the advancements in the development of vaccines against SARS-Cov-2, are briefly highlighted in this paper.

2. HISTORY OF CORONAVIRUS

Under an electron microscope, coronaviruses look as crowns due to spike-like projections on their surface, which are enclosed positive sense RNA viruses that range in diameter from 60 to 140 nm.[36]. Humans are infected with four coronaviruses: HKU1, NL63, 229E, and OC43. These viruses typically cause mild respiratory illnesses. In the last 20 years, there have been two instances where animal beta coronaviruses have spread to people and caused serious illness[37]. Humans are infected with four coronaviruses: HKU1, NL63, 229E, and OC43. These viruses typically cause mild respiratory illnesses. In the last 20 years, there have been two instances where animal beta coronaviruses have spread to people and caused serious illness. The first such incidence was in 2002– 2003 when a novel coronavirus of the β genus with its origin in bats passed over to humans via the intermediary host of palm civet cats in the Guangdong province of China[38]. This virus, identified as severe acute respiratory syndrome coronavirus afflicted 8422 persons predominantly in China and Hong Kong and caused 916 fatalities (mortality rate 11%) before being contained[39]. In 2012, nearly ten years later, the Middle East respiratory syndrome coronavirus (MERS-CoV), which is similarly bat-borne, appeared in Saudi Arabia using dromedary camels as the intermediate host. It infected 2494 individuals and killed 858 of them (34 percent mortality rate).[40].

3. EPIDEMIOLOGY

Over 600 million instances of confirmed COVID-19 have been reported worldwide as of December 2022, with the virus having impacted almost every region.[41,42]. In a non-lockdown population, the basic reproduction number (R0) of the original wild type SARS-CoV-2 has been estimated to be between 2.2 and 3.3, meaning that each sick person typically generates two to three new infections.[9,43]. The official COVID-19 death toll as of December 2022 was over six million worldwide.[42,44].

Since many mild or asymptomatic instances are not being tested, which causes the apparent mortality rate to be skewed upward, it is hypothesized that the true case fatality rate is lower than this.[45]. The Chinese Center for Disease Control and Prevention (CCDC) examined all 44,672 instances detected up until February 11, 2020, in a study. Of them, almost 80% were categorized as "mild," while about 1% were asymptomatic.[46]. Another study examined the clinical features of COVID-19 individuals who had positive test results from close connections. On chest CT scans, almost 30% of those close contacts with COVID-19 never showed any symptoms or alterations. The others displayed CT alterations, but around 20% of them reported experiencing symptoms while in the hospital, and none of them experienced serious illness.[47] This implies that a significant portion of COVID-19 carriers do not exhibit any symptoms. Males accounted for 55–60% of COVID-19 patients in China, with a median age of 47 [45,48].

Over 13 billion vaccination doses had been given worldwide as of December 2022.[49].

4. THE ORIGIN OF THE VIRUS

Coronaviruses were unknown to cause severe illnesses in people until 2002. This situation altered when SARS-CoV appeared in a southern Chinese livestock market, affecting almost 8,000 individuals and resulting in 774 deaths globally. [50,51] A novel coronavirus was discovered in 2012 to be the cause of the Middle East respiratory syndrome (MERS-CoV), which killed 838 people and infected over 2428 others.[52]Before infecting humans, SARS-CoV and MERS-CoV first hopped to another mammalian host, the dromedary camel (Camelus dromedarius) for MERS-CoV and the civet of Himalayan palms (Paguma larvata) for SARS-CoV. [53,54]. The third beta-coronavirus to infect humans is SARS-CoV-2. When it was discovered in late 2019, it most likely came from bats and gradually acquired mutations that allowed it to spread zoonotic diseases.[55].

Given that the bat coronavirus RaTG13 shares 98% of the amino acid sequence of the S protein and 93.1% of the nucleotide sequence of the S gene, it appears to be the closest relative of SARS-CoV-2.[55,56]. It is yet unknown how SARS-CoV-2 (or its direct ancestor) is spread from bats to people, either directly or via a different animal species.[57] Five patients had their entire SARS-CoV-2 genomic sequences taken early in the outbreak, and they were nearly identical, sharing 79.6% of the SARS-CoV sequences.[17,58] The virus was first known as the novel coronavirus 2019 (2019-nCoV). The International Committee of Virus Taxonomy's Coronavirus Study Group formally designated it SARS-CoV-2 on February 11, 2020, after phylogenetic analyses revealed similarities to SARS-CoV.[59]

5. STRUCTURE OF THE SARS CoV 2

Animal species frequently harbor the diverse family of positive-sense RNA viruses known as enveloped coronaviruses (CoVs). They infect multiple species, frequently in a pleomorphic form, and have a full genome size of about 30 kilobases in length and 40 nm to 200 nm in diameter.[60] Based on their chromosomal structure, these are divided into four main groups: α, β, γ, and δ. Only mammals are poisoned by the α and β CoVs. The beta coronaviruses include SARS-CoV-2 and MERS-CoV-2. Prior to producing new viral proteins, the virus adheres to the host species using a five-step process that includes attachment, penetration, biosynthesis, maturation, and release.[61].

According to genetic analysis, the SARS-CoV-2 virus may have developed from a bat-derived strain. Furthermore, further research is required to determine how viruses spread from bats to people[62]. This kind of virus has been shown to be dangerous to people, even causing death, and it infects birds and mammals.[63]. Four structural proteins—the E, M, N, and S-S-

spike glycoproteins—have been found in these viruses.[64]. The S protein is the most important of them. When the spike protein binds to the host cells' membrane receptor, it facilitates the fusion with the cellular membrane and functions as a recognition factor.[65].

It is found on the outside of the virion. Several researchers have used the protein data bank's accessible structures to simulate and validate the SARS-CoV2 spike protein in order to obtain a thorough understanding of the invasion of COVID-19.[66]. In order to comprehend how the spike protein binds to the host cell membrane, they subsequently conducted molecular docking tests to assess its affinity against other receptors. One of the main components of infection is the S protein on the virus's surface. Viral entrance is facilitated by this trimeric class I TM glycoprotein[67]. During viral infection, it facilitates cell adhesion, fusion, and receptor recognition[68]. The S protein undergoes significant structural change after the virus interacts with the host cell, which enables the virus to fuse with the host cell membrane. In order to avoid detection by the host immune system during entry, the spikes are covered in polysaccharide molecules.[69].

The fundamental unit via which the S protein attaches to the receptor is the trimer of the S protein, which is found on the viral envelope's surface.[70,71] The S protein is an inactive precursor in its original state. Target cell proteases cleave the S protein into S1 and S2 subunits to activate it during viral infection.[72] which, following viral entrance into target cells, is required to activate the membrane fusion domain.[73]. Cellular proteases cleave the S protein of SARS-CoV-2 into S1 and S2 subunits, just like they do for other coronaviruses. The S2 domain mostly comprises the heptad repeat (HR) domain, which includes HR1 and HR2, which is intimately linked to virus fusion, whereas the S1 domain contains the Receptor binding domain (RBD), which is primarily in charge of the virus's binding to the receptor.[74].

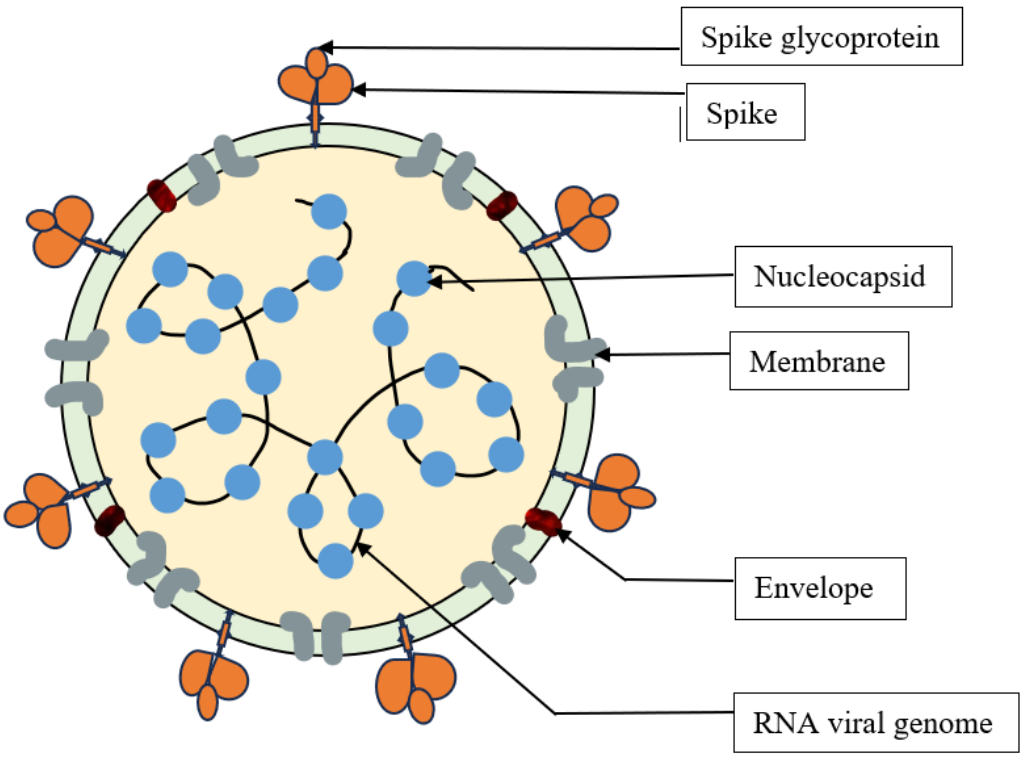


Figure 1. A structure of Respiratory Syndrome (SARS) coronavirus

6. THE VIRUS: TAXONOMICAL CLASSIFICATION

Within the family Coronaviridae, which has two subfamilies (Coronavirinae and Torovirinae), members of the subfamily Coronaviruses are categorized into four genera, and SARS-CoV-2 is a member of the order Nidovirales. The four genera are:

(a) HCoV-229E and HCoV-NL63 are human coronaviruses that are found in alphacoronavirus;

(b)Beta coronaviruses include Middle Eastern respiratory syndrome coronavirus (MERS-CoV), HCoV-OC43, Severe Acute Respiratory Syndrome human coronavirus (SARS-HCoV), and HCoV-HKU1; (c) The gamma coronavirus comprises avian and whale viruses, (d)The delta coronavirus comprises viruses that have been isolated from birds and pigs.[75].

Along with SARS-CoV and MERS-CoV, two extremely dangerous viruses, SARS-CoV-2 is a member of the beta coronavirus family. The enveloped, positive-sense single-stranded RNA (+sRNA) virus is known as SARS-CoV-2.[76].SARS-CoV-2 is regarded as a new beta coronavirus that infects humans. According to phylogenetic analysis of the SARS-CoV-2 genome, the virus is genetically different from SARS-CoV (with roughly 79% similarity) and MERS-CoV, but it is closely related (with 88% identity) to two bat-derived SARS-like coronaviruses that were collected in eastern China in 2018 (bat-SL-CoVZC45 and bat-SL-CoVZXC21).[2]. A subsequent investigation using the genome sequences of SARS-CoV-2, RaTG13, and SARS-CoV revealed that, with 96.2% overall genome sequence identity, the virus is more closely related to Bat CoV RaTG13, a bat corona virus that was previously identified in Rhinolophus affinis from Yunnan Province. According to a study, the genome of SARS-CoV-2 showed no signs of recombination events from other bat-borne viruses, including Bat CoV RaTG13, SARS-CoV, and SARSr-CoVs.[25]. These results collectively imply that bats may have been the virus's original host. [2,25] To determine whether any intermediary hosts have helped spread the virus to people, more research is necessary. For a number of reasons, bats are unlikely to be the mammal directly responsible for the virus's spread to humans. [2]

1)No bats were found or sold at Huanan Seafood Wholesale Market, despite the fact that a variety of non-aquatic creatures, including mammals, were for sale;

(2) The relatively long branch (sequence identity of less than 90%) of SARS-CoV-2 and its close relatives, bat-SL-CoVZC45 and bat-SL-CoVZXC21, indicates that those viruses are not SARS-CoV-2's direct ancestors; and

(3) Other species have served as the intermediate host for other coronaviruses, such as SARS-CoV and MERS-CoV, for which the bat is the natural reservoir (civets and probably camels, respectively). However, bats can spread diseases to people without always requiring a host in between. In Bangladesh, for instance, bats that shed into raw date palm sap are the source of the Nipah virus. [77]

7. MODES OF TRANSMISSION OF CORONAVIRUS (SARS COV-2)

The WHO states that contact routes and respiratory droplets are the two main ways that SARS-CoV-2 is spread based on available data. When a person is within one meter of someone who is coughing or sneezing and is exposed to infectious respiratory droplets, droplet transmission happens through direct touch[78]. The person is at risk of having their mouth, nose, eyes, and other mucous membranes exposed to the droplets if they are within this distance. Indirect contact through fomites on surfaces in the immediate vicinity of the infected individual can also result in transmission[79]. When aerosol-generating operations such as endotracheal intubation, cardiac resuscitation, nebulized treatment administration, and others are carried out, airborne transmission may be conceivable.[80]. During the pre-symptomatic

incubation phase, the virus may spread. More than half of the residents with positive test results for SARS-CoV-2-2 infections were pre-symptomatic, according to a study conducted in a nursing home, and they most likely helped spread the virus.[81]According to certain research, asymptomatic transmission—that is, transmission in patients who never exhibit symptoms—can also happen.[82,83]. For SARS-CoV-2 infection in the early phases of the pandemic in China, the basic reproductive number (R0), which is the projected average number of subsequent infectious cases that one infectious case can generate, was estimated to be between 2.2 and 2.7 in terms of infectivity. This indicates that 2.2–2.7 persons can contract SARS-CoV-2 from a single infected individual.[9] [6].

As the epidemic progresses, particularly when improved control methods are implemented, this number could alter.[9]. When several independent investigations were critically compared, the R0 for SARS-CoV was calculated to be approximately 3.[83].

However, because infected patients were successfully isolated, the SARS-CoV outbreak was more controlled than the current pandemic.[9]In South Korea and Saudi Arabia, the estimated R0 for MERS-CoV ranged from 2 to 5. [84]

8. ETIOLOGY

The World Health Organization (WHO) acknowledged on January 9, 2020, that SARS-CoV-2 was the virus that caused COVID-19 (the virus was then known as 2019-nCoV).[85,86]. Together with the original severe acute respiratory syndrome coronavirus (SARS-CoV-1), which causes SARS, it is one of only two strains of the SARS-CoV species known to cause illness in humans.It belongs to one of the genera of the Coronaviridae family of viruses, the Beta coronaviruses. Humans, mammals, and birds all harbor coronaviruses, which are enclosed single-stranded RNA viruses. Intestinal, lung, hepatic, and central nervous system disorders are caused by these viruses.SARS-CoV-2 is a zoonotic infection, like many others that affect humans. The virus's most likely ultimate origin is a bat coronavirus, which is the closest animal coronavirus by genomic sequence. [33,87,88]. Snakes are another way that the sickness can spread.[18]

9. PRECLINICAL STUDIES

With limits in comprehending pathogenesis, antigenic drift, and virus evolution in this system, cell lines and/or ganoids provide a quick approach for researching the interactions and infection processes of the virus. Therefore, the benefit of using animal models is that they allow researchers to examine virus replication in relation to an organism's physiological symptoms.[89]

Even though FDA restrictions allow for time savings, animal models will be crucial to preclinical research on SARS-CoV-2 vaccines and antiviral medications. SARS-CoV-2 can infect animal models of nonhuman primates, including as African green monkeys, rhesus monkeys, and cynomolgus monkeys, resulting in severe lesions and histological alterations in critical organs. The African green monkey exhibits more respiratory-related symptoms, while the rhesus monkey is more sensitive.[90,91]. The ACE2 receptor in common marmosets, Syrian hamsters, and rhesus macaques is remarkably comparable, reaching 100% in rhesus macaques.[90]. When it comes to SARS-CoV-2 spike proteins, the hamster ACE2 has the strongest affinity. Apoptosis occurs later in the infection process, although diffuse alveolar damage occurs early due to the animal's increased viral load. Due to variations in just two ACE2 amino acids, ferrets are more vulnerable to the virus than cats.[92]. Ferrets are an animal model that could be used to assess the effectiveness of vaccines since the virus affects their upper respiratory tract.[93]. Mice are good models for preclinical research because of their

availability and tiny size. The ACE2 receptor in mice is less like that of human ACE2 and has a lower binding affinity for the spike protein of SARS-CoV-2 viruses.

Thus, in order to investigate the virus's pathogenesis and transmission, as well as to assess antiviral medications and vaccine advancements, mouse-adapted SARS-CoV-2 strains must be created in order to generate mild to severe illnesses that are appropriate for research. [94]

10. CLINICAL DATA (Signs and symptoms)

Acute respiratory distress syndrome, multiple organ dysfunction, and asymptomatic condition are only a few of the clinical manifestations of COVID-19.[95] For RT-PCR, a number of collection routes have been introduced, including urine, feces, oropharyngeal swab specimens, and pharyngeal swab specimens.[96,97]. Compared to nasopharyngeal swabs and sputum specimens, fecal and urine collection is simpler, and the number and quality of the samples can be easily ascertained, which improves the diagnosis of patients who do not exhibit any symptoms.[33]. The typical symptoms of COVID-19 include cough, asthenia, dyspnea, and fever (>37.8OC).[98,99]. but Positive stool test results were not associated with gastrointestinal problems or the severity of the lung infection in patients. [97] and there are some persons who don't exhibit any symptoms.[98].

It has been documented that both younger and older patients have myocardial, hepatic, renal, and altered mental condition.[100] There have also been some reports of non-persistent coughing, hoarse viral voice, nausea and vomiting, shortness of breath, nasal discharge or congestion, headache, wheezing, muscle aches, diarrhea, and loss of taste and smell.[99]. The primary indicators of the disease's beginning in youngsters are headache, vomiting, and abdominal pain.[101,102]. A regular summary of corona virus symptoms demonstrates how symptoms worsen over time in normal patients and how COVID-19 progresses from one severe illness to another.

Day 1: The patient has a fever, exhaustion, muscle soreness, and a dry cough on the first day of the symptoms. A few days prior to the onset of symptoms, a small percentage of individuals may feel nausea and diarrhea.

Day 5: Patients who are elderly or have a pre-existing medical condition may experience breathing difficulties.

Day 7: These are the patient symptoms that result in hospitalization, according to a study from Wuhan University.

Day 8: According to the Chinese CDC, 15% of patients experience acute respiratory distress syndrome (ARDS) on day eight, which is a disease in which fluid builds up in the lungs and is typically fatal. This typically occurs under extreme situations.

Day 10: When symptoms intensify due to the disease's progression, the patient is sent to the intensive care unit. More stomach pain and appetite loss are likely to be experienced by those with less severe symptoms. Only a tiny percentage perishes. The mortality rate at the moment is about 2%.

Day 17: Typically, patients who recover are released from the hospital after two and a half weeks. Finding the signs in the early stages of the infection is challenging, though. Usually, this appears after five to six days. [103]

According to a study, the PCR test came back negative in several patients whose CT scans proved they had COVID-19.[104] However, some COVID-19-positive patients do not exhibit any of the aforementioned symptoms, and the emergence of new symptoms complicates the diagnosis.[105]

10.1 Abdominal symptoms

Without the typical symptoms of COVID-19, a 55-year-old man was admitted to the hospital with a left iliac fossa stomach discomfort; a CT scan revealed no notable respiratory system abnormalities. In a different instance, an 84-year-old man was sent to the hospital due to mild diarrhea without vomiting, nausea, or stomach pain, as well as a 6-day temperature of 38°C. The COVID-19 infection is definitely confirmed by a chest CT scan that showed many ground-glass and crazy-paving pulmonary opacities with multifocal, primarily peripheral, bilateral, and posterior distribution, primarily in the lower lobes.[106]

10.2 Hypertension

Even though hypertension is present in 30% of hospitalized COVID-19 patients, the prevalence of hypertension in the age-matched healthy population is thought to be within the same range[107]. Thus, these results do not support the theory that hypertension (and associated treatment with ACE2 inhibitors/ARB) increases the risk of severe COVID-19 infection. In individuals with SARS-CoV-2, it is advised to avoid starting a new angiotensin receptor blocker (ARB) therapy or increasing the dosage of existing ARB medications.[108,109].

10.3 Renal dysfunction

As putative SARS-CoV-2 host cells, podocytes and proximal convoluted tubules exhibit significant ACE2 and TMPRSS gene co-expression. In people with COVID-19, severe renal dysfunction is one of the deadly consequences. According to pathophysiological studies, this virus-related consequence may have cytopathic effects.[110,111]According to reports, between 0.5 and 19% of COVID-19 patients experience acute kidney injury. In COVID-19 investigations, contrast-enhanced imaging (CT and MRI) should be utilized more cautiously since patients are more susceptible to contrast-induced nephropathy when their renal function is compromised. [112,113]

10.4 Diabetes

Data from published studies indicate that patients with COVID-19 have a higher than average incidence of diabetes mellitus (DM).[44,114–121]. Diabetes is thought to be a risk factor in and of itself for more intensive care unit admissions, ventilator requirements, and ultimately death. [122,123] . It can be argued that individuals with diabetes have a markedly increased risk of contracting COVID-19 and SARS-CoV-2. It's possible that DM patients' increased ACE2 expression increases their susceptibility to these infections.[124].

Additionally, comparatively elevated ACE2 expression in the pancreatic islets may be a factor in COVID-19 patients' hyperglycemia.[125]. A girl with no clinical signs was admitted to the hospital. The urine test came back positive for COVID-19, but the throat swab came back negative by RT-PCR. The throat swab tested positive following antiviral and symptomatic supportive therapies. Both tests came back negative in the second and third weeks, but a month later the patient was feeling better and the throat swab RT-PCR came out negative.[95].

10.5 Cancer

Findings from a study on cancer patients suggested that they may be more prone to infection than people without the disease. The COVID-19 death rate was higher among cancer patients with poorer prognoses for women and those who were older[126]. Combining antiviral medications with hydroxychloroquine (HCQ) appears to be more effective than using HCQ alone. [127]. In another study, Chinese cancer patients experienced severe clinical outcomes as a result of the infection. [128]. Additionally, 10.7% of cancer patients with a virus exhibited symptoms, according to the findings.[129,130].

10.6 Hematological symptoms

According to pathological research on the pathophysiology of SARS-CoV-2, the COVID-19 illness was actually hypersensitivity pneumonitis rather than viral pneumonia. [131] High numbers of cytokines are released into the circulation system by SARS-CoV-2, which triggers a cytokine storm (hyperactive immune response) and causes systemic problems in several organs. When pro-inflammatory cytokines are overproduced and the patient's blood oxygenation capacity is reduced, SARS-CoV-2 pneumonia can result in multi-organ failure. Septic shock, difficult-to-correct metabolic acidosis, and coagulation failure are further signs of severe cases.[132–137].

10.7 Autoimmune diseases

Anti-SARS-CoV-2 IgG and IgM antibodies were not found in serum samples from patients with autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome. This suggests that autoantibodies and SARS-CoV-2 antibodies do not cross-react. [138,139].

10.8 Cardiac manifestation

One transmembrane aminopeptidase that SARS-CoV-2 targets is called ACE1. It is strongly expressed in the heart and is linked to the onset of hypertension. Therefore, the likelihood of myocarditis or cardiovascular injury is also thought to be a sign of COVID-19. Additionally, five confirmed SARS-CoV-2 individuals with extensive cardiac damage due to infection were documented in one clinical investigation[140]. Elevated levels of biochemical markers, such as cardiac creatine kinase, troponin I, lactate dehydrogenase, and α-hydroxybutyrate dehydrogenase, are typically indicative of myocardial damage. [113,141,142].

SARS-CoV-2 When a patient has pneumonia, their blood's oxygenation capacity is reduced and pro-inflammatory cytokines are overproduced, which can lead to multiorgan failure. Septic shock, difficult-to-correct metabolic acidosis, and coagulation failure are further signs of severe cases.[133–137].

10.9 Neurological discoveries

The coronavirus family can enter the central nervous system (CNS) by the circulation or neuronal retrograde pathway, causing meningitis or encephalitis with associated mortality and morbidity. Acute viral encephalitis can impact body temperament, mental status, abnormal motor movement, irregular behavior/speech, and focal neurological irregularities like flaccid paralysis, hemiparesis, paresthesia, or seizures, but it can also go undetected due to the absence of symptoms.[143].

The CNS can be attacked by SARSCoV-2 through the circulation or the cribriform plate of the ethmoid bone. Additionally, it can harm nerve tissues by interacting with ACE2 receptors. Hyposmia and anosmia are among the other problems that could result from COVID-19 brain connection through the cribriform plate.[144–146].

11. COVID-19 and pregnancy

According to recent research, the primary clinical indications of COVID-19 infection in pregnant women are fever and cough, and these symptoms are identical to those of individuals who are not pregnant. Additionally, it has been demonstrated that pregnant women are more vulnerable to COVID-19 and its complications, and they may even get quite sick.[147] Although there isn't enough proof to support vertical transmission, it's still possible for COVID-19 or SARS infections to spread from mother to kid.[148–152].

11.1 Classification Of Covid-19 Patients

Table 1. Four distinct categories are used to classify COVID-19 patients:

Asymptomatic	COVID nucleic acid test positive. Without any clinical symptoms or signs and the chest imaging is normal
Mild	Symptoms of acute upper respiratory tract infection (fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing) or digestive symptoms (nausea, vomiting, abdominal pain, diarrhoea)
Moderate	Pneumonia (frequent fever, cough) with no obvious hypoxemia, chest CT with lesions.
Severe	Pneumonia with hypoxemia (SpO2 < 92%)
Critical	Acute respiratory distress syndrome (ARDS), may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury[153]

11.2 Pathogenesis Of Covid-19

Patients with COVID-19 infections, which target the respiratory system and cause severe pneumonia, exhibit ground-glass opacities and rapid heart damage.[154]. Additionally, these patients had significantly elevated blood levels of cytokines and chemokines. ACE2 expression in cells is downregulated when coronavirus spike proteins bind to them. Therefore, angiotensin II can be converted to the vasodilator heptapeptide angiotensin 1–7 with less ACE2.[155,156]. Severe lung damage and increased hypertension may result from this. When the cell is under stress, the SARS-CoV-2 S protein can identify and attach to the GRP78 SBDβ, allowing the virus to enter.[157]. Consequently, tumor tissues, inflammatory tissues, and pathogen-infected cells all have elevated levels of CD147 expression.[158]. In cells, SARS-CoV-2 showed enhanced infectivity when TMPRSS2 was present.[73]. A possible cleavage site for furan proteases is present in the spike glycoprotein.[9,43,159] Because furin is highly expressed in respiratory tract cells, SARS-CoV-2 is more contagious. The pathophysiology of coronavirus has been thoroughly examined and generally framed in light of the four potential entrance points: ACE2 receptors, Furin-mediated, GRP78-mediated, and CD147 (Basigin-mediated).

11.3 Risk Factors

Adult male patients, whose median age is between 34 and 59 years, are the most likely to have SARS-CoV-2 infection.[82,114,115,160]. Additionally, those with long-term comorbid conditions like diabetes, cardiovascular, and cerebrovascular illnesses are more susceptible to contracting SARS-CoV-2.[95]. Adults over 60 and those with certain underlying disorders, such as diabetes and cardiovascular and cerebrovascular diseases, account for the largest percentage of severe cases.[82,115] Severe symptoms may also be linked to bacterial and fungal confections.[95] Children under the age of 15 have reported less COVID-19 instances.[82,114,115,160].

No incidences of COVID-19 were found in children younger than 15 in a Wuhan study of 425 individuals that was released on January 29.[9,161]However, as of January 2020, 28 pediatric patients had been reported.Although the clinical characteristics of infected pediatric patients vary, the majority have a good prognosis and have experienced moderate symptoms without fever or pneumonia.[162]. Another investigation discovered that a youngster was asymptomatic despite having radiographic ground-glass lung opacities.[163].

In conclusion, children may be less susceptible to infection than adults or, if infected, may exhibit less severe symptoms; as a result, it is possible that their parents will not seek

treatment, which could result in an underestimation of the incidence of COVID-19 in this age group.

11.4 Diagnosis

Through diagnosis, suspicious individuals can determine if they are contaminated or not. Receiving a diagnosis can help them get the care they require and take steps to reduce their risk of spreading the infection to others. Within the recent 14 days, the doctor may also take into account whether the patient traveled to or resided in any places where COVID-19 is still spreading, or if they had close contact with someone who had been diagnosed with the virus. [164]. The China National Health Commission uses one of the following techniques to confirm SARS-CoV-2 infection and identify COVID-19 disease based on clinical manifestations and epidemiological history: High-throughput genome sequencing, the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test, and the serological assessment of antiviral immunoglobulin M (IgM) and G (IgG) antibodies[162,165].

11.5 Diagnosis in Suspected COVID-19 Cases

Instances where any one of the epidemiological history criteria and any two of the clinical symptom criteria are met should be assumed to be SARS-CoV-2 infection.

epidemiological history, which includes instances that occurred within 14 days prior to the onset of the disease and involved travel or residency in adjacent locations with continuous local transmission; cases with a history of contact with respiratory symptoms or feverish people who have previously interacted with patients from the epidemic city or nearby areas; cases connected to a family outbreak or close contact with COVID-19 cases; and newborns born to specific COVID-19 mothers.

Clinical symptoms include: i-) fever (some patients may have a low-grade fever or normal temperature), dry cough, and exhaustion; ii-) lung imaging results; iii-) a normal or decreased leukocyte count, or a decreased number of lymphocytes during the early stages of the COVID-19 infection; iv-) no other infectious agents are detected, fully explaining the symptoms.[20,162].

11.6 Confirmation of COVID-19 Diagnosis

Patients under suspicion who meet any of the following requirements:

- RT-PCR revealed that blood or airway samples were positive for SARS-CoV-2;
- The genetic sequencing of these samples showed a high degree of homology with the SARS-CoV-2 genome.[162,166].

11.7 Laboratory Evaluation (RT-PCR vs. Serology)

These days, RT-PCR is a recognized standard technique for detecting COVID-19 infection. Nevertheless, this lab test is costly and time-consuming.[167]. RT-PCR is used to identify SARS-CoV-2 RNA. Samples from sputum, lower airway secretions, stool, blood, and throat swabs (nasopharyngeal in children) could be examined for SARS-CoV-2 ribonucleic acids. Research has shown that the nasal cavity has larger viral loads than the throat, and there is no difference in the viral burden between people who have symptoms and those who don't. [168].

It is not necessary to collect an oropharyngeal swab, but if you do, you should place it in the same container as the nasopharyngeal swab specimen. In several patients that were later shown to be positive for SARS-CoV-2, negative RT-PCR results from oropharyngeal swabs have been reported, irrespective of CT findings suggestive of viral pneumonia. To check for SARS-CoV-2, the American CDC advises collecting a nasopharyngeal swab. [169]. Sputum

induction is not recommended; sputum should only be collected from cases with productive cough. Recollection and analysis from multiple airway sites are recommended by the WHO if initial testing is negative but there is still uncertainty regarding COVID-19. Because SARS-CoV-2 ribonucleic acid testing in the lab can produce false-negative results, serological examination of virus-specific IgG and IgM antibodies should be used as a diagnostic alternative.[170]. In a case with positive IgG and IgM antibodies against the virus and negative four-time RT-PCR assays for SARS-CoV-2, typical clinical symptoms and radiographic lung abnormalities were shown.[165].

Some SARS-CoV-2 infected cases have been demonstrated to be asymptomatic even when RT-PCR tests are confirmed to be positive, and some cases that recovered from COVID-19 illness may still have positive RT-PCR results at follow-up[171]. Other laboratory tests, such as biochemistry and CBC, are usually nonspecific, and the leukocyte count is often low or normal. There may be lymphopenia; severe disease has been linked to a lymphocyte count less than 1.000. The thrombocyte count is either slightly low or normally normal. Procalcitonin values are usually normal, while CRP and ESR are elevated in the majority of patients. A bacterial co-infection may be indicated by an increased procalcitonin level. Elevated levels of the following parameters may be associated with severe disease: ALT/AST, prothrombin time, creatinine, D-dimer, CPK, LDH, myohemeoglobin, and ferritin.[114,162,172]**.**

Serum procalcitonin levels are typically normal in hospitalized pneumonia cases, but they are more likely to rise in cases requiring intensive care unit (ICU) management. It has been demonstrated that higher D-dimer levels and more severe lymphopenia are associated with death.[95]. Although bilateral infiltrations are typically seen on lung X-rays (CXRs), they can also seem normal in the early stages of the illness. The CT scan of the chest is more precise and sensitive. Infiltrates, ground-glass opacities, and sub-segmental consolidation are typically seen on lung CT scans. Lymphadenopathy and pleural effusion/thickening are less frequent anomalies. Multiple small plaques and interstitial alterations are visible in the lung periphery on thorax CT scans during the early stages of COVID-19 disease. These conditions worsen to bilateral multiple ground-glass opacity and/or infiltrating shadows. In extreme situations, pulmonary consolidation may occur. Pleural effusion is not often seen.[162,173]. In suspected and/or asymptomatic instances with negative RT-PCR, pathologic lung CT imaging has also been used to detect COVID-19; many of these individuals show positive PCR upon repeating the test.[174].

12. Treatments

Despite certain vaccinations and existing medications for the potential treatment of people, there are now, as far as we know, no clear-cut and comprehensive antiviral medications for COVID-19. Researchers and scientists, including those in the biotech and pharmaceutical sectors worldwide, are conducting war-like studies every day to create novel corona virus vaccines and medications.[175,176].

However, the FDA has only approved one treatment for this illness, a medication called remdesivir, and studies indicate that patients only slightly improve from it.[177]. Therefore, remaining at home, cleaning your hands, wearing a face mask, and getting enough sleep are the greatest first-line measures against this illness. We outlined a few possible remedies for this recently discovered virus in our review.

12.1. Supportive Therapy

In essence, treatment is symptomatic and supportive. Ensuring enough isolation to prevent the transmission of other contacted people, cases, and healthcare personnel is the first step. Suspected cases should either self-isolate at home or be isolated in a single room based on their medical circumstances, as advised by the specialists. It is possible to court confirmed patients in the same ward. Immediately admit critical patients to the intensive care unit.

Common tactics include palliative care and bed rest, maintaining water-electrolyte balance and homeostasis, ensuring adequate calorie and water intake, monitoring vital signs and oxygen saturation, keeping the airway clear, and adding oxygen when necessary.[162,178].

12.1.1 Vitamins

Vitamin C helps treat pneumonia and common colds. vitamin C reduces pro-inflammatory cytokine RNA expression in obese people In vitro. Additionally, in HIV-infected patients, the combination of vitamins C and E lowers the viral load and oxidative stress. Additionally, the intracellular type I IFN system, which carries out the antiviral action, can be stimulated by vitamin C.

Vitamin D reducing the cytokine storm, controlling adaptive immunity, and promoting T cell induction, this vitamin lowers the risk of viral infection and mortality. Therefore, maintaining the ideal level of vitamin D in the bloodstream is preferable for those who are at high risk of contracting COVID-19.[179,180].

Vitamin E and A acute effects of vitamin E on the immune system include enhancing the activation of DC, naïve T-lymphocytes, and natural-killer cells as well as preventing the synthesis of pro-inflammatory cytokines like TNF, IL-1, and IL-6. The innate and adaptive immune systems, cytokine generation, differentiation, and other processes can all be regulated by vitamin A and its metabolites.[181].

12.2 Therapeutic agents and inhibitors against COVID-19

Presenting some of the potential and repurposed medications for the treatment of COVID-19 is our goal here.

12.2.1 Antiviral drugs

Figure 3 lists the most significant antiviral medications used to treat the COVID-19 virus; these are covered in more depth below.

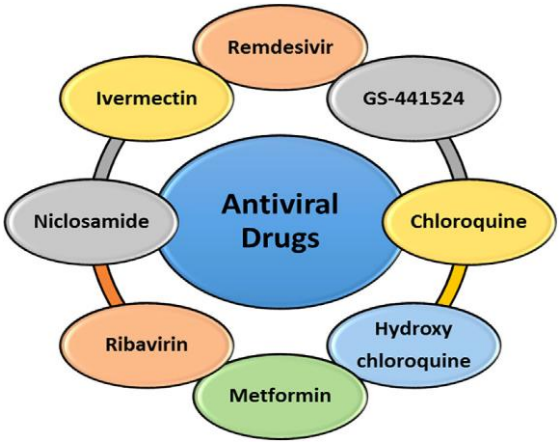


Figure 3. Antiviral Drugs Against Covid-19.

Remdesivir

In 2017, the broad-spectrum antiviral medication Remdesivir (GS-5734) was created. As a monophosphate prodrug, it is a member of the nucleotide analog class. It was utilized to treat the Ebola virus sickness because of its low half maximum effective concentration (EC50) and host polymerase selectivity against the virus. By blocking viral RNA polymerase and

preventing viral exonuclease from proofreading, this medication, which is an adenosine analog, reduces the generation of viral RNA.[182]. Additionally, additional investigation showed strong antiviral efficacy against the SARS-CoV and MERS-CoV viruses, especially human coronavirus 229E. [183–187]

Currently under observation in multisite clinical trials, it is the only medication approved by the FDA to treat SARS-CoV-2. *In vitro* and *in vivo* investigations have shown that GS-5734 possesses antiviral properties against coronaviruses with favorable effectiveness and little harmful side effects.[188–191]. According to one review, emetine and remdesivir work in concert to prevent SARS-CoV-2 multiplication in vitro. [192].

Additionally, it was shown that remdesivir and chloroquine (CQ) were effective in inhibiting COVID-19.[193]. Additionally, Remdesivir has been granted an emergency authorization by the U.S. FDA to speed up SARS-CoV-2 treatment. [194].

GS-441524

Remdesivir's parent nucleoside is the antiviral medication GS-441524. GS-441524 has been shown to have antiviral action against the Marburg virus, the feline infectious peritonitis virus, and the SARS coronavirus (SARS-CoV). This medication has shown positive results in a number of *in-vitro* and *in-vivo* trials against COVID-19 using mouse and nonhuman primate animal models.[195,196]. However, because of its ease of synthesis and in vivo effectiveness in the veterinary setting, GS-441524 was chosen over remdesivir for the treatment of SARS-CoV-2 in a different study based on a more thorough pharmacokinetic rationale. [197].

Chloroquine

An antiviral medication called CQ has long been used to prevent and cure malaria. It has also shown in vitro action against the replication of certain coronaviruses, including SARS-CoV-2.[195,198,199].

This medication's safety and tolerability have already received approval. [200] It was discovered that CQ prevents viruses from entering cells by inhibiting endosomal acidification, proteolytic processing, and glycosylation of host receptors. Additionally, by reducing cytokine production and inhibiting host cell autophagy and lysosomal activity, it modifies immunity.[201,202]As a result, this compound was proposed as a possible medication to treat COVID-19.[203]. However, current clinical data could not demonstrate the effectiveness of this medication (with or without amacrolide) in COVID-19 patients, despite the fact that ventricular arrhythmias were more common and hospital survival was worse.[204,205] The most recent version of the Coronavirus Drug and Treatment Tracker (October 7, 2021) states that this medication is not regarded as promising, indicating that preliminary data indicates that these treatments are ineffective.[206].

Hydroxychloroquine

HCQ is a more effective, safer, and less toxic derivative of CQ that has antiviral and antimalarial properties. Nowadays, alopecia areata, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis, autoimmune disorders, and anti-phospholipid syndrome are all commonly treated with it.[207,208]

Using the same mechanisms of action as CQ, this medication directly prevents viruses from entering cells. Therefore, it has been proposed as an antiviral medication to treat a number of coronaviruses, particularly SARS-CoV-2. [188,189,208,209].

The clinical effectiveness of HCQ in conjunction with azithromycin *in vivo* was documented in early clinical trials.[210,211].

However, additional trials did not support the use of HCQ (with or without a macrolide) in patients hospitalized with COVID-19, and the patients also experienced negative side effects.[212–216].

Azithromycin strengthened the impact of HCQ in lowering the viral load in COVID-19 patients, according to an open-label nonrandomized clinical investigation.[217]. Lastly, when the medication is taken to treat COVID-19, the FDA cautions that it may cause a number of severe negative effects on the heart and other organs. A WHO expert panel strongly recommended against using HCQ in all patients on March 2, noting that the medication was no longer a priority for research. [218]

Metformin

When metformin was first introduced as an anti-influenza drug, one of its acknowledged adverse effects was glucose lowering. This medication may be an HIV infection and has pleiotropic effects. At the molecular level, metformin activates hepatocytes by phosphorylating AMP-activated protein kinase (AMPK)[219]. RBD in the spike protein allows the SARS-CoV-2 to attach to the ACE2 receptor and enter the host cell. Acute lung injury is thought to be caused by ACE2 via autophagy and the AMPK pathway. Therefore, the phosphorylation of ACE2 can modify its conformation and function and limit viral entrance[220]. Regarding this, a retrospective investigation showed that the death rate among COVID-19 patients with diabetes was reduced by metformin treatment.[221]

Ribavirin

For the treatment of COVID-19, ribavirin, an analog of guanosine, is advised due to its antiviral properties. In the case of MERS-CoV, the effectiveness of ribavirin and IFN alfa together in terms of virus removal and patient survival was documented. However, among hospitalized patients with severe or critical conditions, ribavirin treatment did not significantly improve outcomes as compared to the control group. COVID-19[222–224].

Niclosamide

The FDA-approved anthelminthic medication niclosamide exhibits a number of antiviral properties. This drug's effectiveness against ZIKV, HCV, MERS-CoV, and SARS-CoV has been studied. Nicosamide may decrease autophagy, viral replication, and receptor-mediated endocytosis as an antiviral strategy against SARS-CoV-2.[225,226]. It is necessary to assess niclosamide's therapeutic effectiveness against COVID-19.

Ivermectin

The FDA authorised ivermectin, a broad-spectrum antiparasitic. Numerous viruses, including the dengue virus, Zika virus, yellow fever virus, SARS-CoV-2, and others, have been shown to be susceptible to its *in vitro* effectiveness. Nevertheless, this medication has certain adverse effects, including neurotoxicity.[227]. Within 48 hours of adding this COVID-19 inhibitor to Vero-hSLAM cells, the amount of viral RNA had decreased by more than 5000 times. However, extending the duration—up to 72 hours—did not lead to a greater decrease in viral replication. Lastly, a study including 1500 patients revealed that ivermectin had no advantages.[228,229]

12.2.2 Calcineurin inhibitors

Cyclosporine (cyclosporin)

One of the immunosuppressive medications used to prevent organ transplant rejection is cyclosporine, also known as a calcineurin inhibitor. It has been suggested to be used against COVID-19 because it attaches to cyclophilins in cells, which in turn prevents the replication

of other corona viruses. [230,231]. However, additional research should take clinical trials into account.

12.2.3 Cyclophilin inhibitors

Alisporivir

Derived from cyclosporine, alisporivir is a non-immunosuppressive cyclophilin inhibitor. This inhibitor prevents four distinct coronaviruses, including SARS and MERS, from replicating.[232]. It has been suggested as a possible therapy option for COVID-19 since it also inhibits SARS-CoV-2 *in vitro*.[233].

12.2.4 HCV inhibitors

Sofosbuvir

Sofosbuvir is a clinically approved drug against the HCV. The concept that sofosbuvir can efficiently suppress the SARSCoV-2 RdRp is supported by the strong sequence and structural similarities in the RdRp of the HCV and SARS-CoV-2 viruses. Furthermore, because this medication has been used for a long time to treat and eradicate chronic HCV infections in patients, its safety profile is well known. Therefore, sofosbuvir has been proposed as a treatment for SARS-CoV-2.[234,235]

12.2.5 HIV protease inhibitors

Lopinavir/ritonavir (LPV/r)

Another antiretroviral that is a member of the protease inhibitor class is ritonavir (RTV), which increases the plasma half-life of LPV in order to stabilize it. Lopinavir (LPV) is an antiretroviral that inhibits the activity of the protease. The combination of these medications resulted in lopinavir/ritonavir (LPV/r) approved by the U.S. FDA and is used to treat HIV. By blocking the 3-chymotrypsin-like protease (3CLpro), also referred to as major protease (Mpro), it has also been demonstrated to exhibit *in vitro* and *in vivo* effects on other novel coronaviruses, including SARS and MERS.[236–239]. Nevertheless, there was no support for using LPV/r to treat COVID-19.[240–243] The effectiveness of combining LPV-RTV with ribavirin and IFN alfa has been investigated in the context of MERS-CoV. Nevertheless, an LPV/RTV trial study conducted on patients hospitalized with severe COVID-19 revealed no advantages to LPV-RTV treatment over normal care. [244]

Darunavir/cobicistat

Due to their similar mechanisms of action, this combination may be a viable substitute for LPV/RTV. However, this HIV-1 protease inhibitor may not have clinically meaningful anti-SARS-CoV-2 effect, according to a single-center, randomized, open-label trial conducted on mild individuals with confirmed COVID-19. Therefore, additional research is required to examine its function.[245].

Nelfinavir

Another HIV-1 protease inhibitor, nelfinavir, decreases SARS-CoV-2 replication in vitro, making it a viable medication for COVID-19 treatment.[246] Additionally, this medication might prevent SARS-CoV-2 spike-mediated cell fusion. [247]. In Vero E6 cells, one study showed that nelfinavir was highly effective against SARS-CoV-2. However, more research is required as a possible COVID-19 treatment. [248].

12.2.6 Anti-influenza drugs

Favipiravir

Favipiravir is a prodrug of a purine nucleotide and a broad-spectrum antiviral medication[249]. In Japan, it was used to combat novel influenza. This medication seems to work by inhibiting the RNA-dependent RNA polymerase, which stops the spread of viruses.

In preclinical investigations, it demonstrated activity against various RNA viruses and shown good efficacy in treating the influenza and Ebola viruses. It has been suggested that favipiravir be used to treat COVID-19 due to its in vitro efficacy against SARS-CoV-2, which has an EC50 value of 61.88 μm/L in Vero E6 cells, its relatively safe use, and its positive results in early clinical trials. But additional study is required.[250–253]

Arbidol

Another anti-influenza medication is arbidol, which inhibits membrane fusion. For the treatment of influenza A and B infections as well as infections caused by other arboviruses, this medication is licensed in China and Russia. Adults with COVID-19 are prescribed arbidol.[254,255]. One study revealed that COVID-19 treatment with Arbidol monotherapy is superior than LPV/RTV[256]

Oseltamivir

OThe use of oseltamivir against influenza A and influenza B was authorized. This medication targets neuraminidase, which is found on the virus's surface. Clinical trials are being conducted to treat COVID-19 with oseltamivir in conjunction with other medications such favipiravir and CQ.[257]

12.2.7 Antibiotics

Azithromycin

Bronchitis, pneumonia, and *Mycobacterium avium* complex infection are just a few of the bacterial illnesses that can be treated with azithromycin, an antibiotic that is a member of the macrolide class. Through its function as an anisotropic lipophilic weak base, it controlled the pH of endosomes and the trans-Golgi network. In early clinical trials, it has also proven successful against SARS-CoV-2 when paired with HCQ.[258–261]

12.2.8 Monoclonal antibodies

Currently, several mAbs are being investigated as potential COVID-19 treatments.[262] Compared to traditional low molecular-mass medications, monoclonal antibody therapies also offer a number of benefits. Because monoclonal antibodies have high specificities, there is less chance of off-target action and unfavorable patient reactions. Therapeutic mAbs' extended half-life, which permits infrequent dose delivery, provides an additional benefit[263].

MAb therapies can be utilized to reduce hospitalization rates in outpatients at high risk of severe COVID-19 because of their infrequent dosage.[264]. Thus far, it has been demonstrated that monoclonal antibodies used to combat COVID-19 are safe and that serious side effects are uncommon.

However, a variety of immediate or delayed adverse effects are known to occur with therapeutic mAbs. The most often reported side effects in the case of COVID-19 mAbs are those related to injection sites and infusion[265]. Most often, infusion-related responses manifest as fever, chills, flushing, nausea, pruritus, and rashes. Usually, 30 to 60 minutes after the infusion starts, symptoms appear. Reactions brought on by infusion are typically self-limiting. Stopping the infusion and managing the symptoms are the two main components of treatment. Most of the time, the infusion can be resumed when the symptoms have subsided, albeit more slowly.[266]. By taking medication beforehand, increasing the infusion rate gradually, and making sure the patient is hydrated and diurestic, the risk of infusion responses can be reduced.[267]

12.3 Other potential therapies

12.3.1. Alternative drug therapy

However, professionals from Siddha, Ayurveda, homeopathy, Unani, and other fields are working tirelessly to find a potential treatment for COVID-19. Certain groups of people, especially in southern India, employ the siddha method of drinking "kabasura kudineer," a beverage meant to treat respiratory issues.[268,269] In addition, a number of other people incorporate pepper, ginger, lemon, turmeric, and other foods that enhance immunity into their everyday diet.

12.3.2 Chinese folk medicine

Therapies employed in earlier epidemics can help reduce the sickness caused by SARS-CoV-2 and serve as a foundation for novel treatments. This is because certain Chinese folk medicine has been shown to have antiviral effectiveness based on prior coronavirus outbreaks. Because helicase is essential for viral replication, it can be regarded as a potential therapeutic target. Baicalein, scutellarein, and myricetin are appropriate compounds that can prevent SARS-CoV-1 nsP13 from hydrolyzing. Additionally, it was shown that the amentoflavone and bi-flavonoid were efficient against MERS-CoV helicasens P13.[270].

Triterpene glycyrrhizin (GL) has a number of biological uses and may be used as an antiviral medication to treat COVID-19. This medication is thought to have some antiviral properties, inhibiting the virus's ability to connect to the ACE2 receptor, downregulating the expression of proinflammatory cytokines, and causing the body to produce more IFN.[271]. GL frequently appears in Chinese traditional medicine.[272].

12.3.3 Aptamer-based therapy

Scientists have been interested in aptamer as an antibiotic substitute in recent years. These oligonucleotides, which include RNA, ssDNA, and peptide molecules, have a unique three-dimensional structure and bind to their targets with great sensitivity and affinity. Aptamers made for influenza viruses can be studied for SARS-CoV-2 therapy because coronaviruses and orthomyxoviridae (influenza viruses) are RNA viruses with a similar mode of infection[273]. A22 is a DNA-type aptamer that protects against H5N1 influenza. In BALB/c mice, this aptamer decreased the viral load by as much as 90%. C7-35M, which protects against influenza H9N2, is another illustration of a DNA-type aptamer. Viral infections were suppressed by this aptamer in a dose-dependent manner.[274]

12.3.4 Small-interfering RNA

One type of double-stranded, non-coding RNA molecule is called small-interfering RNA (siRNA). This molecule is 20–25 base pairs long. It has been used thus far for the treatment of genetic diseases, viruses, and cancer since it can control the expression of genes. The use of siRNA shown efficacious in the SARS and MERS cases. Consequently, this strategy might be helpful for treating COVID-19.[275]. However, this strategy is limited by the need to create an efficient delivery system.

12.3.5 Mesenchymal stem cell therapy

Type 2 diabetes, autoimmune illnesses, spinal cord injuries, and a few other conditions are all commonly treated using mesenchymal stem cell (MSC) therapy. It has also been proposed recently to employ MSCs in the clinical management of H5N1 virus infections. MSCs prevent pulmonary fibrosis and treat lung dysfunction by protecting alveolar epithelial cells through their immunomodulatory action.[276].

12.3.6 Bacillus Calmette–Guerin vaccination

According to some reports, the Bacillus Calmette–Guerin (BCG) vaccine provides extensive defense against respiratory infections. It was found that nations without universal BCG immunization programs, such the United States, Italy, and the Netherlands, have been

more negatively impacted than those with established and universal BCG vaccination programs. [277].

12.3.7. Immunotherapy

The transfusion of plasma from patients who have recovered from a SARS-CoV-2 infection to infected patients or patients at high risk of infection is known as convalescent plasma (CP) therapy, and it has been used with moderate success during the COVID-19 pandemic. Passive immunization, particularly with CP therapy, has shown potential as a treatment during past corona virus outbreaks. As a result, the therapy has been proposed as a possible therapeutic strategy for COVID-19 patients.[278].

Even though the U.S. FDA approved the treatment through an Emergency Use Authorization (EUA), numerous follow-up studies have either showed no discernible benefits after the drug was administered or have only demonstrated improvements in patients who were extremely or dangerously ill.[279–281]

12.4 Vaccine strategy

It is difficult to design a vaccination against SARS-CoV-2. For instance, RNA viruses have a high rate of mutation, which could cause the produced vaccine to lose its effectiveness quickly. A perfect vaccine should also promote long-lasting protection, herd immunity, and a reduction in transmission. Approximately 67% of the population would need to be vaccinated against SARSCoV-2 in order to achieve herd immunity. Among the primary approaches for vaccine design are protein subunits, RNA, DNA, non-replicating and replicating vectors, inactivated virus, and attenuated virus. [282]

The WHO stated that 276 vaccinations were under development, 109 were undergoing clinical testing, and 24 were being used as of early April 2022.[283]. We divided these vaccination tactics into two main platforms for easier comprehension:

- Classic vaccine platforms and
- Next-generation vaccine platforms.

12.4.1 Classic vaccine platforms

We can include vaccinations based on viruses and proteins in this group. Smallpox and other illnesses were successfully eradicated due to these traditional vaccination systems. However, it takes a lot of time to use these platforms, thus the creation of a vaccine for this pandemic needs to happen fast.[284]. One type of vaccine based on viruses is a whole-inactivated virus. The present influenza is combated with this tactic. This type of vaccine is simple to make and safe. Moreover, it elicited powerful serum neutralizing antibodies. However, they may cause sickness in extremely immune-suppressed persons. BBIBP-CorV (Chinese firm Sinopharm), CoronaVac (Chinese company Sinovac), and Covaxin (made by Bharat Biotech) employed this tactic in the category of recognized or approved vaccines. China and India are responsible for the development of the three vaccines indicated (Table 4). The BBIBP-CorV vaccine has been approved in China, Bahrain, the United Arab Emirates, and other countries, and its efficacy has been reported to be 78.1%. CoronaVac's effectiveness ranges from 50.65% in a Brazil trial to 83.5% in a Turkey trial. China and other nations have approved the injection of this vaccination. The effectiveness of Covaxin was recorded 77.8% and it was the first COVID-19 vaccine produced in India to gain emergency approval[285].

Another vaccine that was created using this approach is the BIV1-CovIran vaccine. Preclinical study has highlighted the BIV1-CovIran vaccine as a viable option to generate a strong and effective immune response that may be a promising and practicable vaccination to protect against SARS-CoV-2 infection[286]. This vaccine's immunogenicity has been reported

to be around 90%, and Iran has authorized its emergency use. There is also the classic platform of a live-attenuated virus. The measles, mumps, rubella, and polio vaccinations are examples of live-attenuated virus vaccines. The creation of this sort of vaccine may be rapid. Reversion by recombination or mutation is feasible, though. The M-protein, or membrane protein, the E-protein, or envelope protein, and the S-protein, or spike protein, are the three surface-exposed proteins of SARS-CoV-2. The S-protein stands out among them as a potential vaccine candidate. In addition to the full-length S-protein, potential vaccine candidates include the S1 domain, RBD, and NTD. Cross-protection can be achieved by developing a subunit vaccine based on the S-protein, which is conserved in both SARS and MERS. The hepatitis B, tetanus, pertussis, and diphtheria vaccines were developed using this approach. This type of vaccine stimulates both humoral and cellular immunity and is safe. But they might be too costly.[287]. The only vaccines based on proteins that have been permitted or approved in the United States and Russia, respectively, are Novavax and EpiVacCorona (Vector Institute). It is unknown if the EpiVacCorona vaccination is effective (Table 4).[288]

12.4.2 Next-generation vaccine platforms

Sequence information is used to design these vaccinations. This group includes vaccinations based on nucleic acids and viral vectors. The generation of endogenous antigens and the promotion of humoral and cellular immune responses make the viral vector a potentially effective vaccine design approach.[289].

The Russian-designed nonreplicating viral vector (Ad5 and Ad26) is called Sputnik V (Gamaleya Research Institute). This vaccination has an effectiveness of roughly 91.6% and is one of the authorized or permitted vaccines. (Table 4). The British-Swedish corporation AstraZeneca produces the vaccine Vaxzevria, which is based on the chimpanzee adenovirus, or ChAdOx1. The vaccination is 100% effective against severe or critical COVID-19 and 74% effective against symptomatic COVID-19. Ad5 was utilized by Convidecia (a Chinese company CanSino Biologics) to create a COVID-19 vaccine that had an efficacy of roughly 65.28%. Ad26.COV2. The third coronavirus vaccine that is offered in the US is S (Johnson & Johnson's vaccine). This vaccine's effectiveness is roughly 72% in the US, 68% in Brazil, and 64% in South Africa.[290].

DNA and RNA vaccination methods are safe and easy to create and manufacture. Nevertheless, the DNA vaccination approach has many drawbacks, such as decreased toxicity and immune response. However, RNA vaccines are not stable in physical environments.[291] Pfizer-BioNTech is a successful vaccine developer that employs an mRNA-based vaccine method in spite of all the aforementioned drawbacks. With a 91% effectiveness rate, this vaccine is currently administered in the US, UK, Bahrain, Canada, Mexico, and other nations. (Table 2). The second vaccination that employed this tactic was Spikevax, also known as mRNA-1273 (Boston-based Company Moderna). About 93.2% of people who receive this vaccine avoid getting COVID-19, and 98.2% avoid getting severe sickness. [292]

Table 2. Different authorized or approved vaccine strategies against SARS-CoV-2.

No	Brand	Type	Developers	Origin Country	Approval
1	BNT162b2	mRNA-based vaccine	Fosun Pharma, Pfizer, and BioNTech	Multinational	Approved in the United States and other countries Emergency use in E.U. and other countries.

2	mRNA-1273 or Spikevax	mRNA-based vaccine	Moderna	The United States	Approved in Switzerland Emergency use in the United States, E.U., other countries
3	Sputnik V	Ad26, Ad5	Gamaleya Research Institute	Russia	Emergency use in Russia and other countries
4	Vaxzevia	ChAdOx1	Oxford-AstraZeneca	British-Swedish	Approved in Brazil Emergency use in the UK, E.U., and other countries
5	Ad26.COV2.S	Ad26	Johnson & Johnson	The United States	Emergency use in the United States, E.U., and other countries
6	BBIBP-CorV	Inactivated	Sinopharm-Wuhan	China	Approved in China, UAE, and Bahrain Emergency use in other countries
7	CoronaVac	Inactivated	Sinovac	China	Approved in China Emergency use in other countries
8	Covaxin	Inactivated	Bharat Biotech	India	Emergency use in India and other countries
9	9 BIV1-CovIran	Inactivated	Amirabad Virology Lab, Shifa Pharmed Industrial Group	Iran	Emergency use in Iran

Many more vaccines are in the third stage of clinical trials, in addition to those that have been fully authorized or licensed for use in emergencies (mentioned above). Table 3 provides a summary of these vaccinations. [293]

Table 3. The list of vaccine candidates at phase 3 clinical trials

No	Brand	Type	Developers	Origin Country	Approval
1	Convidecia	Ads	CanSino	China	Approved in China Emergency use in other countries
2	EpiVacCorona and Aurora-CoV	Protein	Vector Institute	Russia	Approved in Turkmenistan Early use in Russia
3	NVX-CoV2373	Protein	Novavax	The United States	----------
4	Sinopharm	Inactivated	Sinopharm-Wuhan	China	Approved in China Limited use in UAE

12.5 Prevention & Precaution of COVID-19

Prevention is essential for this virus because there are currently no recognized treatments for it. This virus's non-specific characteristics, infectivity even before symptoms appear during the incubation period, transmission from asymptomatic individuals, lengthy incubation period, tropism for mucosal surfaces like the conjunctiva, prolonged illness duration, and transmission even after clinical recovery are some of its characteristics that make prevention challenging. [294]. In order to prevent secondary infections, stop human-to-human transmission to close contacts and healthcare professionals, and stop further international spread, people should stay informed about the most recent information on the COVID-19 outbreak provided by the WHO and follow the instructions of their local health authority. The majority of infected persons recover from a mild illness, but some people may have a more

severe infection. Take the following actions to safeguard others and maintain your health: [295,296].

Take steps to protect yourself

- After visiting a public place, blowing your nose, sneezing, or coughing, wash your hands thoroughly and frequently for at least 20 seconds with soap and water, or use an alcohol-based hand rub (a hand sanitizer that contains at least 60% alcohol). Cover your hands completely and rub them together until they do not dry.
- Avoid touching your mouth, nose, or eyes with unwashed hands because doing so can allow the virus to enter your body and make you ill. Hands can take up viruses via their frequent contact with various surfaces.
- Stay away from people who are coughing or sneezing and practice social distancing by keeping a minimum of one meter or three feet between you and them. Small droplets that may contain the COVID-19 virus are released from the lips or nose of infected people when they cough or sneeze. These droplets can be inhaled by the individual.[297,298].
- Stay away from big events and crowds.

Take steps to protect others

- If you are feeling ill, stay at home unless you plan to visit a doctor.
- Consult your doctor online and get medical help if you develop a cough, fever, or trouble breathing.
- Avoid using public transit if you're ill.
- Use tissue paper to cover your mouth and nose whenever you cough or sneeze.
- Immediately wash your hands with antiseptic soap and water and dispose off used tissues in the trash.

When you are with other people (e.g., sharing a room or car), wear a facemask and, if at all feasible, remain segregated in a different room from family and pets. When the people who are taking care of you enter your room, they should wear a facemask (facemasks may be scarce and should be reserved for caregivers). If you are unable to wear one (for example, because it is making it difficult for you to breathe) then you should cover your coughs and sneezes.

- For a while, remain at home and do as your doctor directs.
- Avoid sharing dishes, glasses, blankets, and other household goods if you're ill.
- Use toilets and a restroom away from the family if at all possible.
- Before disinfecting, clean any filthy surfaces with water and detergent or antiseptic soap.
- Every day, sanitize surfaces that are often touched. Desks, telephones, keyboards, sinks, faucets, tables, doorknobs, light switches, countertops, and handles are all included in this.[299,300].
- Determine and Separate Possible Cases
- To reduce the risk of infection spreading to other patients and medical personnel, identify possible cases as soon as feasible before beginning clinical care and isolate suspected individuals from those with confirmed COVID-19 cases.
- Avoid coming into direct touch with bodily secretions, such as respiratory secretions, during physical examinations or exposure.

For example, Move potentially contagious individuals to isolation rooms, and shut the doors. Keep a safe distance between employees, clients, and other guests in a workplace, especially from the locations of people who could spread illness.

- Pharmacies should set aside and prepare an appropriate area in case a patient or group of patients has to be isolated.
- COVID-19 is unlikely to be present in the majority of patients who visit community pharmacies. Pharmacies should follow their best practices and routinely manage the risks of cross-infection to staff and other patients if they have coughs, colds, or flu-like symptoms that are not related to COVID-19, travel, or contact history.
- Limit the amount of people who can access isolation locations, such as a patient's room if COVID-19 has been suspected or confirmed.
- Use extra engineering and administrative controls to keep employees away from close contact with the infected individual for safe work practices.[301].

13. Conclusions

It is obvious that the current COVID-19 outbreak is a global public health issue. The world's greatest challenge is SARS-CoV-2. The coronavirus is rapidly spreading throughout most countries, including America, Italy, Spain, India, and others. Our understanding of the pathogen, how it infects cells and produces disease, and the clinical features of the disease has rapidly advancedCOVID-19 still has a lot of unanswered potential questions. As it is obvious via our literature study, there are cases where patients confirmed with COVID-19 infection show no chest CT abnormalities, contrasting with subclinical infection presenting with positive imaging findings on CT. It is necessary to ascertain the clinical effects of using chest CT to screen asymptomatic patients.

The existence of any potential advantage on clinical outcomes must be more thoroughly examined in light of the known financial costs and ionizing radiation exposure related to CT scanning. There was discussion of the several molecular techniques used in the diagnosis of COVID-19, including those based on proteins and nucleic acids, as well as POC and X-rays. Countries worldwide should focus more on disease surveillance systems and expand their readiness and response activities, including the creation of quick response teams and the expansion of the national laboratory system, in light of the illness's rapid spread. None of the medications that were tested against COVID-19 were able to stop the virus invasion. Therefore, aside from prospective vaccines that lower the maximum infection rate in people, no curative medications have been produced as of yet.

Meanwhile, researchers worldwide are striving to create COVID-19 vaccines and viable treatments. In order to fully comprehend human SARS-CoV-2 infections and the zoonotic transmission of CoVs through clinical symptoms, more research is required. However, governments are being forced to reopen their economies due to the pandemic's devastating economic effects, which poses a problem for public health. At the moment, effective public health policies and social distancing are the options for reducing viral transmission.

Author Contributions

Conceptualization, Vivek Kumar and Monika Kumari; methodology, Vivek Kumar; formal analysis, Vivek Kumar and Monika Kumari; investigation, Vivek Kumar, Monika Kumari, and Geetanjali Mehara; data curation, Monika Kumari and Geetanjali Mehara; writing—original draft preparation, Vivek Kumar; writing—review and editing, Monika Kumari and

Geetanjali Mehara; visualization, Vivek Kumar and Geetanjali Mehara; validation, Monika Kumari and Geetanjali Mehara; supervision, Vivek Kumar; project administration, Vivek Kumar; resources, Vivek Kumar; literature acquisition, Monika Kumari and Geetanjali Mehara. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable.

Funding

This research received no external funding.

Acknowledgments

This section should recognize any **assistance, support, or contributions** received that **do not.**

Conflicts of Interest

No **conflicts of interest**

Abbreviations

Abbreviation	Definition
ACE2	Angiotensin-Converting Enzyme 2
ADE	Antibody-Dependent Enhancement
ALT	Alanine Aminotransferase
AMPK	AMP-Activated Protein Kinase
ARB	Angiotensin Receptor Blocker
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
CBC	Complete Blood Count
CCDC	Chinese Center for Disease Control and Prevention
CNS	Central Nervous System
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CQ	Chloroquine
CRP	C-Reactive Protein
CT	Computed Tomography
CXR	Chest X-Ray
DC	Dendritic Cell
DM	Diabetes Mellitus
EC50	Half-Maximal Effective Concentration
ESR	Erythrocyte Sedimentation Rate

FDA	Food and Drug Administration
GL	Glycyrrhizin
GRP78	Glucose-Regulated Protein 78
HCoV	Human Coronavirus
HCQ	Hydroxychloroquine
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heptad Repeat
ICU	Intensive Care Unit
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
LDH	Lactate Dehydrogenase
LPV/r	Lopinavir/Ritonavir
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
Mpro	Main Protease
mAbs	Monoclonal Antibodies
MRI	Magnetic Resonance Imaging
NCIP	Novel Coronavirus-Infected Pneumonia
PCR	Polymerase Chain Reaction
RBD	Receptor Binding Domain
RdRp	RNA-Dependent RNA Polymerase
RNA	Ribonucleic Acid
R0	Basic Reproduction Number
rRT-PCR	Real-Time Reverse Transcription Polymerase Chain Reaction
RT-PCR	Reverse Transcription Polymerase Chain Reaction
RTV	Ritonavir
SARS	Severe Acute Respiratory Syndrome
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBD	Substrate Binding Domain
SpO_2	Peripheral Oxygen Saturation
ssDNA	Single-Stranded Deoxyribonucleic Acid
ssRNA	Single-Stranded Ribonucleic Acid
TMPRSS2	Transmembrane Protease Serine 2
TNF	Tumor Necrosis Factor
WHO	World Health Organization
ZIKV	Zika Virus

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