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*Review*

# Potential Drug Targets and Treatment Options for Covid-19: A Review

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## Abstract

**Background**: A novel virulent coronavirus is what causes Novel Corona-virus Disease 2019 (nCOVID 19). It results in severe respiratory distress syndrome and potentially fatal infectious pneumonia. On March 12, 2020, the World Health Organization first labeled it a pandemic, which was then followed on the same day by a community health emergency of global concern. Vaccines against this deadly virus are now being created. Many drugs with different uses have been repurposed and tested for the prevention and treatment of the infection.

**Objective**: The purpose of this review is to provide an in-depth analysis of data on possible pharmacological targets and available coronavirus treatments.

**Methods**: Following the review protocol, a literature search was conducted.

**Results:** Chloroquine phosphate and hydroxychloroquine, Remdesivir, and Lopinavir-Ritonavir in combination with or without interferon and convalescent plasma therapy are the main treatment candidates, according to the World Health Organization. This review article has elaborated on the current evidence of prospective pharmacological targets and related ongoing research, including inflammatory chemicals, bioactive peptides, beta cells, platelets, and the Angiotensin I Converting Enzyme 2 Receptor. This information was gathered from published journals. In addition, stories of medications and biological products like interferons and vaccinations that are utilized or could be utilized have been provided.

**Conclusion:** There are a variety of pharmacological targets and therapeutic strategies that need more study.

**Keywords:** COVID-19; Drug targets; Inflammation; Treatment Options; Vaccines

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# Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused emergent coronavirus illness 2019 (COVID-19) poses an enormous challenge for healthcare systems around the world. The disease's progression and its capacity to quickly cause widespread infection have significant effects that call for active infection prevention and control measures. The virus penetrates its target cells by a pH-sensitive endocytosis pathway, as earlier research showed (5).

Within 1-2 weeks of the disease's beginning, patients suddenly present with worsening symptoms. Small peripheral blood lymphocytes, primarily natural killer cells, and a low lymphocyte count in lymphoid body areas will accompany it. A large number of eosinophils, the formation of hyaline membrane, a high concentration of mono- and poly-nucleated cells, pneumocyte hyperplasia, and the solidification of interstitial fluids are all associated with the injury to the alveoli from a histological perspective. In the aforementioned pathogenic conditions across COVID-19, oxidative stress, inflammation, and post-virus entry apoptosis all play detrimental roles (6).

For COVID-19, there is currently no definite and effective therapy option. The Mayo Clinic's recommendations state that the focus of current therapy is on respiratory and symptomatic care. Investigations are being conducted on several potential vaccines and medications based on the S protein (3). Anti-inflammatory medications (8), antimalarial pharmaceuticals (9), convalescent plasma therapy (10), traditional Chinese medicine (11), viral cycle blockers, virus deactivating antibodies, and small interfering RNAs are some more potential treatment approaches being considered (12).

# Potential Drug targets

## Pivotal inflammatory pathways

The prognosis of the disease is caused by several uncontrolled routes and mechanisms. Receptor tyrosine kinases (15, 16), growth factor receptors (17–20), IL-6 receptor (21–25), IFN–6 (six), TNF– receptor (26), TLR (27), JAK/STAT pathway (28), cytokines (29–32), macrophage activation (33), and mammalian target of rapamycin (34), are a few of these (34, 35). Drugs that target these pathways will therefore be essential.

## Bioactive peptides

TMPRSS2 is required for proteolytic activation of the spike protein upon viral entry into a human cell via the ACE2 receptor. It is crucial to assess bioactive peptides for their ability to block this biological function. A peptide-based screening analysis revealed that TMPRSS2 preferentially favors substrates with arginine over lysine. Additionally, hydrophobic amino acids bind to TMPRSS2's expansive hydrophobic S1 pocket (42). Targeting ACE2 and TMPRSS2 communication will therefore be crucial.

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## B-cells

Since modest COVID-19 was only seen in patients with agammaglobulinemia, it is assumed that B lymphocytes are crucial players in the SARS-CoV-2-induced inflammation. Additionally, it has been discovered that children appear to be more susceptible to SARS-CoV-2 in the early stages of infection. This may be because, compared to B cells in adults, children's B cells can quickly manufacture normal antibodies in response to accidental exposure to novel viruses (43, 44).

## Platelets

According to studies, platelet TLR4 receptors were weakened and caused platelet stacking in the liver and lungs. Angiotensin II (45), which can be released by SARS-CoV-2 upon entrance from ACE-2 and may start platelet degranulation, might cause inflammation and platelet loss by buildup in distant microvascular beds. Thrombocytopenia and intravascular coagulopathy may result from these effects (46). Additionally, the virus binds with platelet CD13, degranulates, and produces cytokines that activate several inflammatory pathways.

## Monocyte-macrophage differentiation

According to a study on the pathogenesis of coronavirus, the infection alters the morphology and inflammatory phenotypes of peripheral blood monocytes (48). Additionally, peripheral body fluid monocyte-derived macrophages were identified as the major macrophage subdivision in the majority of unembellished COVID-19 patients by single-cell RNA sequencing of lung bronchoalveolar immune cells. Numerous pre-clinical and clinical experimental attempts have shown that monitoring the impact of this type of cytokine allows for the monitoring of destructive inflammation (50).

## Cyclophilin A and CD147

Cyclophilin A is one of the crucial proteins in coronavirus replication. The inhibitor of this protein, cyclosporine A, can successfully reduce viral replication. This medication also has immunosuppressive properties. The virus also enters host cells using the CD147-S protein, speeding up the infection (32, 51, 52).

## Neutrophil Extracellular Traps (NETs) and Damage-Associated Molecular Patterns

Although it is challenging to adequately manage, the ongoing tissue inflammation caused by the COVID-19 infection requires prompt care. Therefore, attacking the immune system is always crucial to reducing the illness's indications and symptoms. The activation of neutrophils is one of the principal objectives. NETosis and autophagy can be induced by a variety of chemicals, some of which are quick activators. This chemical is secreted by the injured lung cells, which may once more activate the immune system. Therefore, it is crucial and a reasonable goal to prevent the operation of these molecular entities (53).

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### RNA-Dependent RNA Polymerase

RNA-dependent RNA polymerase (RdRP) is one of the viral enzymes for reproduction once the virus is inside the host. This enzyme is a prospective target for medication development to treat coronavirus infection. The enzyme's additional benefit is that it lacks host cell homologs, allowing for the development of efficient SARSCoV-2 RdRP blockers (54).

## Treatments options

Covid-19 is being treated in many ways, both with currently available medications and through the creation of novel products based on the pathogenesis and replication mechanisms of the virus. The following explains a few.

# Acetazolamide

With its signs and symptoms, this deadly viral infection also causes acute kidney impairment in several ways. It is a sign of the severity of the illness and is detrimental to the patient's survival. There is currently no well-established prophylactic method to lessen the severity of kidney damage. For patients who have a high risk of acquiring severe COVID-19 infection, preventive low-dose acetazolamide medication may offer protection by preventing virus assault and replication (5).

## Antivirals

### Lopinavir/ritonavir

An enzyme called protease is necessary for viral maturation and replication. Drugs like the ritonavir-lopinavir combination suppress the division of Gag-Pol polyproteins by blocking this enzyme. This will result in the production of non-contagious viral particles, which is confirmed by in-vitro experimental results (59). (60). This demonstrates that these medications can be used to treat SARS-CoV-2 infection (61-63). These medication classes are now used to treat both adults and children who have an advanced human immunodeficiency virus infection.

### Ribavirin

After being triphosphorylated, the broad-spectrum antiviral drug ribavirin can inhibit the RNA polymerase of the influenza virus (64). In research on rhesus macaques, the administration of IFN-2b along with ribavirin significantly boosted the former's anti-MERS-CoV activity (65). According to studies done on animals or people, this substance prevented SARS-CoV from multiplying (66). These findings suggest that this medication may be an alternative for treating coronaviruses.

### Remdesivir

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Remdesivir showed potent anti-filovirus efficacy. Additionally, results from animal studies showed that RNA-dependent RNA synthetase was inhibited (67, 68). Remdesivir is effective against the respiratory syncytial virus, coronavirus, Nipah virus, and Hendra viruses, according to subsequent investigations (69). The scientific community reported that this drug was successfully used to treat the first COVID-19 patient in the US (70). Additionally, remdesivir medication given to infected rhesus macaques in the early stages of the infection has been demonstrated to be effective. Additionally, it might prevent pneumonia from becoming harmful (71).

## Biological products

These compounds primarily act to activate the host's defense system, giving it the ability to combat the virus. Active efforts are being made in China to find and create these kinds of anti-SARS-CoV-2 products. IFN, stem cells, and regenerative plasma are some of them.

## Stem cells

Treatment with these cell types will promote the repair of tissue damage by regulating the host defense system and halting the spread of inflammation, particularly in the lungs. Scientific data has shown that mesenchymal stem cells have positive therapeutic effects (78). Currently, MSCs and NK cells are the main targets of stem cell-based therapies. According to these results, the ratio of neutrophils to lymphocytes is also drastically reduced, along with the levels of IL-6 and CRP.

## Vaccines

Vaccines have a vital role in reducing the risk of infection and the severity of illnesses (68). As previous research has demonstrated (79), there are various ways to reduce the severity of infections brought on by SARS-CoV and MERS-CoV. The creation and development of vaccines take more time; it includes the isolation and selection of virus strains, in vitro and in vivo tests, clinical trials, and administrative approval. A total of 115 COVID-19 vaccines, 78 of which were approved for use as of April 8, 2020, were candidates for development. Five of these candidates advanced to the stage of development based on humans. Numerous vaccine varieties (including inactivated, recombinant protein, adenovirus vector, attenuated influenza virus vector live, and nucleic acid) are being thoroughly researched because the virus practically affects every region of the world (80).

## Convalescent plasma

According to research, plasma exchange therapy patients had decreased levels of CRP and IL-6, as well as better lymphocytes and prothrombin times; however, tocilizumab-treated patients' inflammatory markers did not decrease (81). For patients with severe COVID-19, there was also improvement in oxygen saturation, oxygenation index, and inflammatory signs 72 hours after CP infusion (82).

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## Pirfenidone

Idiopathic pulmonary fibrosis is treated with this antifibrotic medication in clinical settings (83, 84). The downregulation of several cytokines, including transforming growth factor (TGF)–1, connective tissue growth factor, platelet-derived growth factors, and TNF—, is one of the hypothesized mechanisms of action (85-89). The expression of the ACE receptor, the main cellular receptor for coronavirus, is downregulated as a result of this agent's ability to scavenge reactive oxygen species. Pirfenidone is a viable COVID-19 therapeutic option because of its anti-apoptotic and anti-fibrotic properties (90-92).

## Zinc supplementation

In aged or immunocompromised patients, zinc restores immunological function and enhances antiviral activity. Zn can have synergistic benefits when combined with conventional antiviral medication.

Zn is effective against different viruses due to physical processes such as virus attachment, infection, and uncoating. Zn will prevent the virus from entering the cell because it may shield or stabilize the cell membrane. Therefore, it might be hypothesized that Zn administration could be employed for COVID-19 prevention and treatment (93).

## Micro-RNA

MiRNAs obstruct the translation pathways by mRNA degradation or blockage by binding to a specific site in ORFs and/or UTRs. Targeted genes will be downregulated or suppressed as a result (94). A new strategy for treatment that combines a variety of miRNAs and 3 UTR may be created (95).

## Green tea and black tea polyphenols are

Tea was tested for its potential antiviral properties using the polyphenols epigallocatechin-3-gallate (EGCG) and theaflavins; the results revealed promising effects against viruses like positive-sense single-stranded RNA viruses. According to recent discoveries, there are binding sites in SARS-CoV-2. Theaflavin-3,3′-gallate, one of the two phenols, in particular, displayed a wonderful interaction with the SARS-CoV3CLpro receptor (96).

## AntagomiRs

Chemically created molecules called antagomiRs can stop a cytokine storm in addition to having a wider variety of activities. They can be injected systemically as a polymer-based nanoparticle that targets miRNAs that are highly associated with inflammatory processes (97, 98). (48).

## Doxycycline

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Doxycycline can take the place of azithromycin because there are some undesirable effects when azithromycin is used in combination with hydroxychloroquine. Doxycycline demonstrated anti-inflammatory properties against several RNA viruses together with other antiviral medications. The mixture improved clinical outcomes and reduced cytokine storms (100). The potential processes could be secondary to intracellular zinc finger antiviral protein transcriptional upregulation (101, 102).

### Metronidazole

Metronidazole reduced levels of several cytokines in preclinical trials, including IL8 (108), IL6 (109), IL1B (110), TNF (111), and interferon (IFN), as well as C-reactive protein (109). It may also lessen reactive oxygen species produced by neutrophils (112).

### Double-Barreled CRISPR Technology

Additionally, new management strategies like CRISPR-Cas-associated gene editing technology may be taken into consideration. The CRISPR-Cas system was discovered in bacteria, and it offers the host cell a built-in defense against invading viruses (113, 114). The host defensive mechanism against viruses is provided when bacteria create a particular CRISPR that attaches to and cleaves one or more areas of the invading viral genetic material (114).

## Conclusion

Numerous problems caused by the COVID-19 pandemic call for an immediate international response. Inflammatory pathways, beta cells, bioactive peptides, platelets, and CD147 were all listed as potential therapeutic targets in this review. A review of the function of doxycycline, metronidazole, and different antivirals in the treatment of COVID-19 was conducted. Further, extensive research is necessary because these drugs have potential benefits.

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