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Review Article

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A Generalized Overview of the Possible Pharmacotherapy and Treatments against SARS-CoV-2

Syed Sajidul Islam [1]*, Sayka Alam [1], Tiluttoma Khan Rajib [1], Nasrin Akhter [2], Md. Zahidul Islam [1]

[1] Department of Biotechnology and Genetic Engineering, Faculty of Biological Sciences, Jahangirnagar University, Savar, Dhaka-1342, BANGLADESH
[2] Department of Biomedical Engineering, Khulna University of Engineering & Technology, Khulna-9203, BANGLADESH
***Corresponding Author:** intro.syed@gmail.com

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ABSTRACT

A highly pathogenic viral infection with several symptoms have been reported such as fever, cough, breathing difficulty, fatigue, headache, failure of taste or smell sensation, sore throat, congestion and diarrhoea in December, 2019 in Wuhan, China. In 30th January, 2020 World Health Organization (WHO) declared the outbreak of coronavirus disease to be a Public Health Emergency of global Concern. This virus is highly contagious and can be transmitted after close contact with an infected patient, and has quickly spread globally. In this pandemic, several types of drugs, non-drugs treatment, and their combination are being used to manage the coronavirus disease (COVID-19) affected patients which caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although none of them are officially recommended by any national and international committee such as U.S. Food and Drug Administration (USFDA) because the efficacy and the safety aspects of these treatments are still unidentified and extensively investigated. Different types of potential pharmacotherapy and treatments such as antimalarial, antiviral, antibiotics and many more are presently undertaking clinical-trials to prove their effectiveness in COVID-19 and some of them also showing promising results. This narrative review article summarizes some potential drugs used for the symptoms of coronavirus disease such as antivirals, antibiotics, antimalarial, anti-inflammatory and possible treatments such as neutralizing antibodies from convalescent plasma, umbilical cord mesenchymal stem cells (UC-MSCs) against SARS-CoV-2.

Keywords: COVID-19, WHO, pandemic, SARS-CoV-2, pharmacotherapy

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INTRODUCTION

In December, 2019 numerous patients with pneumonia associated symptoms have been reported in Wuhan, China's Hubei province [1,2]. Majority of the patients identified with the symptoms believed to be originated in the local Huanan sea-food wholesale market. Primarily, patients had developed pneumonia like respiratory infection with rising acute respiratory distress syndrome (ARDS), acute respiratory failure and different severe complications. Finally, the Chinese Center for Disease Control and Prevention (CDC) identified a novel coronavirus from the specimen collected from throat swab of the patient suffering from pneumonia due to unknown cause by RT-PCR. On the first week of January, 2020 the disease named as 2019-nCoV by The World Health Organization (WHO) [3]. SARS-CoV-2 is a nonsegmented enveloped RNA virus belongs to the genus Betacoronavirus of the subfamily Orthocoronavirinae in the family Coronaviridae [4]. Most infections due to coronavirus are mild and more than 10000 lives were affected in the past two decades due to the Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) with the mortality rates of 37% for MERS-CoV and 10% for the SARS-CoV [5-7]. This new RNA virus is highly contagious and spreads worldwide rapidly. The outbreak was declared by WHO after reported to spread in 18 countries outside China and now it has spread to more than hundred countries (up to July, 2020) with many more countries reporting human-to-human transmission. The virus is pleomorphic in nature and the genome of SARS-CoV-2 was rapidly sequenced therefore enable to proper and early diagnosis and there are no established or approved treatment strategies till now. At this time, there is no concrete authentication from randomized clinical trials (RCTs) that supports any prophylactic preventive therapeutic and more than 300 clinical trials on 2019-nCoV are on the way [8]. In this narrative study, we did a comprehensive review on the basis of current evidence regarding proposed preventive and therapeutic treatments, and medication available for 2019-nCoV till July, 2020 and provide various pharmacotherapies against this novel pandemic coronavirus.

Table 1. Some pharmacotherapy and drugs against 2019-nCoV

Pharmacotherapy	Drug name
Antimalaria	Chloroquine
Antibiotics	Doxycycline, Levofloxacin, Azithromycin, Carrimycin and Teicoplanin
Antiviral	Ribavirin, Favipiravir, Nitazoxanide, Remdesivir, Interferon type-1, Arbidol, Nelfinavir, and Lopinavir
Kinase Inhibitor	Ruxolitinib
Antiparasitics	Ivermectin
Anti-inflammatory	Dexamethasone and Corticosteroid
Antifungal	Itraconazole
Immunosuppressant	Thalidomide and Leflunomide
Monoclonal antibodies	Tocilizumab and Clazakizumab
Vaccine	BCG vaccine and ChAdOx1 nCoV-19 vaccine
Other	Dipyridamole, Vitamin C, Ulinastatin and Pirfenidone
Antibiotic+antimalaria	Azithromycin+hydroxychloroquine
Antimalaria+antiparasitics	Hydroxychloroquine+ivermectin
Antiviral combination	Lopinavir+ritonavir

CLASSIFICATION OF MEDICATION AND TREATMENTS IN NOVEL CORONAVIRUS (2019-nCoV)

Symptoms of coronavirus disease 19 (COVID-19) vary from moderate to extreme, including fever, dry cough, sore throat, and shortness of breath. In this review article, treatments and medications to control the symptoms of 2019-nCoV have been divided into two groups. Which are-

1. Pharmacotherapy
2. Non-drug treatment

The pharmacotherapy group can be subdivided into several small groups such as antimalaria, antiviral, antibiotics, antiparasitics, antifungal, anti-inflammatory, kinase inhibitor, immunosuppressant, monoclonal antibodies, steroid, antithrombotic, vaccines and other. The non-drug group is defined as Advanced Therapy Medicinal Products (ATMP) which can also be subdivided into other small subgroups such as Neutralizing antibodies from Convalescent plasma, Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) and Compound amino acids.

Pharmacotherapy

At this moment, there is no precise treatment and medication recommended for coronavirus disease (COVID-19) and currently no vaccines is available [9]. A report on different types of experimental treatments and its classification has been published by The World Health Organization (WHO) on 28th April, 2020 [9]. This report suggested some drugs that are tried on patients to reduce the observed symptoms, i.e. to ensure that the body does not go into cytokines crisis - which is made the patients go into emergency condition. These drugs which have been suggested are classified into antimalaria, antiviral, antibiotics, antiparasitics, antifungal, anti-inflammatory, kinase inhibitor, immunosuppressant, monoclonal antibodies and vaccines based on this WHO R&D Blueprint COVID-19 report [9]. **Table 1** simply introduced the potential drugs such as Chloroquine as an antimalarial type; Favipiravir, Ribavirin, Remdesivir, Lopinavir as antiviral types; Doxycycline, Carrimycin, Azithromycin as antibiotics and so on. Moreover, the table also depicts some potential combination therapies such as Hydroxychloroquine+azithromycin as a combination of antimalaria and antibiotics; Antimalaria+antiparasitics as a combination of Hydroxychloroquine and ivermectin; Antiviral combination as Lopinavir and ritonavir. Although the accuracy and fitness of all these drugs has not been fully verified at this time and many of them under clinical trials [10,11].

Chloroquine

Chloroquine is a small-molecule agent which is an active drug against malaria, autoimmune diseases, and exerts antiviral activity against viruses [12]. Chloroquine weak bases, that, in their non-protonated form, penetrate and concentrate within acidic intracellular organelles like endosomes and lysosomes [15]. When chloroquine analogs are protonated and raises the endosomal pH, resulting in prevention of endosomal trafficking, dysfunctional cellular enzymes, and impaired protein synthesis along with restraining the glycosylation of ACE2 (ACE2 is the receptor for the SARS-CoV-2 virus which allows it to infect the cell) receptor which prevents SARS-CoV-2 receptor binding and spread of the infection [12,15]. It is inexpensive and suggested by the government and organizer of clinical trials as a safe, effective and promising drug to treat malaria and antiviral agents such as SARS-CoV-2 [13]. In a previous study, Chloroquine has shown antiviral activities against viruses such as, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), Human immunodeficiency virus (HIV), Ebola virus, Hendra virus, including Nipah virus. [13]. Chloroquine shows antiviral activities against SARS, interfering with glycosylation of the cellular receptor of SARS which acts as an antiviral agent against the SARS-CoV2 in Vero E6 cells and thus, is now in medical observations (ChiCTR2000029609) [13]. In China, patients were administered with chloroquine and found that chloroquine inhibits the aggravation of COVID-19. Both the specialist from the organizer and government of medical observations suggested that chloroquine is a potential candidate for fighting against SARS-CoV-2 [13]. The drug may put down the cytokine storm by obstructing the production and release of TNF and IL-6 [14]. Adults aged between 18 to 65 in China were treated by Chloroquine phosphate by the following dosage: if weight more than 50 kg required 500 mg each time, two times a day for 7 days; if weight less than 50 kg required 500 mg each time on the first and second days, twice a day, and required 500 mg each time on the third to seventh days, once a day [14] The negative impacts of Chloroquine and hydroxychloroquine are nausea, abdominal

cramping, vomiting, and diarrhea along with the metallic taste. Chloroquine has a higher risk of retinopathy than hydroxychloroquine only when it is taken for a longer dose. These drugs are contraindicated for the cardiac patient and the patient who have QTc prolongation and the resultant risk of ventricular arrhythmias [15, 16] Clinical data from more than 100 patients from 10 different hospitals in China during the current COVID-19 outbreak indicated the superiority of chloroquine which were proposed to consider for its effectiveness in averting COVID-19 [15]. Chloroquine can also exhibit dermatologic effects like drug eruptions, lichenoid reactions, and photosensitivity [12, 15]. Some adverse effects of using hydroxychloroquine and chloroquine may cause tinnitus, mood swing, hypoglycemia, hemolytic anemia, and headaches [16].

Doxycycline

Doxycycline is a derivative of tetracycline that exerts both anti-viral and anti-inflammatory activity. The anti-viral activities of doxycycline are the result of transcriptional up-regulation of intracellular zinc-finger antiviral protein (ZAP) [17]. ZAP eliminates cytoplasmic mRNA by binding to specific mRNA [18]. Mechanism of action of doxycycline as an anti-inflammatory drug by reducing the pro-inflammatory cytokines such as Interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) [19]. A number of IL-6 receptor antibodies are currently under review for their effectiveness and safety, with no conclusive findings available at the moment. In-vitro experiments have revealed that doxycycline exerts anti-inflammatory activity with inhibitory action on metalloproteases at low (20-40 mg / day) and high (100-200 mg / day) doses and modulating effects of pro-inflammatory cytokines such as Interleukin-6 (IL-6), Interleukin-8 (IL-8), and tumor necrosis factor-alpha [20]. For the anti-inflammatory and anti-viral effects, doxycycline can be a possible therapeutic in coronavirus disease treatment. However, there are some adverse effects of doxycycline: abdominal cramp, nausea, vomiting, diarrhea, gastritis, and rash. It is forbidden to use during pregnancy and in children [20].

Levofloxacin

A fluoroquinolone antibacterial agent Levofloxacin is the L-isomer of ofloxacin [21]. This broad spectrum antibacterial has been permitted to use in the United States for the treatment of acute bacterial infection like: sinusitis, upper respiratory tract infection, community-acquired pneumonia, acute pyelonephritis and urinary tract infections [21]. Levofloxacin along with moxifloxacin (another antibiotcs) have been characterized as 1st line therapeutic for the treatment of severe community acquired pneumonia and levofloxacin shows multiple immunomodulatory actions by inhibiting the TNF- α and IL-1 like pro-inflammatory cytokines which leads to the reduction of the inflammatory response [22]. Interestingly, observational studies have proposed that levofloxacin employs regulatory activity of antioxidant and nitric oxide (NO) in the animal model of H1N1 influenza virus mediated lung injury and most importantly improves survival [23]. Based on the possible antiviral activity, advantageous pharmacokinetic properties, immune-modulatory properties and good safety profile I. Karampela et al. proposed the usage of respiratory fluoroquinolones as adjuncts to treat the patients affected with SARS-CoV-2 associated pneumonia [22]. To explore the therapeutic effect of respiratory fluoroquinolones (levofloxacin) as an adjunct potential treatment, clinical trials must conduct under large groups of people to find out the accuracy and fitness.

Azithromycin

Azithromycin (AZ) is a wide-range of macrolide antibiotic has in vitro viral properties such as increasing level of interferons along with interferon-stimulated proteins, reducing viral replication, viral release, and also blocking the entrance into the host cell; a lengthy half-life, and a huge amount of distribution for treating the infections like bronchitis, pneumonia, and MAC (Mycobacterium avium complex) infection and the most widely prescribed against respiratory infections [24-28]. It has also been reported to increase QT interval (QT interval is an estimation prepared on an electrocardiogram which is used for assessment of some of the heart's electrical properties) and incidence of TdP29-35 (Torsades de pointes) but the amalgamation with either chloroquine or hydroxychloroquine could be assumed to raise the probability of Torsades de pointes (TdP) [29,30]. Patients receiving the drugs are in crucial demand for precise, large scale studies and risk-benefit analysis before starting COVID-19 therapeutics, along with proper attention to clinical interactions, cardiac manifestations, scheduled electrocardiograms, and electrolyte observation [31]. The patients of COVID-19 treated by chloroquine or hydroxychloroquine with and without azithromycin is the largest reported cohort.[29] During treatment, patients were marked increase in the QT intervals but very few patients had the medications with discontinued hydroxychloroquine prematurely due to QT prolongation in seven patients with average QTc of 504.4 ± 39.5 ms [29, 31]. Azithromycin is also known to have immune-modulating and antiviral properties [24,32]. Azithromycin is a drug, approved by the FDA which is being used internationally off-label for the treatment of COVID-19 patients by the mixture of hydroxychloroquine and azithromycin against SARS-CoV-2, as the combination may have a very limited in vitro and in vivo data suggesting a synergistic effect and also found that Azithromycin has the therapeutic against COVID-19 apart from the hydroxychloroquine. The research group of New Mexico University did the study [24,27,33]. At the end of March, an online observation was conducted where 33% of an international board of medical consultants personally prescribed chloroquine or hydroxychloroquine, and 41% announced the same for azithromycin to resist SARS-Cov2 and among them, those who have been treated COVID-19 patients, 32% believe that azithromycin is the most efficacious treatment and 37% believe that chloroquine or hydroxychloroquine for the same [26]. Recently, a clinical study was conducted by P. Gautret, J.-C. Lagier and P. Parola et al., in France stated that 100% of patients medicated with the combination of hydroxychloroquine and azithromycin, had virological clearance and tested negative PCR results in nasopharyngeal samples at 6 post-inclusion [34,35]. It shows that combined treatment of COVID-19 with hydroxychloroquine and azithromycin raises the possibility of negative-PCR in patients which is based on limited published data whereas, 70% of hydroxychloroquine-treated patients were virologically cured compared to the combination of hydroxychloroquine and azithromycin [35]. So, for better understanding, excluding the medical observations of P. Gautret et al., and more medical studies are looking over the consequences of azithromycin in COVID-19 and found that azithromycin destroys asexual blood stage parasites by blocking the ribosomal 50S subunit and acts also as an inhibitor of red blood cell (RBC) invasion [25,35,36]. The adverse side effects of azithromycin are gastrointestinal upset, prolongation of the QT interval, pruritus, nausea, headache, hypoglycemia, idiosyncratic hypersensitivity reactions, neuropsychiatric effects, and drug-drug interactions [30,33].

Treatment of long duration includes neuropathy, restrictive cardiomyopathy, retinopathy, cardiac conduction disturbances, and vacuolar myopathy which are negligible within the context of treatment of SARS-CoV-2 but are also relevant if they're used for extended prophylaxis [30]. However, as an antimicrobial agent, azithromycin has immense therapeutic value for the treatment of COVID-19 patients and can influence the course of viral infections. More clinical studies need to be carried out with azithromycin as it has the potential to influence clinical outcomes and acts as prophylaxis for reducing the infections [27,28].

Carrimycin

Carrimycin is an antibiotic with superior activity, mainly use in the in mycobacterium tuberculosis infection resistance including some drug-resistant bacteria [37]. In a recent study, carrimycin along with other pharmacological agents such as tetrandrine, chloroquine, damageprevir, umifenovir (arbidol) have been shown potential therapeutic activity and are under clinical trials for a promising drug against COVID-19 pandemic [38]. Some basic treatments along with carrimycin are in a phase IV clinical trial under a group of 520 patients in a Chinese hospital (Identifier: NCT04286503) and the primary outcome measures: (1) Fever to normal time (day); (2) Pulmonary inflammation resolution time (HRCT) (day); and (3) Negative conversion (%) of SARS-CoV-2 RNA in gargle (throat swabs) at the end of treatment. The adverse effects and secondary efficiency outcomes were also observed [39].

Teicoplanin

Teicoplanin (TCP), a glycopeptide antibiotic that is analogous to vancomycin which is commonly used for treating bacterial infections, it was indicated to be active in-vitro against SARS-CoV and could be used against corona virus diseases as a therapeutic arsenal [40-42]. The antibiotic is normally applied to treat infections of Gram-positive bacteria, in particular staphylococcal infections, that are useful against viruses such as influenza virus, hepatitis C virus, flavivirus, Ebola, and human immunodeficiency virus (HIV), as well as coronaviruses such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [40,41]. Teicoplanin (TCP) is a broad spectrum antibacterial drug and coagulase-negative staphylococci have been reported to be resistant against teicoplanin [42]. In the early stages, teicoplanin acts on the life cycle of the coronaviruses by preventing the low-pH cleavage of the viral spike protein by cathepsin L in the late endosomes, thereby averting the release of the viral genomic RNA and further viral replication cycle. However, Cathepsin L needs the entry of the novel coronavirus into the cell and the S-protein region found in the novel coronavirus known as target teicoplanin [43]. Zhang *et al.* suggested that cleavage site cathepsin L is conserved between SARS-CoV and 2019-nCoV S protein [43]. Teicoplanin blocks the SARS and MERS envelope pseudotyped viruses as well as Ebola virus of the entrance into the cell cytoplasm [12]. As teicoplanin absorbs poorly after oral administration so the drug is widely distributed into body tissue and is eliminated primarily in renal [42]. The adverse effects have included: irreversible ototoxicity, gram-positive bacteremia, endocarditis, osteomyelitis, allergic reaction which can cause maculopapular rashes in the body, pain at the intramuscular injection site, the rising of aminotransferases and severe skin reactions [42,44]. The optimum dosing regimens and concentrations of therapeutic serum drugs were not well-known and the treatment of infectious diseases by teicoplanin is encouraged to have a further inquiry into this molecule's antiviral activity on SARS-CoV-2 suggested as another possible option for COVID-19 treatment [40,42].

Ribavirin

Ribavirin is an antiviral drug which is a guanosine analog. It has been used as a therapeutic drug against hepatitis C virus (HCV), hepatitis B, Respiratory Syncytial Virus (RSV) infection, and viral hemorrhagic fevers [12,13]. It was developed for treating SARS or MERS affected patients [13]. Some previous study showed that for the treatment of SARS-CoV-1 infection with lower risk of ARDS (acute respiratory distress syndrome), ribavirin was used which as combination of LPV/RTV (Lopinavir/Ritonavir). For treating SARS-CoV-2, a current in vitro investigation presented that ribavirin is needed with high effective concentration which is EC50 = 109.50 μM and antiviral activity against SARS-CoV had been evaluated at a concentration of 50 mg/mL which reduces hemoglobin that is harmful to the patients with respiratory distress [12,45]. The most frequent negative impacts of this drug were hemolytic anemia in high dose treatment (61%), hypocalcemia (58%), and hypomagnesemia (46%). Ribavirin could be a teratogen exerting embryonic toxicity. So, the use of systemic and barrier contraception must be strictly imposed [3]. However, in the treatment of coronavirus disease, ribavirin was administered in combined with pegylated interferon (ChiCTR2000029387) with lower doses which stimulated the innate antiviral responses and minimized side effects [13]. Ribavirin in combination therapies with interferon should be monitored. Ribavirin with other immunosuppressive therapeutics, especially azathioprine or IFN can cause pancytopenia [13,15]. So, certain therapies should be used carefully as it can cause toxicities [15].

Favipiravir

Favipiravir (T-705) is an RdRp (RNA dependent RNA polymerase is the most multifaceted enzymes of RNA viruses that is crucial for genome replication and carrying out transcription) inhibitor and guanine analog approved for treatment which is effective in vitro against oseltamivir resistant influenza A, B, and C viruses [12,13]. This moreover can viably repress the replication of Ebola, norovirus, yellow fever, enterovirus, and chikungunya viruses [13]. One can get it under the brand names Avigan, Abigan, and FabiFlu. It is a derivative of pyrazinecarboxamide having action against RNA viruses. Favipiravir is easy to recognize in many RNA viruses, as a viral RNA polymerase substrate when it is transformed into phosphoribosylated in active form [12]. Recent results of the clinical study proposed that it has a promising potency in the treatment of SARS-CoV-2 infection in Vero E6 cells showing effective antiviral activity (EC50 = 61.88 μM) (EC50 is Half maximal effective concentration) [12,13]. Also, patients with coronavirus disease infection are being treated with combination therapy and randomized trials to assess the effectiveness of favipiravir+interferon-α (ChiCTR2000029600) and favipiravir+baloxavir marboxil (ChiCTR2000029544) [12]. The prescribed dosage of favipiravir is orally 1600 mg twice daily on day 1, orally 600 mg twice daily on day 2-5, and 600 mg once on day 6 against influenza virus [12]. However, favipiravir isn't efficacious in primary human airway cells and therefore uncertain in influenza treatment [46]. Evidence showed that using Favipiravir during pregnancy can harm the baby [47].

Nitazoxanide

Nitazoxanide is a 2-(acetyloxy)-N-(5-nitro-2- thiazolyl) benzamide which was first synthesized in the early 1970s on the scaffold of niclosamide with an approval from USFDA (U.S. Food and Drug Administration) indicate its anti-protozoal task in treating diarrhea caused by Giardia lamblia and Giardia parvum [15,48]. Nitazoxanide is a wide-range of antiviral drug whose development is undergoing for the treatment of influenza, other coronaviruses, other viral respiratory infections, and it is also active against gram-positive and gram-negative anaerobic bacteria [15,49]. Nitazoxanide is one of the promising results in vitro to treat coronavirus disease which is also known as tizoxanide [50,51]. It is an anthelmintic drug and it is being repurposed for use in the treatment of viral respiratory infections which are currently undergoing phase-3 clinical development to treat acute uncomplicated influenza [49,51]. In particular, to treat subjects with acute uncomplicated influenza infection detected by RT-PCR or baseline culture. On evidence from the Phase 2b/3 trial, Nitazoxanide extended-release tablets (600 mg) administered twice daily for 5 days are being used in Phase 3 clinical development [49]. Nitazoxanide's most usual negative impacts are abdominal, gastrointestinal pain, headache and nausea. Patients may also suffer from eye and urine discoloration, dizziness, diarrhea, gastroesophageal reflux disease, skin rash, or hives. The patients receiving placebo versus low-dose nitazoxanide versus high-dose nitazoxanide are reported to have headache and diarrhea for the treatment of viral respiratory infection without any significant result is recorded for these three classes [15]. Nitazoxanide is being investigated in conjunction with oseltamivir and also as monotherapy [49]. So, it is important to investigate the safety of nitazoxanide for further trial and researches are needed [50].

Remdesivir

Remdesivir (GS-5734) is a monophosphate precursor that impedes viral RNA polymerases which have been manifested in vitro activity against SARS-CoV-2. Remedesivir sustains metabolism to an active C-adenosine nucleoside triphosphate analog which has a broad antiviral spectrum and it includes filoviruses, pneumoviruses, paramyxoviruses, and coronaviruses such as MERS-CoV, SARS-CoV, and SARS-CoV-2 [8,15,52,53]. The chemical structure is compared with tenofovir alafenamide which is an approved HIV reverse transcriptase inhibitor and contains an investigational antiviral agent that goes through the phase 3 clinical trials of COVID-19 treatment. [13,15]. At first, it was developed to treat hemorrhagic fever due to the Ebola virus outbreak as it has low EC50 which shows host polymerase selectivity against the virus [8,12]. The drug has appeared as the most promising candidate to treat patients with infection of two phases III clinical trials (NCT04252664 and NCT04257656) which were initiated to test the efficacy of remdesivir in patients affected by SARS-CoV-2 [13]. This promising and optimistic antiviral drug targets viral RNA dependent RNA polymerase (RdRp) avoiding the proofreading by viral exoribonuclease which results in premature termination of viral RNA transcription [12]. Due to its broad-spectrum, remdesivir is a potential drug for COVID-19 which has shown in vitro activity against several nCoVs and also SARS-CoV-2 accompanied by half-maximum effective concentrations (EC50) and (EC90) values of 0.77 μM and 1.76 μM, respectively [8,12]. Grein, J.et. al has been reported that severe COVID-19 patients with severe respiratory distress while receiving oxygen support or breathing atmospheric air, both were administered with either remdesivir (200 mg on day 1 and 100 mg on days 2-10 in single daily infusions) or for 10 days the exact amount of placebo infusions [52,54]. The clinical adverse effects have been reported: nausea, rectal hemorrhage, hepatic toxicity, gastroparesis, increased hepatic enzymes, diarrhea, rash, renal impairment, anemia or decreased hemoglobin; vomiting, acute kidney injury, creatinine clearance, increased blood creatinine; pyrexia; hyperglycemia and increased aminotransferase levels including alanine aminotransferase, constipation, hypoalbuminemia, thrombocytopenia and in the placebo group, the most common were hypoalbuminemia, anemia, hypokalaemia, constipation, increased aspartate aminotransferase, increased total bilirubin, and increased blood lipids [12,52,53,54]. Patients with critical COVID-19 have been noticed with liver dysfunction along with septic shock, acute kidney injury, hypotension, and also multiple organ dysfunction syndromes [15, 52]. The National Institutes of Health is financing an adaptive, randomized, and placebo-controlled trial that will help to understand the efficacy of the drug. The results from RCTs are predicted, the incorporation of remdesivir for the treatment of COVID-19 may be contemplated. Moreover, the drug is not approved by the FDA currently [8]. Besides, the high mortality rate despite using remdesivir, clears the fact that the antiviral drug alone is not enough for the treatment and all the deaths during the survey were judged by the site to be not related to the intervention [53,54]. However, the therapeutic effectiveness and safety of this drug still need to be proved and the evaluation of antiviral agents in combination with other therapeutic approaches should be continued to improve the condition of the patients affected by SARS-CoV-2 [13,54].

Interferon type-1

Viruses evolved strategies to antagonize the Antiviral actions of interferons (IFNs). Interferon type- 1 (IFN-1) elect a set of cytokines consisting of the ubiquitous subtypes α and β along with the subtypes ε, ω and κ [55]. These interferons are secreted by a number of cell varieties, particularly plasmacytoid dendritic cells after the viral constituents are recognized by pattern recognition receptors [56]. During a viral infection, Interferon type-1 is one of the earliest cytokines being produced. The interferon-α / β receptor (IFNAR) found in most cell types at the plasma membrane typically recognizes them. Interferon-stimulated genes (ISGs), including pattern recognition receptors (PRRs), which sensitize the cells to pathogens; decreases the fluidity of the membrane, preventing viral membrane coalition and antivirals that precisely impede one stage of the viral cycle [57,58]. According to the IFN - I immunomodulative properties, it plays a vital role in the antiviral immunity as well as various diseases treatment [59]. The treatment of IFN-I has been studied against SARS-CoV and MERS-CoV coronaviruses [60], and they are closely associated with the SARS-CoV-2 coronavirus while presenting similar properties. However, they have some differences in their pathological and epidemiological actions [61]. IFN-I could be efficacious in treating SARS-CoV-2 because previous research on SARS-CoV or MERS-CoV coronaviruses indicates that the most important interferon subtype should be IFNβ, and to optimize antiviral treatment and prevent adverse reactions then IFN-I should be issued as quickly as possible [62]. Moreover, COVID-19 pathology proposes that SARS-CoV-2 stimulates an immoderate antiviral response caused by IFN-I, which leads to tissue damage. It is suggested that treatment with IFN-I should be restricted to the preliminary infection stages [63]. Anti-interferon medications can be used in the late phases to alleviate the pathology [64]. Since the safety of the IFN-I treatment has already been examined

in numerous clinical trials, and it is expected to give more precise information on this treatment in the near future research [65].

Arbidol

Arbidol(ethyl-6-bromo-4-[(dimethylamino)methyl]-5-hydroxy-1-methyl-2-[(phenylthio)methyl]-indole-3-carboxylate hydrochloride monohydrate) is a potential wide-range of antiviral agent shows activity against a variety of enveloped and nonenveloped viruses [66]. It has been found that a limited number of coronavirus disease affected patients treated with a combined therapy of arbidol and lopinavir/ritonavir shows recovery [67,68]. In a current clinical study, 50 patients with corona virus diseases were selected and divided into two groups. Among 36 patients were treated with rotinavir/ritonavir, commonly known as rotinavir/ritonavir group, and 14 patients were treated with arbidol, commonly known as arbidol group. Interestingly, after the two weeks of admission in the hospital, the arbidol group patients were recovered and the viral load was undetectable in all the cases (patients). But 44.1 % of patients who have taken lopinavir/ritonavir have been detected with the viral load. Patients in the lopinavir/ritonavir group had a lengthy period of positive RNA test comparing with arbidal group [69]. Although the appropriateness of the usage of arbidol in COVID-19 affected patients have not yet been determined but its significance in COVID-19 treatment should be further researched in the future.

Nelfinavir

Nelfinavir mesylate is generated as an anti-human immunodeficiency virus (HIV) protease inhibitor, originally established to be used in combination with HIV targeting antivirals through different mechanisms. With the advancement of recently developed antiviral combinations for HIV, nelfinavir mesylate reportedly inhibited severe Acute Respiratory Syndrome (SARS) replication and cytopathic effects in cell culture [15,70]. Previously, the structure and function S glycoprotein of SARS in transient transfection-membrane fusion assessment were investigated [71,72]. SARS CoV-2 S (Sn) has been reported to cause profound S-mediated membrane fusion compared to the cell fusion produced by transient expression of SARS (So) [70]. The probability of binding nelfinavir to the S2 amino terminus within the S trimer was revealed by in-silico docking experiments thus; it may straightly prevent the formation of the heptad-repeat complex that results in S-mediated membrane fusion [70]. There are some major negative impacts of using nelfinavir, which causes nausea, gastrointestinal intolerance, flatulence, primarily diarrhea, and some non-specific rashes [15]. Further research and study are recommended.

Lopinavir

Lopinavir is a “novel inhibitor” of the protease produced from ritonavir and medication for the patients infected with human immunodeficiency virus-1 (HIV-1) [73]. Lopinavir is an aspartic acid protease inhibitor that is co-formulated with ritonavir to improve the pharmaco-kinetic function and half-life of lopinavir by inhibiting CYP450 [15]. Chu et al. stated that clinical and in vitro studies had shown anti-SARS-CoV activity of lopinavir [74]. The lopinavir is relatively safe and could be easily mobilized against COVID-19 [75]. The dosage of lopinavir should be given: 400 mg/100 mg for adults, 2 times/day but considering that the patients unable to swallow the tablets should not be chewed or crushed it [76]. An oral suspension must be arranged for delivery through a nasogastric tube for the patients who have limited oral access or intubated. Lopinavir treatment may lead to intolerable gastrointestinal toxicity, diarrhea and certain adverse effects that are especially important to intensive care unit (ICU) patients. It also includes hepatitis, fatal pancreatitis and hepatic decompensation in patients with pre-existing liver disease, which needs routine monitoring of liver functions and supporting antimotility and antiemetic drugs [15].

Ruxolitinib

Ruxolitinib is a Janus-associated kinase 1/2 (JAK 1/2) inhibitor and might be a potential therapeutic for severe coronavirus disease affected patients [77]. A recent investigation found that adding ruxolitinib to standard of care (SoC) treatment could significantly reduce the cytokine storm characterized in critical coronavirus disease condition which justified the use of ruxolitinib to lessen systemic inflammation [78,79]. Another randomized controlled trial on a total number of forty-three patients proposed that ruxolitinib with the addition of standard of care treatment was not associated with significant clinical improvement but there was a numerical rapid clinical improvement in ruxolitinib recipients. Although there was no statistical difference witnessed among them. But it showed significant chest computed tomography improvement and rapid improvement from lymphopenia in the patients [80]. The potency of ruxolitinib for the possible treatment of coronavirus disease was encouraging and future trials with ruxolitinib in a larger population might get an anticipated result.

Ivermectin

Ivermectin is a wide range of antiparasitic FDA (Food and Drug Administration) approved drug which causes paralysis by the influx of chloride-ions through cell membranes in many arthropods and nematodes [81,82]. It is a potent macro-cyclic lactone, showing potential microfilaricidal activity against major filarial parasites of humans and, currently a drug of choice for human onchocerciasis [82]. It has the potentiality in reducing malaria transmission by mosquito killing which is under review in several trials worldwide [83]. Caly et al. recently proposed that ivermectin has in vitro wide spectrum antiviral activity and is a potent inhibitor against SARS-CoV-2 replication. This study stated that they infected Vero/hSLAM cells with SARS-CoV-2 isolated from Australia for 48 hours in addition of 5 μM ivermectin, which shows 5,000-fold reduction in SARS-CoV-2 RNA levels when it is comparing with the controls [84]. Although another report examined the clinical importance of the concentrations measured by Caly et al. and expressed skeptical observations. Because in-vitro study leads to clinical failures in the most of the cases and it needs to verify the accurate concentrations if macrolytic lactone classes are used in the treatment of corona virus affected patients [85]. We need to be concerned with the negative impact that this drug could produce in the treatment of coronavirus disease and phase 1 clinical trials must be conducted before treating patients with ivermectin. Because a recent metaanalysis stated that there is no enough data to support a proposal for its usage in high concentrations [86].

Dexamethasone

Dexamethasone is a widely accessible corticosteroid that plays a major role in reducing the mortality rate in critically sick coronavirus disease patients and as well as reduces the activity of pro-inflammatory transcription factors as well as the cytokine storm. [87] Glucocorticoid receptors (GC-R) of corticosteroid bind to the pro-inflammatory transcription factors (e.g. AP-1 and NFKB) and inhibit the activity. It

can also block cytokine sites [88]. Dexamethasone plays a role in decreasing the mortality rate in critically sick corona virus affected cases [87]. Dexamethasone is an immunosuppressive drug having several impacts on multiple immune cells. For example, they antagonize macrophage differentiation, inhibit T-cell activation by inhibiting interleukins 2, 3, 4, and 6, and affect the function of dendritic cells [89].

Corticosteroids

Corticosteroids, methyl-prednisolone, are proposed as adjunctive therapies, for the patients of the novel coronavirus [8]. Corticosteroids are found disputed that employment of glucocorticoids must make sure as a result of glucocorticoids could considerably improve the clinical symptoms of respiratory disease, reduce the degree of malady progression, and additionally accelerate the absorption of internal organ lesions; however, it cannot shorten the length of hospital keep but Methylprednisolone is commonly used for patients with fast malady progression or severe unhealthiness [90]. This is wide accustomed for treating acute community gained disease to avert viscus injury as it has restrictive dreadful consequences and general inflammations rather like rheumatic diseases, which could function as a bridge to specific economical antiviral medical aid for COVID-19 [41,91]. The corticosteroids provide a potent medicament choice that prolongs the viral shedding time and maintains a systemic anti-inflammatory state which will reduce the precipitation of acute respiratory distress syndrome (ARDS), dyspnea, and acute pneumonia and antiviral immune reactions also [92,93]. An associate quantity of forty to eighty mg of methylprednisolone per day is often considered, and also the total daily dose shouldn't exceed 2 mg/kg (Weak recommendation) in keeping with the severity of the disease [90]. Researchers found that agent polymer of SARS-CoV2 reaches its peak throughout the first week then step by step decreases which immune plasma protein and IgM begins to rise from the tenth day, so most patients have anti-viral antibodies by the fourteenth day [93]. The negative impacts include delayed viral clearance, raised risk of secondary infection, pneumonia, hyperglycemia, psychosis, avascular necrosis, chronic-obstructivepulmonary disease exacerbation, or refractory shock [8,94]. The research confirms the inefficiency of corticosteroid usage on viral infections like MERS-Co-V, SARS-Co-V, and H1N1 virus as corticosteroids might speed up recovery from coronavirus disease still, many clinical trials proves whether the employment of corticosteroids can decrease coronavirus disease related death [41,93]. Long-time management of high dosage of corticosteroids within the primary phases of treatment also has adverse effects [41]. Though the World Health Organization (WHO) states that on the clinical administration of extreme acute infection when SARS-CoV-2 infection is guessed that corticosteroids should be averted except when the patient has symptoms like acute or moderate ARDS, septic shock or sepsis, or another excuse [41,91,92,94].

Itraconazole

Itraconazole is an extremely active triazole anti-fungal substance used to treat onychomycosis, blastomycosis, histoplasmosis and amphotericin B-refractory aspergillosis [95]. It is mainly used against Candida albicans and other Candida species, which includes many resistant to fluconazole [96,97]. In a recent study, the usage of antifungal therapeutics itraconazole (ITZ) in the treatment of COVID-19 suggests that it has a wide range of antiviral efficacy against the Picornaviridae family which infects vertebrates including mammals and birds [98]. It also shows antiviral activity against some enveloped RNA viral infections such as influenza-A virus [99,100].

Thalidomide

Thalidomide or N-phthalimidoglutarimide [C13 O4 N2 H9] is used for the treatment of erythema nodosum leprosum and multiple myeloma [101]. But when it was first developed for treating pregnant women with morning sickness, teratogenic effects such as inner and outer malformations of the ear and ocular anomalies found on children and later removed from market [101]. Thalidomide is involved in various adaptive and innate immune responses including downregulating the phagocytic function of immune cells, inhibiting cyclooxygenase enzyme 2 (COX), and Prostaglandin E2 (PGE2) and reducing TNF-α production by human blood monocytes [102]. A study recently showed that thalidomide has been used for a corona virus affected patients along with low-dose methylprednisolone. The dose was 100 mg for thalidomide and 40 mg for methylprednisolone. The patient's condition improved without showing any adverse effect [103]. Though the anti-inflammatory and the immunomodulatory functions make this drug a promising one to treat COVID-19 affected patients, the teratogenic effect should be taken into serious consideration [104].

Leflunomide

Leflunomide is a potent immunosuppressant which shows anti-inflammatory activity by inhibiting the pyrimidine biosynthesis in rapidly dividing cells [105]. It is an isoxazole derivative that has been used in rheumatoid and psoriatic arthritis patients as a disease modifying antirheumatic drug (DMARD) [106-109]. However, a recent study on humans reported that human dihydroorotate dehydrogenase (DHODH) inhibitors have antiviral activity as well as an inhibitory role in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in infected cells. The study evaluated leflunomide which was used to treat an insignificant number of corona virus affected patients [110]. Another study proposed that leflunomide or teriflunomide could be potent therapeutic with a therapeutic range of 6-26 μM of teriflunomide in patients infected with SARS-CoV-2 [111]. A controlled non-random clinical trial has been conducted in a Chinese hospital that demonstrated the accuracy and safety of leflunomide and presented the effectiveness by enhancing the clearance of SARS-CoV-2 in patients affected with refractory COVID-19. Although the course of treatment of 14-28 days with leflunomide tolerance is admissible [112]. However, further studies must be carried out in a large numbers of people to ensure the effectiveness in COVID-19 affected patients.

Tocilizumab

Tocilizumab (TCZ) is a genetically engineered humanized anti-human Interleukin-6(IL-6) monoclonal receptor antibody that recognizes both the membrane bound and the soluble IL-6 receptor (IL-6R) type and explicitly hinders the actions of IL-6 [113]. The activation of large numbers of macrophages and T-lymphocytes has occurred when the patients are affected by coronaviruses and thus, produces cytokines for instance interleukin-6 (IL-6) that can attach to the IL-6 receptor on the target cells and causes severe inflammatory response as well as cytokines storm in lungs and different types of organs. TCZ can bind to the IL-6 receptor and prohibiting IL-6 from binding to its receptor, making it unable to inflict immune-damage on target cells [114]. A recent research indicated that a single dose of tocilizumab could not improve the patient's critical conditions, although

glucocorticoid is combined with it. But when low doses of tocilizumab are used repeatedly, there might be an improvement in critically ill patients. Seriously sick patients might be benefited by a single dose of TCZ with about 10 times higher IL-6, and moderately sick patients might also be benefited from repetitive TCZ therapy with a very elevated level of IL-6. The study recommended repeated TCZ dosages for severely ill patients with high IL-6 [115]. Although this study is observed with a sufficient number of corona virus affected patients, but it must be evaluated with caution, and further research must be undertaken to identify the effectiveness of TCZ on COVID-19 patients.

Clazakizumab

Clazakizumab is a high affinity and specific monoclonal antibody against human interleukin-6 (IL-6) [116] and might be a potential therapeutic agent by averting the cytokine response to the SARS-CoV-2 in COVID-19. A massive inflammatory response, namely cytokine storm, with significant cytokine dysregulation is detected after SARS-CoV-2 infections [117]. An excessive amount of cytokines can cause secondary hemophagocytic lymphohistiocytosis, which will damage the organs and tissues [118]. Interleukin-6 is a cytokine that exhibits cytokine pleiotropy and contributes to the activation of an innate immune response, acute phase reaction, and certain other defensive actions. An excessive amount of IL-6 production can cause chronic inflammation [119], which is followed by serious infections, including the pandemic of H1N1 influenza [120]. On a clinical investigation of 69 infected patients with coronavirus disease, the application of IL-6 as a potential biological marker has been suggested [121]. Clazakizumab is a monoclonal IgG1 antibody against human IL-6, instead of the IL-6 receptor [122]. At present, randomized placebo-controlled clinical investigations are examining the efficiency of clazakizumab in the treatment of SARS-CoV-2 pneumonia affected patients at Cedars Sinai Medical Center and NYU Langone Medical Center [123,124]. Clazakizumab has some negative impacts, which are dose dependent including mild infections, increasing the level of aminotransferase and cholesterol, decreasing platelet and neutrophil counts [125]. Clazakizumab might be a safe choice for monitoring the characteristics of cytokine storm for serious COVID-19 pneumonia patients, including transplant recipients, but further clinical investigations must be conducted for the accuracy and efficacy [125].

Bacillus Calmette-Guérin (BCG) vaccine

Bacillus Calmette-Guérin (BCG) vaccine was developed in 1921 against tuberculosis [126]. There lies a positive relationship between BCG vaccination and the decreased mortality rate among coronavirus disease affected patients [127]. A recent study suggested that, countries with BCG policies had lower mortality rates and the countries which never had a BCG policy had a greater mortality rate [127]. This is because BCG provides heterologous immunity provided by T cells cross-reactive between different viruses [128]. Those T- cells will secrete cytokines to kill pathogens directly or activate macrophages [128]. Another mechanism provided by BCG is termed as 'trained immunity' that confers nonspecific immune memory. Trained immunity also involves in cellular reprogramming through epigenetic changes [129]. Epigenetic reprogramming leads to an increased expression of cytokine production in response to non-related pathogens [129]. For the long- term effects of heterologous immunity and trained immunity BCG vaccine might be a promising treatment for COVID-19.

ChAdOx1 nCoV-19 vaccine

Chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-1) is a bacterial artificial chromosome (BAC) derived vector vaccine [130]. A wild type chimpanzee adenovirus isolate Y25 was used to develop this vaccine. Then E1/E3 region was deleted to develop vector ChAdY25 and E4 region was deleted to improve virus yield. This manipulation is associated with homologous recombination [130]. After vaccinating mice with ChAdOx1 nCoV-19 vaccine particular neutralizing antibodies were noticed. Vaccination in rhesus macaques helped to understand that it prevents replication of viruses in the lower respiratory tract [131]. According to a study, phase 1/2, participant-blinded, randomized controlled trial among the 1077 participants has been exhibited promising results of ChAdOx1 nCoV-1. Patients were administered with a dose of 5×10^5 viral particles and shown mild or moderate adverse effects which were reduced by prophylactic paracetamol [132]. All these events make this vaccine a potential one for fighting against COVID-19.

Dipyridamole

2,6-bis-diethanolamino-4,8-dipiperidinopyrimido-(5,4-d)-pyrimidine is a pyrimidopyrimidine derivative which is commonly known as dipyridamole, a U.S. FDA approved drug [133]. Dipyridamole (DIP) is an anti-platelet compound which increases intracellular cAMP/cGMP by inhibiting phosphodiesterase (PDE) [134]. Dipyridamole could be a potential drug for the corona virus disease affected patients. It expresses a wide range of antiviral activity against the positive stranded RNA viruses [135]. A clinical study was conducted involving 31 patients in two separate Chinese hospitals. The first hospital recruited 12 patients and 10 controls, and the second hospital recruited 2 patients and 7 controls. Standard treatment was given to all of the patients in compliance with the recommendations of the General Office of National Health Committee. All the patients were treated in separate isolation wards. However, the selected ward patients from the two hospitals were treated with DIP and the other ward patients from the two hospitals were treated without the DIP adjunct therapy as controls. The clinical study found some significant information regarding the treatment with DIP. Extremely sick patients with coronavirus disease treated with dipyridamole adjunctive therapy increases the clinical recovery, remission rates, improves the coagulation profiles, and facilitates the recovery of immune cells. Again the death rates of the control group patients (23.5%) was greater than the death rates of the DIP adjunct therapy treated patients (7.1%) [136]. Although the efficiency and accuracy of dipyridamole adjunct therapy to treat the coronavirus disease affected patients is still not approved by any national or international committee but further research should be conducted on its therapeutic application in coronavirus disease.

Vitamin C

A potential therapeutic agent against COVID-19 might be Vitamin C because it has multiple impacts on the human immune system [137]. Vitamin C is an antioxidant and a reducing agent working as a co-factor in catalyzed reactions of Fe2 + -dependent dioxygenases and Cu+-dependent monooxygenases [138]. Although it is found that regular intake of vitamin C around 1 gram per day (1 g/day) cannot escape the upper respiratory tract infections (URTIs) which was a meta-analysis of 29 controlled trials under 11,306 participants. However, the duration of infections in adults and in children reduced by 8% and 14% respectively [139]. So far no evidence has been found to conclude that

vitamin C against coronavirus disease would be absolutely ineffective [137]. Furthermore, a meta-analysis found that vitamin C reduced the time spent in the Intensive Care Unit (ICU) by 8% which was analyzed with 1,722 patients in ICU [140]. There's also evidence that vitamin C levels in critically sick patients are declining significantly [140,141]. A healthy individual can maintain a normal level of plasma by taking 0.1 g/day of vitamin C [142] as it is a safe and affordable nutrient essential for the body [143].

Ulinastatin

Ulinastatin is a glycoprotein which extracted and purified from fresh human urine, the anti-inflammatory agent in our body that is used in the treatment of pancreatitis and acute circulatory failure, and for the cytokine storm for COVID-19 as well [14,144-147]. Ulinastatin is a serine protease inhibitor with anti-inflammatory properties and has superb opportunities for the treatment of SARS-CoV2 infection, as it protects the vascular endothelium by blocking the generation and releases of inflammatory substances [144,147]. It decreases the levels of pro-inflammatory factors such as TNF-α, IFN-γ, and IL-6, and raises the level of anti-inflammatory factor IL-10 [14,147]. Ulinastatin promotes the balance between pro-inflammatory and anti-inflammatory reactions in humans and therefore hinders the cytokine storm caused by the vicious cycle of inflammation [14]. There were no adverse events observed rather the patients with abnormal liver function were improved instead of deteriorating after treatment with the creatinine levels being normal before and after ulinastatin treatment. Overall Ulinastatin could be considered with decent safety profiles for use along with other anti-viral drugs concurrently to treat severe or critical COVID-19 cases that have great potential for application and further study is recommended [14,147].

Pirfenidone

In the pandemic, corona virus-infected patients have symptoms extending from the upper-respiratory tract to severe acute respiratory distress syndrome [148]. COVID-19 primarily injures the vascular endothelium and neglecting may eventually cause multi-organ failure to a coronavirus (COVID-19) patient with acute respiratory distress syndrome (ARDS) [149]. The fundamental reason behind the mortality and morbidity in coronavirus disease affected patients is ARDS. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an antifibrotic agent that has adverse effects and has been permitted for patients with minor to a moderate condition for the medication of Idiopathic Pulmonary Fibrosis (IPF). A recent hypothesis has suggested that pirfenidone might be a potent therapeutic for the treatments of coronavirus disease because it could down-regulate ACE receptors expression, reduction of inflammation and improve oxidative stress, protect pneumocytes, and other cells from COVID-19 invasion. Although it has not yet been tried for the treatment of corona virus-infected patients [150]. Another research-based on epidemiological results and scientific literature suggested that pirfenidone could be used as monotherapy or along with other anti-inflammatory drugs to treat COVID-19 patients to avoid serious complications during viral infection [151]. It may have therapeutic potential to prevent or reduce fibrotic lung lesions of the ongoing COVID-19 infection but further research must be carried out to ensure the accuracy and efficiency of pirfenidone in treating patients with coronavirus disease.

Combined Drugs

Azithromycin+hydroxychloroquine

Hydroxychloroquine (HCQ) is a potential antimalarial agent that has several immunomodulatory effects [152], and azithromycin is an antibacterial agent that is a semi-synthetic, acid-stable derivative of erythromycin with a wide range of activity [153]. Hydroxychloroquine with azithromycin has been considered as possible remedying drug in treating the corona virus disease affected patients [154]. A recent clinical study was conducted on 1438 corona virus disease affected patients in USA, those receiving both hydroxychloroquine and azithromycin. Interestingly, the patients receiving both hydroxychloroquine and azithromycin have death rate of 25.7%. Although the patients receiving only hydroxychloroquine have a mortality rate of 19.9% and patients receiving only azithromycin have mortality rate of 10.0% [154]. However, there was no significant association with differences in in-hospital death rate when treating patients with the combined usage of azithromycin and hydroxychloroquine [154]. But another study conducted on France suggested that a combination of hydroxychloroquine and azithromycin exhibited a synergistic effect. Because azithromycin has been shown to prevent severe infections in the respiratory tract when patients suffering from viral infection [155], and effective in vitro against Ebola virus and Zika virus [156-158]. However, further exploration should be conducted to know whether combined therapy of azithromycin and hydroxychloroquine is more effective in coronavirus disease affected patients.

Hydroxychloroquine+ivermectin

Ivermectin, a potential medication used in treating various neglected tropical disease, and Hydroxychloroquine (HCQ), an anti-malarial agent considered as an immunomodulator rather than immunosuppressant which is used to treat patients with autoimmune diseases [159-161]. In the COVID-19 pandemic, vaccines have not yet been invented (up to July, 2020) but we need effective drugs to treat the infected patients. In this situation, two drugs mentioned above have considered as a potential candidate against corona virus disease. It has been found in a study that hydroxychloroquine could interfere with the glycosylation of angiotensin-converting enzyme-2, resulting in reduced binding efficacy between angiotensin-converting enzyme-2 in host cells and the spike proteins of SARS-CoV-2 [161]. The virus attachment with the host cell could be blocked using HCQ by cleaving coronavirus surface spike proteins through the inhibition of protease activity [161]. On the other hand, the antiparasitic activity of ivermectin may suppress the replication of various RNA viruses by interfering on importin- α / β -dependent nuclear transport of viral proteins [162]. A recent hypothesis suggested that ivermectin and HCQ could act in a significant way as ivermectin may reduce the replication of the viruses and HCQ may inhibit the access of the virus into the host cell by acting as a barrier. Although no in-vivo and in vitro research has been carried out yet on the combined effect of hydroxychloroquine and ivermectin in corona virus disease [163].

Lopinavir+ritonavir

Lopinavir, a type 1 aspartate protease-inhibitor of HIV has inhibitory activity invitro against severe acute respiratory syndrome corona virus (SARS-CoV) which causes severe acute respiratory syndrome (SARS) in human [164-166]. Ritonavir is used with lopinavir to improve its plasma half-life through the prevention of cytochrome

P450. A research suggests that the application of lopinavir-ritonavir (400 mg and 100 mg, respectively) with ribavirin decreased the adverse clinical consequences (acute respiratory distress syndrome [ARDS] or death) as well as viral activity among SARS affected patients (164). Activity against MERS-CoV was shown in animal models and invitro by lopnivir and it has been suggested in some case studies that the combine medication of lopinavir+ritonavir with interferon alfa and ribavirin which resulted in virological clearance and survival [167-171]. In total, 199 patients suffering from severe acute respiratory syndrome corona virus 2 (SARS-CoV2) infections in a hospital underwent a clinical trial applying lopinavir plus ritonavir group and standard-care group. However, no benefits were observed in adult patients with severe coronavirus disease using lopinavir plus ritonavir treatment apart from the standard-care [172].

Types of Non-drug Treatment

In this review, treatments and medication for COVID-19 is divided into two sections among types of non-drug is one of them. There are different types of experimental non-drug treatment and methods can found in the report published by The World Health Organization (WHO) although all of these treatments have not been yet approved and endorsed. These treatments are in the experimental and clinical phase, and efficacy have not been determined [10,11]. They are-

1. Neutralizing antibodies from Convalescent plasma
2. Umbilical Cord Mesenchymal Stem Cells (UC-MSCs)
3. Compound amino acids and others

Neutralizing antibodies from convalescent plasma

Neutralizing antibodies (NAbs), anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins can be obtained from plasma given by the donors using apheresis procedure [173]. The Spike(S) protein's S1 domain of CoVs forms a globular structure that mediates the interaction of the S protein with angiotensin-converting enzyme 2 (ACE2) which is its receptor [174]. The S protein is the major inducer of Nabs [175]. Anti-SARS-CoV nAbs bind to the viruses receptor binding domain (RBD). This binding, blocks the viral receptor binding domain (RBD) and the cellular ACE2 receptor interaction which neutralizes viral infection [176]. But plasma therapy is not without risk. Some elements of plasma might react with the patient's immune system. Plasma therapy can be associated with a mild fever. Some patients may develop allergic reactions and life-threatening bronchospasm [177]. Again, with some patients, an evanescent facial red spot was seen with no adverse reaction [178].

Umbilical Cord Mesenchymal Stem Cells (UC-MSCs)

The immunomodulatory effects as well as anti-microbial actions of Mesenchymal Stem Cells may play an important function in treating coronavirus affected patients [179]. MSCs secrete anti-microbial peptides (AMPs) for example, human β-defensin-2 (hBD-2), cathelicidin LL-37, lipocalin-2 (Lcn2) and hepcidin. These AMPs are involved in the elimination of microorganisms from the body [180]. Umbilical cord stem cells (UC-MSCs) have faster doubling times, more plasticity, more potency, and can be extracted noninvasively [179]. These characteristics make UC-MSCs more advisable while treating COVID-19 patients. A study showed that a patient with high fever, shortness of breath, weakness and low oxygen saturation was treated with UC-MSCs. Both fever and shortness of breath disappeared, count of CD8+T cell, CD4+T cell and CD3+T cell were amplified, the plasma CRP levels and the inflammatory factors (TNF-α and IL-6) have been reduced. The patient was tested negative after six days of administration [181].

Compound amino acids and others

Drugs from natural resources such as plant derive drugs can be potential in COVID-19 treatment. In silico-based study suggested that medicinal plant-derived compounds such as naringenin, quercetin, curcumin, kaempferol, oleuropein, catechin, luteolin-7-glucoside, demethoxycurcumin, epicatechin-gallate and apigenin-7-glucoside can inhibit main protease (Mpro) of COVID-19. They have the lowest binding energies and inhibition constants which make them potential compounds fighting against COVID-19 [182]. Another in-silico based study showed that antimicrobial activity of stilbene based compound resveratrol is the most promising candidate for COVID-19 treatment [183]. Baicalin a derivative of medicinal plant Scutellaria baicalensis Georgi showed antiviral activity to fight against the Coronaviradae family [184]. According to clinical evidence, 1063 volunteers used Sang-Ju-Yin and Yu-Ping-Feng-San (Traditional Chinese Medicine herbal extract) and none of them were infected [185]. These studies may pave the way for drug development. However further research is important to test the efficacy of these compounds.

CONCLUSION

Coronavirus disease is extremely communicable viral infection caused by severe acute respiratory syndrome coronavirus 2 and genomic study exposed that SARS-CoV-2 is phylogenetically correlated to severe acute respiratory syndrome-like (SARS-like) bat viruses**.** It is highly human-human transmittable pneumonia associated virus that has not yet been eliminated**.** On 30th January, 2020 the pandemic of coronavirus disease has been declared as a Public Health Emergency of International Concern by The World Health Organization (WHO). COVID-19 may be interrupted by the application of a robust system for early detection, isolation, immediate treatment, and contact detection**.** Although so far no vaccine (up to July, 2020) or accurate treatment has come out to treat the COVID-19 affected patients. Although many researchers and investigators are examining many potential candidate drugs against COVID-19 and also many ongoing clinical-trials are being conducted to find an accurate drug in treating the affected patients. In this review, we have noted many candidate drugs and also some non-drug treatment methods. These treatments are not being yet verified by any national committee and research organization for the treatment of coronavirus disease affected patients. All these candidate drugs and proposed treatments require evaluation in clinical trials to know about the potential efficacy and safety. We do not guarantee that these drugs will work effectively but they might have the potentiality to fight against corona virus disease.

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