

---

## Therapeutic Management for Covid-19: A Pandemic Disease – An Evidence Based Design

Sairam Pasam<sup>1</sup>, Vasudha Bakshi<sup>2</sup>, Narender Boggula<sup>2\*</sup>

<sup>1</sup>Samskruti College of Pharmacy, Kondapur, Ghatkesar, Hyderabad, Telangana, India.

<sup>2</sup>School of Pharmacy, Anurag University, Venkatapur, Ghatkesar, Hyderabad, Telangana, India.

**\*Corresponding Author**

Email Id: narender.b987@gmail.com

---

### ABSTRACT

Since the 2019 novel coronavirus disease (COVID-19) outbreak originated from Wuhan, Hubei Province, China, at the end of 2019, it has become a clinical threat to the general population worldwide. Among people infected with the novel coronavirus (2019-nCoV), the intensive management of the critically ill patients in intensive care unit (ICU) needs substantial medical resource. The unexpected pandemic set off by the novel coronavirus 2019 (COVID-19) has caused severe panic among people worldwide. COVID-19 has created havoc, and scientists and physicians are urged to test the efficiency and safety of drugs used to treat this disease. In such a pandemic situation, various steps have been taken by the government to control and prevent the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This pandemic situation has forced scientists to rework strategies to combat infectious diseases through drugs, treatment, and control measures. COVID-19 treatment requires both limiting viral multiplication and neutralizing tissue damage induced by an inappropriate immune reaction.

Currently, various diagnostic kits to test for COVID-19 are available, and repurposing therapeutics for COVID-19 has shown to be clinically effective. More research is required for further understanding of the influence of diagnostics and therapeutic approaches to develop vaccines and drugs for COVID-19. Currently, no medication is recommended to treat COVID-19, and no cure is available. Anti-biotics aren't effective against viral infections such as COVID-19. Researchers are testing a variety of possible treatments. The FDA granted permission for some medications approved for other diseases to be used to treat severe COVID-19 when no other options are available. SARS-CoV-2 is a newly emerging human infectious coronavirus that causes COVID-19, which has been recognized as a pandemic by the World Health Organization (WHO) on March 11 2020. There is still no vaccine or definitive treatment for this virus because its pathogenesis and proliferation pathways are still unknown. Therefore, in this article, new potential COVID-19 therapies are briefly reviewed. Currently, various diagnostic kits to test for COVID-19 are available and several repurposing therapeutics for COVID-19 have shown to be clinically effective. In addition, global institutions and companies have begun to develop vaccines for the prevention of COVID-19. We hope that this review will provide useful and most updated therapeutic drugs to prevent, control, and treat COVID-19 patients until the approval of vaccines and specific drugs targeting SARS-CoV-2.

**Keywords:** COVID-19, SARS-CoV-2, current diagnostics, remdesivir, hydroxychloroquine, convalescent plasma therapy, acute respiratory distress syndrome (ARDS).

---

## **INTRODUCTION**

The world has seen the onset of a pandemic of a new infectious disease from December 2019. This has been formally named as the Corona Virus Infectious Disease (COVID)-19 by a consensus group of WHO experts. Numerous clusters of patients started to surface in Wuhan, Hubei Province, China in mid-December 2019. They presented with features of a viral respiratory illness with complaints of fever, cough, headache and breathlessness. Some of the patients had evidence of respiratory failure, shock, acute respiratory distress syndrome (ARDS) and sepsis [1, 2].

The current global pandemic due to the highly contagious COVID-19 infection is rapidly spreading in many countries with a high number of deaths. Many communities and countries have enforced restrictions, permitting only essential activities. Health systems around the globe are currently preparing to manage the surge of the influx of critically ill patients. During this phase, care providers, administrators, and policymakers work in concert to understand and combat this deadly pandemic. The current knowledge about COVID-19 is limited but rapidly evolving. During this outbreak, the medical community used evidence gleaned from past outbreaks of SARS-CoV and MERS-CoV to predict COVID-19's behaviour, clinical presentation and treatment. In addition, corona viruses are known to cause signs and symptoms of multi-organ system damage, many of which are subtle and can go unnoticed by trained medical professionals. Furthermore, frontline healthcare personnel lack a comprehensive review of the numerous clinical pulmonary and extra-pulmonary manifestations of deadly corona viruses making self-education time consuming [3-5].

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is a newly emerging human infectious coronavirus, originated in Wuhan, China, and has been spreading rapidly in China and other countries since December 2019. The World Health Organization (WHO) also declared a global emergency on January 31<sup>st</sup> due to increasing concerns over its fast spread, and on March 11<sup>th</sup> the disease was recognized as a pandemic. Since the bases for pathogenesis of this virus and its proliferation is unclear, there is still no vaccine or definitive treatment against it. Thus, medications used against SARS-CoV-2 are mainly based on their effectiveness on earlier strains of coronavirus, SARS-CoV and MERS-CoV. Therefore, the immediate introduction of potential COVID-19 treatments can be essential and salvaging. In this article, new potential COVID-19 therapies are briefly reviewed [6,7].

In the absence of definitive and specific treatment regimens, strategies including early diagnosis, timely reporting, isolation, and supportive treatments are important line of actions against COVID-19 infections. Current social practices including timely release of epidemic information and maintenance of social orders and personal practices such as improving personal hygiene, wearing facial coverings or masks, adequate rest, and keeping rooms well ventilated remain some of first line of actions against COVID-19 pandemic [8,9].

At present, the treatments of patients with SARS-CoV-2 infection are mainly repurposing the available therapeutic drugs and based on symptomatic conditions. Considering ARDS, followed by secondary infections, antibiotics, antiviral therapy, systemic corticosteroids, and anti-inflammatory drugs (including anti-arthritis drugs) are often used in the treatment regimens. In addition to anti-viral interferers and anti-biotics, neuraminidase inhibitors, RNA synthesis inhibitors, convalescent plasma, and traditional herbal medicines have also been

utilized in the treatment of COVID-19. Nevertheless, the efficacy of these treatment regimens remains to be verified by appropriately designed clinical trials [10,11].

### **Prevention of COVID-19 Entry and its Transmission**

WHO Director General constitutes a Public Health Emergency of International Concern for the outbreak of COVID-19, recommends the options to prevent the disease in new areas and possible reduction in human-to-human transmission to curtail its further spread that can be achieved by the strict quarantine, which involves the movement restriction or separation from the rest of the population with sustained and intense hygiene measures. Avoiding mass gatherings in enclosed spaces, maintaining the distance of at least 1 meter from any person with respiratory symptoms (e.g., coughing, sneezing), wearing a medical mask for an adequate level of protection combined with hand hygiene frequently by using an alcohol-based hand rub or soap is recommended [12]. The people who develop respiratory complications during quarantine period should be specially treated and managed as a suspected case of COVID-19 and further tests should be required to confirm whether positive or negative. The front-line healthcare personnel must use the personal protective equipment (PPE) includes N95 or FFP2 standard masks, gowns, gloves, eye protection shields to protect themselves, patients, and others when providing the care [13].

### **The Current Update and Possible Treatment Options for Management of COVID-19**

Renin angiotensin system (RAS) inhibitors in SARS-CoV-2 patients RAS and ACE2 inhibitors are widely used in treating patients with hypertension. As described earlier ACE2 is the target receptor for SARSCoV-2 and is highly expressed in epithelial cells in the oral mucosa. Additionally, this protein is widely expressed in immune reactive cells such as macrophages, lungs, blood vessels and intestine. Clinical findings suggest that circulating ACE2 levels were significantly increased in diabetic and cardiovascular patients, however, this protein is aberrantly expressed with ACE inhibitors lisinopril alone. But the ACE2 activity is not altered correspondingly, while cardiac ACE2 mRNA expression was increased with RAS receptor inhibitor losartan. Combination of losartan and lisinopril did not affect the ACE2 activity compared with Losartan alone, but on other side, ACE2 mRNA was highly expressed with losartan alone. Thus, there is a lack of correlation between up and down expression of ACE2 mRNA with ACE2 activity [14-16].

However, there is a debate on the use of RAS and ACE inhibitors in SARS-CoV-2 pneumonia infections and few clinical trials are going on for the usage of Losartan among patients who have not previously administered with RAS inhibitors and are either hospitalized or not hospitalized. The selective ACE2 inhibitor DX600 might show beneficial results in SARS-CoV-2 infections; however, its clinical significance in COVID-19 has not evaluated. Further, in one promising study, circulating recombinant human soluble ACE2 protein upon intravenous administration produced significant blockade of initial stages of SARS-CoV-2 viral entry and infections by preventing the binding of viral spike protein onto cell host cell surface ACE2 receptor [17, 18].

### **Vaccines**

The epidemics of SARS (2003), MERS (2012) and the recent SARS-2 (2019) has generated a lot of interest in the preventive strategies like the drug chemoprophylaxis for health care individuals and close contacts of index patients of the COVID-19. The role of drugs has been discussed in a separate section. After the SARS epidemic in 2003, various researchers all

over world got in the effort of developing a candidate vaccine for the same. There are about 43 vaccines that have been developed. However, most of them are in the pre-clinical phase. They are yet to undergo phase 1 randomized trials in humans [18-20].

These vaccines are DNA, inactivated, live attenuated vaccines (LAV), viral vector based (non-replicating) protein sub-unit vaccines and other 6 unknown vaccine types. One of the RNA based vaccines (LNP-encapsulated mRNA) has been made available for the phase 1 clinical trial in humans. This vaccine has been developed by collaborative effort of scientists at NIAID/NIH and a biotechnology company (Moderna Therapeutics) in USA. The clinical trial began in mid-March 2020 and has already enrolled few patients in Seattle, USA (NCT04283461). It will study the efficacy and adverse reactions of the candidate vaccine in 45 adult volunteers from 18 to 55 years of age. Another vaccine that has gone in phase 1 clinical trial is a non-replicating viral vector vaccine (ChiCTR2000030906). It has been bioengineered by using an adenovirus vector (type 5) at Beijing Institute of Biotechnology and CanSino Biological Inc. It uses the same platform as was used for developing a vaccine for Ebola virus. However, this is just the beginning and it will take 12-18 months for the trial to complete and have the data to interpret for antibody response and long-term efficacy [21, 22].

### **Anti-malarial drugs**

Chloroquine and hydroxychloroquine are the class of quinoline derivatives and widely used to treat malaria caused by *Plasmodium vivax*, *P. malariae*, and *P. ovale*. It is the active constituent of the bark of *Cinchona* (*Cinchona officinalis*) plant. Apart from malaria, chloroquine and hydroxychloroquine can be used to treat amoebiasis and other autoimmune disorders such as rheumatoid arthritis and lupus erythematosus syndrome. Chloroquine and its derivative hydroxychloroquine inhibit the heme polymerase in malarial trophozoites, resisting the conversion of heme to hemozoin. Plasmodium species continue to accumulate toxic heme, killing the parasite and exhibits antimalarial activity. Whereas the anti-viral activity of Chloroquine is exerted by diffusing into the host cells and accumulating in endosomes, lysosomes and Galgi complexes, where it is converted into protonated form, then this moiety is deposited in organelles and further involve in raising the surrounding pH. The raised pH in endosomes and lysosomes prevent viral fusion and inhibits the viral entry by endocytosis into the cells. ACE2 is the target receptor for SARS-CoV and SARS-CoV-2 for viral fusion, however, chloroquine does not affect the ACE2 levels but downregulated the terminal glycosylation of ACE2. Insufficient glycosylation of ACE2 offers inefficiency to bind with SARS-CoV-2 viral spike proteins and inhibits viral fusi. Some authors reported chloroquine inhibited the endocytosis mediated cell uptake of SARS-CoV-2 by suppressing the phosphatidylinositol binding clathrin assembly protein (PICALM) [23].

In the field of nanomedicine, chloroquine/hydroxychloroquine has been used extensively to understand the mechanism of nanoparticles uptake into cells. It was used as inhibitor of nanoparticles uptake via endocytosis pathway. Similar kind of viral particle entry through endocytosis route is proposed to be inhibited by chloroquine. The combination of chloroquine or its derivative hydroxychloroquine with drugs like remdesivir or azithromycin demonstrated to produce beneficial effects against this novel virus. However, its use in SARS-CoV-2 therapy has not been approved by US FDA and there are multiple clinical trials going on to evaluate the efficacy of chloroquine/hydroxychloroquine [24].

Apart from therapeutic benefits, chloroquine exerts various side effects such as fever, chills, loss of appetite, blurred vision and insomnia. Additionally, few reports indicated that chloroquine exerts proarrhythmic effects by increasing the QT interval in the ECG patterns and decreasing the heart rate. This drug cannot be indicated for the patients who suffer from retinopathy and porphyria. Based on the promising evidences, Chloroquine may become suitable drug for SARS-CoV-2 disease. Further, to improve the efficacy, hydroxychloroquine may be used in place of chloroquine. There were reports suggested the superior anti-viral effects of hydroxychloroquine compared to chloroquine with better safety profiles. Further, the combinational approach along with other antiviral drugs may be designed to evaluate the efficacy. Other anti-malarial drugs such as artesunate and artemisone found to be effective against human cytomegaloviruses, but effect of these compounds on SARS-CoV-2 needs to be evaluated. Moreover, the severe inflammatory cytokine storm observed in multiple organs may be curtailed by chloroquine due to its immunomodulatory effects [24].

### **Anti-bacterial and Anthelmintic Drugs**

Azithromycin is a renowned antibacterial drug belongs to the class of macrolide antibiotics. It shows antibacterial activity by binding to bacterial 50s ribosomal subunit and represses the protein synthesis. It is commonly used in the treatment of pneumonia, sinusitis, Lyme disease, skin infections and sexually transmitted diseases. Apart from anti-bacterial activity, Azithromycin has antiviral activity observed in bronchial epithelial cells infected with rhinovirus, where it increased the production of interferon-stimulated genes. Additionally, its anti-viral activity was reported against Zika virus in human glial cells, where it prevented the virus induced alterations in fetal brain. Also, the combination of hydroxychloroquine and azithromycin was found to be effective in SARS-CoV-2 associated pneumonia, where this combination significantly decreased the virus load and involved in the elimination of virus [26].

Energetics based modeling suggests that this drug combination might show the effect on SARS-CoV-2 spike-ACE2 complex. Recently Pfizer has reported the necessary data of azithromycin for SARS-CoV-2 clinical trials. Another anti-biotic and anti-tuberculosis drug carrimycin being tested to treat the SARS-CoV-2 patients, currently, it is under clinical trials, however, its safety and efficacy need to be established in COVID-19 patients. The fluoroquinolone anti-bacterial drug ciprofloxacin is used to treat respiratory tract infections. Apart from its anti-bacterial activity, it can reduce the replication of polyoma BK virus. Ciprofloxacin reduced the viral load with IC<sub>50</sub> value (50% virus inhibitory concentration) of  $216.67 \pm 16.7 \mu\text{g/ml}$ , whereas, coumermycin showed the IC<sub>50</sub> value of  $10.6 \pm 3.9 \mu\text{g/ml}$ . The aminoglycoside anti-biotics including neomycin, kasugamycin, and streptomycin inhibited herpes simplex, influenza A and Zika virus replication by upregulating the interferon stimulated genes (ISGs). The polyether antibiotic CP-44161 is recommended to treat varicella-zoster virus infections and also it inhibited the proliferation of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). However, this anti-biotics were not tested on SARS-CoV-2 [27].

Few anti-biotics which exhibits anti-viral properties like distamycin a, netropsin, ehrlichin, teicoplanin, rifampicin, and doxycycline. The US-FDA approved anthelmintic drug niclosamide is also explored as an anti-cancer, anti-bacterial and anti-viral agent. Also, it was found to be effective as a protease inhibitor in shedding the SARS-CoV and MERS-CoV replication and viral antigen synthesis was suppressed by niclosamide at  $1.56 \mu\text{M}$ . It might be

a good pharmacological agent to treat SARS-CoV-2 infections as well and studies may be designed to evaluate the same in vitro and clinical conditions. The FDA approved anti-parasitic drug ivermectin is widely used as an essential medicine to treat lymphatic filariasis, strongiloidiasis, ascariasis, head lice, scabies, and river blindness etc. Ivermectin was tested for its repurposing antiviral activity against SARS-CoV-2, where it has shown excellent antiviral activity. The in vitro results suggest that Ivermectin reduced viral RNA load >5000 fold with 5  $\mu$ M concentration at 48 h. It might be a good repurposing drug in treating SARS-CoV-2 infections and further studies are required for this specific use [28].

### **Anti-viral Therapy**

An American biotechnology company Gilead Sciences developed the anti-viral drug remdesivir against Ebola virus. Remdesivir exerts broad-spectrum anti-viral activity and showed beneficial results in SARS-CoV and MERS-CoV induced respiratory infections. It has been recommended to administer to SARS-CoV-2 infected patients in United States of America, Europe, and Japan, where physicians found the beneficial results. But it is not yet approved by the drug regulators for treating the patients who are suffering from SARS-CoV-2. Remdesivir is a prodrug and is metabolised to its active form, which is a nucleotide analogue inhibitor of RNA-dependent RNA polymerases. It interferes with the viral RNA polymerase activity and further inhibits the viral exoribonuclease involved in proofreading and ultimately causes the deprivation of viral RNA production [29].

Remdesivir was tested in clinical isolates of SARS-CoV-2 *in vitro*, where it exhibited significant anti-viral activity. Further, it was also tested in combination with chloroquine and found to be effective against COVID-19. However, the data available is limited on remdesivir and further studies need to be conducted to prove its essential role in treating COVID-19 along with its drug-drug interactions and contraindications. Oseltamivir is recommended to treat and prevention of Influenza A and Influenza B viruses. It belongs to the class of neuraminidase inhibitors and acts as a competitive inhibitor of neuraminidase enzyme present in influenza virus and prevents the respiratory tract infections. This enzyme involved in the cleavage of the sialic acid which is an important component of glycoproteins present on the surface of human cells and helps new virions to exit the cells [30].

The therapeutic potential of oseltamivir on SARS-CoV-2 infections needs to be evaluated. Few of the combinational drugs such as ritonavir are being evaluated together with oseltamivir, these are under the clinical trials now. Coronaviruses are associated with different types of proteases such as main protease (Mpro) also known as 3 chymotrypsin-like protease (3CLpro), papain-like proteases (PLpro) and transmembrane protease, serine 2 (TMPRSS2). Mpro involved in viral replication and plays a pivotal role in processing the polyproteins, which are translated from its RNA [31].

Apart from these, remdesivir, saquinavir and darunavir, as well as flavone and coumarin derivatives were found to be effective against SARS-CoV-2 Mpro. Another SARS-CoV-2 protease PLpro plays an important role in viral replication and survival, which mainly involved in cleaving the viral polyproteins a/b. Camostat mesylate is TMPRSS2 inhibitor, is involved in proteolytic processing of spike proteins and it suppressed the SARS-2-S-driven fusion into Caco-2 and Vero-TMPRSS2 cells and might be effective in COVID-19 therapy. Other protease inhibitors include lopinavir and ritonavir were found to be effective in SARS-CoV infections and also these drugs are currently under the clinical trials for testing the

efficacy and safety against SARS-CoV-2. Investigators performed an open-label randomized trial at Wuhan hospital, China. They have given the treatment to adult SARS-CoV-2 patients with oral lopinavir and ritonavir (400 and 100 mg, respectively) twice daily for 14 days. They found that lopinavir and ritonavir combination was significantly effective against SARS-CoV-2. However, further studies are needed to draw a clear conclusion on the usage of the combination of lopinavir and ritonavir in SARS-CoV-2 [31, 32].

The nucleoside analogue ribavirin has extensive activity against DNA and RNA viruses and it is used to treat SARS-CoV patients. The exact anti-viral mechanism of ribavirin has been studied for decades and it is still unclear. Ribavirin usage is associated with the major side effect of anaemia which is found in 27–59% of patients. The importance of Ribavirin for fighting against SARS-CoV-2 was evaluated in combination with protease inhibitors and corticosteroids. This drug has been showing significant results with sofosbuvir and this combination is under the clinical trials. The nucleotide analogue sofosbuvir is used to treat hepatitis C and it is recommended in combination with ribavirin, velpatasvir, and voxilaprevir. Molecular docking studies of RNA dependent RNA polymerase model suggest that sofosbuvir in combination with ribavirin and remdesivir could exhibit possible therapeutic effects in SARS-CoV-2 [33].

Basically, sofosbuvir is a prodrug, which converts into active metabolite and serve as a defective substrate for the non-structural protein 5B (NS5B) of RNA dependent RNA polymerase and further inhibits RNA synthesis. Sofosbuvir and other combinations will be tested in the view of adverse effects such as pruritis, upper respiratory tract infections, and lymphopenia. The short-term anti-coagulant, anti-viral and anti-bacterial drug nafamostat mesylate inhibits Spike protein induced membrane fusion in MERS-CoV and also researchers suggested that using nafamostat alone or with combination of anti-viral drugs could be a safe approach in treating COVID-19 [34].

### **Umifenovir (Arbidol)**

Umifenovir (branded as Arbidol), is a small indole-derivative molecule and is approved for the prophylaxis and treatment of influenza and other respiratory viral infections. It also showed inhibitory activity against other viruses, enveloped or not, responsible for emerging or globally prevalent infectious diseases such as hepatitis B and C. In addition, arbidol has been reported to have anti-viral activity against the pathogen of SARS, and the effect of arbidol mesylate—a derivative of arbidol, was almost five times higher than arbidol in reducing the reproduction of SARS in cells *in vitro*. It has been claimed that arbidol was effective against 2019-nCoV *in vitro*. A randomized multicenter controlled clinical trial of arbidol in patients with 2019-nCoV is in progress in China [35].

### **Corticosteroids**

The use of corticosteroids in the treatment of ARDS is controversial. Observational data in SARS suggest that immunomodulation with regimens of high-dose methylprednisolone might be helpful in modulating inflammatory responses and lung damage. On the other hand, other studies showed that use of steroids is associated with increased risk for bacterial infection, increased mortality, and even antiviral resistance in influenza-associated pneumonia or ARDS. Moreover, multiple studies have reported that corticosteroid treatment is associated with delayed viral shedding in hospitalized patients without significant change in 90-day mortality. Corticosteroid therapy in patients with MERS was shown to be not associated with

a difference in mortality, but associated with delayed MERS coronavirus RNA clearance. The early use of parenteral glucocorticoids therapy for fever reduction and pneumonia prevention has been shown to increase the risk for critical disease or death from H1N1 infection. The currently limited clinical research does not support the use of corticosteroids in the treatment of ARDS in COVID-19 patients to improve the outcome of patients. The WHO recommended that corticosteroids should not be used in the treatment of viral pneumonia or ARDS. There is no convincing proof for the therapeutic benefits of corticosteroids in the treatment of COVID-19, which still need to be demonstrated in clinical research [36].

### **Thymosin alpha-1**

Thymosin alpha-1 is a thymic peptide hormone with significant benefits in restoring the homeostasis of the host immune system. It is chemically synthesized and used in diseases with impaired immune system. It has been reported that the low lymphocyte count is associated with the poor prognosis of septic patients. The use of thymosin alpha-1 therapy in combination with conventional medical therapies was effective in improving clinical outcomes and reducing mortality in severe sepsis. In addition, thymosin alpha-1 can enhance the immune responses of SARS patients and help to limit the spreading of SARS. Therefore, although there is no clinical evidence showing the beneficial effects of thymosin alpha-1 in COVID-2019, it has been recommended to be used for some patients to enhance cellular immunity for the resistance of viral infection [37, 38].

### **Cyclosporine A**

Cyclosporine A is widely used in transplantation and autoimmune disorders due to its immunosuppressive effect. Cyclophilin A as a key member of immunophilins is the cellular receptor for cyclosporine A. The inhibition of cyclophilins by cyclosporine A could block the replication of coronavirus, including SARS-CoV. Therefore, non-immunosuppressive derivatives of cyclosporine A might serve as broad-range CoV inhibitors applicable against emerging virus like 2019-nCoV, which still needs to be confirmed by clinical studies in the future [39].

### **Effect of Interferons**

The 166 amino acid sequence of Interferon alfacon-1 is produced by recombinant DNA technology, which is the class of non-naturally occurring type-I interferon. Interferon alfacon-1 acts as anticancer and antiviral agent. The therapeutic effect of Interferon alfacon-1 was observed in leukemia, melanoma, HIV/AIDS related Kaposi's sarcoma, and hepatitis C. It is also found to be effective in SARS-CoV and also tested in SARS-CoV-2 in combination with corticosteroids.

Interferon alfacon-1 shows antiviral activity by binding to interferon receptors type 1 including IFNAR1 and IFNAR2c. Further, it initiates the dimerization and activates the Janus kinase 1 (Jak1) and tyrosine kinase 2 (Tyk2) phosphorylation. The signal transducers and activators of transcription 1 and 2 (STAT1 and STAT2) bind to the phosphorylated IFNAR and initiate the expression of immunomodulators and antiviral protein expression including protein kinase R (PKR) and 2'-5' oligoadenylate synthase (2'-5' OAS). Additional clinical studies are required to approve this drug for SARSCoV-2 therapy. There are multiple reports on the antiviral activity of IFN- $\alpha$  and IFN- $\beta$ , and combinations of IFN- $\alpha/\beta$ , IFN- $\beta$  1a and IFN- $\gamma$  against SARS-CoV and these agents might be also effective against SARS-CoV-2 too, which need to be evaluated in suitable studies [39-41].

## **Convalescent Plasma and Neutralizing Anti-bodies**

The US FDA has approved the emergency investigational use of convalescent plasma for the treatment of critically ill patients with COVID-19. Convalescent plasma is collected from COVID-19 recovered individuals who are eligible for blood donation. The traditional screening protocol for blood donation should be satisfied. In addition, the plasma should be collected from people with a prior confirmed diagnosis of COVID-19 who have resolved their symptoms at least 14 days prior to donation. In addition, they should have negative PCR for SARS-CoV-2 and high SARS-CoV-2 neutralizing anti-body titers. Takeda pharmaceutical company is also developing an anti-SARS-CoV2 polyclonal hyperimmune globulin (TAK-888) [40].

The use of convalescent plasma resulted in a shorter hospital stay and reduced mortality in SARS 73 and H1N1 influenza.<sup>74</sup> It has also been used during Ebola and MERS outbreaks. A preliminary report of a series of five patients with severe COVID19 pneumonia complicated by ARDS showed that administration of convalescent plasma containing neutralizing antibody (SARS-CoV-2 IgG titers greater than 1:1000 by ELISA and neutralizing antibody titer >40) led to clinical improvement.<sup>27</sup> There was a normalization of body temperature in four patients within three days, the sequential organ failure assessment score (SOFA) decreased, and viral load declined to negativity by day 12.

ARDS resolved within 12 days in four patients. These preliminary findings are promising, but the small number and the uncontrolled nature of this study calls for further evaluation of this treatment modality in randomized controlled clinical trials. Several groups, including investigators from our institution and other academic institutions, are collaborating to achieve a common goal of developing convalescent plasma as a viable treatment of critically ill patients with COVID-19 [40, 41].

## **Therapeutic importance of Amniotic Fluid Cells and Convalescent Plasma in SARS-CoV-2 ARDS Infections**

Amniotic fluid cells are the possible source of stem cells for clinical purposes such as fetal therapies and regenerative medicine, where they proliferate rapidly can differentiate into different cells. The human amniotic fluid is approved by US-FDA for tissue injury and also used to treat inflammatory and fibrotic diseases.

The researchers from the University of Utah tested the nebulized and/or intravenous purified amniotic fluid in SARS-CoV-2 patients, where it reduced the respiratory inflammatory responses observed with this novel pandemic virus. Recently they received the approvals from regulatory bodies to perform the clinical trials. Recently, the US-FDA allowed medical practitioners and physicians to use convalescent plasma in emergency to treat critical ill SARS-CoV-2 patients and few of the clinical studies are also initiated for the use of anti-SARS-CoV-2 and convalescent plasma [13, 23, 40].

## **Monoclonal Anti-bodies**

Monoclonal antibodies are currently used for diagnostic and therapeutic purposes. Various monoclonal antibodies are approved by USFDA to treat cancer and autoimmune disorders. Additionally, few of monoclonal antibodies are tried to treat SARS-CoV-2 infections such as bevacizumab, tocilizumab, and meplazumab etc [41].

## Natural Products and Dietary Supplements

Our diet contains a lot of vitamins, minerals, carbohydrates, proteins, fats, and lipids and they play an important role in maintaining the homeostasis in our body and play important role in maintaining the immunity. Additionally, our diet contains various biological active natural products and they exert multiple pharmacological properties such as anti-cancer, anti-oxidant, anti-inflammatory, anti-diabetic, anti-bacterial, anti-viral and anti-fungal properties etc. The battery of proinflammatory cytokines is responsible for the cytokine storm, which is involved in manifestation of severe acute lung injury, this is the main cause for SARS-CoV-2 induced morbidity and mortality.

The active constituent of turmeric, curcumin exhibits wider pharmacological activities such as anti-bacterial, anti-viral, anti-cancer, anti-diabetic properties. Curcumin inhibited pro-inflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$  level and suppressed the cytokine storm in Ebola virus infected experimental models. Additionally, Curcumin also inhibited the SARS-CoV replication and the effective concentration (EC<sub>50</sub> value) was found to be around 10  $\mu$ M and also acted as a protease inhibitor. Thus, it might be effective against SARS-CoV-2 infections, where intravenous (i.v.) route of administration in suitable formulation form may enhance the better bioavailability. Similarly, a thorough search across all the natural products needs to be evaluated for their direct anti-viral effects and their potential role in controlling severe inflammatory responses observed in COVID-19 induced pneumonia. Dose study of Curcumin shows that Curcumin does not show any toxic effect if consume 12g/day over 3 months. According to other studies' doses of 1,200–2100 mg of curcumin per day for 2–6 weeks there is no toxic or adverse effect occurs.

The Indian traditional plant neem (*Azadirachta indica*) and its parts such as leaves, seeds, flowers, barks and routes are widely using in various diseases. Ancient people believe that it is a Sarva roga nivarini (the cure for all diseases). Methanolic extract of neem leaves exhibited anti-viral activity against HSV-1 infections by glycoprotein mediated viral fusion. Nimbolide is an active constituent of Neem tree explored as a pharmacological modulator in treating various diseases such as cancer, diabetes, and inflammatory diseases. TNF- $\alpha$  is a pleiotropic cytokine involved in activation of various signaling cascade and this cytokine might be playing role in respiratory failure associated with COVID-19 mediated pneumonia. Nimbolide is found to be TNF- $\alpha$  inhibitor and also suppresses the nuclear translocation of p65 NF- $\kappa$ B and HDAC-3 and inhibited the cytokine storm observed in ARDS experimental model. Thus, it might show beneficial effects in SARSCoV-2 infections by direct anti-viral activity or indirect supportive therapy by controlling the inflammatory cytokine storm. This natural product may have clinical significance in inflammation associated with viral diseases [2, 6, 41].

The other natural product Withaferin A is isolated from Ashwagandha (*Withania somnifera*) and widely used to treat various diseases such as cancer, fibrosis, and inflammatory disorders. It has shown the antiviral activity against Herpes Simplex virus 1 and 2, which may show plausible effects against COVID-19. Andrographolide is a diterpenoid isolated from *Andrographis paniculata*, which has been employed in treating various diseases such as cancer and inflammatory diseases. Apart from anti-inflammatory activity, Andrographolide exhibits immunomodulatory effect by increasing the level of cytotoxic T cells, NK cells, phagocytic cells, and phagocytic cells, and shows the broad spectral antiviral activity against various deadliest viruses. Recent computational analysis data suggest that Andrographolide

and its derivatives chrysin-7-O- $\beta$ -glucuronide might produce therapeutic effects against SARS-CoV-2 pneumonia infections. Quercetin is widely present in leaf vegetables, red onions, seeds, and grains, which is a plant flavonol from the flavonoid group of polyphenols and employed as a pharmacological agent in treating inflammation and cancer. It has shown the anti-viral activity against Dengue virus by inhibiting the viral replication without affecting its attachment and entry process. Also, quercetin inhibited the SARS-CoV entry into the host cells and exhibited the anti-viral activity against HIV-luc/SARS with EC<sub>50</sub> value of 83.4  $\mu$ M. The US-FDA approved drug ingredient, Quercetin might show therapeutic activity against SARS-CoV-2 [36, 39].

### **Vitamin C (Ascorbic Acid)**

Vitamin C is an essential nutrient and plays significant roles within the human body. It can neutralize free radicals and assist to prevent or reverse cellular damage as a potent anti-oxidant agent. It is also involved in some biological processes, many of which are associated with immune health. Moreover, vitamin C appears to be effective as an antiviral agent, especially against influenza viruses. Many studies showed that vitamin C positively affects the development and maturation of T lymphocytes and NK (natural killer) cells involved in the immune response to viral agents. It also contributes to the inhibition of reactive oxygen species (ROS) production and to the remodulation of the cytokine network typical of systemic inflammatory syndrome. Given this background, a phase II clinical trial is initiated in China to evaluate high-dose IV vitamin C in ICU patients with severe COVID-19-associated pneumonia. Some hospitals have reported giving infected patients 1500 mg of vitamin C as supportive treatment. High-dose IV vitamin C has been given in the treatment of 50 moderate to severe COVID-19 patients in China. The doses varied between 2 and 10 g per day, given over a period of 8-10 h IV infusion. The oxygenation index was improved in real time and all the patients eventually recovered and were discharged. Moreover, high-dose (1.5 mg/kg body weight) vitamin C has been used for several decades clinically and an NIH panel also documented clearly that this dose regimen is safe and has no major side effects [10, 17].

### **Colchicine**

Colchicine is an anti-inflammatory drug commonly used for gout management and a variety of other conditions sharing similar pathophysiology. Its mechanisms of action are related to interfering with migration of neutrophils to sites of inflammation and blocking the inflammasome complex in both neutrophils and monocytes, thus reducing IL-1 $\beta$  activation. Colchicine also has inhibitory effects on macrophages via the inhibition of the NACHT-LRRPYD-containing protein 3 (NALP3) inflammasome and pore formation activated by purinergic receptors P2X7 and P2X2. There may also be beneficial effects on endothelial function due to colchicine's antifibrotic activities. Some patients with COVID-19 present with myopathies and colchicine has been shown to reduce inflammation in the cardiac myocytes [38, 40].

### **Infection Control in SARS-CoV-2**

The predominant mode of person-to-person transmission in SARS-CoV-2 infection is by close contact with infected individuals generating respiratory droplets. The virus is capable of staying active on inanimate surfaces for several hours, making fomite transmission likely. Airborne transmission though possible, does not appear to be a major mechanism. This has particular implications due to shortage of personal protective equipment in various settings. Aerosol-generating procedures may generate smaller particles which may stay in the air for a

longer time. Distant spread of such particles to produce secondary infection seems unlikely [41, 42]

## **CONCLUSION**

To date, there is no proven effective drug or immunomodulator therapy for the management of COVID-19. As this SARS-CoV-2 pandemic escalates, the search for an effective treatment regimen is at the forefront of clinical medicine and research.

The current COVID-19 pandemic is the third major global illness due to a novel coronavirus. Understanding COVID-19 along with the other known novel coronaviruses places the newest coronavirus in context. We presented the similarities and differences in pathogenesis, manifestations, and outcomes with respect to a spectrum of extra-pulmonary organ systems. Increasing knowledge about COVID-19 literature will aid in earlier recognition and more effective therapy. Coronavirus infections have led to few epidemics and a new pandemic in last 2 decades. The infections vary in clinical manifestations from self-limiting viral respiratory tract infections or gastroenteritis to severe form like the SARS-CoV-1, MERS and the recent SARS-CoV-2 infections. These have led to a significant morbidity and mortality and a global economic crisis. Newer developments in therapeutics, preventive therapy in the form of chemoprophylaxis and vaccines are underway. Newer information about the molecular mechanisms, clinical manifestations, epidemiological pattern and preventive public measures is available each week in all the scientific or medical journals. In addition, lot of input is being provided by electronic and print media for public awareness. Only few articles published in the initial phase of COVID-19 epidemic have been cited to maintain brevity of the article. It will not be appropriate if a little note is not made about the unsung heroes of this pandemic. The world's 'new heroes' are the medical workers. The doctors, nurses, paramedical staff and other health care workers who are directly or indirectly involved with patient care in isolation wards and critical care areas. They risk their own lives, knowing that there are no effective drugs or vaccines available at present.

Over the past 50 years, in the pre-SARS era, many different CoVs have been identified that caused a wide variety of human and veterinary diseases. In particular, the human CoVs were found to cause mild respiratory diseases. In November 2002, SARS-CoV infection was emerged in Guangdong Province of China, identified to be fatal resulting in ARDS, which became a pandemic in 37 countries with over 8000 reported cases and 800 deaths. This deadly SARS virus was found to be originated from horseshoe bats that transmitted to pangolins before reaching humans. At that time no specific drugs or vaccines were available and only preventive measures were implemented to limit the transmission rate by maintaining social distance, quarantine, travel restrictions, patient isolation. In 2012, another zoonotic CoV were identified from Saudi Arabia postulated to have originated from the dromedary camels which infected 2494 people and 858 deaths were reported, In late December 2019, a recent global outbreak, a novel CoV strain has been evolved which is linked to a seafood market in Wuhan, Hubei Province, China with the symptoms varying from mild respiratory illness and pneumonia in most of the patients, to fatal consequences that progresses to ARDS by the induction of a pro-inflammatory cytokine storm. As of 8 April 2020, approximately 1.43 million cases of COVID-19 have been confirmed worldwide, and this pandemic is rapidly escalating all around the globe and most of the countries implemented the most restrictive mass quarantines that led to severe global socioeconomic disruption which has become the greatest concern of WHO. As of now, there are no specific approved drugs for

treating SARS-CoV-2 and currently, physicians are using the repurposing drugs such as chloroquine/hydroxychloroquine, remdesivir, tocilizumab, azithromycin, dexamethasone, acetaminophen etc., and they are showing plausible results, however more studies are required for specific use against SARS-CoV-2. Moreover, immune boosters such as Vitamin C, Zinc and other natural products are suggested in preventing the viral infections. Additionally, scientists are developing the new antiviral drugs and vaccines, and few are under the clinical trials. Apart from traditional drug therapy, medical practitioners are transfusing the convalescent plasma to rescue the critically ill patients with successful outcome in viral load reduction; Also, MSCs were effective for treatment with encouraging improvement with fewer side effects. Thus, there is a lot of scope to develop antiviral drugs and vaccines against SARS-CoV-2; there is a need for vigorous effort on the vaccine development and exploration of potential antiviral treatment regimens. Simultaneously, the primary and intermediate host and mechanism of its cross-species spread and human interface needs to be investigated. Owing to the fact that new CoV viruses will continue to evolve on the basis of their ability to undergo frequent recombination's of their genomes, mutations, the propensity to infect multiple species and the increasing human-animal interface, the strict legislations should be made to prohibit the consumption and farming of terrestrial wild animals to prevent the future outbreaks.

## **DECLARATIONS**

### **Author Contributions**

All authors contributed to data collection, drafting or revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

### **Competing Interest Statement**

All authors declare that there is no conflict of interests regarding publication of this paper.

### **Financial Support and Sponsorship**

None.

### **Ethical Approval**

No.

## **REFERENCES**

- 1) Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *BMJ Quality & Safety*. 2003; 12(1):18-23.
- 2) Loveday H, Wilson J, Pratt R, Golsorkhi M, Tingle A, Bak A, et al. National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *Journal of Hospital Infection*. 2014; 86:S1-70.
- 3) Jeppala Sripriya, A Vishal Reddy, Nellutla Shalini, Narender Boggula. Novel Coronavirus Disease (Covid-19): A Literature Based Review. *Research and Advances in Pharmacy and Life Sciences*. 2020; 2(2):9-20.
- 4) Pratt R, Pellowe C, Wilson J, Loveday H, Harper P, Jones S, et al. National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *Journal of Hospital Infection*. 2007; 65:S1-59.
- 5) Pratt RJ, Pellowe C, Loveday H, Robinson N, Smith G, Barrett S, et al. The epic project: developing national evidence-based guidelines for preventing healthcare associated

- infections. Phase I: Guidelines for preventing hospital-acquired infections. Department of Health (England). The Journal of Hospital Infection. 2001; 47:S3-82.
- 6) Kasturi Jahnavi, Bere Jyostna, Karangula Jyoshika, Ilavarapu Ashwitha, Diddiga Amulya, Kannekanti Chaitanya, Boggula Narender. Remdesivir: A Critical Review. J Pharm Adv Res, 2021; 4(6):1285-1295.
  - 7) Gough D, Thomas J, Oliver S. Clarifying differences between review designs and methods. Systematic Reviews. 2012; 1(1):28.
  - 8) Pellowe CM PRJ, Loveday HP, Harper P, Robinson N, Jones SRLJ. The epic project. Updating the evidence-base for national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England: a report with recommendations. British Journal of Infection Control 2004;5(6).
  - 9) Lin MY, Bonten MJ. The dilemma of assessment bias in infection control research. Clinical Infectious Diseases. 2012; 54(9): 1342-1347.
  - 10) Dinesh Kaul. An overview of coronaviruses including the SARS-2 coronavirus e Molecular biology, epidemiology and clinical implications. Current Medicine Research and Practice. 2020; 10:54-64.
  - 11) Venkatesh Pooladanda, Sowjanya Thatikonda, Chandraiah Godugu. The current understanding and potential therapeutic options to combat COVID-19. Life Sciences. 2020; 254:117765.
  - 12) Jyostna Bere, Naga Dharani Jonnalagadda, Lavanya Kappari, Vedhavathi Kappari, Jyoshika Karangula, Narender Boggula. 2-Deoxy-D-glucose: An update review. Journal for Innovative Development in Pharmaceutical and Technical Science. 2021; 4(5):68-78.
  - 13) Syed Ismail Jabiullah, Jainendra Kumar Battineni, Vasudha Bakshi, Narender Boggula. *Tinospora cordifolia*: A medicinal plant: A review. Journal of Medicinal Plants Studies 2018; 6(6): 226-230.
  - 14) Jahan I, Onay A. Potentials of plant-based substance to inhabit and probable cure for the COVID-19. Turk J Biol. 2020; 44(3):228–241.
  - 15) Matias T, Dominski FH, Marks DF. Human needs in COVID-19 isolation. Journal of health psychology. 2020; 25(7):871–882.
  - 16) Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ. Health Perspect. 2001; 109(S1):69-75.
  - 17) Bandyopadhyay U, Biswas K, Chattopadhyay I, Banerjee RK. Biological activities and medicinal properties of neem (*Azadirachta indica*). Curr Sci. 2002; 82(11):1336-1345.
  - 18) Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020; 579(7798):265-269.
  - 19) Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents. 2020; 55(3):105924.
  - 20) Hoever G, Baltina L, Michaelis M, Kondratenko R, Baltina L, Tolstikov GA, et al. Antiviral activity of glycyrrhizic acid derivatives against SARS– coronavirus. Journal of medicinal chemistry. 2005; 48(4):1256-1259.
  - 21) Giannella M, Alonso M, Garcia de Viedma D, et al. Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients. Clin Microbiol Infect. 2011; 17(8):1160–1165.
  - 22) Wang Y, Guo Q, Yan Z, et al. Factors associated with prolonged viral shedding in patients with avian influenza A(H7N9) virus infection. J Infect Dis. 2018; 217(11):1708–1717.

- 23) Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;382(8):727–733.
- 24) Hui DS, Azhar I, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—the latest, novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis.* 2019; 2020(91):264–266.
- 25) Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020; 395(10224):565–574.
- 26) Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA.* 2003; 289(21):2801–2809.
- 27) Yeung KS, Yamanaka GA, Meanwell NA. Severe acute respiratory syndrome coronavirus entry into host cells: opportunities for therapeutic intervention. *Med Res Rev.* 2006; 26(4):414–433.
- 28) Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with Middle East respiratory syndrome. *Am J Respir Crit Care Med.* 2018; 197(6):757–767.
- 29) Han K, Ma H, An X, et al. Early use of glucocorticoids was a risk factor for critical disease and death from pH1N1 infection. *Clin Infect Dis.* 2011; 53(4):326–333.
- 30) Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA.* 2009; 302(17):1872–1879.
- 31) Du CY, Zheng KY, Bi CW, et al. Yu Ping Feng San, an ancient Chinese herbal decoction, induces gene expression of anti-viral proteins and inhibits neuraminidase activity. *Phytother Res.* 2015; 29(5):656–661.
- 32) Dyal J, Gross R, Kindrachuk J, et al. Middle East respiratory syndrome and severe acute respiratory syndrome: current therapeutic options and potential targets for novel therapies. *Drugs.* 2017; 77(18):1935-1966.
- 33) Dong Kim K, Zhao J, Auh S, Yang X, Du P, Tang H, et al. Adaptive immune cells temper initial innate responses. *Nat Med.* 2007; 13(10):1248–1252.
- 34) Nishimura H, Yamaya M. A synthetic serine protease inhibitor, Nafamostat Mesilate, is a drug potentially applicable to the treatment of ebola virus disease. *Tohoku J Exp Med.* 2015; 237(1):45–50.
- 35) Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antivir Res.* 2014; 110:94–103.
- 36) de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrob Agents Chemother.* 2014; 58:4875-4884.
- 37) Chan JF, Yao Y, Yeung ML, et al. Treatment with Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. *J Infect Dis.* 2015; 212:1904-1913.
- 38) Westover JB, Sefing EJ, Bailey KW, et al. Low-dose ribavirin potentiates the antiviral activity of favipiravir against hemorrhagic fever viruses. *Antiviral research.* 2016; 126:62-68.
- 39) Sarma P, Prajapat M, Avti P, Kaur H, Kumar S, Medhi B. Therapeutic options for the treatment of 2019-novel coronavirus: An evidence-based approach. *Indian J Pharmacol.* 2020; 52:1-5.

- 40) Shashwat Garg, Himanshu Joshi, Harmanjot Kaur, Swati Verma, Amandeep Singh Bhatia, T Venkatachalam. Curcumin - A Immunomodulators against COVID-19. *International Journal of Pharmacy and Pharmaceutical Research*, 2020; 18(2):417-426.
- 41) Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis*. 2011; 52(4):447-456.
- 42) Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020; 395(10223):473-475.