



Therapeutic Options for Treating COVID-19

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Abstract

COVID-19, instigated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused the pandemic. This disease provoked with its epicenter in China. Belonging to the *Coronaviridae* family of viruses, it is a new strain of β -type of coronavirus. The World Health Organization (WHO) declared its name as 'SARS-CoV-2'. Also, in January 2020, the WHO declared COVID-19 as a sixth public-health emergency of international suffering. Lack of etymology, precautionary measures, and specified drug or vaccination for this viral infection are few of the main reasons for the epidemic. Hence, there was an extensive need for the scientists throughout the globe to work on it. Some potential inhibitors have been reported to possibly treat COVID-19 affected patients. Likewise, a new technique, which is the Plasma Therapy, is used in the treatment. In this context, this review aims to summarize the epidemiology, virology, mode of dissemination, treatment, and prevention measures of COVID-19.

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The outbreak of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late December 2019 in Wuhan. Since its emergence on December 31, 2019, to June 13, 2020, it has affected nearly 8 million people across the globe out of which more than 430,000 succumbed to death,^[1] and the toll is increasing at an alarming rate, and at the same time, it has greatly impacted almost every walk of life, mainly public and psychological health,^[2] maternity and child care,^[3] energy and environment,^[4] business and economy,^[5] education,^[6] and several others.

SARS-CoV-2 shows its toxicity by targeting the host cells through the viral structural spike (S) protein and binds to the angiotensin-converting enzyme 2 (ACE2) receptor. After integration into the host cell, the viral particles replicate their RNA and synthesize proteins *via* their own RNA-dependent RNA polymerase (RdRp), and viral particles are released, leading to the onset of disease.^[7] At present, there is neither a single specific antiviral therapy, clinical treatments, or therapeutic strategies to treat COVID-19 nor

vaccines available to immune the body against the SARS-CoV-2: all available options are only supportive treatments. The mode of attachment, integration, replication, and protein synthesis of viral particles provide the potential targets for developing specific drugs. The potential of some available drugs with their known antiviral activities and effectiveness against influenza, SARS, MERS, Ebola, and other human coronaviruses have been tested in-vitro, in mice models, and clinical isolates, even few of them have been directly used on COVID-19 patients on 'trial and error' basis, both alone and in different combinations. Such drugs show their effect by targeting the different stages of life-cycle of the virus, either directly or through targeting the key molecules, such as enzyme or receptors, required for successful completion of life-cycle. Herein, we summarize four-classes of potential therapeutic options, including the specific drugs which can potentially prevent the (1) attachment, (2) integration, and (3) protein synthesis by viral particles, and (4) the non-drug-based therapies, to prevent the onset of COVID-19.

The ACE2 receptors in the lower respiratory tract (LRT), mainly present on the epithelial cells of the lungs, intestine, and kidney are primarily targeted by the SARS-CoV-2 infection;^[8] thus a drug which can potentially inhibit the ACE or an angiotensin receptor blocker (ARB) could potentially minimize the invasion of viral particles.^[9] A study reported that statins target the host response to infection rather than the virus itself, indicating that a

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combination of ARB and statins could potentially accelerate the homeostasis and augment a self-recovery of COVID-19 patients.^[10] Another class of drugs that could be potentially used are the immunomodulatory drugs, which revoke the immune system by augmenting or reducing its ability to produce antibodies or sensitized cells that recognize and react with the antigen mediating their production, thus preventing the integration of antigen to the cell. Different drugs such as Chloroquine, Hydroxychloroquine, Azithromycin, Ruxolitinib, as well as monoclonal antibodies, are available as potential immunomodulatory drugs to treat COVID-19. Some of these drugs, such as Chloroquine and Hydroxychloroquine, have known antiviral activities and show their immunomodulatory effects by attenuating the cytokine production and inhibiting the autophagy and lysosomal activity in the host cells.^[11,12] These drugs also prevent the entry of virus particles by inhibiting the glycosylation of cellular receptors, proteolytic processing, and endosomal acidification; for example, Chloroquine increases the endosomal pH and interferes with the glycosylation of the cellular receptors of SARS-CoV.^[13] In an in-vitro study, Chloroquine effectively inhibited the SARS-CoV-2 with an EC₅₀ in the low micromolar range, while the Hydroxychloroquine showed its activity with a slightly lower EC₅₀, after 24 h growth.^[14] Chloroquine improved the radiological findings, enhanced the viral clearance, and reduced the diseases progression,^[15] while Hydroxychloroquine and Ruxolitinib potentially control the cytokine storm and reduce the clinical recovery time in COVID-19 patients.^[14,16,17] Similarly, Azithromycin, in combination with Hydroxychloroquine, effectively minimized the virus load in COVID-19 patients.^[18] In addition to such immunomodulatory drugs, the use of monoclonal antibodies that target the key inflammatory cytokines and other aspects of innate immune response could also be used to treat COVID-19. Usually, an amplified immune response and cytokine release lead to pathophysiology of organ damage, mainly lungs and liver,^[19] thus necessitating the suppression of immune response. To this end, using the Tocilizumab, which is a monoclonal antibody interleukin 6 (IL-6) receptor antagonist, effectively dampens the infection and improved the clinical outcome such as respiratory function and defervescence in COVID-19 patients.^[20] In addition to revoking the immune system, the integration of viral particles into the host cells *via* S protein can also be prevented by inhibiting the host's type-2 transmembrane serine protease (TMPRSS2).^[21] Two drugs, Lopinavir/Ritonavir (LPV/RTV) and Darnunavir have known to inhibit the activity of papain-like protease and 3-chymotrypsin-like protease,^[22] however, these have not been really tested against SARS-CoV-2, while some preliminary studies of using these drugs are mostly comprised of case reports and small retrospective and non-randomized cohort studies,^[23] thus do not provide conclusive evidence of their effectiveness against the COVID-19. Similarly, the FDA-approved

antiparasitic drug Ivermectin boosts the immune system by producing various ILs, activates the production of superoxide, and augment the lymphocytes response to the mitogens.^[24] The third class of antiviral drugs targets the RdRp to prevent protein synthesis by the integrated virus particles. After successful attachment and integration into the host cells, the virus replicates and synthesizes its own proteins by using the RdRp, also named as nsp12; thus, this enzyme has been the main target of various antiviral drugs, such as Remdesivir, Favipiravir, and Ribavirin, to minimize the level of infection even after the invasion of the virus. Among these, Remdesivir which targets the RdRp and induces a premature termination of transcription of viral RNA,^[25] has shown promising impact, both alone^[26] and in combination with Chloroquine and Interferon- β by blocking the replication of virus genome and showed effective recovery of patients,^[27,28] with acceptable safety, favorable pharmacokinetic profiles, and acceptable clinical efficacy against moderate-to-severe infections. Likewise, Favipiravir inhibits the activity of RdRp and halts the replication of viral RNA in host cells, as indicated by a preliminary in-vitro study against the SARS-CoV-2 when used with an EC₅₀ of 61.88 μ M/L in Vero E6 cells.^[28] It significantly improved the recovery within seven days in COVID-19 patients with moderate infections; however, it did not show a significant effect in severe or combined severe/moderate infections.^[29] Similarly, Ribavirin has proven effective against the SARS-CoV at higher concentrations, indicating its potential against SARS-CoV-2 if used at higher concentrations and in combination therapy; however, its side effects such as hematologic and liver toxicity^[30] rank it lower in the priority list of available options for treating COVID-19 despite its recommendation by the National Health Commission and State Administration of Traditional Chinese Medicine in 7th edition of their report "Novel Coronavirus Pneumonia Diagnosis and Treatment Plan".^[31] In addition to the above-mentioned therapeutic options, there are several other drugs which can be useful in treating COVID-19. For example, Teicoplanin and Lipoglycopeptides can potentially prevent the entry of viral particles into the cytoplasm and inhibit the transcription and replication-component virus-like particles.^[32]

In addition to various drugs, other therapeutic options, such as using convalescent plasma and inhaling nitric oxide, could also be utilized and have shown some promising results. For example, the plasma or hyperimmune immunoglobulins therapy involving the injection of plasma containing the antibodies harvested from the recovered patients can potentially free the viruses and infected cell immune.^[33] After the successful preliminary studies of using convalescent plasma,^[34] FDA released the guidance for requesting an emergency investigation of the application of the new drug screening the donors for COVID-19 convalescent plasma;^[35] however, the current commercial immunoglobulins preparation likely lacks the protective

antibodies against SARS-CoV-2, thus warranting further investigation and efficiency trials amid the increasing pool of COVID-19 patients. Similarly, the inhalation of nitric oxide can potentially reverse pulmonary hypertension and improved hypoxia, thus reducing the ventilator support;^[36] however, it is not recommended if other therapeutic options are available.

Among the above-mentioned and several other drugs, some have already been withdrawn after showing adverse reactions even after demonstrating promising clinical outcomes. The most-effective and long-term therapy for preventing a future outbreak of COVID-19 is the development of vaccines, and several commercial and government-supported companies are already working on it.

Conflict of interest

All authors declare no competing financial conflict of interest associated with the publication of this work.

Supporting Information

There is no additional supporting information for this paper.

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