COVID-19: The Unprecedented Malady- A Holistic Review

Viney Chawla¹,²*, and Pooja A. Chawla²,

¹Department of Pharmaceutics, University Institute of Pharmaceutical Sciences and Research, Baba Farid University of Health Sciences, Faridkot, Punjab, India; ²Department of Pharmaceutical Chemistry, ISF College of Pharmacy, GT Road, Moga, Punjab, India

Abstract: Background: Coronavirus disease (COVID-19) is spreading rapidly at an unprecedented scale across continents and has emerged as the single biggest risk the world has faced in modern times. Some scientists are comparing it to Spanish flu that created havoc around a century ago. The fear of death by COVID-19 looms large in the world today. The disease has reached devastating proportions since its first reports in December 2019. Doctors are having a difficult time dealing with this challenge and the microbiologists are having sleepless nights to bring about an effective vaccine for this disease.

Methods: A number of research and review articles have been exhaustively reviewed. The collected data has been meticulously analyzed and documented.

Conclusion: This paper reviews the different types of coronaviruses, the structure of SARS-CoV-2 responsible for COVID-19, its transmission, and virulence. Further, the article discusses the diagnosis, signs and symptoms like fever, breathlessness, cough, potential loss of taste or smell, sneezing, runny nose, fatigue, headache, sore throat and different treatment approaches including drug repurposing being tried by doctors around the globe that may come handy in the management of disease symptoms. The article describes the use of remdesivir, ribavarin, lopinavir, favipiravir, hydroxychloroquine, chloroquine, and tocilizumab among others in treating COVID-19.

Keywords: Coronavirus disease, COVID-19, chloroquine, diagnosis, SARS CoV-2 structure, pandemic, drug repurposing.

1. INTRODUCTION

Coronavirus disease (COVID-19) has been declared a pandemic by the World Health Organization [1]. On January 30, 2020, the WHO has declared COVID-19 as the sixth public health emergency of international concern. It is causing havoc throughout the world and has spread to more than 210 countries. As on date 16th April 2020, it has claimed 144858 lives globally [2]. Scientists and doctors are hard-pressed to find a useful remedy to treat this nightmarish disease which is characterized by high fever, headache and diarrhea. Further, the inflammatory process in the interstitial space and in the alveolar space of lung parenchyma reduces the transfer of gases between systemic circulation and alveolar space [3]. The spread of the disease in exorbitant proportions has put many countries in a lockdown stage. Predictions regarding the severity of coronavirus disease were largely ignored. Some authors had predicted long back (2007) regarding the presence of coronavirus in horseshoe bats and feared that the habit of consuming exotic mammals may prove to be a ticking bomb. Largely their predictions have come true [4].

1.1. Family of Corona Viruses

Coronaviruses belong to the category of enveloped RNA viruses which are frequently distributed in humans, other mammals, and birds [5-6]. Their ability to cause respiratory, hepatic, enteric, and neurologic diseases makes them quite dangerous [7-8]. The occurrence of disease in human beings can chiefly be attributed to their six strains [9]. These six strains can be divided into two categories, whereas the first four of them (namely HKU1, NL63, OC43, and 229E) are 10-20% of respiratory diseases [10-20]. These four strains cause common cold like symptoms in immunocompromised patients. The latter two strains are responsible for more serious and fatal diseases. It is imperative to mention that severe acute respiratory syndrome outbreaks in the People’s Republic of China during 2002 and 2013 can be attributed to SARS-CoV [21-23]. On the other hand, MERS-CoV was the causative agent for a similar outbreak in Middle East countries during 2012 [24]. The tendency to alter their genomes coupled with their widespread distribution and exceptionally high genetic diversity has made coronaviruses more lethal than expected [25-26]. Although the assessments of mortality are poor, studies equate asymptomatic carriers to symptomatic patients [10, 16]. Coronaviruses are members of the order Nidovirales and subfamily Orthocoronavirinae. This subfamily is divided into four genera: Alphacoronavirus,
Betacoronavirus, Gammacoronavirus, and Deltacoronavirus. Alphacoronavirus and Betacoronavirus have a general tendency of infecting the mammals whereas the other two tend to infect birds with few of them occasionally infecting mammals [27].

1.2. Coronavirus Structure

SARS CoV-2 is a type of RNA virus from the family of coronaviruses (Fig. 1), primarily resulting in a respiratory system infection. Pneumonia is one such primary finding for COVID-19 [28-30].

![Structure of SARS CoV-2 virus.](image)

Coronaviruses are large polymorphic spherical particles (radius 60 nm) with bulbous projections at the surface [31-32]. Their outer surface is often enveloped by a surface glycoprotein which is responsible for imparting them with their characteristic appearance of a crown (Latin: corona).

The viral envelope consists of a lipid bilayer where the membrane (M), envelope (E) and spike (S) structural proteins are attached [33]. Members of the betacoronavirus family also possess a surface protein akin to a small spike [34]. This protein is known as hemagglutinin esterase (HE).

The innermost and continuous beads on a string like structure are composed of nucleocapsid (N) proteins bound to a positive-sense single-stranded RNA genome [32,35]. When outside a host cell, the virus is protected by nucleocapsid, membrane proteins, and lipid bilayer envelope [36].

1.3. Life Cycle of Coronavirus

The infection starts with attachment of viral spike (S) glycoprotein to its complementary host cell receptor followed by cleavage of host protease, thus activating the receptor attached spike protein. This process allows the viral entry into the host cell either by endocytosis or direct fusion of viral envelope with a membrane of the host cell [37]. After entry, the virus particle uncoats itself, thus releasing its genome into the cytoplasm [38]. The coronavirus RNA attaches to host cell ribosomes leading to translation through host cell producing long-chain polyproteins which are cleaved by its protease into multiple nonstructural proteins [39]. The aggregation of these nonstructural proteins results in the formation of a multiprotein replicase-transcriptase complex (RTC). The direct replication and transcription of RNA from an RNA strand takes place through RNA-dependent RNA polymerase (RdRp) replicase transcriptase. Another nonstructural protein, exoribonuclease facilitates replication by proofreading [40]. The transcription of the viral genome into positive sense mRNAs is carried out through this complex [41]. The host cell’s ribosomes translate these mRNAs into structural and various accessory proteins inside the endoplasmic reticulum. The viral structural proteins S, E, and M assemble in the Golgi apparatus, thus binding to the nucleocapsid. The release of the daughter virus particle from the host cell takes place by exocytosis [38].

Since the S glycoprotein of the coronavirus is exposed to the surface and facilitates its entry to host cells, scientists have frequently attempted to bring about neutralizing antibodies (Abs) against this antigen (S glycoprotein). The entry of SARS-CoV S into the cells is facilitated by the ACE2 enzyme owing to structural similarities of their receptor-binding domains [40].

1.4. Transmission

The spread of human coronavirus from person to person often takes place through respiratory fluids like mucus. They can spread in more than one ways including:

- Dispersal of droplets into the atmosphere when one coughs or sneezes in the absence of protective gear like mask.
- Handshake or occasional touch with an infected person.
- Touching surfaces or objects having viral load and later touching own eyes, mouth or nose.

All individuals are likely to be infected by coronaviruses at some point in time during their life. The ability of viruses to mutate effectively makes them so contagious. Transmission may be prevented by staying at home and taking rest while being symptomatic. Social distancing is the key to prevention. It is advisable to use protective gear like mask, tissue, or handkerchief to cover the mouth and nose while coughing or sneezing which can certainly help prevent transmission. Disposal of any tissues after use and maintaining hygiene around the premises is of paramount importance [41].

1.5. Organs Involved

Different body organs are affected by COVID-19 in many ways.

1.5.1. The Lungs

COVID-19 is a respiratory disease wherein the virus invades the lung cells which are of two categories: mucus making and others with hair-like structures called cilia. It is the luminal side of the lungs that is attacked by the virus leading to the release of progeny viruses [42-43]. Breath-
lessness coupled with pneumonia in left and right lung has been reported in many patients. Phase two is characterized by attempts on part of the immune system to reverse the damage and repair the lung tissue. Under stress, the immune system goes out of control and kills anything on its way including healthy cells, thus the damage may exceed the repair. The lungs are clogged up worsening pneumonia. Progressing towards the third stage, the condition of lungs worsens leading to respiratory failure. The lungs get holes thus acquiring “a honeycomb-like appearance” which stiffens the lungs. The patients have to struggle for breathing and thus need to be put on a ventilator.

The permeability of the membranes between the air sacs and blood vessels increases due to inflammation filling the lungs with fluid, thus decreasing the ability to oxygenate the blood which ultimately leads to death.

1.5.2. Nervous System

The central nervous system can be attacked by the new coronavirus in more ways than one, sometimes leading to irreversible damages or even death. Genetic sequencing has been used to confirm the presence of SARS-CoV-2 coronavirus in the cerebrospinal fluid [44]. Health workers working at Wuhan opined that many patients developed neurological symptoms. Broadly these symptoms were classified into CNS symptoms and PNS symptoms. Vertigo, disturbed consciousness, headache and epilepsy constitute CNS symptoms, whereas anorexia, ageusia and anosmia are the symptoms of the peripheral nervous system. As many as 25 percent of patients were reported to have CNS symptoms with frequency decreasing in the following order: dizziness (17%)-> headache (13%) > impaired consciousness (8%)-> cerebrovascular problems (3%) > ataxia and seizures (0.5% each) [45]. Seizures either with meningitis or encephalitis [46] or with focal status epilepticus [47] have also been reported by other researchers. These seizures in COVID-19 patients may be attributed to reduced oxygen supply to the brain, organ failure or cerebral damage.

1.5.3. The Digestive System

The virus responsible for COVID-19 bears structural similarity to SARS-CoV and has a tendency to attack human host cells through its ability to bind with the ACE-2 receptor, thus bringing about extensive liver tissue damage [48]. The digestive symptoms associated with COVID-19 may be attributed to the ability of the virus to cause disturbances in the normal composition of gut microflora which being linked to the mucosal immune system may bring about respiratory tract flora disorders. The so-called gut-lung axis phenomenon is responsible for appetite loss and diarrhea [49-52]. Traces of viral nucleic acid were found in stool testing of nearly 53.4 percent subjects [53-55].

1.5.4. Blood Storm

Hypotension compromised WBC and platelet count and increased levels of hepatic enzymes are often associated with all types of coronaviruses having a zoonotic origin. Patients diagnosed with COVID-19 have an increased risk of thrombosis and pulmonary embolism. Some authors have reported VTE: DVT or PE in patients with COVID-19 [56-57]. Few reports of acute kidney injury and cardiac arrest have also been documented. The human immune system employs cytokines (which are proteins by nature) to act as an alarm beacon and bring about necrosis of infected tissues so that the healthy tissues can be protected. Under attack from a coronavirus infection, there is unregulated dumping of cytokines in the lungs by the immune system. The cytokine storm translates into inflammation leading to weakened pulmonary blood vessels and fluid seepage through the air sacs. Further, Inflammation associated with a cytokine storm begins at a local site and spreads throughout the body via the systemic circulation thus bringing about unprecedented systemic issues in different organs. In full-blown cases of COVID-19, this cytokine response together with compromised oxygen pumping capacity can result in multiple organ failure. This may be due to the presence of certain underlying conditions like heart disease or diabetes [58].

1.5.5. Heart

Individuals who are 65 or above with a history of elevated blood pressure or coronary heart disease stand higher chances of being infected and tend to show more severe symptoms. The prime target of the coronavirus is lungs but a diseased heart that is already struggling for oxygenated blood may be affected badly. It is also anticipated (speculated) though not confirmed, that ACE inhibitors and angiotensin receptor blockers (ARBs) increase the chances of severe COVID-19 infections. This can be attributed to elevated levels of ACE-2 often observed in individuals treated with ACE inhibitors and ARBs since the SARS-CoV-2 virus binds to this enzyme to infect the host cells. An increased level of ACE-2 receptors in such patients would mean an increased number of binding sites for coronavirus S proteins [59].

Wang et al. presented a case report of 138 hospitalized COVID-19 patients among which 14.1% had baseline cardiovascular disease, and 31.1% had hypertension [60]. Huang et al. reported data of 41 patients wherein 14.6% had baseline cardiovascular disease and a similar percentage presented with hypertension [61]. While in a larger cohort of 416 patients, 30.5% had hypertension, 10.6% had coronary artery disease, and 5.3% had cardiovascular disease [62]. Prognostic significance of CVD was amply illustrated with a cohort of 191 patients, where 30% had hypertension and constituted 48% of non-survivors, whereas CVD was present in 8% who constituted 13% of non-survivors [63].

1.5.6. Liver

After entering the bloodstream, the virus can swim to any part of the body. Coronavirus can very easily get into the liver which is a highly vascular organ. Alternatively, the collateral damage of hepatic cells may be an autoimmune response to the inflammatory response brought about by a viral attack.

As the disease progresses, patients record elevated levels of serum glutamic oxaloacetic acid transaminase (SGOT) and serum glutamic pyruvic acid transaminase (SGPT) thus indicating higher rates of liver dysfunction [62,64-65]. Impairment of the liver can be a direct consequence of drug hepatotoxicity [66].
1.5.7. Kidneys

The kidneys have been reported to be affected causing acute renal injury due to novel coronavirus in SARS patients though uncommon but fatal. Acute renal impairment proved fatal in 91.7% of patients suffering from SARS as per a study in 2005. Kidneys act as blood filters and each kidney is equipped with about 800,000 nephrons which are the most affected by zoonotic coronaviruses. The WHO has reported that during the SARS outbreak, the kidney tubules were heavily infected and inflamed by the deadly virus. If the virus gets entrapped in the cell and replicates there, it may lead to fatal injury. However, it is still unclear that the virus replicates there or not. The acute kidney injury could be due to various causes including hypotension, sepsis, antibiotics, metabolic disturbance, multiple organ failure, being put to a ventilator for a long time, or more likely due to autoimmune intervention [67].

The National Institute of Health (NIH) suggests that some people are more at risk of severe complications than others. The risk can increase for those with an underlying health condition, such as heart disease, diabetes, and lung disease. The geriatric population is also at risk of severe illness from coronavirus. Other groups at risk include people with HIV, pregnant women, and people with asthma. The typical findings associated with major organs regarding COVID-19 are presented in Table 1.

1.6. Diagnosis

The U.S. CDC has developed criteria for persons under investigation (PUI) [68]. If a person is deemed a PUI, immediate prevention and infection control measures are undertaken. Epidemiological factors are used to assess the requirement of testing. These include close contact with a COVID-19 positive patient within 14 days of symptoms or travel history to an infected area within 14 days of symptom onset. The WHO recommends collecting samples from both the upper and lower respiratory tracts. This can be achieved through expectorated sputum, bronchoalveolar lavage, or endotracheal aspirate [68]. These samples are then assessed for viral RNA using the polymerase chain reaction (PCR). If a positive test result is achieved, it is recommended to repeat the test for re-verification purposes. A negative test with a strong clinical suspicion also warrants repeat testing [69]. Quick diagnosis of COVID-19 is also based on the measurement of IgG and IgM antibodies in human serum or plasma. Whenever possible, portable X-ray equipment should be used so that the transportation of the patients is kept to a minimum. In order to reduce the chances of transmission from established COVID-19 patients to health workers or other individuals, it is advisable to use dedicated radiography equipment [70].

It is easier to predict evolution towards a more severe form of disease through serial procalcitonin measurement. There is a feasible explanation for this evidence. The production and release into the circulation of procalcitonin from extrathyroidal sources are enormously amplified during bacterial infections, actively sustained by enhanced concentrations of interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6 [71]. Nevertheless, the synthesis of this biomarker is inhibited by elevated levels of interferon (INF)-γ during viral infections. Real-time PCR was used to target unique regions in the spike protein of SARS-CoV-2. The set of primers which were designed at the Indian Institute of Technology, Delhi, tend to bind to regions conserved in over 200 fully sequenced SARS-CoV-2 genomes. The sensitivity of this assay was reportedly comparable to commercially available kits. The assay is based on the identification of unique regions in SARS-CoV-2 which are absent in other human coronaviruses thus providing an opportunity to specifically detect SARS-CoV-2 [72].

1.7. Signs and Symptoms

The incubation period for COVID-19 is 2-14 days. The number and severity of symptoms do vary from person-to-person. However, in isolated cases, it may lead to death. Accordingly, the patients are classified as mild, serious, or critical. Common symptoms include fever, breathlessness, cough, potential loss of taste or smell, sneezing, runny nose, fatigue, headache, sore throat, pneumonia-like symptoms, and exacerbated asthma [2].

2. TREATMENT APPROACHES

2.1. Prevention

As per recommendations of WHO, the infection can be brought under control through avoidance of person to person contact, especially the ones who came up with stated symptoms. It is advisable to wash hands frequently and to avoid contact with ill people or their environment and avoiding unprotected contact with farms or wild animals. On the other hand, it is expected from patients to exercise self-control in coughing/sneezing and cover their mouth and nose while doing so. They are advised for frequent hand washing. It is

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Organ Involved</th>
<th>Typical Findings</th>
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<tbody>
<tr>
<td>1</td>
<td>Lungs</td>
<td>Subpleural ground glass opacities followed by consolidation</td>
</tr>
<tr>
<td>2</td>
<td>Brain</td>
<td>Cerebral edema, elevated levels of D-dimer and severe platelet reduction</td>
</tr>
<tr>
<td>3</td>
<td>Liver</td>
<td>Elevated levels of SGOT and SGPT</td>
</tr>
<tr>
<td>4</td>
<td>Kidneys</td>
<td>Acute renal injury</td>
</tr>
<tr>
<td>5</td>
<td>Heart</td>
<td>Elevated levels of proinflammatory cytokines, myocardial damage</td>
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</table>
obligatory on part of hospitals, especially the emergency facilities to adopt frequent disinfection and sanitization [73].

Isolation of those affected and the use of personal protective equipment (PPE) are the mainstays to block transmission of this pathogen, which is presumed through respiratory droplets. Fourteen days quarantine is applied to subjects coming from endemic areas or who came in touch with confirmed cases [74].

2.1. Role of Vitamins

Vitamin C or L-ascorbic acid not only improves immunity but also plays a pleiotropic physiological role. When given in high doses through the intravenous route, it is known to offer protection during sepsis-induced ARDS. It cuts down on the number of hours a patient is put on mechanical ventilation [75].

2.1.2. Vitamin D

The alveolar damage arising out as a consequence of ARDS may be minimized by the administration of Vitamin D since it helps to regenerate endothelial lining [76].

2.2. Treatment

2.2.1. Medication

Although it is difficult to test and approve a new drug overnight for effective treatment of COVID-19, the physicians are managing the cases with antipyretics, fluids, oxygen and antithrombotic agents. Further, a number of existing drugs have been tried for symptomatic management of this disease. This essentially makes the basis of so-called drug repurposing. It makes it easier for doctors if the drug considered for repurposing is already on the WHO list of essential drugs because of their easy availability. The following category of drugs may be possibly used for the management of COVID-19.

2.2.2. Adenosine Nucleotide Analogues

One such drug is remdesivir which exhibits potential for use against COVID-19. With favorable in vitro antiviral activity of remdesivir, it has been further tested in animal models of different viral infections. In a rhesus monkey model of Ebola virus disease, daily administration of 10 mg/kg remdesivir for 12 days profoundly suppressed the replication of the Ebola virus and protected all infected animals against this lethal infection [77]. Besides, in a mouse model of SARS-CoV infection, prophylactic and early therapeutic dosing of remdesivir therapy effectively decreased viral load in lungs and improved pulmonary function [78]. Further, as per the latest report, remdesivir has shown promise in 68 percent of COVID-19 patients. Thirty-six out of 53 patients who received the drug on compassionate use grounds showed signs of clinical improvement in terms of improvement in oxygen support class over a median follow up of 18 days [79]. Remdesivir is a prodrug of a nucleotide analogue that is intracellularly metabolized to an analogue of adenosine triphosphate that inhibits viral RNA polymerases. The activity of remdesivir can be attributed to the fact that SARS-CoV and SARS-CoV-2 share 82% RNA sequence similarity, their RNA-dependent RNA polymerase (RdRp) share 96% sequence similarity [80-82]. Therefore, the drugs targeting viral RdRp proteins of SARS-CoV are likely to be effective for SARS-CoV-2.

Ribavirin is another nucleoside analogue which is known to act by inhibiting viral RNA synthesis and mRNA capping. When given with interferon to patients of MERS, it has shown mixed results [80].

2.2.3. 4-Amino Quinolines

In this category, two drugs namely chloroquine and hydroxychloroquine are the mainstay of COVID-19 management. Chloroquine is approved for prophylaxis and treatment of malaria [83]. It has emerged as an effective antiviral agent against RNA viruses as diverse as rabies virus [84], poliovirus [85], HIV [86-88], hepatitis A virus [89-90], hepatitis C virus [91], influenza A and B viruses [92-95], influenza A H5N1 virus [96], Chikungunya virus [97-99], Dengue virus [100-101], Zika virus [102], Lassa virus [103], Hendra and Nipah viruses [104-105], Crimean–Congo hemorrhagic fever virus [106], and Ebola virus [107] as well as various DNA viruses such as hepatitis B virus [108] and herpes simplex virus [109].

Chloroquine can act through more than one mechanisms depending upon the pathogen being studied. Chloroquine interferes with the binding of viral particles to the surface cell receptors thereby inhibiting an important step of the viral cycle. It can also control the fusion and uncoating steps of the viral cycle by alkalizing the phagolysosome [110]. Binding of viruses involves an important step of ligand recognition. Sialic acid which is prevalent at the ends of sugar chains found on cell transmembrane plays an important role in ligand recognition. Chloroquine interferes with the biosynthesis of sialic acid by inhibiting the enzyme quinone reductase 2 which is a structural neighbor of UDP-N-acetylgalcosamine [111-113]. Scientists have attributed the efficacy of chloroquine against SARS-CoV-1 to its ability to bring about a fall in the glycosylation of a virus cell surface receptor, the angiotensin-converting enzyme 2 (ACE2) [114]. Recently, Devaux et al. have highlighted the antiviral efficacy of chloroquine against coronavirus [115].

Hydroxychloroquine is another successful example of drug repurposing. Gautret et al. contemplated the possibility of COVID-19 containment through concomitant administration of hydroxychloroquine and azithromycin consequent upon a clinical trial [116].

2.2.4. Protease Inhibitors

This category of drugs blocks viral maturation and their entry into host cells. Camostat mesylate is known to block the SARS-CoV-2 virus in vitro in lung cells [117]. Another protease inhibitor, Lopinavir/Ritonavir which is already approved for HIV-1 treatment has been repurposed with success against SARS-CoV-1 both in vitro and human studies [118]. The current Chinese guidelines for COVID-19 treatment include a PO 50 mg-200 mg dose BID for a duration of 10 days. The lopinavir and ritonavir are used as a regimen single-agent or combination with either ribavirin or interferon-α [119].

Darunavir/Cobicistat is also an approved drug for the treatment of HIV-1 but its efficacy against coronaviruses of other diseases is yet to be established.
2.2.5. RNA Polymerase Inhibitors

Drugs like favipiravir inhibit viral RNA dependent polymerase. They are known to possess broad-spectrum antiviral activity against influenza, arenavirus, bunyavirus and filovirus. For the RdRp target in the genus Betacoronavirus (to which SARS-CoV-2 belongs), there are other potential drugs or compounds, including penciclovir, galidesivir, 6'-fluorinated aristeromycin analogs, and acyclovir fleximer analogs [120].

2.2.6. Fusion Inhibitors

Umifenovir can be a potential drug owing to its ability to inhibit fusion between viral and cellular membranes. It is quite effective against other coronaviruses. Currently, it is being used orally in China at a dose of 200 mg TDS for a duration of 10 days [119].

2.2.7. Viral Endonuclease Inhibitors

Baloxivir marboxil is a drug which belongs to this class and inhibits the multiplication of the virus. It is approved for oral use against influenza of uncomplicated type [117].

2.2.8. Monoclonal Antibodies

As discussed previously there is unregulated dumping of cytokines into the lungs by the immune system. This cytokine storm is blocked by monoclonal antibodies like tocilizumab, sarilumab, eculizumab. These agents also block interleukin-6, an important mediator in the inflammation process following infection by the coronaviruses. Out of these, tocilizumab is reported to reduce pyrexia and oxygen requirement in COVID-19 patients. Since it is approved for rheumatoid arthritis, tocilizumab is an ideal candidate for drug repurposing [121].

2.2.9. Replication Inhibitors

2.2.9.1. Inhibiting IMPα/β1-mediated Nuclear Import of Viral Proteins

Another example of repurposing is Ivermectin which has shown promise as an in vitro inhibitor of SARS-CoV-2 [122]. This drug is FDA approved for the treatment of parasitic infections and is widely available because of being in the WHO model list of essential medicines. It is known to presumably act by inhibiting IMPα/β1-mediated nuclear import of viral proteins [123].

2.2.9.2. Preventing the Release of Genomic Viral RNA

A drug named Teicoplanin which was effective against Staphylococci had also shown promise in inhibiting the preliminary stages of MERS coronavirus in human beings. It acts by inhibiting the replication cycle of the virus through its ability to prevent the release of genomic viral RNA [124-125]. Table 2 presents major treatment options and their mechanism of action.

2.2.9.3. Stimulation of Intrinsic Antiviral Immunity

Cytokines, interferon-β1 and aerosolized interferon α help the body fight the disease because of their ability to stimulate the innate antiviral immunity. MERS-CoV appears to be more sensitive than SARS-CoV in vitro studies. Anti-MERS-CoV action was noted in animal studies [121].

2.2.9.4. Neuraminidase Inhibitor

Oseltamivir is a drug that belongs to this class and inhibits replication of the virus. Although there are no past reports of its activity against coronaviruses, it can be used as an adjunct therapy. Lopinavir 200 mg and ritonavir 50 mg, when given in a combination twice a day, have been proven beneficial for the treatment of COVID patients by Indian doctors. Additionally, the patients were also given chloroquine and oseltamivir [126].

CONCLUSION

The alarming increase in the number of coronavirus disease patients warrants immediate steps to be taken to control this pandemic. Whereas several clinical trials are going on towards developing a vaccine against it but it may take quite some time before it sees the light of the day. Till that time, management of the disease with existing antiviral drugs and exhaustive steps towards its prevention through social distancing and hygienic etiquettes are imperative for better management.

Table 2. Treatment options for COVID-19.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Treatment Option</th>
<th>Mechanism of Action</th>
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<tbody>
<tr>
<td>1.</td>
<td>Remedesivir</td>
<td>Inhibits viral RNA polymerases</td>
</tr>
<tr>
<td>2.</td>
<td>Chloroquine</td>
<td>Interferes with the binding of viral particle to the surface cell receptors</td>
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<tr>
<td>3.</td>
<td>Lopinavir</td>
<td>Blocks viral maturation and their entry into host cells</td>
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<tr>
<td>4.</td>
<td>Favipiravir</td>
<td>Inhibits viral RNA dependent polymerase</td>
</tr>
<tr>
<td>5.</td>
<td>Baloxivir marboxil</td>
<td>Inhibits multiplication of the virus</td>
</tr>
<tr>
<td>6.</td>
<td>Teicoplanin</td>
<td>Inhibits the viral replication cycle</td>
</tr>
<tr>
<td>7.</td>
<td>Ivermectin</td>
<td>Inhibitor of SARS-CoV-2 replication</td>
</tr>
<tr>
<td>8.</td>
<td>Tocilizumab</td>
<td>Blocks cytokine storm</td>
</tr>
<tr>
<td>9.</td>
<td>Umifenovir</td>
<td>Inhibits fusion between viral and cellular membranes</td>
</tr>
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</table>
LIST OF ABBREVIATIONS

ACE = Angiotensin Converting Enzyme
ARBs = Angiotensin Receptor Blockers
ARDS = Acute Respiratory Disease Syndrome
CNS = Central Nervous System
CoV = Corona Virus
COVID = Corona Virus Disease
CVD = Cardio Vascular Disease
DVT = Deep Vein Thrombosis
HIV = Human Immunodeficiency Virus
Ig = Immunoglobulin
IMP = Importin
MERS = Middle East Respiratory Syndrome
NIH = National Institute of Health
PCR = Polymerase Chain Reaction
PE = Pulmonary Embolism
PNS = Peripheral Nervous System
PO = Per Oral
RdRp = RNA-dependent RNA polymerase
RNA = Ribonucleic Acid
RTC = Replicase-Transcriptase Complex
SARS = Severe Acute Respiratory Syndrome
SGOT = Serum Glutamic Oxaloacetic acid Transaminase
SGPT = Serum Glutamic Pyruvic acid Transaminase
TDS = Ter in Die Sumenda (three times a day)
TNF = Tissue Necrosis Factor
US CDC = United States Centre for Disease Control
VTE = Venous Thromboembolism
WBC = White Blood Cells
WHO = World Health Organization

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