CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.3972085

Available online at: http://www.iajps.com *Review Article*

AN UPDATED REVIEW OF POTENTIAL THERAPEUTIC AGENTS AGAINST COVID-19

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Article Received: June 2020 **Accepted:** July 2020 **Published:** August 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, antimalarials, 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.

Keywords: Coronavirus, SARS-CoV-2, COVID-19, treatment, therapeutic agents, drugs

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Please cite this article in press Shahzaib Ahmad et al, ***An Updated Review Of Potential Therapeutic Agents Against Covid-19.,*** *Indo Am. J. P. Sci, 2020; 07(08).*

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 China1. 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 20202. 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 Coronavirus3. 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 date4. 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 cure5.

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 from January 10, 2020, to April 10, 2020. The authors reviewed all these articles, 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. Then the screening was completed without bias following PRISMA guidelines. We included only clinical trial reports, in vitro studies, and review articles.

Tables:

Study	Method	Therapeutic agents	Mechanism of Action
Chen et al (2020) [6]	Brief Review	Convalescent Plasma	Suppresses viremia which peaks in first week of illness
Dong et al (2020) [7]	a) In vito	INF alpha, Lopinavir /Ritonavir, Ribavirin , Chloroquine, Arabidol	SARS-CoV-2 reproduction inhibitor
	b) In vitro	Favipiravir	Anti-influenza drug, RNA polymerase inhibitor
	c) In vitro	Remedesivir	Nucleoside analogue
	d) In vitro	Darunavir	HIV Protease inhibitor, inhibits viral replication
	e) In vitro	Imatinib	Blocks the fusion of virus with endosomal membrane
Cortegiani et al (2020) [8]	Brief review	Chloroquine	Increases endosomal pH and interfere with the glycosylation of cellular receptor of SARS-CoV-2 results in blocking virus infection. Enhances antiviral effect in vivo via immune modulant effect
Stebbing et al (2020) [9]	a) Brief review	Baricitinib, fedratinib, ruxolitinib, Sunitinib, erlotinib,	JAK-STAT signaling inhibitor effective against elevated levels of cytokines
XU et al [10]	Screening	Tocilizumab	Binds sIL-6R and mIL-6R and inhibits 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	Targets trimeric spike (S) glycoprotein of SARS-CoV-2
Liu et al (2020) [16]	In vitro	Hydroxychloroquine	The antiviral less toxic derivative of CQ
Shen et al (2020)[17]	Clinical Trial	Convaalescent Plasma	Reduces viremia
Nicholas Moore [18]	In vitro and experimental data	Chloroquine	Inhibits coronavirus replication
Ali Rismanbaf [19]	Review	Chloroquine, Remdesivir, Teicoplanin, Lopinavir, Remdesivir, Atazanavir, Efavirenz Ritonavir, Lithium, ACE inhibitors and many others	Reduces viral infection due to SARS-CoV-2
Sanders et al. [20]	a) In vitro	Chloroquine phosphate	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
	b) In vitro	Hydroxychloroquine sulfate	Hydroxychloroquine shares the same mechanism of action as chloroquine
	c)In vitro	Lopinavir/ritonavir	3CL protease
	d)In vitro	Umifenovir	S protein/ACE2 membrane fusion inhibitor
	e) In vitro	Favipiravir, Remdesivir	RNA polymerase inhibitor
	f) In vitro	Tocilizumab	IL-6 inhibition- reduction in cytokine storm
Yavuz et al. (2020) [21]	a) In vitro and clinical trial	Remdesivir	Adenosine nucleotide analog, prodrug, RdRp inhibitor
	b) In vitro and clinical trial	Favipiravir	Guanosinenucleotid analogue, prodrug, RdRp inhibitor
	c) In vitro and clinical trial	Lopinavir / Ritonavir	Protease inhibitor
	d) In vitro and clinical trial	Hydroxychloroquine	Viral inhibitor

	e) In vitro and clinical trial	Chloroquine	Viral inhibitor
	f) In vitro	Nitazoxanide	Amplifies cytoplasmic RNA sensing, Interference with host-regulates pathways involved in viral replication, and interferes with type I IFN pathways
	g) In vitro	Ivermectin	Inhibits importin 1 heterodimer thus blocks nuclear import of host and viral protein
Gautret et al (2020) [22]	a) non-randomized clinical trial	Hydroxychloroquine	Increases pH of endosomes required for virus-cell fusion and block the glycosylation of cellular receptors of ACE-2
	b) non-randomized clinical trial	Azithromycin	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
Devaux et al [26]	In vitro study	Chloroquine	Anti viral activity
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	Antioxidant and increase glutathione synthesis thus decreasing viral load, anti-inflammatory
Bimonte et al. [35]	a) In vitro and clinical trial	Lopinavir/ritonavir Ribavirin	Protease inhibitor Nucleoside analog inhibiting viral replication and protein synthesis
	b) In vitro and clinical trial	Chloroquine phosphate	Inhibition of SARS-CoV-2
	c) In vitro and clinical trial	Remdesivir	Adenosine nucleotide analogue, prodrug, RdRp inhibitor
	d) Review	Neuraminidase inhibitors	Blocks neuraminidase enzyme
	e) In vitro and clinical	Tocilizumab	Recombinant humanized

	trial		monoclonal antibody binding to IL 6 receptors both soluble and membrane bounded
ANDREOU et al [36]	a) In vitro	Copper and N-acetylcysteine (NAC)	Anti oxidant and anti-inflammatory
	b) In vitro	Remdesivir	RNA polymerase inhibitor
	c) In vitro	Colchicine	Anti-inflammatory
	d) In vitro	Nitric Oxide (NO)	Vasodilatory effects on pulmonary vessels
Lopes et al [37]	Randomized trial	Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	Decreases 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	Inhibits both the NTPase and RNA helicase activities of SARS-CoV-2
Palanques-Pastor et al [40]	Clinical trial	siltuximab	IL-6 blockers
Pandey et al [41]	a) In vitro	Metal ions	Protease inhibitor
	b) Clinical trial	Chloroquine	Inhibits COVID-19
	c) Clinical trial	Hydroxychloroquine	Same as Chloroquine
	d) Clinical trial	Lopinavir and Ritonavir	Protease inhibitor
	e) Clinical trial	Remdesivir	Adenosine nucleotide analog inhibits viral replication
	f) Clinical trial	Ribavirin	Viral protein synthesis inhibitor
	g) In vitro	Arabidol	Viricidal
	h) In vitro	Favipiravir	RNA polymerase inhibitor
	i) In vitro	Darunavir	Inhibits viral replication
	j) Review	Oseltamivir	Prevents release of virus from infected cell
	k) In vitro	Interferons	SARS-CoV-2 inhibitors
	l) In vitro	Azithromycin	Interferes with viral entry
	m) In vitro	Teicoplanin	Inhibits viral entry
	n) In vitro	Sirolimus	Inhibits IL 2 dependent lymphocyte proliferation by inhibiting mammalian kinase
	o) In vitro	Baricitinib	Janus kinase (JAK) inhibitor
	p) In vitro	Cyclosporine	Reduces viral load by binding with RNA dependent RNA polymerase of virus
	q) In vitro and clinical trial	Tocilizumab	Recombinant humanized monoclonal antibody
	r) In vitro	Ivermectin	Inhibits viral replication
	s) In vitro	ACE 2 inhibitors	Blocking viral entry
	t) Clinical trial	Convalescent plasma	Suppresses viremia
	u) In vitro	Tetracycline	Antiviral activity, decreases severity of infection

Ibáñez et al [42]	In vitro and clinical trial	Hydroxychloroquine and chloroquine	Inhibits 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, enhances 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
Chu et al [50]	In vitro	Lopinavir/ritonavir	Inhibit cytopathic effect of the SARS CoV2
Vellingiri et al [51]	a) Brief review	Ribavirin	Inhibit RNA polymerase of the virus
	b) Brief review	Sofosbuvir	Nucleotide polymerase inhibitor
	c) Brief review	Lopinavir/Ritonavir	Protease inhibitor
	d) Brief review	Remdesivir	Causes premature termination by entering the nascent viral RNA
	e) Brief review	Chloroquine	Immune modulating properties
	f) Brief review	Favipiravir	Anti-viral drug
	g) Brief review	Indian medicinal plant	Provide raw material for antiviral effects
W Zhang et al [52]	a) Brief review	Glucocorticoids	Immunomodulatory therapy
	b) Brief review	Tocilizumab	Recombinant humanized monoclonal antibody binding with IL 6 receptors
	c)Brief review	JAK inhibitors	Interferes with cytokine and reduce inflammation
	d)Brief review	Chloroquine, Hydroxychloroquine	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	Reduces viremia
Yang Z et al [56]	Clinical trial	Dexamethasone	Anti-inflammatory

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, an anti-helminthic drug, targets glutamate-gated chloride channels causing hyperpolarization and paralysis of the parasite. It acts through various other unknown mechanisms. It inhibits viral entry into the cell when used to treat viral infections. In vitro study of the drugs showed that ~5000-fold reduction in viral load is made 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 the hospitalized patient[41]. However, in vivo and clinical studies needed for the individual therapy for ivermectin.

Imatinib:

Imatinib (Gleevec), a chemotherapeutic drug, 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 (Actemra) is the first humanized recombinant monoclonal antibody used to treat inflammatory and autoimmune conditions. It binds with soluble IL-6 receptors and inhibits IL-6 mediated response, including T-cell activation and tissue fibrosis. 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]. Phase 3 clinical trial in COVID 19 patients showed tocilizumab treatment was more likely to yield clinical improvement. [10] A multicentered study is conducted on COVID-19 patients having pneumonia (n=330) to check the efficacy and safety of tocilizumab. [35] 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 the clinical condition[41]. Tocilizumab was administered 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 of the lungs 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:

China researchers reported in vitro activity of darunavir suggests that it can be used to inhibit SARS CoV 2 infection. 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. Cobicistat, when used in combination with darunavir, enhances its activity. [41]

Remdesivir:

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 showed its meaningful activity 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] In vitro, it showed its potency 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 Remdesivir 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, its broad-spectrum antiviral activity is identified. 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 in 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 of therapy41.

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. 13Also, 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 is 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 delays 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 so far is that dexamethasone didn't improve the condition in the patients who didn't require respiratory support. However, for patients on oxygen therapy and ventilator, results are promising. Death reduced in patients on a ventilator by one-third and by one-fifth in patient required oxygen therapy.[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 trials of interferons are being conducted41. 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 load22. Pandey et al. briefly reviewed the clinical trials using Azithromycin41.

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 is evident that cyclosporin can be a potential treatment against SARS-CoV-245. Pandey et al. stated that the cyclosporine potentially prevents the cytokine storm, thus preventing organ damage due to the excessive release of cytokines41. 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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