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Possible treatment and strategies for COVID-19: review and assessment

N. TRIVEDI[1], A. VERMA[2], D. KUMAR[3]

[1]Department of Neurological Sciences, University of Nebraska Medical Center, Nebraska Medical Center, Omaha, NE, USA
[2]Clinical and Experimental Therapeutics, College of Pharmacy, University of Georgia and Charlie Norwood VA Medical Center, Augusta, GA, USA
[3]Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Nebraska Medical Center, Omaha, NE, USA

Abstract. – The coronavirus disease 2019 (COVID-19) is declared as an international emergency in 2020. Its prevalence and fatality rate are rapidly increasing but the medication options are still limited for this perilous disease. The emergent outbreak of COVID-19 triggered by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) keeps propagating globally. The present scenario has emphasized the requirement for therapeutic opportunities to relive and overcome this latest pandemic. Despite the fact, the deteriorating developments of COVID-19, there is no drug certified to have considerable effects in the medical treatment for COVID-19 patients. The COVID-19 pandemic requests for the rapid testing of new treatment approaches. Based on the evidence, hydroxychloroquine is the first medicine opted for the treatment of disease. Umifenovir, remdesivir, and favipiravir are deemed the most hopeful antiviral agent by improving the health of infected patients. The dexamethasone is a first known steroid medicine that can save the lives of seriously ill patients, and it is shown in a randomized clinical trial by the United Kingdom that it reduced the death rate in COVID-19 patients. The current review recapitulates the existing evidence of possible therapeutic drugs, peptides, humanized antibodies, convulsant plasma, and vaccination that has revealed potential in fighting COVID-19 infections. Many randomized and controlled clinical trials are taking place to further validate these agent's safety and effectiveness in curing COVID-19.

Key Words:
COVID-19, Remdesivir, Dexamethasone, SDRV-003, LCB1.

Introduction

A Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was initially recognized and assigned as COVID-19 infection[1]. National Health Commission of China confirmed the information of the first appearance of COVID-19 in pneumonia patients appeared in the city of Wuhan in China in December, 2019[2]. Initially, pneumonia patients expressed the normal respiratory infection which rapidly transformed into acute respiratory syndrome[3]. Now it has broken all the borders infecting more than 23 million people worldwide. Globally, the deaths by this COVID-19 pandemic are more than one million.

There is very urgent requirement to invent novel antiviral drug and effective vaccines against COVID-19. Additionally, economic problem has been produced by this pandemic so rapid interference is required to control the spreading of COVID-19. In instance, previous research and treatment that were used in Severe Acute Respiratory Syndrome Coronavirus (named, SARC-CoV) and Middle East Respiratory Syndrome coronavirus (named MERS-CoV) could provide some prospect to step up the consequential treatment against COVID-19. Based on evidence, Food and Drug Administration (FDA) approved some drugs that has been already used in the treatment of SARC-CoV and MERC-COV. Primary opted treatment for COVID-19, the lopinavir, is an antiretroviral (ARV) drug that is used for HIV-1 treatment and that has been used for COVID-19 in combination with ritonavir (potent anti-HIV drug). This lopinavir-ritonavir combination showed to be efficient against COVID-19[4]. Remdesivir was also used for the treatment of SARC-CoV and MERC-COV. Remdesivir showed the most promising effect against COVID-19[5]. Favipi-

Corresponding Author: Devendra Kumar, Ph.D; e-mail: devendra.kumar@unmc.edu; kumardevendradubey@gmail.com

ravir was previously used for the treatment of Influenza and Ebola and also revealed potential against COVID-19. Anti-malarial drug hydroxychloroquine has shown more promising results against COVID-19 and it is used in higher frequency. Alone and in combination, these drugs have been trailed to treat COVID-19 infected patients[6-8]. Despite the antiviral therapy, dexamethasone has shown the little relief against COVID-19. In the initial clinical trial, it reduced the death by one-third on severe patients that were on ventilator[9]. Some other drugs like ivermectin ribavirin, nitazoxanide and umifenovir were also using worldwide, as shown in Table I.

Convalescent plasma was collected from people recovered from COVID-19 infection. That showed reliable effect to treat the COVID-19 patients without showing adverse effect. Thus, it might be useful to test the safety and efficacy, FDA has approved for clinical trial for COVID-19 treatment. The vaccine is the last hope. Vaccine development is typically a long game. Already, more than ten vaccines against COVID-19 are in clinical trials. We will have to wait and see how things play out[10].

However, medication options and standard treatment for COVID-19 are restricted. Herein, we reviewed the supportive roles of several antivirals, some antibiotics and some therapeutic peptides that have tested their efficacy in the worldwide treatment of COVID-19.

Agents Used to Treat COVID-19

Remdesivir

Remdesivir (GS-5734) was developed by Gilead Sciences (Foster City, CA, USA). It is an adenosine triphosphate analog and that has been used to treat for coronavirus and Ebola virus[7]. Remdesivir stops the viral replication by inhibiting the essential replicating enzymes RNA dependent RNA Polymerase. It promotes the premature termination of viral transcription by eluding the proofreading activity of exoribonuclease[11]. That's why remdesivir has the broad spectrum activity against many viruses, including, SARS-CoV, and MERS-CoV[4,5]. Clinical pharmacokinetics (PK) data have not been determined for better dosage regimen yet. Moreover, safety data on human are available online[12]. It is now in phase 3 clinical trial for severe and moderate COVID-19 infected patients for finding out the clinical efficacy[13]. Its report will come out soon. Remdesivir has already shown the successful inhibition with sub micromolar concentration in tissue culture experiment against human CoV, and Zoonotic CoV[14,15]. Similar efficacy was also found in MERS-CoV infected nonhuman primate (rhesus monkey)[16]. Presently, more than 24 clinical trials are ongoing on COVID-19 patients. It may give the direction for potential treatment for COVID-19 infected patients[17]. Based on research outcomes remidesivir was recommended as a hopeful op-

Table I. Mechanisms of action of potential agents used for COVID-19 treatment.

	Drug	Mechanism of action
1	Remdesivir	Inhibition of the RNA dependent RNA Polymerase
2	Favipiravir	Inhibition of the RNA dependent RNA Polymerase
3	Ribavirin	Inhibition of the RNA dependent RNA Polymerase
4	Interferons	Inhibition of Viral Exocytosis
5	Lopinavir/ritonavir	Inhibition of Protease Enzyme
6	Chloroquine, Hydroxychloroquine	Inhibition of Endosomal Acidification
7	Dexamethasone	Regulate Cytokines Formation
8	Umifenovir	Inhibition to Critical Membrane Fusion
9	Tetracyclines	Inhibition of Bacterial Translation
10	Tocilizumab	Regulate Cytokines Formation
11	Itolizumab	CD6 Inhibitor
12	Teicoplanin	Inhibition of cathepsin L
13	Meplazumab	Inhibition of CD147
14	Eculizumab	Inhibition of C5 Complement Protein
15	AMY101	Inhibition of C3 Complement Protein
16	Nitazoxanide	Inhibition of Neuraminidase Enzyme
17	Ivermectin	Inhibition of Replication
18	SDRV-003	Regulate Cytokines Formation
19	LCB1	Neutralizing Protein

tion for the treatment of COVID-19 even though its safety and efficacy data in human are still required through clinical trials.

Favipiravir

Favipiravir is an antiviral drug named as Avigan or T-705 that was used for the treatment of influenza infection in 2014 in Japan[18]. Favipiravir was also used for the treatment of Ebola virus in 2014, in the absence of standard cure for Ebola[19]. Based on the safety and efficacy in clinical trial it was finally approved for the treatment of Ebola virus infection[20-22]. Favipiravir directly inhibits viral transcription by inhibiting RNA polymerase[23]. It was noticed that favipiravir also showed the immune response in viral clearance in nonhuman primates[24]. Other studies[25,26] have also described that active metabolite of favipiravir (favipiravirribofuranosyl-50-triphosphate) directly inhibited the RNA dependent RNA polymerase in cells. That drug might be one option for treating for COVID-19. The clinical evidence for the efficacy and safety was observed in open label, nonrandomized control clinical trial[27]. Currently, 18 clinical trials are running in various phase of development for the treatment of COVID-19[28]. Recently, phase-3 clinical trials for COVID-19 favipiravir with tablets was initiated in India, and it is expecting the complete study results will come out soon[29]. The clearance has granted Appili Therapeutics for evaluating phase to clinical trial for the safety and efficacy of favipiravir in the tablets form to control COVID-19 in long-term care services. FDA has given approval to Appili Therapeutics to an investigation for broad-spectrum antiviral therapy favipiravir.

Lopinavir/ritonavir

Lopinavir (Kaletra) is potent anti-HIV drug that is used to treat HIV infection in combination with ritonavir. Ritonavir inhibits the drug metabolism of lopinavir to improve the PK (half-life) and activity. Infectious Diseases Society of America (IDSA) recommended ritonavir-boosted combination therapy for HCV patients as first line therapy[30]. Lopinavir/ritonavir have shown anti SARS-CoV-2 activity *in vitro* by inhibiting the protease in Vero E6 cells[31]. In a comparative study[32], lopinavir-ritonavir in combination with ribavirin exhibited a risk in SARS-CoV. Moreover, SARS patients disclosed that Lopinavir-ritonavir plays an important role to explain the clinical consequences and in combination with IFN enhanced clinical outcomes on some MERS patients[33]. Lopinavir-ritonavir was found to 40% decrease in the risk of MERS infection[34]. In India, EMR division has advised the dosing schedule for this drug combination for clinical management of COVID-19[35]. One randomized open-label clinical trial[36] for lopinavir-ritonavir is conducted on 199 patients, of whom 99 were appointed to the treatment group, and 100 received the standard of care. The authors did not find more advantage of lopinavir-ritonavir to clinical benefits beyond the standard of care, while it was found to have benefit for some secondary endpoints. The efficacy of the lopinavir-ritonavir was approved, and future trials will verify the results[36]. Currently, 64 clinical trials are proceeding for lopinavir-ritonavir along with other drug involvements, and the majority of them are at the initial stage of the progress[37].

Ribavirin

Ribavirin is a broad spectrum antiviral drug which is developed by Bausch Health Companies (Bridgewater Township, NJ, USA). It is a guanosine analogue used to treat several viral diseases. In combination with interferon, it has been used as treatment option for chronic hepatitis C. It was also used as treatment option for SARS-CoV-1 in combination with lopinavir-ritonavir. It showed lower risk and decreased death in ARDS infection (Acute respiratory distress syndrome) in combination with than lopinavir-ritonavir only[32]. However, in recent *in-vitro* studies, ribavirin showed the high effective concentration against COVID-19[38,39]. Nonetheless, ribavirin showed an unexpected adverse effect, which was very harmful to ADRS patients[4].

Chloroquine, Hydroxychloroquine

The two aminoquinolines, chloroquine (CQ) and hydroxychloroquine (HCQ) are mostly used for treating malaria and rheumatic diseases. They were recommended as a primary treatment option for the COVID-19 infection in the initial stage[40-43]. CQ and HCQ have weak diprotic properties and they could raise the pH inside the endosome while fusing the virus to host cell[44]. Recently, both drugs have shown the activity against the COVID-19 in Vero E6 cells[45]. Several clinical trials were preceded in China for CQ and HCQ on COVID-19 infected patients to find out the efficacy and safety. One of them[46] disclosed that hopeful results in reduction the diseases progression.

Meanwhile one clinical trial was conducted in France for finding the clinical efficacy of HCQ used different doses, and in combination with azithromycin on COVID-19 infected patients. The

clinical manifestation revealed that treated rate was significantly higher in HQC used in combination with azithromycin[47]. Even though this study revealed promising results, more extensive clinical data are required to authenticate the clinical efficacy and safety of HQC with azithromycin[48]. Likewise, postexposure prophylaxis clinical trial (NCT04308668) using oral dosing regimen has been conducted in USA. The result will come out soon.

Umifenovir

Umifenovir, is also known as Arbidol, is a broad-spectrum antiviral agent, developed by Russian Research Chemical and Pharmaceutical Institute. Umifenovir was demonstrated as a therapeutic option for many viral diseases[49]. The principal site of action of umifenovir was to prevent the fusion of endosome membrane to virus particles[50-52]. In the influenza virus case, umifenovir was discovered to interact with virus hemagglutinin and enhance the hemagglutinin stability, thus inhibiting the hemagglutinin transition into functional state[53]. Umifenovir also revealed the immunomodulatory effect, such as IFN induction and macrophage activation[54]. Lopinavir-ritonavir and umifenovir was previously used to treat acute SARC-CoV in the clinical practice; however, their effectiveness remains divisive. The clinical safety and efficacy of the umifenovir monotherapy were analyzed in COVID-19 patients and compared with lopinavir-ritonavir therapy. Umifenovir was found better than lopinavir-ritonavir for treating COVID-19[55]. Similarly, Central Drug Research Institute (CDRI) has acquired the approval for proceeding the phase III clinical trial of umifenovir. In this randomized, double-blind, placebo-controlled trial, the efficacy, safety, and tolerability of umifenovir will be tested. The results shall be reported soon.

Nitazoxanide

Nitazoxanide is a broad-spectrum antiparasitic and broad-spectrum antiviral drug. Nitazoxanide has exhibited effective *in-vitro* activity against SARS-CoV-2 and MERS-CoV in Vero E6 cells. The efficacy was believed on the bases of its involvement in regulation of viral replication instead of specific metabolic pathways[56]. Nitazoxanide inhibits the viral infection by enhancing the specific host mechanism[57]. While, the *in-vitro* activity of nitazoxanide against the SARC-CoV-2 is suggesting that more clinical data are needed to estimate the efficacy and safety against COVID-19[31,58]. While assessing the efficacy of nitazoxanide alone and in combination with HQ, it reduced the requirement of insidious ventilator support for COVID-19 patients. Currently, many clinical trials for nitazoxanide are proceeding with various doses to treat COVID-19 patients[59]. Although the results are not encouraging or unavailable yet, FDA has given the approval to Azidus Brasil for nitazoxanide to proceed phase II clinical trial[60].

Ivermectin

Ivermectin is as effective as albendazole, antiparasitic agent that was approved by FDA. Ivermectin has shown the activity against many viruses[61-66]. Recently, one *in-vitro* study[67] showed that ivermectin strongly inhibited the replication of COVID-19. Its antiviral activity may play essential role and provide as a potential candidate to treat COVID-19[68,69]. Finally FDA announced a statement for self-administration of ivermectin in COVID-19 patients[70].

Interferons

Interferon (IFN) is a broad-spectrum antiviral agent that inhibits the viral replication by interacting with toll-like receptor (TLR)[71]. Type III IFNs (IFN-λs) was identified in 2003, it established independently to perform antiviral resistance in cells[72,73]. Furthermore, a member of this family (IFN-λ4) was discovered in 2013[74]. Type IFNs have been used to treat critically ill patients by chronic hepatitis C virus and hepatitis B virus-infected people. It may have the capability to protect patients during outbreaks of other viruses. IFN-λ was found to be more effective with less increase in inflammation and tissue damage[75,76], and potentially restricted viral spreading from the nasal epithelium to the upper respiratory tract[77], with efficacy as compared to IFNα-based therapies[78]. IFNα and β exhibited activity against the SARS-CoV *in-vitro*[79,80]. IFNβ demonstrated the potential action in diminishing MERS-CoV replication[81,82]. Mostly type I IFN showed the fast decrease of viral load in mild to moderate COVID-19 patients. In the severe COVID-19 infection, IFN showed the antiviral response with elevated lungs cytokine levels, weakened the T cell response and acute clinical relapse[83].

Dexamethasone

The FDA approved dexamethasone as a spectrum immunosuppressor in 1958. It is 30 times more potent with longer duration than cor-

tisone and reduces the ability of B cells to synthesize antibodies[84]. Dexamethasone regulates cytokine's damaging effects by limiting the formation of cytokine[85]. Additionally, dexamethasone stops macrophages and natural killer cells from clearance secondary nosocomial pathogens[86]. Clinical evidence does not endorse the use of corticosteroids in COVID-19 infection[87]. Even though corticosteroid has been accompanying the rise of the viral load, it continued the viral load even after survival of patient from SARS-CoV[88]. By contrast, a clinical trial showed that dexamethasone saved life seriously ill COVID-19 infected patients in United kingdom (UK)[9]. UK government declared that dexamethasone was allowed as an immediate treatment option for hospitalized patients that were seriously ill and on ventilator[89]. WHO added the dexamethasone in the vital medicine list that is readily available at low cost. In USA, NIH issued the guideline to recommend the dexamethasone as a treatment option of COVID-19 infected patients [90,91].

Tetracyclines

Tetracycline is an antibiotic used to treat several infections. It is sold as Sumycin and other names. Tetracycline can be used as a possible treatment option for COVID-19 patients because its well-known activity to decrease the level of inflammatory cytokines such as IL-1b and IL-6[92]. Both IL-1b and IL-6 levels were significantly increased in the body of patients during COVID-19 infection [93]. Tetracycline also showed that it diminished the inflammatory agent in the circulation by activation of protein kinase C and induction of the programmed cell death[94]. Investigators proposed that tetracycline must be a better therapeutic option to treat inflammatory disorders[94,95]. Previously it is documented to use for the treatment of HIV, Nile virus and viral encephalitis diseases[96] and also used for prevention of septic shock induced by ARDS[97]. Based on combinatorial molecular simulation analysis, doxycycline and minocycline were selected, as a potent inhibitor COVID-19 infection[98].

Tocilizumab

Tocilizumab (named; Actemra) is a recombinant monoclonal antibody that was developed by Roche pharmaceuticals (Basel, Switzerland). Tocilizumab is basically used to treat rheumatoid arthritis. It was designed as IL-6 receptor blocker to inhibit the binding of IL-6 to its receptor thus alleviating cytokine release syndrome. IL-6 significantly increases in concentration in the body of patients when COVID-19 infection is exposed[93]. This is why tocilizumab is used as therapeutic option for treating COVID-19 patients[70,99]. In COVID-19 infected patients, T-lymphocyte and macrophages produce IL-6 and cause the cytokine storm and severe inflammatory responses in lungs and other tissues. Tocilizumab has the highest binding affinity to IL-6 receptor and makes the receptor incapable to bind IL-6 and lessens the inflammatory response and finally obstructs the IL-6 signal transduction pathway. Consequently, it is basically turned into an efficient therapeutic drug for the treatment of severe COVID-19 infected patients[100,101]. FDA has given the approval to Genentech for proceeding the phase III clinical trial of intravenous tocilizumab to assess the safety and efficacy on adult patients infected with severe COVID-19[102].

Itolizumab

Itolizumab (named, Alzumab) is a recombinant monoclonal antibody against for CD6 (Cluster of Differentiation 6) of IgG1 (Immunoglobulin G1). It was developed for the treatment of psoriatic patients[103]. Itolizumab have shown the effect of regulating the downstream pathways, and then, a reduction of inflammatory cytokines, such as, IFN-γ, TNF-α and IL-6[104-106]. On the basis of the mode of action, it could be used as treatment option for COVID-19 infection[107]. It showed the reduction of IL-6 in critically ill patients[108]. The biopharmaceutical company Biocon has procured approval for itolizumab from the DGCI (Drugs Controller General of India) for the emergency use in COVID-19 patients[109]. Cuban regulatory agency (CEMED) has given approval for the trial on the basis of prospective use of itolizumab for COVID-19.

Teicoplanin

Teicoplanin (named; Targocid) was developed by Sanofi Pharmaceuticals (Paris, France). It is an antiviral drug that can inhibit the replication and transcription of the competent virus. It also worked against the MERS and SARS as well[110]. Mechanistic investigations revealed that teicoplanin specifically inhibits the activity of host cell's cathepsin L and cathepsin B; these proteins are accountable for cleaving the viral glycoprotein allowing contact of the receptor-binding domain of its core genome and consequent release into the cytoplasm of the host cell[111,112]. COVID-19 is also the cathepsin L dependent virus. Therefore, the-

se studies suggested that the teicoplanin could be used as therapeutic option for treating COVID-19. According to Ceccarelli et al[113], teicoplanin has a therapeutic effect in COVID-19 infected subjects. Nevertheless, one study[114] revealed first-time real-life report on the use of teicoplanin *in vivo* in subjects affected by COVID-19 and the outcomes appear fairly acceptable when compared with a previous report from the same geographical area. Teicoplanin was recommended as a hopeful option for the treatment of COVID-19 even though its safety and efficacy data in human is still required.

Meplazumab

Meplazumab is a humanized monoclonal antibody that works against the CD147. It efficiently inhibited the virus replication in Vero E6 cells[115]. Based on this evidence, one study has been conducted to determine the clinical outcomes using meplazumab by treating the COVID-19 infected patients. In this open-label concurrent controlled trial, meplazumab revealed improvement in the COVID-19 infected patients[116]. It was previously reported[117] that meplazumab exhibited activity against the Chauge-Strauss syndrome (Characterized by eosinophilic vasculitis, pulmonary infiltration, sinusitis, neuropathy, and asthma). Phase I clinical trial (NCT04369586) in healthy volunteer of maplazumab for injection has been completed for finding the safety, efficacy, tolerability, PK characteristics and dosage regimen for Phase II clinical trial[118]. One open study for phase I and phase II clinical trial is running in USA to find the safety and efficacy of meplazumab injection in COVID-19 infected patients (NCT04275245). This trial will be completed in December 2020[119]. Meplazumab can be used as therapeutic option to treat COVID-19 patients.

Eculizumab

Eculizumab (Soliris, Alexion Pharma International, Zürich, Switzerland), a human monoclonal antibody is a highly selective and effective complement C5 binding protein with high affinity. It prevents cleavage to C5a and C5b and inhibits the production of the membrane attack complex (MAC) C5b-9 to lysis the cell[120]. Interestingly, the C5 blockade reveals an indirect immunoprotective action by preserving early complement components. Eculizumab revealed to be an effective therapeutic option for hematological and neuroinflammatory diseases[120-123]. Evermore, evidence[124] indicates that complement is also a key mediator of lung damage through viral infections, and notably during CoV infection. Thus, activation of compliments is also an effective factor in COVID-19 infection. Consequently, eculizumab might work as an emergency therapy to treat COVID-19 patients associated with ARDS. Some studies[125,126] supported the eculizumab use a treatment for severe COVID-19. It is approved for continuing the clinical trial. Some studies [127,128] were conducted for eculizumab in combination with ruxolitinib for confirming the efficacy in severe COVID-19 patients.

AMY101

AMY101 is a highly selective complement C3 inhibitor that was developed by Amyndas Pharmaceuticals[129-131]. It is a small sized cyclic peptide that showed more promising efficacy in NHP[132]. AMY101 has successfully completed the phase I clinical with acceptable safety and tolerability, and now it is in phase II clinical trial (NCT04395456)[133,134]. Some studies[128,135] have shown the proinflammatory response by the activation of Compliment system (C3) in COVID-19 patients. AMY101 could be unique therapeutic option to overwhelm the complement mediated inflammatory response in COVID-19 patients. Recent clinical study[136], AMY101 showed the safety and efficacy in patients with severe ARDS due to COVID-19 infection.

ARDS-003

Cannabinoid (CBD) is also a possible treatment for severe COVID-19 patients. It was designed as an injectable form to treat a serious case of coronavirus "acute respiratory distress syndrome (ARDS)". This syndrome triggered cytokine storm which created signal to produce more inflammation. It will have the advantage of impacting several pro-inflammatory signaling pathways, by enhancing the effectiveness of the drug to rapidly dampen the cytokines release and prevent the acute outcomes like ARDS. It is related to flood the lungs with fluid. The cannabinoid drug named, ARDS-003, has been approved for the phase I clinical trial. It is still being tested by Tetra Bio-Pharma[137]. Initially, FDA emphasized that the nonclinical study results were appropriate for starting study in COVID-19 infected patients[138].

LCB1

LCB1 showed the SARS-CoV-2 neutralizing antibody. It is a computer designed mini-protein

that has been synthesized by the researchers of University of Washington School of Medicine. It binds tightly to SARS-CoV-2 spikes proteins and impede it from infecting cells. LCB1 showed to protect the Vero E6 cells from SARS-CoV-2 infection. The synthetic antiviral candidates were designed to stop infection by interfering with the mechanism that coronavirus use to break into and enter cells. LCB1 is currently being assessed in rodents[139]. These hyper stable mini-binders provide starting point for COVID-19 therapeutics[140].

Convalescent Plasma

Convalescent plasma (CP) is an effective therapeutic option to treat COVID-19 infected patients. The efficacy of convalescent plasma transfusion (CPT) has been reassessed. However, no specific antiviral agents are available for its treatment, so we should explore CPT's feasibility to rescue the severe patients. Salazar et al[141] showed that out of 25 patients, nine showed improvement within seven days, while other patients had improvement in 14 or couple of days as evaluated by discharge or at least a one-point development on the modified clinical scale. Duan et al[142] also showed that 10 severely ill patients having a single dose (200 ml) of CPT could considerably maintain or increase the counteracting antibodies leading to improvement in efficacy in 3 days and disappearance of disease in 7 days. Shen et al[143], also described that CPT had a positive effect on sever and critically ill patients. Sometimes, CPT can result in transfusion related adverse events, like allergic reactions, transfusion-related dyspnea, and transfusion-related acute lung injury. Nevertheless, in most of the studies, it is shown that most patients tolerate CPT well[144]. Based on studies on COVID-19 patient having CPT treatment, we can say that CPT can reduce the mortality rate in a critically ill patient. Indeed, after CPT, there is a beneficial effect on clinical symptoms, disappearance of SARS-CoV-2 and increase in counteracting antibody titers. Convalescent plasma therapy has the potential to cure COVID-19[145]. Limited clinical data suggest that it is safe, clinically effective and reduces mortality. However, there is an urgent need to establish multicenter clinical trial studies to establish its efficacy to COVID-19 patients. U.S. FDA released a EUA (emergency use authorization) for investigational CP for treating COVID-19 infected patients. The EUA approves the distribution of COVID-19 CP in the USA for the treatment of hospitalized patients with COVID-19 infection[146].

Vaccine Development

Vaccine is the most important therapeutic option to cure the COVID-19 infection. Vaccine is a very urgent need to prevent COVID-19 super spreading. Several companies are developing DNA, RNA, protein, and vectored vaccines. Nucleic acid based vaccines can be produced quickly on the basis of viral sequences, which permits a rapid path to the clinic[147-150]. According to Jackson et al[149], the mRNA vaccine named, mRNA-1273, created to protect COVID-19, was in general safe and tolerated and produced counteracting antibodies action in hale and hearty people. Moderna is proceeding phase I clinical trial approved by NIH. mRNA-1273 is designed to induce neutralizing antibodies directed to the "spike" protein, a portion of coronavirus, which is used to bind to and enter human cells[151,152]. Scientists are also working on a vaccine that may targets COVID-19, it can be given in one dose *via* the nasal way instead of intramuscular injection. It is shown that the nasal route produced a strong immune response in mice susceptible to the novel coronavirus[153].

In total, WHO lists more than 100 candidates in preclinical development while fifteen or more vaccines are in a various phase of clinical trials (Table II), while many infectious disease experts say that even 18 months is an extremely forceful schedule for the first vaccine to come. Few optimists suppose that hundreds of millions of doses of vaccine might be ready to come out by the end of 2020[10]. Global demand for any effective vaccines, when they are ready, will bring its own difficulties. Distribution, delivery, and administration need to be answered.

Herbal Medication

In recent times, many medicinal plants with proven antiviral and related beneficial effects are present and can be considered as an alternative approach to prevent high-risk population suffering from COVID-19. It is also shown in studies carried out by in-silico[154,155] that particular meditational plant is showing antiviral activities. In China during COVID-19 outbreak, some traditional medicine were generally used, like Astragali Radix (Huangqi), Saposhnikoviae Radix (Fangfeng), Glycyrrhizae Radix Et Rhizoma (Gancao), Atractylodis Macrocephalae Rhizoma (Baizhu)[156,157]. Some products of cannabinoids were also used as a treatment option to control the inflammatory response[158-160]. All articles reporting the use of Herbal Medicine to treat viral disease and/or their pharmacological evaluation were

Table II. COVID-19 vaccines in clinical trials.

S.N.	Name	Developmental Status	Properties	Developer
1	mRNA-1273	Phase 3	mRNA vaccine	Moderna and NIAID
2	BNT162	Phase 1/2	mRNA vaccine	BioNTech and Pfize
3	INO-4800	Phase 1	DNA vaccine	Inovio Pharmaceutical
4	AZD1222	Phase 2b/3	Adenovirus vaccine	University of Oxford and AstraZeneca
5	Ad5-nCoV	Phase 2	Adenovirus vaccine	CanSino Biologics
6	Unnamed	Phase 1/2	Inactivated virus	Wuhan Institute of Biological Products and Sinopharm
7	Unnamed	Phase 1/2	Inactivated virus	Beijing Institute of Biological Products and Sinopharm
8	PiCoVacc	Phase 1/2	Inactivated virus, plus adjuvant	Sinovac
9	Unnamed	Phase 1	Inactivated virus	Institute of Medical Biology and Chinese Academy of Medical Sciences
10	NVX-CoV2373	Phase 1/2	Protein subunit	Novavax
11	Sputnik V	Phase 3	adenovirus vaccine Institute of Epidemiology and Microbiology	Gamaleya Research
12	Covaxin	Phase 1	Inactivated vaccine with alum as adjuvant	Bharat Biotech and ICMR
13	ZyCoV-D	Phase 2	DNA vaccine	Zyuds Cadila
14	CDX-005	Phase 1	Live-attenuated	UK's Oxford University, a manufacturing partner of which is India's Serum Institute
15	ChAdOx1 nCoV-19	Phase 1/2	Adenovirus	Centre for Clinical Vaccinology and Tropical Medicine, University of Oxford; NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton; Clinical Research Facility, Imperial College London; St Georges University of London and University Hospital NHS Foundation Trust; and University Hospitals Bristol and Weston NHS Foundation Trust)

retained for further analysis. Therefore, there is a need to complete the data regarding the evidence based and use of herbal preparation in the management and treatment of COVID-19.

Conclusions

Present review defines that the different strategies mentioned above are having different way of action and properties, in tackling the COVID-19. The consumption of single drug may possibly not be more effectual to treat fatal virus. Therefore, combination of antivirals with different mode of action perhaps could be more effective but along with their adverse effects can not be underestimated. The spread of COVID-19 is ongoing but still there is not any antiviral treatment available. Consequently, there is an urgent need to develop antivirals to counteract this pandemic. Healthcare professionals and scientific community currently demonstrated several agents with efficiency to COVID-19 viruses. Latest testimonies for managing COVID-19 are going to be uncovered shortly. No drug may be superior or inferior, however, the use of single drug may not be effective enough to control this deadly virus, by keeping in mind the PK and drug metabolism, the use of combination of antivirals with different mechanism of action may be more effective.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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