EJMO

DOI: 10.14744/ejmo.2020.52538
EJMO 2020;4(4):265–285


Review

# Various Evidence-Based Hypothetical and Experimental Treatment Approaches and Their Effectiveness against COVID-19 Worldwide: A Comprehensive Literature Review

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## Abstract

Several drugs are presently undergoing clinical studies to investigate their efficacy and safety in the handling of 2019 coronavirus disease (COVID-19). Despite of the fact, certain encouraging results have been obtained thus far, however, these treatments have resulted in controversy as these are not based on data generated from direct conventional clinical trials. As the legal requirement for approval of drug is "substantial" evidence of effectiveness demonstrated through controlled clinical trials and requires a large portion of time. A number of clinical trials are currently in progress to evaluate possible therapies, but the worldwide reaction to the COVID-19 outbreak has been mostly restricted to monitoring/suppression. In the meantime, scientists are struggling to discover antivirals specific to the virus either by screening/testing available broad-spectrum antiviral drugs or redevelopment of newer particular drugs based on individual coronavirus (CoV) genome. Upto date, the hypothetical and experimental treatment approaches against COVID-19 that are tested or being testing are the use of antimalarial and antibiotics, antivirals, anti-parasitic, immunomodulators, anticoagulant treatment, antihypertensive, chinese traditional medicines and others (high temperature and high humidity) as well as vaccines development. This review summarized all the literature-based treatment approaches in various ways that are implementing for the management or treatment of COVID-19.

**Keywords:** COVID-19, existing therapies, SARS-CoV-2, treatment approaches, vaccines development.

***Cite This Article:*** *Naveed M, Uddin S, Abdullah KS, Ishaq SE, Ahmad T. Various Evidence-Based Hypothetical and Experimental Treatment Approaches and Their Effectiveness against COVID-19 Worldwide: A Comprehensive Literature Review. EJMO 2020;4(4):265–285.*

COVID-19 is a contagious disease emerged by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it was primarily recognized in 2019 in Wuhan, China and has led to the 2019–20 coronavirus pandemic declared by world health organization(WHO) and a Public Health Emergency of International Concern (PHEIC).[1, 2] Coronaviruses (CoVs) are a big family of viruses[3] that results in a variety of illness ranging from common cold to more serious diseases i.e. Middle East Respiratory Syndrome [MERS] and Severe Acute Respiratory Syndrome [SARS]. It has many types which damage respiratory system and gastrointestinal system.[3] Certain well-known CoVs are present in ani-

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**Submitted Date:** May 05, 2020 **Accepted Date:** June 14, 2020 **Available Online Date:** August 06, 2020

mals that have not so far affected humans. A novel CoV-2 (nCoV-2) is a newer strain that has not been formerly recognized in humans. The WHO China Country Office was notified of a cluster of pneumonia cases of unidentified origin in Wuhan City on 31 December 2019. A nCoV-2 was isolated and determined as the causative virus by Chinese authorities on 7 January.[4, 5] Later, the disease was officially named as COVID-19 on 11 February, 2020.[6, 7] Generally, COVID-19 patients with pneumonia have a fever, and the temperature above 38 degrees with symptoms such as dry cough, fatigue, dyspnea, difficulty breathing, and frost-glass-like symptoms in the lungs.[8-10] The disease is highly transmittable[10, 11] and ever since it has spread worldwide quickly[1] and become a world-wide public health challenge.[6] As of May 05, 2020 more than 3, 517, 345 cases have been reported, and more than 243, 401 have lost their lives within 215 countries, areas or territories.[12]

The COVID-19 is transmitted through inhalational route or due to contact with large infected droplets eliminated while coughing/sneezing by symptomatic as well as asymptomatic patients.[13, 14] It can be diagnosed from various respiratory samples (such as nasopharyngeal swab, throat swab, endotracheal aspirates, sputum and bronchoalveolar lavage) through particular molecular tests.[13] In several severe cases, the virus can also be identified in the stool and blood. Comparatively, the nasal cavity has more viral loads than the throat with same viral burden within symptomatic and asymptomatic people.[15] The patients can be contagious until the symptoms remain and even after recovery.[13] The mechanism by which the virus gets entry to the respiratory mucosa has recognized to be the angiotensin receptor (ACE)-2.[16] A study demonstrated that in the pathogenesis of COVID-19, a cytokine storm occurred[6] such as tumour necrosis factor (TNF)-α, interleukins-(IL)-2, (IL)-6,(IL)-7, (IL)-10 etc. resulting in the severity and progression of disease.[6, 7, 17] In brief, the inspiration of droplets containing SARS-CoV-2 infects ACE-2 expressing target cells like alveolar (type)-2 cells or other unidentified target cells. Intensified replication of virus occurs due to inhibition of anti-viral IFN (interferon) responses by the virus. The enrolment of neutrophils and monocytes/macrophages results in the induction of pro-inflammatory cytokines that results in immunopathology of lungs and prognosis of disease.[18] Additionally, the presence of inflammatory mediators induces febrile responses by binding with its respective receptor present in the hypothalamus, results in pyrexia.[19]

Right now, due to lack of vaccine or specific antiviral treatment for human and animal CoVs, urgent identification of drug treatments for the response to the COVID-19 outbreak is the utmost requirement.[20] However, until now some of general methods have been practiced or still being practicing to discover the potential treatment for COVID-19. These methods include evaluation of available broad-spectrum antiviral drugs by means of standard assays, which have been consumed for treating other viral infections,[21] screening of a chemical library comprising various current compounds/databases, containing information related transcription characteristics in distinct cell lines,[22] and reinforcement of newer specific drugs based on the genome and biophysical chemistry of respective coronaviruses.[23] Upto date, several treatment options (Table 1) have been hypothesized and various drugs have been tested such as some existing antimalarial, antivirals, antibiotics, anti-inflammatory, immunomodulators and some traditional treatment against COVID-19. Some of them have been achieved promising results so far.[24] However, the efficacy and safety of these drugs for COVID-19 still require to be further proved by clinical experiments. This review article summarized upto date various hypothetical and experimental treatment approaches against SARS-CoV-2 with evidence in details.

## Methods

### Search and Selection Strategy

A thorough literature search was conducted on recently published studies regarding treatment of COVID-19 which have published since the outbreak. Related articles, some editorial, letter to editor and correspondence which described about the current treatment process and drugs options for COVID-19 infection were extracted from scientific databases including Google Scholar, Medline, PubMed, and Science Direct with keywords "Covid-19 treatment", "Treatment for Covid-19", "Covid-19 AND Treatment", "Current drug treatments for Covid-19", "Antimalarial AND Covid-19", "Antivirals AND Covid-19", "NSAIDs AND Covid-19", "Chinese traditional medicine AND Covid-19", "Immunosuppressant AND Covid-19", "Anticancer AND Covid-19", Vaccine AND Covid-19".EndNote X 7.2.1 software was used for referencing and to exclude duplicates from searched data.

## Treatment Approaches Against COVID-19

### Antimalarial

#### Chloroquine

Chloroquine is a medication utilized to inhibit and treat malaria and is effective as an anti-inflammatory drug for treating lupus erythematosus and rheumatoid arthritis.[25] It's in vitro antiviral activity has been recognized since the end of 1960's and the growth of many various viruses can be repressed in cell culture by chloroquine, including the SARSCoV.[26] Recently, precise pre-clinical proof and expert ideas recommend possible use against SARS-CoV-2 and a search in trial registries demonstrates that 23 clinical trials were conducted just in China until March 2020.[27] It has been progressively learnt that the anti-inflammatory and anti-viral actions of chloroquine may share in the treatment

**Table 1.** Different treatment approaches and their effectiveness against COVID-19

| Drug Name | Indications | Effectiveness against COVID-19 |
|---|---|---|
| Chloroquine | –Anti-malarial<br>–Anti-inflammatory | –Increases endosomal pH and interferes with the glycosylation of cellular receptor of SARS-CoV |
| | | –Effective in ( EC50) of 1.13 & 5.47 μM in vitro |
| | | –Suggested dose: 500 mg twice daily for 10 days |
| Hydroxychloroquine (HCQ) | –Analog of chloroquine | –Similar to chloroquine, HCQ alters the pH and confers antiviral effects |
| | –Anti-malarial | –More potent agent than chloroquine in inhibiting SARS-CoV-2 in vitro |
| | –Anti-rheumatic | –Effective in EC50 of 0.72 μM in vitro |
| | | –A loading dose of 400 mg twice daily give orally, followed by a maintenance dose of 200 mg given twice daily for 4 day suggested for COVID-19 |
| Hydroxychloroquine (HCQ) + | –Anti-bacterial activity | –After 6 days of treatment with HCQ (600 mg/day) + AZM (500 mg for 1 day |
| Azithromycin (AZM) | –Immunomodulatory effects | followed by 250 mg/day upto 4 days) showed 100 % nasopharyngeal clearance of virus in human |
| Remdesivir | –Broad spectrum antiviral<br>–Adenosine nucleotide analogues | –A highly potent WHO recommended drug with confirmed inhibiting activity against SARS-coV-2 by blocking the viral RNA polymerases |
| | | –A 10 days treatment course with 200 mg loading dose on day 1 and 100 mg daily I/V up to remaining 9 days |
| Lopinavir/ritonavir (LPV/r) | –Antiretrovirals | –The antiretrovirals in combination has the capacity to combat CoV-19 by |
| | –Protease inhibitors | hitting the viral protease and stopping its replication |
| | –Approved for HIV-1 treatment | –Mostly efficient in mild corona virus cases with oral dosage of 200/50 mg 2×BID for 7 days |
| Oseltamivir | –Antiviral | –No evidence in SARS and MERS |
| | –Neuraminidase inhibitor<br>–Anti-influenza agent | –Very few mild COVID-19 reported cases got cured with Oseltamivir along with antibiotics and supportive care |
| | | –Suggested dosage in mild cases include 4-6mg/kg with 800mg HCQ each day orally |
| Duranavir | –Antiviral | –No significant results against COVID-19 |
| | –HIV Protease inhibitors<br>–Anti-HIV medication | –The drug cannot block properly the viral protease, also require very high dosage confirmed from several trials |
| | | –Used under trials at recommended oral dose of 800mg every 8 hours in combination with Ritonavir (200mg) and Oseltamivir (300mg) per day |
| Favipiravir | –Broad-spectrum antiviral<br>–RNA polymerase inhibitors | –Showed some potency against CoV infection with lesser adverse effects than against influenza lopinavir/ritonavir |
| | | –Considered for experimental tests with loading dose of 2400 mg on day 1 and maintenance dose of 1200mg every 8 hours in combination with |
| | | Lopinavir (800mg), Ritonavir (200mg) per day |
| Umifenovir/Arbidol | –Antiviral | –Effective against viral entry to host cell |
| | –Membrane fusion inhibitor<br>–influenza treatment drug | –Can effectively inhibit COVID-19 infection at a concentration of 10-30 μM in vitro |
| | | –A seven-day treatment course of 200mg dose three times a day is suggested |
| Ribavirin | –Antiviral<br>–Anti-RSV | –Showed positive outcomes during the previous outbreaks of MERS and SARS |
| | | –Currently conducted clinical trials proved the potential efficacy of ribavirin with recommended dose of 500mg IV BID or TID |
| | –Anti-HCV | –However, some experts are recommending to be used in combination with other antivirals (IFN-α or LPV/r) for better results |
| Ivermectin | –Antiparasitic | –In vitro the solo treatment is strong enough to effect nearly 5000-fold drop in virus concentration at 48h in cell culture |
| | –Nuclear transport inhibitor | –Therefore, full attention with priority basis clinical trials to be needed to get evidence-based results about this emerging drug |

**Table 1.** CONT.

| Drug Name | Indications | Effectiveness against COVID-19 |
|---|---|---|
| NSAIDs | –Anti-inflammatory | –It's use has been controversial in COVID-19<br>–Link with respiratory and CVS adverse events<br>–Among them, Indomethacin has reported a strong antiviral activity in-vivo and in human SARS-CoV at a dose concentration of 1 mg/kg |
| Corticosteroids (Glucocorticoids) | –Inflammatory modulators | –Various studies recommended the use of corticosteroids as preferred over NSAIDS for COVID-19 treatment<br>–However, WHO has not recommended its routine administrations in patients with COVID-19 |
| Combining anti-viral and | –Janus kinase inhibitor | –Baricitinib, Fedratinib and Ruxolitinib were expected to be beneficial in COVID-19 anti-inflammatory treatments<br>–It was also expected that combinations of Baricitinib with direct-acting antivirals i.e. ((LPV/r, Remdesivir) might diminish viral replication |
| Tocilizumab | –Immunosuppressant<br>–Anti-IL-6 receptor<br>–Anti-rheumatoid arthritis | –An effective drug in severe individuals with COVID-19<br>–Reduced fever and oxygen requirement in COVID-19<br>–Phase II clinical trial study launched on March 20 2020 holding in Italy in COVID-19 patients group received a dose of 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours by intravenous infusion |
| BCG Vaccine | –Attenuated antitubercular vaccine | –Stimulate immune system to produce specific immunoglobulin against virus<br>–Postulated that until a specific vaccine is developed, SARS-CoV-2 vulnerable populations could be immunized with BCG vaccines to attain heterologous nonspecific protection from the new coronavirus |
| Monoclonal antibody therapy | –Passive (IgG) immunoglobulin-G<br>–Immunotherapy | –There are many reported monoclonal antibodies directing the RBD region of S protein of SARS-CoV and MERS CoV which showed promising results in vitro and in vivo that could be theoretically effective against COVID19 |
| Plasma therapy | –I.V immunoglobulin treatment<br>–Passive (IgG) immunoglobulin-G | –Neutralization of COVID19 particles through stimulation of antibody-dependent cellular cytotoxicity or phagocytosis<br>–Suggested dose is 1 unit (500 ml) convalescent plasma introduce directly after the onset of symptoms |
| Interferon (IFN) alpha 2b | –Immunomodulators<br>–Antiviral | –Interferon is known to have cured more than 1,500 patients with coronavirus and is among the drugs of choice for the WHO<br>–The suggested method for administration of IFN-α is vapor inhalation at a dose of 5 million U (and 2 mL of sterile water for injection) for adults, 2 times/day. |
| Anti-cytokines | –IL-6 & TNF- α inhibitors<br>–Anti-inflammatory<br>–Immunomodulators | –Anti-cytokines can manage CoV-19-induced (CRS) Cytokine release syndrome which is a deadly multiple organ dysfunction in the body of CoV-19 patients<br>–Some of the anti-interleukin drugs in treating COVID-19 CRS are under experimental testing and trials |
| Anticoagulant treatment | –Coagulation disorders | –The use of anticoagulant for severe coronavirus disease 2019 (COVID-19) treatment has been recommended in patients with coagulopathy<br>–LMWH is the best and used as prophylactic dose due to its anti-inflammatory effect, its ability to prevent DIC and SIC |
| Antihypertensive drugs | –Lowering Blood Pressure | –Regardless of the absence of proof, there have been thoughts for both the continuation and termination of ACE-Is, AR-Bs, or both throughout the treatment for COVID-19 in patients with hypertension |
| Traditional chinese medicines (CM) | –Traditional uses | –Previous clinical evidence on CM prevention for similar public health emergencies such as SARS and H1N1 influenza has been reported<br>–Recently, a highly suspected case of novel coronavirus pneumonia were recovered with the use of CM |

**Table 1.** CONT.

| Drug Name | Indications | Effectiveness against COVID-19 |
|---|---|---|
| Temperature and Humidity | –Environmental factor | –Few studies conveyed that the COVID -19 was associated to the climatological factors, which reduced with the temperature growing |

COVID-1 (2019 coronavirus disease), SARS-CoV (severe acute respiratory syndrome coronavirus), EC50 (Half maximal effective concentration), WHO (World Health organization), SARS (Severe Acute Respiratory Syndrome), MERS (Middle East Respiratory Syndrome), HIV (Human Immunodeficiency Virus), HCV (Hepatitis C Virus), RSV (Respiratory Synctial Virus), BID (bis in die/two times), TID (ter in die/ Three times), H1N1 (Hemagglutinin Type 1 and Neuraminidase Type 1 (influenza strain), ACE-Is (Angiotension converting Enzyme inhibitors), AR-Bs (Angiotension Receptor Blockers), LMWH (Low Molecular Weight Heparin), DIC (Disseminated intravascular coagulation), SIC (Sepsis-Induced Coagulopathy), RBD (Receptor-Binding Domain).

of patients with novel COVID-19 and these actions have directed to several trials instantly in the face of international health emergency.[28] Chloroquine elevates endosomal pH and interferes with the glycosylation of cells surface receptor of SARS-CoV and thus it has the potency to prevent viral infection.[29]

The early in vitro studies found that chloroquine could stop COVID-19 infection by low micro molar (μM) concentration, with a half-maximal effectual concentration (EC50) of 1.13 μM and a half-cytotoxic concentration (CC50) more than 100 μM.[25, 29] Similarly, in the study by Yao et al.,[30] in-vitro chloroquine was shown to have an inhibitory effect on SARS-CoV-2 with an EC50 value of 5.47μM. There were some consequent clinical trials have been quickly established in China to examine the effectiveness and safety of chloroquine or hydroxychloroquine in treating COVID-19 related pneumonia in >10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo.[31] A Chinese research including >100 individuals of COVID-19 found chloroquine higher than to the control group in reducing symptom period, aggravation of pneumonia involving radiological enhancement and promoting virus-negative seroconversion without any serious side effects.[25] This was the first human experiment ever directed with chloroquine against COVID-19. This early outcome led China to insert chloroquine in the treatment and prevention of COVID-19 pneumonia.[28]

Furthermore, a meeting was conducted on February 15, 2020; contributors including professionals from governmental and regulatory authorities and organizers of clinical experimental research came to a recommendation that chloroquine phosphate has potent action against COVID-19.[25] The drug is recommended for addition in the next version of the Guidelines for the Diagnosis, Treatment, and Prevention of Pneumonia Caused by COVID-19 allotted by the National Health Commission of the People's Republic of China[25, 28] in which they stated that chloroquine should be administer in a dose of 500 mg of chloroquine two times daily for 10 days in mild to severe COVID-19 pneumonia.[28]

Moreover, on 17 February 2020, the State Council of China briefed that chloroquine phosphate had demonstrated noticeable efficacy and adequate safety in treating COVID-19 related pneumonia in multicenter clinical trials organized in China.[31] Furthermore, the effectiveness of chloroquine has been reported by the "editorial written by French researchers",[32] "expert consensus published by a multicenter collaboration group of Guangdong Province",[33] "Dutch Center of Disease control (CDC),[26] "Italian Society of Infectious and Tropical disease".[34] All these published literatures and clinical trials are summarized by Nitesh et al.[26, 34] and Cortegiani et al.[27]

## Hydroxychloroquine

Hydroxychloroquine (HCQ) is an analog of chloroquine and a less toxic aminoquinoline that has less fears about drug-drug interactions.[30, 35] Like chloroquine, HCQ changes the pH and shows its antiviral effects. In addition, HCQ has a modifying effect on activated immune cells, decrease the expression of Toll-like receptors (TLRs) which leads to downregulation of TLR-mediated signal transduction, and lowering the interleukin-6 production.[36] In the former SARS outbreak, HCQ was described to have anti-SARS-CoV activity in vitro. This suggests that HCQ may be a potential pharmacological agent for the treatment of COVID-19 infection.[30] Another reports determined that HCQ effectively inhibited both the entrance, transportation and the post-entrance stages of SARS-CoV-2 as that of chloroquine and one study found HCQ to be a more potent agent than chloroquine in inhibiting SARS-CoV-2 in vitro.[30, 37]

Several clinical trials are currently investigating the use of HCQ to treat SARS-CoV-2 infection.[30] Up till February 23, 2020, there were 7 clinical trial studies found in Chinese Clinical Trial Registry (http://www.chictr.org.cn) for using HCQ to cure COVID-19.[37] In one of those seven trials, a placebo controlled randomized research of two different doses of HCQ in 62 patients with radiological findings of pneumonia but without serious hypoxia, showed small enhancements in body fever and cough in the treatment group of higher dose.[38] Conversely, the endpoints de-

scribed in the published protocol varied from those specified, the outcome in the low dose group were not defined, and the trial looks to have been discontinued before the due time.[39] A previous non-randomized research of HCQ, published in preprint, apparently supported efficiency in 20 individuals, but the trial plan was weak and the results uncertain: six individuals gave up the treatment arm (2 due to an admission in intensive care unit (ICU) and 1 because he died); the degree of efficacy was viral load, not a clinical endpoint; and evaluations were made on day 6 after initiating the treatment.[40] Supporters, including US President Donald Trump, claimed that HCQ is broadly used and harmless. It is now approved by the US Food and Drug Administration (FDA) for use[41] and also supported by the Indian Council for Medical Research.[28] However, no drug is certain to be harmless or free of side effects, and wide use of HCQ will expose some users to rare adverse reaction events.[42]

In a study by Yao et al.,[30] theanti-SARS-CoV-2 activity of HCQ was investigated in vitro by means of SARS-CoV-2 infected Vero cells. HCQ (EC50=0.72 μM) was showed to be more potent than chloroquine (EC50=5.47 μM) in vitro. This was demonstrated by the EC50 values for HCQ always being smaller than the EC50 values for chloroquine, indicating that HCQ has a more potent antiviral activity.[30] On the basis of HCQ's superior antiviral and prophylactic activity, as well as its more tolerable safety profile in comparison to chloroquine, it was believed that HCQ may be a promising drug for the treatment of SARS-CoV-2 infection.[30, 43] Depending on PBPK (Physiologically-Based Pharmaco Kinetic) models results, a loading dose of 400 mg two times daily of HCQ sulfate administered orally, followed by a maintenance dose of 200 mg given twice daily for 4 days was recommended for SARS-CoV-2 infection.[30] Moreover, a Central Clinical Task Force from Korea who have treated 27 cases of SARS-CoV-2 infection recommend using Hydroxychloroquine 400 mg orally per day for 7-10 days, in moderate to severe case of COVID-19.[28]

## Antimalarial and Antibiotic

### Hydroxychloroquine and Azithromycin

Some of the old drugs such as Macrolides were anticipated for their effectiveness against COVID-19, based on the structure based selection of drugs for specific identification of SAR-CoV-2 protease inhibitors. Macrolides (MAC) such as erythromycin, clarithromycin, and azithromycin (AZM) not only have anti-bacterial activity but also have immunomodulatory effects, including anti-inflammatory effects. Latterly, macrolides have gained robust attention because of their anti-viral effects. Recent studies reported the effectiveness of AZM administration in combination with HCQ.[40] Moreover, it is noteworthy to mention the promising effects of macrolides either administered alone or in combination with other drugs has paved the way to devise some international strategies to cope the rapid emergence of this viral infection.[44]

In March 2020, a human study (n=36) as an open label non-randomized trial was conducted in Méditerranée Infection University Hospital Institute, Marseill, France by Gautret et al.[40] Twenty of thirty-six received active treatment with a total 600 mg/day of HCQ and their nasopharyngeal swab samples were subjected to test for viral load. Based on their clinical condition, AZM was added to their treatment regimen, about six of these 20 were administered AZM (500 mg for 1 day administration followed by 250 mg/day upto 4 days administration) to prevent bacterial superinfection. Sixteen control patients did not receive these active treatments. Their samples were evaluated on Day-6 for the viral presence or absence, the end point was considered as Day-6 post.[40, 45] The findings of this research explained that HCQ either alone or in combination with AZM exhibited significant effects in abstaining nasopharyngeal viral loads (samples evaluated by PCR), within 3-6 days in COVID-19 subjects as compared to controls.[40] At day 6, out of the 20 treated patients, 100% of HCQ/AZM, 57.1% HCQ only and 12.5% of the control group showed nasopharyngeal clearance of virus.[45] These preliminary findings suggested that the combination treatment of AZM and HCQ could have a synergistic effect.

However, these findings needed to be further explored for the significance of a combination treatment as more effective and safe because of AZM association with QR interval prolongation and arrhythmia, most importantly in outbreak of severe cases. Future studies emphasizing this combination treatment are required, as this combination might be a potential candidate as an antiviral agent against SARS-CoV-2 as well as can be effective in preventing several bacterial super-infection.[40] In addition, every adult patient with COVID-19 in Turkey were initially treated with HCQ and AZM.[46]

## Antiviral Drugs

### Remdesivir

Remdesivir, a prodrug of a nucleotide equivalent that prevents the action of viral RNA polymerases. During the past outbreaks occurred due to members of few other virus families containing Filoviruses (e.g., Ebola) and MERS-CoV (e.g., SARS-CoV) and the antiviral remdesivir is considered to possess broad-spectrum activity against these viruses. It has also been reported from several studies that the

drug holds therapeutic efficacy and prophylactic activity in many nonclinical models of the above coronaviruses.[29, 47, 48] Recently, when there is a race to find a potent drug candidate, remdesivir was also tested in vitro and results has presented that it has prominent activity against SARS-CoV-2 and chosen as a strong candidate. In the late January of this year a chemist Wenshe Ray Liu along with his group members of Texas A&M University were the foremost to recognize remdesivir as a practical medicine to combat COVID-19.[49]

The first case of COVID-19 reported in the US was a young man in Snohomish County in Washington. He was administered with antiviral remdesivir when his condition became severe; and surprisingly the doctors found him well the next day. A Californian patient whose doctors thought to not survive the disease, he was given remdesivir and recovered as well.[50] A study reported a total of 53 infection cases of COVID-19 that were hospitalized in several affected countries, were treated with remdesivir and 68% improvement was observed in clinical conditions of 36 patients. These patients received the drug between January 25 and March 7,2020, in hospitals around the world: 22 in Europe, 22 in the USA and 9 in Japan.[51] A news released by NIH on 25th February of this year has reported that randomized, controlled clinical trial, to assess the security, safety and effectiveness of tentative remdesivir antiviral in adults being hospitalized with COVID-19, has started in Omaha at the University of Nebraska Medical Center (UNMC).[52]

A report published in the journal of NATURE biotechnology stated that the broad-spectrum antiviral "remdesivir has quite high potency against all different CoVs and therefore it is selected as one of the prime and suitable drug candidates to start being tested".[53] WHO in the mid of March had launched an international level mega trial of the 4 most auspicious treatments against CoV including remdesivir on top of list with higher potency and efficacy. According to their study the nCoV-2 is giving this compound a second chance to shine. The original pioneer of remdesivir "Gilead Sciences" developed the drug to combat Ebola and related viruses by blocking the RNA-dependent RNA polymerase of pathogens. A professor named Shibo Jiang from Fudan University in China, who is known for his expertise on CoV therapeutics, stated that "remdesivir has the best potential to be used in clinics" for treatment of COVID-19. A 10 day treatment course with 200 mg loading dose on day 1 and 100 mg daily I/V up to remaining nine days has suggested. [54] A virtual meeting held on 2nd April,2020 among members of EMA's (Human Medicines Committee) provided recommendations on concerned usage of remdesivir as efficient antiviral for COVID-19 medication.[55]

**Lopinavir/ritonavir (LPV/r)**

Lopinavir is an antiretroviral protease inhibitor administered in combination with other antiretrovirals in the treatment of HIV (Human Immunodeficiency Virus)-1 infection. Ritonavir is an inhibitor of the enzymes responsible for lopinavir metabolism, and its co-administration "boosts" lopinavir exposure and antiviral activity.[31] Lopinavir is a peptidomimetic molecule and it contains a hydroxy-ethylene scaffold that imitate the peptide linkage which is characteristically targeted by the HIV-1 protease enzyme and alongside itself cannot be slinter, thus stopping the activity of the HIV-1 protease.[56] Similarly, in COVID-19 the virus needs viral protease to have its replication, so the antiviral medication of lopinavir might be operational by binding to the protease of CoV to hinder virus-related replication. Some of the earlier studies[57, 58] have been displayed that lopinavir could prevent MERS-CoV and SARS-CoV replication.

Recently, it is reported from a case study conducted in Guangdong Center for Disease Prevention and Control, China that a patient with COVID-19 pneumonia was treated with LPV/r (200/50 mg twice daily two tablets) antiviral therapy along with other medical necessities. After the 8 days of treatment, the SARS-CoV-2 nucleic acid test results were negative from his throat and swab samples two times with notable improvement in cough and computed tomographic chest images. The patient has recovered and declared safe and healthy by doctors and was discharged from the hospital.[59] Moreover, another study reported that lopinavir alone or in combination with ritonavir have anti-CoV activity in vitro 20. From the Moscow City Health Department's website, a recommendation published on 25th March, 2020 stated that the experts recommended the (LPV/r) medication successful against mild CoV cases.[18] A Molecular Docking study conducted by Dayer M R et al. in Iran also found that lopinavir is a potent drug against CoV infection.[20] The suggested dosage of lopinavir/ritonavir is 400 mg/100 mg for adults, BID.

**Oseltamivir**

Oseltamivir an FDA approved drug for influenza A and B treatment works by blocking the viral neuraminidase and subsequently prevent the release of viral particles from host cells.[60] In china, clinical trials were established to test oseltamivir alone or with combination of chloroquine and favipiravir as a treatment option for COVID-19.[16, 61] A study conducted by School of Public Health in Hong Kong University stated that the antiviral oseltamivir does not show any notable effects on nCoV-2.[62] Another study documented two retrospective case series about oseltamivir ef-

fectiveness against COVID-19 with contradictory results. In one case series, it is reported that out of 138 patients 124 received oseltamivir with adjusted dose according to the severity of disease but noted no effective outcomes.[63] In the 2nd Case series, Ding et al. reported the clinical characteristics and care for 5 patients being co-infected with both the influenza virus and COVID-19. All of the patients have been treated with antiviral treatment (together with oseltamivir), antibiotics and supportive care. All patients obtained complete recovery and were discharged from hospital.[64] At present, 3 clinical trials of oseltamivir in combination with other medications are being ongoing for the treatment of COVID-19 with estimated completion in next few months.[46]

### Darunavir

Another HIV protease inhibitor, darunavir and the boosting agent cobicistat, is also under evaluation. A study based on circumstantial findings, stated this protease inhibitor has formerly shown great efficacy against SARS associated CoV, though it has not been verified safe and potent for the treatment of COVID-19 and thus additional conformational studies need to investigate. In China, Shanghai Public Health Clinical Center (SPHCC) have worked in collaboration with Zhongnan Hospital to find out some potentially efficient drugs against COVID-19 and to achieve this up to 30 effective and potent compounds including darunavir were examined. Later, SPHCC documented that the drug darunavir was not effective against COVID-19 during a randomized, controlled trial.[65] A report issued in detail by the darunavir/cobicistat manufacturer company "Janssen" about the activity of drug against COVID-19 that it does not bind well to the virus protease and the potency achieved in a lab-dish with much high dose than is attained in the body.[66]

### Favipiravir

Favipiravir is an antiviral medicine which is significantly effective in COVID-19 treatment. The drug prevents viruses from replicating their genetic material. It is a pyrazine carboxamide derivative and initially discovered while examining for drugs to treat influenza. Report from doctors at China's Wuhan University makes more modest claims. They controlled the study of 240 ordinary patients (those who were having mild pneumonia) around Hubei province. Half of them received umifenovir and the remaining favipiravir. They were under observation to examine which group recovered fast. The doctors observed that patient's fevers and coughs disappeared more rapidly on favipiravir but similar number in each group ended up requiring oxygen or ventilator. On the basis of these findings, they concluded that favipiravir is the preferred of the two drugs. During the outbreak in China, a CoV-infected woman in her late 90's after getting antiviral favipiravir therapy soon became better and was discharged from Leishenshan Hospital to observation facility. So far, this was the oldest critical patient that got cured.[67]

Moreover, favipiravir needs consideration because it was accepted for treating novel influenza on 15th Feb 2020 in China. The medicine is now experiencing more clinic trials in the COVID-19 treatment. This medicine is a fresh RNA-dependent RNA polymerase (RdRp) type inhibitor. Along with its anti-influenza action, favipiravir is thought to be proficient of hindering the replication of many RNA viruses.[24] Favipiravir being transformed into an active phosphoribosylated form (favipiravir-RTP) in cells renowned as a substrate through viral RNA polymerase, hence constraining RNA polymerase action.[24] Consequently, favipiravir might possess potential antiviral action against SARS-CoV-2 that is an RNA virus. No significant adverse reactions were noted in the favipiravir treated set of patients, proposing that it had comparatively less unfavorable results than the (LPV/r) group.[24] Moreover, in Turkey intensive care (IC) patients with severe COVID-19 pneumonia had been started the use of favipiravir. Because of its effectiveness against clearance of virus, the health ministry approved it positive safe choice for early stage of pneumonia in hospitalized patients instead of IC unit (ICU) and this was thought to be the reason behind less admission ratio of ICU administration.[46]

### Umifenovir [Fusion peptide (EK1)]

Umifenovir, antiviral medicine for influenza infection mostly consumed in Russia and China with the brand named arbidol and its mechanism of action apply through blocking and inhibition of enveloped virus membrane fusion with host cell membrane, thus prevent virus from cell entry.[68] Umifenovir exhibits modulatory effect on the immune system along with its precise antiviral action against both influenza B and A viruses. This medicine triggers a humoral immune response, encourages interferon-production, and moreover excites the phagocytic function of macrophages.[69] Arbidol was revealed to have a direct antiviral action in early viral reproduction in vitro for SARS-COV, the National Health Commission (NHC) of China for tentative therapy of COVID-19 have included arbidol in the newest version of the "Strategies for the Prevention, Diagnosis, and Treatment of Novel Coronavirus (COVID19)-induced Pneumonia".[70] Arbidol should be administered orally at a dose of 200 mg for adults, 3 times/day. The period of treatment should not exceed 10 days. Recently, there was a study in China has stated that arbidol can effectively inhibit COVID-19 infection at a concentration of 10-30 μM in vitro.[24]

One study reported that four patients with mild or severe 2019-nCoV pneumonia have been cured or have significant improvement in their respiratory symptoms after treatment with combined lopinavir/ritonavir, arbidol, and Shufeng Jiedu Capsule.[71] Moreover, another study in China revealed that arbidol mix with LPV/r might be beneficial to retard the development of lung lesions and minimize the chances of respiratory and gastrointestinal transferring for reducing the viral load of COVID-19.[72] Furthermore, a randomized multicenter controlled clinical trial of arbidol in patients with 2019-nCoV (ChiCTR2000029573) has been initiated in China.[73] In February 2020, an expert Li Lanjuan, from the National Health Commission of China, suggested consuming arbidol in combination with darunavir as a possible treatment. Statement given by experts from China that preliminary tests have revealed darunavir and arbidol might prevent viral replication.[74]

### Ribavirin

Ribavirin, an antiviral medicine typically given to cure Respiratory Synctial Virus (RSV)-infection, some vial hemorrhagic fever and hepatitis C. To treat hepatitis C infection, it is given in combination with few other drugs like simeprevir, sofosbuvir, peginterferon-α2b/2a. Ribavirin being guanosine equivalent consumed to halt viral mRNA capping and viral RNA synthesis, hence, it is known as nucleoside inhibitor. It is a prodrug which after being metabolized bear a resemblance to purine RNA nucleotides. In its later form, it interferes with viral RNA metabolism essential for its replication bringing alterations in RNA-dependent replication more specifically in RNA viruses. These kind of hyper mutation could be fatal to RNA viruses. Similarly, in COVID-19 which is also an RNA virus it can be administered to the patient and was given in the amount nearly 500 mg each time, twice to thrice per day along with IFN-α or (LPV/r).[75]

## Antiparasitic Drugs

### Ivermectin

Ivermectin prevents the growth of the SARS-CoV-2in vitro. The solo treatment is strong enough to effect nearly 5000-fold drop in virus concentration at 48h in cell culture. This drug has an advantage of being approved by FDA for parasitic infections treatment, hence, possess potential for repurposing. The drug is easily accessible thus permits further analysis for potential benefits in humans. Ivermectin works to inhibit nuclear import of host and viral proteins. Essentially, it is considered to restrict many RNA virus infections.[76, 77]

Information suggesting that ivermectin nuclear transport inhibitory activity might be beneficial in conflict of SARS-CoV-2. Vero/hSLAM cells infected with SARS-CoV-2 were used to test the antiviral activity of ivermectin. At 24 h, it has been shown around 93% decrease in viral RNA existing in the supernatant of samples treated with ivermectin in comparison with the vehicle DMSO. Likewise, nearly 99.8% drop in cell-associated viral RNA was experienced with ivermectin treatment.[75]

## Anti-inflammatory Drugs

### NSAIDs

Although, the use of NSAIDs was hypothesized to use against COVID-19 but its use has been a topic of debate and controversy. It is suggested that the use of NSAIDs can increase the risk of cardiovascular (CVS) and respiratory complications which are reported as the most lethal complications of COVID-19.[78] In addition, several studies demonstrated a pragmatic evidence linking NSAIDs with both respiratory and cardiovascular adverse effects in clinical settings, but until now no evidence has been seen relating specifically to people with COVID-19. Further studies are required to demonstrate some reasonable and cautionary strategies for the public to avoid the incidence of these probable adverse effects. Regular NSAIDs use should be avoided as a first line therapy for symptomatic treatment of COVID-19. However, NSAIDS may be recommended for some other symptoms of COVID-19 such as management of musculoskeletal pain and as aspirin may be used for the secondary prevention of CVS disease. The sole study that hypothesized NSAIDs effectiveness in COVID-19 patients, has evaluated indomethacin effects, demonstrating its in-vitro potent anti-viral activity against canine coronavirus. This study reported indomethacin as potent inhibitor of viral replication and protects the host cell from viral damage. This study was further explored in-vivo and in human SARS-CoV at a dose concentration of 1mg/kg.[79, 80]

### Corticosteroids (Glucocorticoids)

Similarly some reports stated that the use of corticosteroids may exacerbate symptoms of coronavirus infection in patients. Meantime, there are some evidences recorded that corticosteroids may exert some beneficial effects in the early acute phase of infection. Various studies recommended the use of corticosteroids as preferred over NSAIDS for COVID-19 treatment.[80] Taken together, key findings are generally emphasizing the use of corticosteroids, especially in regard of the outbreak of the SARC-CoV, as they are well known as inflammatory modulators. Several studies in mice models and human samples[81] and mice[82] reported that corticosteroids such as glucocorticoids has seemed to be effective in diminishing immuno-pathological viral

damage response. Nevertheless, the WHO has not recommended the routine administrations of systemic corticosteroids in patients with COVID-19.[83]

Recently, to investigate the efficacy of corticosteroid treatment in COVID-19 patients, one observational study in the two COVID- 19- designated hospitals in Wuhu, Anhui province, China, was undertaken by Zha et al.[84] Thirty- one SARS- CoV- 2 infected patients were treated at the two designated hospitals. Eleven of 31 patients received corticosteroid treatment but they did not find an association between therapy and outcomes in patients without acute respiratory distress syndrome. The researchers stated that an existing HBV infection may delay SARS-CoV-2 clearance, and this association should be further evaluated.[84] Recommendation from WHO against handling patients with COVID-19 demonstrated that corticosteroid treatment did not improve clinical outcomes for patients with SARS or MERS also even though medical societies in China recommend their sensible use.[85]

Recently a research study conducted in UK at the Queen's Medical Research Institute Edinburgh in 2020 concluded that no distinctive reason occurs to assume that patients with nCoV-2 infection could get the advantage from corticosteroids, apart from this there might be a chance more likely to harm the patient with such treatment.[86] On April 3, 2020, a study published in the Journal of Clinical Endocrinology & Metabolism is warning clinicians and patients that individuals taking glucocorticoids may be at an increased risk if they were to become infected during the pandemic. Furthermore, these endocrinologists have shown concern that patients may be unable to mount a normal stress response with COVID-19.[87]

## Combining Anti-viral and Anti-inflammatory Treatments

A research conducted by medical team at the Imperial College London, UK described a collection of accepted drugs that could possibly prevent endocytosis mediated by clathrin and by this means prevents viral infection to the cells.[88] Baricitinib drug is recognized as inhibitor of Janus kinase (JAK) and it is advised that the drug can be of usage in combating SARS-CoV-2 infections. Along with baricitinib, fedratinib and ruxolitinib were also expected to be beneficial to counter the consequences of the high levels of cytokines characteristically detected in people with COVID-19. To confirm the hypothesis all the three drugs were subjected to proper clinical testing.[10]

After the uncertain outcome of clinical trials, it was concluded that these drugs have not that much potency to lower the rate of viral infection at tolerated doses though they might be capable to decline the inflammatory response of host by hindering JAK. Furthermore, it was expected that combinations of baricitinib with direct-acting antivirals i.e. ((LPV/r, remdesivir) might diminish viral replication, viral infection, plus the unusual host inflammatory response as the drug possesses anti-inflammatory properties,[89] minimal interaction with CYP enzymes and low plasma protein binding.

## Immunomodulators

### Tocilizumab

It is an immunosuppressant drug that approved to treat patient with rheumatoid arthritis[90] and systemic juvenile idiopathic arthritis[91] where it is available as an intravenous (IV) or subcutaneous (SC) formulation. It is a recombinant humanized monoclonal antibodies that acts by specifically binding to cell surface bound IL-6 receptor (mIL6R) and soluble IL-6 receptor (sIL6R) and inhibit signal transduction thus inhibit inflammatory response. Ina study by Xiaoling Xu et al. held in February 2020, 21 critical COVID-19 persons (their average age was 56.8±16.5 years, ranged from 25 to 88 years,) treated with tocilizumab were analyzed. The study stated that tocilizumab efficiently improves clinical signs and suppress the worsening of severe COVID-19 patients. There were no problems associated with tocilizumab administration and no history of illness worsening or death. Hence, tocilizumab is an effective drug in severe individuals with COVID-19, that provided a new therapeutic protocol for this fatal COVID-19 infections.[6] A randomized, placebo-controlled, singled-blind, multicenter, phase II clinical trial study launched on March 20, 2020 holding in Italy with the title of Tocilizumab in COVID-19 Pneumonia (TOCIVID-19). TOCIVID-19 patients in the experimental group received a dose of 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours by IV infusion besides the routine treatment. Patients in the control group also administered routine treatment and the similar dose of a placebo. The trial is expected to conclude by the end of December 2020.[31] In addition, the health ministry of Turkey has offered option regarding the use of tocilizumab in severe COVID-19 ICU patients with cytokine release syndrome.[46]

### BCG Vaccine

The Bacillus Calmette-Guérin (BCG) vaccine is live attenuated vaccines that was developed in the early part of the 20$^{th}$ Century by Albert Calmette and Camille Guérin by subculturing different strains of Mycobacterium tuberculosis and Mycobacterium bovis to protect against tuberculosis. Although, it is thought to reduce the risk of contracting

tuberculosis by approximately 50%, there are some proofs clarified that the BCG vaccine shows non-specific protection and decrease the morbidity and mortality rates of pathogen some of which causes acute respiratory tract infection.[92, 93] In addition, the BCG vaccine can enhance the immune response to other vaccines as well. One study including the administration of the BCG vaccine previous to the influenza vaccine exhibited that antibody titer to the latter was significantly improved[94] which stated that following the BCG inoculation, there was a fast seroconversion and improved pro-inflammatory leukocyte response, and even a modification of cytokine responses against dissimilar pathogens.

The Semmelweis University published on its official website that according to a recent epidemiological study there is a correlation between the use of the BCG and COVID-19 infections and the course of the disease where mortality due to COVID-19 is reduced in countries where there are vaccination of newborns with BCG. On the other hand, in countries where BCG vaccination has been suspended (eg. Spain, France) or compulsory vaccination has never been introduced (eg. Italy), the mortality rate of the viral infection is high.[95] The exact molecular mechanism which activates the BCG vaccination against tuberculosis, COVID-19 and other upper respiratory tract infections is very little known. Data from some animal studies suggest that the pleiotropic protective effect of the BCG vaccine enhances the formation of inflammatory mediators, which boost non-specific antiviral immunity.[96] A recent study published by Gursel et al. hypothesized that BCG vaccination policies adopted by different countries might influence the SARS-CoV-2 transmission patterns and/or COVID-19 associated morbidity and mortality through the vaccine's capacity to confer heterologous protection. In addition, it is postulated that until a specific vaccine is developed, SARS-CoV-2 vulnerable populations could be immunized with BCG vaccines to attain heterologous nonspecific protection from the new coronavirus.[95, 96]

## Monoclonal Antibody Therapy

Monoclonal antibodies (MAs) are a new tool of immunotherapy in infectious disease prevention and it is considered a multipurpose class of pharmaceuticals which have been effectively used by pharmaceutical manufacturing to deliver a competent therapeutic intervention with a highly specific therapy against specific disease.[97] Rapid public health interventions by using MAs are highly essential to stop disease spread and consider as a way to limit COVID-19 pandemic as well as to reduce the likely future outbreaks through its ability to deactivate the virus and stop further infection. Similarly, the early administration or hyper-immune immunoglobulin can possibly decrease the viral infection and disease mortality. The passive MAs act through its ability to identify epitope regions in the foreign virus particle which can reduce the virus replication and disease severity. This passive MA can obtain from the serum of the infected patients or it can be made in the lab.[97-99]

The pathogenic mechanism of COVID-19 start by virus attachment and entry to the host cells through linking of receptor binding domain (RBD) located in the spike protein (S-protein) present on COVID-19 virus membrane and target host cell surface receptors such as Angiotensin converting enzyme 2 (ACE 2) which is the same receptor that utilized by SARS-CoV to enter and attach to the host cell.[100] As both SARS-CoV and COVID-19 viruses use same host cell surface receptor, probable blocking strategies tested to stop virus access to host cell could be used against COVID-19. There are many reported MAs directing the RBD region of S-protein of SARS-CoV and MERS-CoV which showed promising results in vitro and in vivo that could be theoretically effective against COVID-19 as 80R, CR3014, CR3022, F26G18, F26G19, m396, 1A9, 201, 68, 4D4, S230, MERS-4, MERS-27, 4C2, m336, G4, D12, JC57-14, MERS-GD27, MERS-GD33, LCA60, MCA1, CDC2-C2, 7D10 and G2.[97] In addition, to get more effective disease prevention it was recommended to use the mixture of different monoclonal immunoglobulins which identifies different epitopes on the viral surface. So, the Monoclonal antibody cocktail may show extra effective anti-virus activity that can rise the efficiency of the treatment and inhibit the viral escape.[101]

Unfortunately, the use of MAs as therapeutic tool for COVID-19 have some disadvantages during its biosynthesis where the devices that use for manufacturing of MAs are labor exhaustive, expensive and time consuming which outweighs the MAs clinical application especially against emerging pathogen. Although, there is a more growth towards the progress of MAs therapy for CoV infection, no MAs have yet been successfully used.

## Plasma Therapy

Plasma therapy or intravenous immunoglobulin (Ig) treatment which is considered as a kind of passive immunoglobulin-G (IgG) antibodies and it is specific against COVID-19 by stimulating the immune response in newly infected individuals.[102] The presence of this Ig in the serum of infected individuals will help in COVID-19 infection prophylaxis and treatment and it is more effectual when introduce directly after the onset of symptoms. The passive antibodies from human convalescent serum neutralizes COVID-19 microorganisms or their toxins through stimulation of antibody-dependent cellular cytotoxicity or phagocytosis.[103] IgG antibodies strengthen our immune

response by two mechanisms; firstly by its fragment antigen-binding [F(ab')2] portion, that recognizes the antigen and secondly by crystallizable fragment (Fc), that considers significant for stimulation of the immune response by interacting with Fc receptors on B-cells and other innate immune cells. Additionally, the Fc portion also plays a significant role in the activation of complement system and in the killing of microorganisms.[104] Plasma therapy has been used to treat individuals with chronic inflammatory and autoimmune diseases such as chronic lymphocytic leukemia, dermatomyositis, kawasaki disease, multiple sclerosis, lupus, and idiopathic thrombocytopenic purpura.[105-107] Moreover, it has been used as an anti-microbial agent against viruses, bacteria, and fungi in human and experimental models.[108, 109]

The plasma therapy against CoV started during SARS outbreak in HONG KONG where 80 patients were treated with convalescent plasma in 2005 and the study reported that therapy had improved prognosis for all patients within 6 days of plasma administration.[110] Another study in Taiwan published that three patients with SARS were cured with 500 mL therapeutic plasma, resulting in a reducing serum virus titer in all three patients.[98] Ko JH et al. in 2018, showed that three patients with MERS in South Korea were treated with therapeutic plasma, but only two of them had passive antibody in their plasma.[111] During the current pandemic there is a study that therapeutic plasma was utilized for treatment of patients with COVID-19 in China, however, a little information are existing from the epidemic in China and published reports which involved small numbers of patients, the available data recommends that therapeutic plasma administration decrease viral load and was safe. [112] A recent report of 10 patients with severe COVID-19 were treated with therapeutic plasma and all 10 patients had enhancement in symptoms disappearance (e.g. fever, cough, shortness of breath and chest pain) within 1-3 days of administration. They also demonstrated radiological improvement in pulmonary lesions.

Recently drug regulatory authority of Pakistan (DRAP) permits clinical trials of plasma therapy for treatment of COVID-19[113] and there are five clinical trials USA have been projected to estimate human anti-SARS-CoV-2 plasma for the prevention and handling of COVID-19.[114] In addition, Turkey have started convalescent plasma from recovered patients to use for patients who had severe disease.[46] All of the previous and current conclusions suggest that administration of therapeutic plasma is harmless, diminishes viral infection and may improve clinical consequences. Moreover, COVID-19 therapeutic sera could be helpful to treat patients with initial symptoms.

## Interferon (IFN) Alpha 2b

This drug reflects the recombinant form of the protein interferon alpha-2 which was made by recombinant process in Escherichia coli to combat viral infections triggered by the HIV, hepatitis B and C, plus respiratory Papillomatosis. Recently, this medication was used in clinical trials to treat patients with SARS-CoV-2, although there are no published results of those trials in the peer-reviewed scientific literature yet. During this COVID-19 outbreak, China has chosen Cuban drug IFN alpha-2b along with 30 others to treat CoV patients.[115] Luis Herrera Martínez, a scientific and commercial advisor to the President of Bio-Cuba-Farma, stated that the drug "the antiviral interferon alpha 2b has the advantage that in situations like these it has a mechanism to protect itself and its use prevents patients from reaching serious and complicated stage".[116] IFN is known to have cured more than 1,500 patients with CoV and is among the drugs of choice for the WHO.[117] The specific method for administration of IFN-α is vapor inhalation at a dose of 5 million U (and 2 mL of sterile water for injection) for adults, 2 times/day.[24, 54]

## Anti-cytokines

A retrospective observational study conducted in china with the aim to determine alterations of markers of severe COVID-19 patients in peripheral blood, which might be worthy in surveillance of the disease. It was concluded that the baseline level of IL-6 is of close relationship with the seriousness of COVID-19, and the elevated IL-6 was considerably related to the clinical signs of critical patients. Decline of IL-6 was considered to be closely associated to treatment effectiveness. Researchers decided after collective outcome of the study, that the dynamic changes in level of IL-6 could be utilized as a marker for disease monitoring in severe COVID-19 patients.[117] The University of Manchester and Salford Royal Hospital in the UK documented surge of pro-inflammatory cytokines in the blood, together with TNF, interferon γ, interleukin (IL)-1, IL-6 in ICU patients with COVID-19.[118]

A report covering a trial of 21critical COVID-19 patients in China and one case study belonging to France got medical advantage with the anti-IL-6 receptor antibody. Out of many, only few drugs such as adalimumab or infliximab and anti-TNF antibodies have high potency, efficacy, availability, and a well-established safety profile.[119] Recently, a study published by Bingwen liu and his colleagues in Elsevier Journal of autoimmunity proposed a new promising approach to utilize IL-6 blocking agents could manage nCoV-2-induced (CRS) Cytokine release syndrome which is a deadly multiple organ dysfunction in the body of CO-

VID-19 patients and symbolizes a potential therapeutic target.[85] This approach still needs further investigatory research to determine the actual outcome.

### Anticoagulant Treatment

The use of anticoagulant for severe COVID-19 treatment has been recommended by some general proficient agreement 120 due to the risk of disseminated intravascular coagulation (DIC) and venous thromboembolism (VTE). In addition, a previous study identified a first stage of sepsis-associated DIC called "sepsis-induced coagulopathy (SIC)"[121] as well long-term bed-staying and probability of getting hormone therapy increases the risk of VTE in severe COVID-19 cases.[122] There was a study published by Iba et al. has been confirmed that the patient with SIC benefit from anticoagulant therapy.[123] The mechanisms by which COVID-19 can cause coagulopathy complication are by inducing the impairment of endothelial cells function which results in excess thrombin formation and fibrinolysis cessation that specified by a hypercoagulable state in patient with infection such as COVID-19.[124] Furthermore, the hypoxia which reported in severe COVID-19 cases can trigger thrombosis not only through raising blood viscosity, but also through a hypoxia-induced transcription factor-dependent signaling pathway.[125]

A recent lung organ dissection has been found an evidence for presence of obstruction and microthrombosis formation in lung small vessels of serious patient with COVID-19.[126] Low molecular weight heparin (LMWH) was the best and most used as prophylactic dose due to its anti-inflammatory effect, its ability to prevent DIC and SIC.[127] A recent retrospective study in Tongji hospital, Wuhan, Hubei, China reported that anticoagulant treatment chiefly with LMWH seems to cause a better prognosis in severe COVID-19 patients meeting SIC criteria or with noticeably raised D-dimer level.[120] It has been observed that COVID-19 patients with coagulation disorder have higher chances of mortality. For this reason anticoagulant drugs had been added to their treatment algorithm.[46] It is suggested that only the patients with severe COVID19 infection whom need for intensive care treatment and meeting SIC criteria or with severe elevated D-dimer may benefit from anticoagulant therapy.

### Antihypertensive Drugs

Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (AR-Bs) are generally prescribed for patients with high blood pressure (B.P). ACE hydrolyzes angiotensin-I hormone into the vasoconstricting angiotensin-II resulting in high B.P. ACE2 act to neutralize the activity of ACE and lowering B.P by decreasing the amount of angiotensin-II. As ACE2 serves as the co-receptor for SARS-CoV-2, this has created some to hypothesize that reducing the levels of ACE2, in cells, might assess in combating the infection. On the other hand, ACE2 has been revealed to have a shielding effect against virus-induced lung injury by growing the generation of the vasodilator angiotensin (1–7).[128] Both ACE-Is and AR-Bs have been determined in rodent studies to induce ACE2 expression therefore may worsen the severity of CoV infections.[129] However, numerous professional societies and regulatory organizations have suggested continuing standard ACE-Is and AR-Bs therapy. Regardless of the absence of proof, there have been thoughts for both the continuation and termination of ACE-Is, AR-Bs, or both throughout the treatment for COVID-19 in patients with hypertension.[130]

### Traditional Chinese Medicines (CM)

A study reported the historic records for infection prevention in CM along with former clinical evidence on CM prevention for similar public health emergencies such as SARS and H1N1 (Hemagglutinin Type 1 and Neuraminidase Type 1) influenza. Available literature presented that the practice of CM to prevent epidemics of contagious diseases can be traced back to ancient CM practice over centuries, and its effective results were preliminarily demonstrated by modern human clinical researches when applied to SARS and H1N1 influenza epidemics signifying that historical CM experience is a valuable approach.[131]

Based on the complete investigations of the prevention programs allotted by 23 provinces since the COVID-19 outbreak, it is established that the main CM principles in preventing COVID-19 were to tonify qi to defend from external pathogens, discharge heat and disperse wind, and resolve dampness with aroma. It was also related to the features of CHM formulae for preventing "outbreak" in previous times and SARS in 2003.[132] The six most frequently used herbs were Radix (Fangfeng), Glycyrrhizae Radix Et Rhizoma (Gancao), Saposhnikoviae Astragali Radix (Huangqi), Lonicerae Japonicae Flos (Jinyinhua), Atractylodis Macrocephalae Rhizoma (Baizhu), and Forsythiae Fructus (Lianqiao). Astragali Radix (Huangqi), Saposhnikoviae Radix (Fangfeng), and Atractylodis Macrocephalae Rhizoma (Baizhu) are all ingredients of a classical herbal formula Yupingfeng Powder, for tonifying qi to keep from external pathogens.

In Lao, et al's controlled study[132] of CM formula for preventing SARS, Yupingfeng Powder was also the main components. Many findings have confirmed that Yupingfeng Powder has antiviral, anti-inflammatory and immunoregulatory effects.[133] Japonicae Flos (Jinyinhua) and Forsythiae Fructus (Lianqiao) are the main parts of Yinqiao Powder, which is a classical formula used to prevent and treat re-

spiratory infectious diseases in ancient.[134] An experimental investigation found that the consequence of Yinqiao Powder (银翘散) in preventing and treating upper respiratory tract infection could be described by its antibacterial and antiviral properties and improvement of the function of upper respiratory mucosal immune system.[135] A large-scale, multicenter, randomized trial found that Yinqiao Powder along with heat-clearing formula could decrease time to fever perseverance in patients with the H1N1 influenza virus infection.[134]

These days, the National Health Commission of China has not issued a CM prevention program for COVID-19. There may be multiple reasons like, first, according to the CM theory of three-factors concerned treatment (Sanyin Zhiyi, 三因制宜), due to the differences of regional, individual, and seasonal factors in the distribution and occurrence of diseases, these aspects should be measured in prevention and treatment,[136] and second, nonexistence of solid proof of CM formula for COVID-19. However, a single case study by Ren et al. stated that Qingfei paidu decoction is controlling the symptoms of COVID-19.[137] In addition, H.L. Zhang and Y.X.Zhu stated in another single patient case report that the highly suspected case of novel coronavirus pneumonia were recovered with the use of CM.[138] We recommend that the protection should also be given attention to when taking CHM formula to prevent COVID-19, especially when they are used for long time. The people should select the prescriptions under the guidance of CM doctors according to the program issued by provincial health authorities, and avoid taking the prescriptions or herbs with unknown origin and without officially approval.

## Others

### Temperature and Humidity

In order to prevent COVID-19, multiple environmental factors are playing important role to cope this disease. Temperature and humidity are also important in this regard. A research validated an inverse relation between COVID -19 mortality and temperature, while a direct relation with diurnal temperature range (DTR). Multiple research have demonstrated that respiratory diseases mortality elevated with falling temperature,[139] and was strongly linked with decreased temperature.[140] While another research established that both heat and cold effects might have hostile impacts on respiratory mortality.[141] The increased DTR have shown increased risk of mortality for respiratory and cardiovascular diseases by a study conducted in 30 East Asian cities.[142] During cold conditions, the accumulative risk of respiratory, cardiovascular and non-accidental death increased at high DTR values in Tabriz.[143] A time dependent research conducted in Shanghai for the effect of DTR on daily chronic obstructive pulmonary disease (COPD) death rate showed that for each 1°C increase in the 4-day moving average for DTR counted for 1.25% of amplified risk of COPD mortality.

In a demographic research, the outbreak of SARS in Guangdong in 2003 slowly washed-out with the warming weather approaching, and was completely ended until July.[144] It has been recorded that the temperature and its deviations might have affected the SARS plague. A research in south Korea have found that the menace of influenza incidence was considerably elevated with decreased daily temperature and relative low humidity, and a direct significant relationship was perceived for DTR.[145] Further, temperature and DTR have been associated to the death from respiratory diseases. A study confirmed that absolute humidity had significant correlations with influenza viral transmission and survival rates.[146]

Few studies determined that the COVID-19 was associated to the climatological factors, which reduced with the temperature growing,[147] but their effects on the death rate has not been described. Scientists established that respiratory infection was increased during unusually cold and low humidity circumstances,[148] representing decreased humidity might too be a significant risk factor for respiratory diseases. A 25 year research study established that humidity was a significant element of mortality, and low -humidity levels might cause a huge increase in mortality rates, possibly by influenza -related mechanisms, similar to a study carried out in the United States.[149] Epithelial damage and/or reduction of mucociliary clearance can be caused by breathing dry air, and then lead to expose the host more vulnerable to respiratory virus infection; The creation of droplet nuclei is vital for transmission, but exhaled respiratory droplets settle very quickly at high humidity so that it is hard to contribute to influenza virus spread.[150]

## Future Perspective: The Development of Prophylactic COVID-19 Vaccines

The increased pace of SAR-CoV-2 contagions and affected nations, the whole struggle is on making an effective SARCoV-2 vaccine in various countries. Following the standard operating procedures (SOPs) and knowledge from SARS and MERS vaccines development, many research scientist have started working on SAR-CoV-2 vaccine development within only a few weeks after the outbreak. Almost 37 biopharmaceutical companies and academic sectors after two months of this outbreak started competition for the development of prophylactic vaccine by utilizing several techniques including DNA, mRNA, recombinant protein and ad-

enoviral vector.[18] Maximum vital information are needed to be gather for the formation and validation of vaccines, which includes investigating final target antigen(s), correlated-immune protection, animal models, immunization route, production facility, scalability, outbreak forecasting, target product profile (TPP), and target population. Factors like International cooperation as well as technology allocation between experts are too needed and helpful for SARS-CoV-2 vaccine development. Knowledge learnt from Zika was used to speed up the available vaccine during current plague, along with clinical trails the preclinical studies of SAR-CoV-2 vaccine nominees may need to be performed. Although prior of entering into clinical testing, the production process must be asses by some regulatory agencies for preclinical information to make sure volunteers' safety.[151]

Vaccine formation is an expensive and lengthy process. Attention is high, and it normally requires numerous candidates and many years to develop a licensed vaccine.[152] Due to high price and maximum failure rates, researchers usually follow a linear sequence of phases, with manifold breaks for manufacturing-process checks or data analysis. A new pandemic paradigm is required for the developing a vaccine, with a quick start and numerous steps implemented in comparable prior to confirming a successful result of another step, hence, resulting in higher economical risk. For instant, for platforms with experience in humans, phase 1 clinical trials may be able to progress in comparable with testing in animal models. Table 2 contains some of the potential vaccines under clinical trials by different pharmaceutical companies and universities to cope the COVID-19 plague.[153]

## Discussion

This review article is compiled based on the currently published data for the treatment of COVID-19. At present time, there is no an effective vaccine or specific antiviral drugs for coping COVID-19. Thus, alternatively we have to depend on imposing firm precautionary and control trials that diminish the menace of possible disease spread.[6] This article undoubtedly validates that the existing data are not enough to suggest any treatment for abolition of COVID-19 to be used at the clinical level. As the human research are lacking comparative data thus it is very difficult to say whether the patient get treated are because of the use of a specific medicine or the general clinical care gained. Most of the in vitro research, are the indicative of potential valuable effects although the data are too maiden to be utilized as rationale for clinical consumption.[6, 24]

Scientists are finding effective and appropriate vaccine nominees and therapeutics for monitoring the deadly COVID-19. From the recently conducted in vitro study, the results on some human trails against COVID-19 are encouraging since some antiviral, antimalarial and other pharmacological and no-pharmacological treatments were

**Table 2.** The Development of Prophylactic COVID-19 Vaccines

| Platform | Type of Candidate vaccine | Developer | CoV Target | Current stage of Clinical Evaluation or regulatory status of CoV candidate | Same platform for non-CoV candidates |
|---|---|---|---|---|---|
| NonReplicating Viral Vector | Adenovirus Type 5 Vector | CanSino Biological Inc./Beijing Institut of Biotechnology | COVID-19 | Phase2 ChiCTR2000031781 Phase1 ChiCTR2000030906 | Ebola |
| Inactivated | TBD | Osaka University/ BIKEN/NIBIOHN | COVID-19 | Pre-Clinical | |
| Live Attenuated Virus | Deoptimized live attenuated vaccines | Codagenix/Serum Institute of India | COVID-19 | Pre-Clinical | HAV, InfA, ZIKV, FMD, SIV, RSV, DENV |
| NonReplicating Viral Vector | ChAdOx1 | University of Oxford | COVID-19 | Phase 1/2 (not yet recruiting) NCT04324606 | MERS, influenza, TB, Chikungunya, Zika, MenB, plague |
| NonReplicating Viral Vector | Ad26 (alone or with MVA boost) | Janssen Pharmaceutical Companies | COVID-19 | Pre-Clinical | Ebola, HIV, RSV |
| NonReplicating Viral Vector | MVA expressing structural proteins | Centro Nacional Biotecnología (CNB-CSIC), Spain | COVID-19 | Pre-Clinical | HIV, HCV, chikungunya, Ebola, zika, malaria, leishmania |
| Protein Subunit | microneedle arrays S1 subunit | Univ. of Pittsburgh | COVID-19 | Pre-Clinical | MERS |

shown to be highly effective in preventing the infection.[154] Though, the fact that needs careful consideration is the safety profile of all these treatment tactics and required to be verified through properly conducted clinical trials. Therefore, the concentration of the studies may important to be on the direct human clinical approaches in maximum quantity along with in vitro studies to approve the efficacy as well as protection of all pharmacological treatments.

## Conclusion

As the Pandemic situation is spreading in the whole world, scientists around the globe are dynamically discovering medications that would be effective in fighting against COVID-19. At the present, there are not any certified antivirals drugs specific for COVID-19. However, the safety and efficiency of these already available potential drugs in the treatment of COVID-19 are required be confirmed in further preclinical and clinical trials. Furthermore, this viral pandemic needs to be defied with a joined national approach that can be executed rapidly on a very large scale. The capability to mobilize and to stay nimble in adjusting to these challenges is paramount. Municipal buy-in is vital for all residents to abide by the rules and recommendations. Cooperation and sharing knowledge of COVID-19 among countries are imperative to establish more effective policies to control the spread of future pandemic and curtail morbidity and mortality.

**Disclosures**

**Ethics Committee Approval:** Ethics committee approval was not requested for this study.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – M.N., S.U.; Design – M.N., S.U.; Supervision – M.N.; Materials – K.A.; Data collection &/or processing – S.I., T.A.; Analysis and/or interpretation – M.N., S.U.; Literature search – K.A., S.I., T.A.; Writing – M.N., S.U., K.A., S.I., T.A.; Critical review – M.N., S.U., K.A., S.I., T.A.

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