An updated review of potential therapeutic agents against COVID-19

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July 23, 2020

Abstract

Coronavirus disease of 2019 (COVID-19) is a public health emergency of international concern caused by a novel coronavirus, i.e., Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2). Since it is a new virus, an effective remedy against the virus is yet unknown. SARS-CoV-2 is a member of order nidovirales, family coronaviridae. Previously known treatment strategies against Middle East Respiratory Syndrome and Severe Acute Respiratory Syndromes are being tested for their effectiveness against SARS-CoV-2. Thus, various clinical and observational studies aimed at identifying potential therapies against the disease. In our study, we reviewed various drugs along with their mechanism of action including anti-virals, anti-bacterials, glucocorticoids, ACE inhibitors, anti retrovirals, anti-malarials, monoclonal antibodies, plasma and many more. Individual drugs are described and evaluated for their potential to treat SARS-CoV-2 infection. This study offers a brief review of the findings of trials conducted so far. Dexamethasone, convalescent plasma therapy, tocilizumab, remdesivir and combination therapies are found to be beneficial against SARS-CoV-2.

Introduction:

During the last month of the year 2019, certain cases of atypical pneumonia were reported in Huanan Seafood Wholesale Market, Wuhan, a district of Hubei province of China[1]. This idiopathic pneumonia was declared to be caused by a new strain of the coronavirus family, previously unknown to humans, by the research teams. The WHO tentatively named this virus 2019 Novel Corona Virus (nCov-19) in January 2020[2]. Later, the virus was named SARS COV-2 because of the striking resemblance of the genetic sequence of nCoV-19 with the Severe Acute Respiratory Syndrome Coronavirus[3]. This disease has reached almost 213 countries, and territories around the world have reported a total of 12,418,777 cases of COVID-19 that originated from Wuhan, China, and a death toll of 558,082 to date[4]. The details on the pathogenesis of SARS-CoV-2 and its proliferation are uncertain. Hence, no vaccine or treatment guidelines have yet been made for its prevention and cure[5].

Moreover, therapeutic strategies against SARS-CoV-2 depend on the effectiveness of various drugs on other strains of coronavirus, i.e., SARS-CoV and MERS-CoV. Various strategies based on different mechanisms of action are being employed to find a successful treatment agent. Therefore, the review of the COVID- 19 medication is of practical significance. In this study, COVID-19 treatment therapies are thoroughly reviewed.

Methods:

In our study, we extracted the published articles systematically from PubMed, Google Scholar, and EMBASE, using terms “COVID-19”, “SARS-CoV-2”, “nCoV-19” in combination with “treatment,” “therapeutic agents,” “randomized control trials,” “pharmacology,” and “drug therapy” to find articles in which treatment and therapeutic agents against COVID 19 were discussed. All these articles were reviewed by the authors, and related articles were screened out. Out of 6288 articles searched, two authors independently excluded the articles not related to our exclusion criteria unanimously, then the articles for which they dissented whether

those should be included or not, the third author was the tiebreaker, and then the screening was completed without bias. We included only clinical trial reports, in vitro studies, and review articles.

TABLE 1 lies here.....

Results:

Convalescent plasma

Passive immunity is the administration of antibodies against an infective organism for the purpose of prevention and treatment of the disease caused by that agent. Passive immunity has a long-standing history before the development of antimicrobial therapy in the 1940s. However, for certain infections that do not require respondents to antimicrobial therapy, passive immunity is still used for such diseases. An adequate quantity of antibodies must be administered to achieve effective results of the therapy. The protection given by this antibody to the patient depends upon the concentration of the antibodies given and may last for weeks or months. The effectiveness of the sera varies with the type of virus. COVID-19 is an example of such a disease. In the meantime, plasma therapy is used as the best treatment for SARS-COV-2. Experimental studies show that patients with consolidation, extensive lung lesions, Sjogren syndrome, and GGO (GROUND-GLASS OPACIPICATION) treated with plasma therapy discharged healthy from the hospital[55]. According to the study convalescent plasma can be used to prevent diseases among those who are exposed to COVID-19 patients and to treat a patient with early symptoms[24]. However, little information is available on this topic, and fewer patients are used for clinical trials, so more studies and trials are needed.

Ivermectin:

Ivermectin is a broad-spectrum, FDA-approved anti-helminthic drug. It causes hyperpolarization by binding to glutamate-gated chloride channels resulting in paralysis and death of the parasite. It acts through various other unknown mechanisms. Moreover, its anti-viral action is due to its interference with virus entry into the cell. In vitro study of the drugs showed that ~5000-fold reduction in viral load is done by the single dose of ivermectin within 48 hours in cell culture[11]. Clinical trials for the drug are ongoing. These trials aim to determine the efficacy profile, safety, and possible adverse reaction of the combination therapy for hydroxychloroquine and ivermectin in hospitalized patient[41]. However, in vivo and clinical studies needed for the individual therapy for ivermectin.

Imatinib:

Imatinib (Gleevec) is an oral chemotherapeutic drug used for the treatment of various cancers. It acts by blocking tyrosine kinase receptors. The anti-viral activity of the imatinib is because of its ability to inhibit the infusion of virions with the endosomal membrane. Hoffmann et al. indicated that, to enter target cells, SARS-CoV-2 uses ACE2, the cellular protease TMPRSS2, and the SARS-CoV receptor. Imatinib is a potent inhibitor of TMPRSS2 and thus can be used as a treatment option. However, further in-vivo and clinical studies needed with the aim to decide the efficacy profile, safety, and adverse reactions of the drug.

Tocilizumab:

Tocilizumab first humanized recombinant monoclonal antibody used to treat inflammatory and autoimmune conditions. It is an Immunoglobulin belongs to the G1 class (IgG1 class) that interacts with the soluble interleukin 6 receptor (sIL-6R). It is an IL-6 receptor antagonist. IL-6 is a proinflammatory cytokine involved in fibrosis of tissues, metabolism of lipids, T-cells activation. Tocilizumab is FAD approved for the treatment of severe rheumatoid arthritis, systemic juvenile idiopathic arthrit‘is, and the life-threatening CRS associated with chimeric antigen receptor T-cell in pediatric as well as adult patients. Tocilizumab is administered in a dose of 400mg to the COVID-19 patient. Hypertension, gastrointestinal perforations, headaches, and skin reactions are the significant side effects caused by tocilizumab. A dose of 400mg given to 21 COVID-19 patients shows improvement in 91% of patients respiratory function, and successful discharge, with only a single dose[20]. Xu et al. reported in an FDA phase III clinical trials of tocilizumab on patients with COVID-19 that tocilizumab efficiently improve respiratory symptoms and decrease the deterioration of patients.

Under the supervision of IRCCS Institute Nazionale Tumori, IRCCS, Fondazione G. Pascale of Naples, a multicenter study on COVID-19 pneumonia is conducted on 330 patients to test the tolerability and efficacy of tocilizumab in patients with critical COVID-19 pneumonia[35]. To check the efficacy and tolerability of tocilizumab, a multicentered, phase-II, open-labeled, and single-arm clinical trial study has been initiated by the National Cancer Institute, Naples, in treating the patient with COVID-19 pneumonia. A clinical study design to explore the use of tocilizumab in managing COVID-19 patients with suspected pulmonary hyper inflammation has been initiated[41]. It is a randomized, multi-centered, open-label, and two-arm study to test the hypothesis that virus-induced cytokine storm inflammation can be effectively reduced by tocilizumab and results in fast recovery of clinical condition[41]. Tocilizumab has applied intravenously to 20 patients 400 mg once along with the necessary anti-virus treatment. The fever of the patient returned to normal within a few days. Oxygenation was improved by 75%. 90.5% of patients showed a decrease in the opacity lung lesions on CT scans. In addition, In 52.6% of patients, peripheral lymphocytes count normalized. Their data suggest that tocilizumab might prove life-saving in critical patients[30].

Darunavir:

Darunavir is an second-generation HIV-1 protease inhibitor. Researchers in China reported on February 4, 2020, that darunavir could inhibit SARS-CoV-2 infection in vitro. Experimental studies indicated that darunavir at a concentration of 300 μM significantly inhibits in vitro viral replication, and its efficiency was 280-fold in the treated group than that in the untreated group[7]. In trial number NCT04252274[41], darunavir is used in combination with cobicistat for patients with COVID-19 pneumonia. FDA approved this combination therapy for AIDS patients currently. Darunavir is an HIV-1 protease inhibitor, and cobicistat is an inhibitor of cytochrome P450 (CYP3A) that enhance pharmacokinetics and pharmacodynamics of darunavir[41]

Remdesivir:

Formally known as GS-5734, Remdesivir is a prodrug. It is a monophosphate that, through metabolism, forms an active analog (C-adenosine nucleoside triphosphate). Remdesivir is a broad-spectrum anti-viral. The agent was discovered during the trials that screened antimicrobials to find the drug with activity against RNA viruses. It is primarily used to treat Ebola patients in 2015. Now, it is in Phase -II trials to find out its activity against the hemorrhagic fever-induced by the Ebola virus.[41] Remdesivir is an antiviral known to decrease viral replication and hence reduce the viral load. It enters the nascent viral load and causes premature termination. The animal studies on MERS-CoV infected mice showed that the Remdesivir improved the pathological damage and decrease the viral load in the lungs and restore lung functions[41]. Remdesivir is under laboratory trials on cultured cells, animals, and non-human primate models. These trials demonstrated its value as an effective antiviral drug against coronaviruses. An intravenous loading dose of 200mg of remdesivir followed by 100mg for 5 to 10 days proved very useful in current clinical studies[41] Remdesivir is a potent drug for SARS-CoV-2 due to its broad-spectrum activity. It showed its potency in-vitro against several novel coronaviruses, including SARS-CoV-2 with EC50 values of 0.77 μM and an EC90 value of 1.76 μM.[20] Another recent study has shown that Remidesivir blocked viral infection with a half-maximal concentration of 0.77 μM against COVID-19[51].

Chloroquine:

Chloroquine is an anti-malarial drug. It is used to treat chronic inflammatory diseases, including rheumatoid arthritis and systemic lupus erythematosus. Recently, It's broad-spectrum antiviral activity is identified. Chloroquine interferes with the biosynthesis of nucleic acids and caused accumulation of toxic heme metabolite within the parasite, thus killing them. Chloroquine inhibits the production of interleukin-1 and the release of enzymes in the treatment of rheumatoid arthritis. Its anti-viral mechanism of action involves inhibition of glycosylation of SARS-CoV-2 cell receptors blocking viral entering and increasing the pH of endosomes. Chloroquine showed in vitro inhibition of SARS-CoV-2 (EC50 = 1.13 μM). Reports have so far shown that chloroquine phosphate is preferred in managing of pneumonia. It encourages virus-negative transformation and reduces illness duration[41]. 500mg dose of Chloroquine orally once or twice daily proved

very effective[20]. Clinical trials of chloroquine phosphate should be designed in such a way to monitor the possible side effects used by oral use.

Hydroxychloroquine:

Hydroxychloroquine has a similar mechanism of action as chloroquine. Furthermore, Hydroxychloroquine prevents the activation of pro-inflammatory genes. It also reduced the cytokine syndrome via inhibition of T-cell receptors. Anti-inflammatory, as well as the anti-viral role of hydroxychloroquine, proved very potent in combating COVID-19. Hydroxychloroquine is safer than that of chloroquine. EC50 of hydroxychloroquine = 6.14 μM and that of chloroquine is 23.90 μM[20]. The dose of hydroxychloroquine in COVID-19 treatment is 400 mg of loading dose twice for one day, followed by 200 mg twice daily. Dosing needed further studies. Side effects of hydroxychloroquine include hypoglycemia, retinopathy, QTc prolongation, and neuropsychiatric effects. However, no infant ocular toxicity is reported in a review of 12 studies, including 588 pregnant patients[20]. Hydroxychloroquine proved less toxic than chloroquine, but prolonged use is still associated with severe side effects. Considering that most patients are asymptomatic or present with less severe symptoms, the use of dangerous drug Chloroquine and hydroxychloroquine cannot be recommended unless they are proven effective in treatment. Social distancing remains the top priority measure for the prevention of COVID-19.[18]

Siltuximab:

Palanques-Pastor et al suggested the administration of this drug to treat severe SARS CoV-2 infection. This can be achieved due to its interference with IL 6, which in turn leads to decrease binding with its receptors; thus, hyperinflammatory response due to cytokine storm is inhibited. Its half-life suggests that a single intravenous dose can be infused. It is generally well-tolerated, but complete blood count should be done before drug administration. [40]

Favipiravir:

Favipiravir is a drug that directly binds with the enzyme of an RNA virus and inhibits viral infection. This drug has potent anti-influenza activity and has activity against many other RNA viruses. In a controlled and open-label study, 80 confirmed cases of COVID are subjected to a clinical trial in which favipiravir (n=35) is compared with lopinavir/ritonavir (n=45). Both groups received interferon-alpha, and the efficacy of these drugs is compared in both groups. The group which was administered favipiravir shows improvement in symptoms and has less reported adverse effects as compared to the other group.[7] This trial is no longer available due to a lack of authenticity. In another randomized trial, drug Arbidol and favipiravir are compared. [21] Confirmed cases of COVID having moderate and severe infection are subjected to arbidol (n=120) and favipiravir (n=120). Patients having moderate infection show improvement with favipiravir in a week as compared to arbidol. Severely infected patients show no significant improvement. These trials are also not found in the journal due to a lack of placebo.[20]

JAK inhibitors:

Baricitinib is a well-known anti-inflammatory drug and a potent inhibitor of AAK1 involved in endocytosis. The adverse outcome which is reported significantly is upper respiratory tract infection.[9]Although the therapeutic doses reduce inflammation, the infectivity of the virus is not reduced. Therefore, combination therapy can be proved beneficial due to less drug interaction. Combination therapy trials have been initiated. One open-label non-randomized trial uses this therapy to treat moderate and severe patients of COVID-19. Moreover, other trials treat patients with SARS CoV-2 pneumonia with this combination therapy[41].

ACE 2 inhibitors and ARBs:

SARS-CoV-2 binds through ACE 2 receptors found predominantly in the lungs and enters the cells. In a case report, infecting Vero E6 cells with SARS and concomitantly giving human recombinant soluble ACE2 (hrs ACE 2) to check the inhibitory effects of this drug on the viral entry into the cell. The infection is markedly reduced, and similar observations are obtained by infecting human capillary organoids and kidney

organoids. In a prospective study, induced myocardial infarction in rats, which was chronically managed by ATR1 blockers, shows upregulation of cardiac ACE2 receptors. [13]Also, kidney ACE 2 receptors were upregulated in rat studies after this treatment. In humans, this is confirmed by raised urinary ACE 2 levels. Viral entry is responsible for the downregulation of ACE 2 receptors, thereby increasing angiotensin responsible for lung injury. Although this seems paradoxical, ATR1 blockers are therapeutically exploited to prevent acute lung injury. [14]In another randomized clinical trial, confirmed COVID-19 patients (n=500) are treated with ACE 2 inhibitor and ATR1 blockers, and their hospital-stay and disease progression is assessed. This treatment is effective in decreasing the mortality rate as compared to those not taking these drugs.[37]

Colchicine:

In uncontrolled case series, COVID patients (n=9) are treated with colchicine, and the safety of the drug is assessed. Symptoms among most of the patients improved. Early administration of this drug is not beneficial as it impairs the immune response, and it is not effective in the later stages due to organ dysfunctioning by the cytokine storm[53]. There are four ongoing pieces of research on colchicine, which mainly address the topic of losing dose effectiveness in controlling myocardial complications, the response in patients with severe infection, efficacy in pneumonia, and reduction in death rate as a result of short-term treatment with this medicine.[36]

Ribavirin:

Hepatitis B, hepatitis C virus, and RSV infections are treated effectively by ribavirin, which acts as nucleoside analog. A study on Vero cells showed combining ribavirin with interferon-alpha inhibits SARS CoV 2. Ribavirin administration as monotherapy shows that drug resistance is widespread, and combination therapies either with interferon, or lopinavir/ritonavir are fruitful[41]. Another study on Severe SARS-CoV-2 patients treated with ribavirin monotherapy(n=111) and combination therapy (lopinavir/ritonavir) (n=41) shows that later group are at lower risk for developing complications such as acute respiratory distress syndrome and death[7].

Lopinavir/Ritonavir

The same study discussed under the ribavirin section of 41 patients treated with combined therapy had a better safety profile and less severe adverse outcomes. [7]A recent study implies that various drug combinations, in SARS-CoV-2 patients (n=51), including lopinavir/ritonavir were studied and symptoms in these patients were improved[19]. In a case report, a 54-year-old patient who was successfully treated with lopinavir/ritonavir from 10 days of infection shows a decrease in viral loads.[41] In a randomized open-labeled study, COVID patients(n=199) are treated with lopinavir/ritonavir after 13 days from the onset of symptoms. No improvement was reported in these patients because of delay in the administration of these drugs.[20] Further trials are needed to confirm it is efficacy. Various drug interactions and adverse effects limit their use.

Dexamethasone:

A corticosteroid used for its inflammatory role in the patients of COVID-19. Various clinical trials are ongoing to show its efficacy and safety profile. But what we know till now is that dexamethasone doesn't have improve the condition in the patients who don't need respiratory assistance. However, for patients on oxygen therapy and ventilator, results are promising. Death reduced in patient on ventilator by one-third and in patient required oxygen therapy by one-fifth.[56]

Interferons:

Interferons are well-known anti-viral agents that effectively combat viral infections. Pandey et al. briefly described its potential to be used against SARS-CoV-2. Several open-label controlled trails of interferons are being conducted[41]. Interferon monotherapy and combination regimens with other drugs such as

lopinavir/ritonavir and ribavirin are being investigated. The practical role of INF has not been established yet due to insufficient clinical evidence.

Azithromycin:

Azithromycin is a widely used antibiotic for respiratory illness. In our review, we found that Gauret et al. studied the effectiveness of inSARS-CoV-2 infections. In a non-randomized clinical trial, six patients that were previously treated with Hydrochloroquine were administered 500mg on the first day and then 250mg per day subsequently. The findings of the study supported the use of Azithromycin in conjunction with Hydrocholoroqune to effectively decreased the viral load[22]. Pandey et al. briefly reviewed the clinical trials using Azithromycin[41].

Cyclosporine:

Cyclosporine is an immunosuppressive drug derived from natural sources. In the treatment of the SARS-CoV-2 certain studies suggest that the Cyclosporin affects the molecular mechanism of SARS-CoV-2. De Wilde et al. indicates that the siRNA block of the replication of RNA and protein synthesis, thus inhibiting protein synthesis. Therefore, it evident that the cyclosporin can be a potential treatment against SARS-CoV-2[45]. Pandey et al. stated that the cyclosporine potentially prevents the cytokine storm, thus preventing organ damage due to the excessive release of cytokines[41]. However, clinical evidence for the utility of Cyclosporin has not enough supportive evidence to be used as an effective remedy.

Conclusion:

In December 2019, several cases of pneumonia were reported in Wuhan, Hubei province, in China. The agent responsible for this respiratory illness was named SARS-CoV-2. COVID 19 is transmitted to humans through bats and the intermediate host is unknown. People having potential risk factors for this disease are particularly susceptible to this disease. Some develop COVID 19 complications, including acute respiratory distress syndrome, shock, acute renal injury, acute cardiac injury, secondary infection, and death. This disease has reached almost 213 countries /territories/ areas around the world, and it has disturbed the socio-economic status of many countries. This is declared by the World Health Organization(WHO) as a pandemic in March 2020. It has become a public health emergency of international concern (PHEIC) as declared by the World health organization (WHO). Early reported cases had the contact history of the Huanan seafood market. Human to human transmission occurs via respiratory droplets. Social distancing is the only way to reduce the spread of COVID-19. Symptomatic and supportive treatment can help reduce the severity of the disease. They are thus raising the primary concern for controlling this infection. Vaccine for COVID 19 has to go through a vigorous trial process. Potential therapeutic drugs and plasma could help manage patients with mild, moderate, and severe coronavirus disease.

Our article summarizes case reports, case series, randomized control trials, in vitro studies, and prospective drug reviews. Therapeutic strategies are considered for the treatment of COVID 19. As many diseases involve the same molecular basis, investigating the already existing drugs for therapeutic purposes can help us to develop drugs within a short period for COVID 19. This core approach is one strategy to deal with this worldwide pandemic. Due to the slow pace of newly discovered drugs, we consider those drugs with already established pharmacokinetic profile and efficacy in drug reprofiling. Our article covers the repurposed drugs suggested in various journals and the methodological framework suggested by them. The detailed study of their mechanism of action shows that they act by one of these mechanisms, i.e., blocking viral entry, inhibiting endocytosis, decreasing cytokine storm, reducing viremia, by modulating the inflammatory response and viral replication.

Various drugs have been identified for treating SARS CoV 2 infection previously used for other coronavirus diseases. Although the efficacy of these drugs is not established, multiple clinical trials and in vitro studies are being carried out to check the safety profile of these drugs. Combination therapy of various antivirals like lopinavir/ritonavir with ribavirin shows promising results. Little information about convalescent plasma is there, and more clinical trials are needed. Angiotensin-converting enzyme inhibitors or angiotensin receptor

blockers show promising results in decreasing the mortality rate as compared to those not taking these drugs. In critically ill patients, tocilizumab use may prove life-saving. Clinical trials on remdesivir suggest that it has in vitro activity and can act as a potent drug in COVID 19 patients. Possible side effects of chloroquine and hydroxychloroquine limit its use. The combined use of azithromycin and hydroxychloroquine shows promising results. Severe SARS-CoV-2 infection can be managed by steroids, but its routine administration is not recommended. Clinical evidence of these drugs can be established by further studies on animals, cells, and humans.

Among the 50 articles included in our review, most of them are RCT and in vitro studies. Our review provides information on understanding the potential therapeutic strategies and clinical outcomes of using several drugs. Although no specific treatment is available, various strategies are used for managing COVID patients, including antivirals, antibacterial drugs, steroids, oxygen mask, invasive, and non-invasive ventilation. Studies in this domain are needed to control the pandemic.

Acknowledgement:

None/Not applicable

Conflict of interest statement:

The authors declare no conflicts of interest.

Funding information:

Not applicable

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Tables:

Study	Method	Therapeutic agents	Mechanism of Action
Chen et al (2020) [6]	Brief Review	Convalescent Plasma	Suppress viremia which peaks in first week of illness
Dong et al (2020) [7]	a) In vitro b) In vitro c) In vitro d) In vitro e) In vitro	INF alpha, Lopinavir /Ritonavir, Ribavirin , Chloroquine, Arborol Favipiravir Remedesivir Darunavir Imatinib	SARS-CoV Reproduction inhibit Anti-influenza drug, RNA polymerase inhibitor Nucleoside analogue HIV Protease inhibitor, inhibit viral replication blocks the fusion of virus with endosomal membrane
Cortegiani et al (2020) [8]	Brief review	Chloroquine	increase endosomal pH and interfere with the glycosylation of cellular receptor of SARS-CoV results in blocking virus infection. Enhances antiviral effect in vivo via immune modulant effect

Study	Method	Therapeutic agents	Mechanism of Action
Stebbing et al (2020) [9]	a) Brief review b) Brief review	Baricitinib, fedratinib, ruxolitinib Sunitinib, erlotinib,	JAK STAT signaling inhibitor effective against elevated levels of cytokines NAK inhibitor, reduce viral infection in vitro
XU et al [10]	Screening	Tocilizumab	Binds sIL-6R and mIL-6R and inhibit signal transduction
Caly et al (2020) [11]	In vitro	Ivermectin	Inhibits replication of SARS –CoV-2
Monteil et al [12]	In vitro	Human recombinant soluble ACE-2	Blocks growth of SARS-CoV-2
Gurwitz et al (2020) [13]	Review	Losartan	Angiotensin receptor blocker (AT1R), increases ACE expression in SARS –CoV-2 patient
Chen et al (2020) [14]	In vitro	Ledipasvir, Velpatasvir, Sofosbuvir, Etoposide, Diosmin, Hespiridin	Block enzyme and the active site of SARS-CoV-2
Wang et al (2020) [15]	In vitro	Human monoclonal antibody	Targeting trimeric spike (S) glycoprotein of SARS-CoV-2
Liu et al (2020) [16]	In vitro	Hydroxychloroquine	Antiviral less toxic derivative of CQ

Study	Method	Therapeutic agents	Mechanism of Action
Dong et al (2020) [17]	a) In vitro b) In vitro and clinical c)Clinical d)In vitro and clinical e) In vitro f) In vitro g) Animal experiments h) In vitro	INF alpha Lopinavir/Ritonavir Ribavirin Chloroquine Arbidol Favipiravir Remdesivir Darunavir	Inhibits SARS CoV reproduction. FDA approved antiviral-broad spectrum drug used to treat hepatitis Anti SARS CoV activity Nucleoside analog with broad spectrum antiviral activity Anti-malarial blocks SARS CoV infection at low micro molar concentration Antiviral drug used to treat influenza and inhibit SARS-CoV-2 infection Anti influenza drug having RNA dependent RNA polymerase inhibitor activity Broad spectrum antiviral drug act as nucleoside analog reduce viral load in lung tissue Second generation of HIV 1 protease inhibitor inhibit SARS CoV infection
Nicholas Moore [18]	In vitro and experimental data	Chloroquine	Inhibit corona virus replication
Ali Rismanbaf [19]	Review	Chloroquine, Remdesivir, Teicoplanin, Lopinavir, Remdesivir, Atazanavir, Efavirenz Ritonavir, Lithium, ACE inhibitors and many others	Reduce viral infection due to SARS CoV 2

Study	Method	Therapeutic agents	Mechanism of Action
Sanders et al [20]	a) In vitro b) In vitro c)In vitro d)In vitro e) In vitro f) In vitro g) In vitro	Chloroquine phosphate Hydroxychloroquine Sulfate Lopinavir/ritonavir Makeover Remdesivir Favipiravir Tocilizumab	Blockade of viral entry via Inhibition of glycosylation of host receptors, endosomal acidification, and proteolytic processing Immunomodulatory effects through autophagy inhibition of cytokine production, and lysosomal activity in host cells Hydroxychloroquine shares the same mechanism of action as chloroquine 3CL protease S protein/ACE2, membrane fusion inhibitor RNA polymerase inhibitor RNA polymerase inhibitor IL-6 inhibition-reduction in cytokine storm
Yavuz et al (2020) [21]	a) In vitro and clinical trial b) In vitro and clinical trial c)In vitro and clinical trial d)In vitro and clinical trial E) In vitro and clinical trial f) In vitro g) In vitro	Remdesivir Favipiravir Lopinavir/ritonavir Hydroxychloroquine Chloroquine Nitazoxanide Ivermectin	Adenosine nucleotide analogue, prodrug, RdRp inhibitor Guanosinenucleotid analogue, prodrug, RdRp inhibitor Protease inhibitor Increase pH of endosomes required for virus cell fusion and block the glycosylation of cellular receptors of ACE-2 Increase pH of endosomes required for virus cell fusion and block the glycosylation of cellular receptors of ACE-2 Amplifying cytoplasmic RNA sensing, Interference with host-regulated pathways involved in viral replication, and interfere with type I IFN pathways Inhibit importin 1 heterodimer thus block nuclear import of host and viral protein

Study	Method	Therapeutic agents	Mechanism of Action
Gautret et al (2020) [22]	a) non-randomized clinical trial b) non-randomized clinical trial	Hydroxychloroquine Azithromycin	Increase pH of endosomes required for virus cell fusion and block the glycosylation of cellular receptors of ACE-2 In vitro effective against Ebola and Zika virus, combined with hydroxychloroquine to inhibit SARS CoV 2 activity
Gao et al [23]	Brief review	Chloroquine phosphate	Anti-inflammatory and anti-viral activity
Casadevall et al [24]	Perspective	Convalescent sera	Passive immunity
Guo et al [25]	Review	Serum. Remdesivir, IgG, Chloroquine, IFN-alpha, IL-6, Lopinavir/ritonavir	Autophagy inhibition, interference with receptor glycosylation
Zhao et al [26]	In vitro study	Plasma	Antibody response detection in COVID patients
Yao et al [27]	In vitro study	Chloroquine, Hydroxychloroquine	Inhibition of SARS-CoV-2
Fu et al [28]	Review	Immunoglobulins	FcR activation blockage
Vincent et al [29]	In vitro study	Chloroquine	SARS-CoV-2 inhibition
Zhang et al [30]	Structural X-ray analysis	Alpha ketomide inhibitor	Inhibition of M protease
H Zhang et al [31]	Review	Camostat Mesylate	Protease inhibitor
Nguyen et al [32]	Perspective	CRISPR/Cas13d technology	Functional disruption of the virus
Bouadma et al [33]	Review	Remdesivir, corticosteroids	Anti-inflammatory effects
Poe et al [34]	In vivo, in vitro and clinical trials	N-Acetylcysteine	Anti-oxidant and increase glutathione synthesis thus decreasing viral load, anti-inflammatory

Study	Method	Therapeutic agents	Mechanism of Action
Bimonte et al [35]	a) In vitro and clinical trial b) In vitro and clinical trial c)In vitro and clinical trial d)Review e) In vitro and clinical trial	Lopinavir/ritonavir Ribavirin Chloroquine phosphate Remdesivir Neuraminidase inhibitors Tocilizumab	Protease inhibitor Nucleoside anlog inhibiting viral replication and protein synthesis Inhibition of SARS-CoV-2 Adenosine nucleotide analogue, prodrug, RdRp inhibitor Block neuraminidase enzyme Recombinant humanized monoclonal antibody binding to IL 6 receptors both soluble and membrane bounded
ANDREOU et al [36]	a)In vitro b)In vitro c)In vitro d)In vitro	Copper and N-acetylcysteine (NAC) Remdesivir Colchicine Nitric Oxide (NO)	Anti-oxidant and anti-inflammatory RNA polymerase inhibitor anti-inflammatory Vasodilatory effects on pulmonary vessels
Lopes et al [37]	Randomized trial	Angiotensin converting enzyme inhibitors and angiotensin receptor blockers	Decreasing the production of angiotensin and blocking its receptors, reduces lung injury
Ayaz et al [38]	In vitro	Polycomb inhibitors	Plays a role in modulating viral replication by inhibiting replication of viruses
Shu et al [39]	In vitro	Bismuth Salts	Inhibit both the NTPase and RNA helicase activities of SARS-CoV-2
Palanques-Pastor et al [40]	Clinical trial	siltuximab	IL-6 blockers

Study	Method	Therapeutic agents	Mechanism of Action
Pandey et al [41]	a) In vitro b) Clinical trial c)Clinical trial d)Clinical trial e) Clinical trial f) Clinical trial g) In vitro h) In vitro i)In vitro j) Review k) In vitro l)In vitro m)In vitro n) In vitro o) In vitro p) In vitro q) In vitro and clinical trial r) In vitro s) In vitro t) Clinical trial u) In vitro	Metal ions Chloroquine Hydroxychloroquine Lopinavir and Ritonavir Remdesivir Ribavirin Arbidol Favipiravir Darunavir Oseltamivir Interferons Azithromycin Teicoplanin Sirolimus Baricitinib Cyclosporine Tocilizumab Ivermectin ACE 2 inhibitors Convalescent plasma Tetracycline	Protease inhibitor Inhibit COVID 19 Same as Chloroquine Protease inhibitor Adenosine nucleotide analog inhibit viral replication Viral protein synthesis inhibitor Viricidal RNA polymerase inhibitor Inhibit viral replication Prevent release of virus from infected cell SARS CoV 2 inhibitors Interferes with viral entry Inhibits viral entry Inhibit IL 2 dependent lymphocyte proliferation by inhibiting mammalian kinase Janus kinase (JAK) inhibitor Reduce viral load by binding with RNA dependent RNA polymerase of virus Recombinant humanized monoclonal antibody Inhibit viral replication Blocking viral entry Suppress viremia Antiviral activity, Decreases severity of infection
Ibáñez et al [42]	In vitro and clinical trial	Hydroxychloroquine and chloroquine	Inhibit viral entry and anti-inflammatory
Rilinger et al [43]	Perspective	Tocilizumab	Anti-inflammatory
Sarma et al [44]	Clinical trial	Hydroxychloroquine	Blocks viral infection
Wilde et al [45]	In vitro	Cyclosporin A	Inhibited coronavirus replication
Abeygunasekera et al [46]	Brief review	Diethylcarbamazine	Immune modulatory, Enhance antibody production, antiviral activity
Biembengut et al [47]	In silico approach.	Coagulation modifiers	Targeting SARS-CoV-2 main protease Mpro
Irvani et al [48]	Perspective	Interferon Beta 1a, compared to Interferon Beta 1b	
Tan et al [49]	In vitro	Betaferon, Alferon, Multiferon, Wellferon, and ribavirin	Inhibit cytopathic effect in SARS CoV 2

Study	Method	Therapeutic agents	Mechanism of Action
Chu et al [50]	In vitro	Lopinavir/ritonavir	Inhibit cytopathic effect of the SARS CoV2
Vellingiri et al [51]	a) Brief review b) Brief review c)Brief review d)Brief review e) Brief review f) Brief review g) Brief review	Ribavirin Sofosbuvir Lopinavir/Ritonavir Remidesivir Chloroquine Favipiravir Indian medicinal plant	Inhibit RNA polymerase of the virus Nucleotide polymerase inhibitor Protease inhibitor Causes premature termination by entering the nascent viral RNA Immune modulating properties Anti-viral drug Provide raw material for antiviral effects
W Zhang et al [52]	a) Brief review b) Brief review c)Brief review d)Brief review	Glucocorticoids Tocilizumab JAK inhibitors Chloroquine and hydroxychloroquine	Immunomodulatory therapy Recombinant humanized monoclonal antibody binding with IL 6 receptors Interferes with cytokine and reduce inflammation Block viral entry into the cell
Torre et al [53]	Clinical trial	Colchicine	Causes tubulin disruption, anti-inflammatory
Rosenberg et al [54]	Retrospective multicenter cohort study of patients	Hydroxychloroquine or Azithromycin	Suppression of the activity of SARS CoV 2
YE et al [55]	Clinical trial	Convalescent plasma	Reduce viremia
Yang Z et al [56]	Clinical trial	Dexamethasone	Anti-inflammatory