ISSN: 2455-281X

Contents lists available at http://www.albertscience.com

ASIO Journal of Pharmaceutical & Herbal Medicines Research (ASIO-JPHMR)

Volume 6, Issue 2; 2020; 68-77

# A REVIEW ON THE USE OF HERBAL REMEDIES AND CLINICAL THERAPEUTICS FOR THE MANAGEMENT OF COVID-19 PANDEMIC

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## ARTICLE INFO

**Review Article History**
**Received:** 26th September, 2020
**Accepted:** 9th October, 2020

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel coronavirus now referred to as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), which was first identified amid an outbreak of respiratory illness cases in Wuhan City, China. The rapid spread of COVID-19 was characterized as a pandemic by the World Health Organization on 11 March, 2020. As of the time of submission, there were over 36 million confirmed global cases in 188 countries and territories. Around 27 million people had recovered while over one million deaths recorded. The United States, Brazil, and Mexico have been among the countries hardest hit by the pandemic. Currently, there is no dedicated treatment for this disease, due to its broad clinical spectrum. While vaccine and drug development studies are continuing all over the world, available antiviral drugs and clinical therapy options are tested against SARS-CoV-2. Moreover, inspired by previous experience, herbal remedies are considered one of the alternative approaches in the treatment of COVID-19. Some natural herbal compounds have demonstrated encouraging anti-viral properties. Hence, this review of the potency of known antiviral drugs and herbal remedies with proven safety records is a quicker, reliable and more efficient way of developing new drugs or vaccines to combat COVID-19 coronavirus outbreak worldwide.

**Keywords:** *Herbal remedies, clinical therapy, COVID-19, Management, Pandemic, WHO.*



## 1. INTRODUCTION

Infectious diseases are a major global problem and are still causing substantial morbidity and mortality despite considerable developments in medical sciences. Particularly, advancement in anti-viral therapy is hampered by the emergence of mutants capable of overcoming the effects of drugs that target viral components [1]. Coronaviruses (CoV) (Family: Coronaviridae; subfamily: Coronavirinae). Coronavirinae consists of four genera as Alpha-coronavirus, Beta-coronavirus, Gamma-coronavirus and Delta-coronavirus. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which belongs to Beta-coronavirus genus is an enveloped virus containing a single-stranded Ribonucleic Acid (RNA) genome. In genomic analysis, 79% similarity between SARS-CoV-2 and SARS-CoV has been determined [2]. These viruses are pleomorphic particles with sizes ranging from 80 to 120 nm in diameter [3]. Their entire replication cycle takes place in the cytoplasm. Research findings indicated that the CoV envelope is involved in critical aspects of the viral life cycle, and that CoVs lacking CoV envelope make promising vaccine candidates [4].

Coronaviruses are able to cause a number of diseases, including bronchitis, gastroenteritis, hepatitis, systemic diseases, and even death in birds, humans, and other animals [5]. Moreover, CoVs were found to be the causative agents of Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV-2). A novel coronavirus disease 2019 (COVID-19), also referred to as SARS-CoV-2, has caused an international outbreak of acute respiratory illness. The rapid spread of COVID-19 was characterized as a pandemic by the World Health Organization (WHO) on 11 March 2020 [6]. Over 36 million infections confirmed in 188 countries and territories, with over one million fatalities while more than 27 million people have recovered to date. Currently, there are no specific therapeutic agents for this disease, due to its broad clinical spectrum.

Inspired by previous experience, herbal medicine is considered one of the alternative approaches in the treatment of COVID-19. In China, the National Health Commission has declared the use of herbal medicine combined with Western medicine as a treatment for



DOI : 10.2016-19146535/ ; DOI Link :: http://doi-ds.org/doilink/10.2020-85722646/

COVID-19, and has issued many guidelines on herbal medicine-related therapy [7]. To date, there is much clinical evidence that reports favorable effects of the usage of herbal medicine in the treatment of COVID-19 [8]. Several systematic reviews that included evidence from case reports, case series, and observational studies have also been conducted, to study the effectiveness of herbal medicine in the treatment of COVID-19 [9-11]. However, in the hierarchy of systematic reviews, reviews of Randomized Control Trials (RCTs) offer the highest level of evidence.

Currently, there are no approved therapies for either the treatment or prevention of COVID-19. Several national and international research groups are working collaboratively on a variety of preventative and therapeutic interventions. Potential avenues being explored include vaccine development, convalescent plasma, interferon-based therapies, small-molecule drugs, cell based therapies, and monoclonal antibodies (mAbs) [12]. However, drug therapy development is a costly and timely process with a high attrition rate [13]. The speed of the normal drug development pathway is unacceptable in the context of the current global emergency. Therefore, there has been considerable interest in repurposing existing drugs and expediting developmental antiviral treatments, such as those for influenza, hepatitis B virus (HBV), hepatitis C virus (HCV), and filoviruses, to allow more rapid development [12]. The swift genomic sequencing of COVID-19 has facilitated this process, allowing comparison with MERS-CoV, SARS-CoV, and other morbific viruses [14].

Amidst the mounting global concerns about the COVID-19 outbreak, an understanding and knowledge of the herbal remedies and clinical therapies with anti-viral properties is essential for providing an effective management of COVID-19 patients. In response to the request made by WHO, a review of all published reports of treatments used during the 2002/2003 SARS epidemic was necessary to guide future treatment decisions and identify research priorities. Therefore, the aim of this review was to summarize available and recent information on the reported anti-viral activity of both herbal remedies and clinical therapeutics for the management of COVID-19 pandemic.

## 2. DISCUSSION

### Modes of transmission and Incubation period

Since the first COVID-19 patients had a history of direct contact with local Chinese seafood and wild animal market, therefore, the main route of transmission was reported as zoonotic exposure [15]. Bats are known as reservoir hosts of SARS-CoV-2. On the other hand, for zoonotic transport, the intermediate host of SARS-CoV-2 has not been detected accurately yet [16]. Over expression of Angiotensin converting enzyme 2 (ACE2) on the luminal surface of intestinal epithelial cells supports that the first entry of SARS-CoV-2 into the human body might have been through nutrition [17]. Afterwards, transmission from person to person was detected. The virus is transmitted mainly through droplets, direct contact and aerosols. Droplet transmission can be defined as inhalation of respiratory droplets through mouth or nose, when an infected person coughs or sneezes. People can also be infected by touching a virus-contaminated surface or object and then touching their mouth, nose, or eyes [18].

There has not been a report of pets infected with SARS-CoV-2 yet. COVID-19 patients are recommended to limit contact with their animals until more information about the virus is learned [19]. Reference [20] reported that cats and ferrets could be experimentally infected with SARS-CoV-2, but that dogs, pigs, chickens and ducks were not susceptible to SARS-CoV-2. According to this study, cats can spread SARS-CoV-2 by inhalation and transmit it to other cats [20].

The World Health Organization reports that COVID-19 symptoms develop on average 5-6 days after exposure, but this period may be extended to 14 days. For this reason, 14 days which is expressed as the quarantine period is the internationally applied time to monitor and restrict the movement of healthy individuals in contact with the patient with COVID-19 [21].

### Signs and Symptoms of COVID 19 infection

Between 2 to14 days of contracting the deadly COVID-19 coronavirus, symptoms such as mild to severe respiratory illnesses, fever, cough and dyspnoea are observed [22]. Chest computerized tomography (CT) scan can also reveal the presence of bilateral ground-glass opacities in the lungs [23]. Patients with severe infection develop acute respiratory distress syndrome requiring patients' admission into the intensive care unit (ICU) with oxygen therapy too [22]. The mortality rate of patients with early signs of COVID-19 coronavirus infection is about 15% [23].

### Clinical Diagnosis of COVID-19

Reverse Transcription Polymerase Chain Reaction (RT-PCR) is currently the only rapid diagnostic test that can give the necessary sensitivity and specificity that are required for a routine clinical diagnosis such as two-step conventional and one step quantitative RT-PCR techniques were routinely used for coronavirus outbreak [24]. A report from the Center for disease control and prevention (CDC) indicated that real-time RT-PCR may be more sensitive than conventional RT-PCR (Potentially providing a useful technique for detecting virus in the early phases of the diseases) when virus titre is low [25]. Enzyme-linked immunosorbent assay (ELISA) detection of antinucleocapsid protein (NP) antibodies (for peak infection at early stages) was later identified by Canadian investigators as a more reliable and specific method for diagnosing coronavirus [26]. Some diagnostic tests used in the detection of previous coronavirus infections such as serological assays, immunofluorescence assays, ELISA, protein microarray, micro-neutralization assays and Western blot, etc. [27] can also be used as potential diagnostic tools for detecting the presence of COVID-19 in humans.

Chest radiography and computerized tomography (CT) scan of infected patients demonstrate pulmonary involvement. Findings differ depending on the stage of the disease, age of the patient, and immune status. On CT scan, ground glass opacifications and thickening of the interlobular septa can be observed [28]. Lung lesions are more common in patients over the age of 50 compared to younger patients. Clarity of radiographic examination is not as good as CT imaging that reveals the ground glass opacities [29].



DOI : 10.2016-19146535/ ; DOI Link :: http://doi-ds.org/doilink/10.2020-85722646/

**Prevention by physical intervention and simple Hygiene**

Physical interventions like isolation of infected patients, quarantine of suspected victims and physical distancing to curb the spread of COVID-19 are the most effective means of controlling coronavirus infections [30, 31]. The success of coronavirus disease prevention by physical intervention was demonstrated during the last disease epidemics in Singapore with drastic reduction in the secondary infection rate [32]. In Taiwan, the application of Level A quarantine (Individuals with direct contact to coronavirus patients) resulted in the prevention of about 461 additional cases and 62 deaths, the use of Level B quarantine (Travellers from affected areas) reduced the number of new cases and deaths by about 5% [33].

Coronavirus can survive on surfaces for up to six days but can be inactivated by washing with sodium hypochlorite [NaOCl], 75% ethanol [$C_2H_5OH$], and household detergents [32] or chemical disinfectants such as povidone-iodine [34, 35]. Personal protective equipment (Eye goggles, surgical masks or N-95 disposable filtering respirators etc.) are recommended for health care personnel [31]. Airborne precautions should be applied especially when performing aerosol-generating procedures such as intubation [36]. All potentially infectious specimens should be handled and transported with caution, and must be tested in laboratories with WHO Biosafety level 3 (BSL-3) standards [31].

**COVID-19 Comorbidities**

It has been determined that the most severe COVID-19 patients are generally of advanced age and / or have underlying comorbidities such as hypertension, diabetes mellitus (DM), chronic lung and kidney diseases or cancer [18].

**Vaccines against COVID-19**

Vaccines stimulate the body's immune system against infectious pathogens. Hence, they are one of the most effective ways of preventing diseases. However, the development of effective vaccines against COVID-19 may take several months, including the period of safety evaluation. The effective control of coronavirus epidemics in farm animals by vaccines developed from killed (attenuated) viral strains was an indication of the possible breakthrough in the development of novel synthetic vaccines. The Spike (S) protein is currently considered to be one of the most promising targets for coronavirus vaccine development [37], and is being targeted for the development of anti- MERS-CoV vaccines [38], including mucosal vaccine for intranasal administration [39]. This research has been facilitated by the recent development of small animal models that effectively replicate MERS-CoV transmission and symptomatic human diseases [40]. Human MERS-CoV vaccines are also now in development, including Deoxyribonucleic acid (DNA) vaccines, vector-based, live attenuated and protein subunit vaccines [41], many of these vaccines target the S protein [42].

The race for the development of a vaccine for COVID-19 has been on since the genetic sequence of SARS-CoV- 2 was published on January 11, 2020. The first COVID-19 vaccine candidate entered human clinical testing on March 16, 2020 [43]. News outlets on April 14, 2020 announced that the Chinese authorities have just approved 2 vaccine candidates for clinical trials. At present, 115 vaccine candidates are being explored, with 78 confirmed as active and 37 unconfirmed, 73 of 78 confirmed active projects are at the exploratory or preclinical stages [43]. It has been reported that the most advanced candidates have recently moved into clinical development.

Research by scientists at the University of Pittsburgh, School of Medicine and the Graduate School of Public Health in collaboration with CDC, showed that an adenoviral-based vaccine could induce both SARS-CoV-specific T cell and virus-neutralizing antibody responses [44], both responses have been found important for lasting protection. In long-term studies of recovered SARS patients, antibody responses decreased after approximately six years, while T-cell responses persisted, suggesting that the latter is required for long-lasting immunity [45], this also might be the key for production of vaccines aimed at long term prevention of COVID-19 infection.

**Management of COVID-19 Patients**

**Potential Herbal Remedies**

Recent publications show that herbal medicine has been used for the prevention and treatment of COVID-19. Recent clinical evidence also showed the therapeutic effectiveness of traditional medicine in treating different stages of COVID-19. Below are some herbal formulas recommended for the management of COVID – 19.

***Artemisia Annua* Plant**

COVID-Organics is literally an herbal tea or decoction (a hot water extract of the plant *Artemisia Annua)*. A. *annua* is a famous plant in phytochemical circles because it contains artemisinin. Artemisinin is the groundbreaking compound renowned in pharma circles for its inhibitory efficacy on *Plasmodium falciparum*, the parasite that causes malaria. The announcement of the President of Madagascar on 20 April, 2020 about the effectiveness of the "Covid-Organics" was widely covered by the media. It was developed by the Malagasy Institute for Applied Research (IMRA). Distributed in 33 cl bottles or in dry herbal sachets under the brand name "CVO Tambavy", it contains 62% *Artemisia annua* and a mixture, in confidential proportions, of Malagasy medicinal plants used in the composition of traditional remedies as antiseptics and bronchial fluidizers [46].

However, the preventive and curative effectiveness of "CVO Tambavy", proclaimed by government authorities and some infectious disease specialists from the capital, is not unanimous in the Malagasy medical community. The "Houses of Artemisia" network supports this initiative as well as several African countries. Since May 2020, IMRA has been preparing an injectable form for patients in respiratory distress. After having expressed significant reservations, the WHO Director-General ended up accepting to include COVID-Organics in the clinical trials of the "Solidarity Trial" program [46].

**Traditional Chinese Medicine**

In China, Traditional Chinese Medicine (TCM) has played an important role in the battle against COVID-19. In late January 2020, the National Administration of Traditional Chinese Medicine (NATCM) organized an urgent study section to identify effective prescriptions of TCM for prevention and treatment of COVID-19. Based on symptoms observed in early COVID-19 patients, several



DOI : 10.2016-19146535/ ; DOI Link :: http://doi-ds.org/doilink/10.2020-85722646/

TCM formulae were developed, among which the Lung Cleansing and Detoxifying Decoction (LCDD) was one of the most widely used, and clinically studied. LCDD is a combined formula developed based on four classical formulae described in the Treatise on Cold Pathogenic and back by colonists from all over the world could be cultivated and studied [47].

**Citri Reticulatae Pericarpium and Glycyrrhizae Radix et Rhizoma**

Analytical results by reference [48] has shown that Citri Reticulatae Pericarpium and Glycyrrhizae Radix et Rhizoma has the strongest correlations among herbs. Both herbs are often prescribed together in herbal formulae [49]. In the theory of traditional medicine, Citri Reticulatae Pericarpium regulates the Qi (energy) nourishes the spleen, and dry dampness to resolve phlegm whereas Glycyrrhizae Radix et Rhizoma tonifies the Qi and enhances the function of Citri Reticulatae Pericarpium in resolving phlegm and reducing cough [50]. Additionally, a prior study on the distribution patterns of herbs used for respiratory disease treatment using data mining methods also reported that Glycyrrhizae Radix et Rhizoma was often grouped with Citri Reticulatae Pericarpium [51]. Studies also showed that the herb Citri Reticulatae Pericarpium has anti-inflammatory and anti-asthmatic properties which may relieve fever, soothe cough and dyspnea, stimulate appetite, as well as enhance the immune system [52, 53]. Particularly, the recommended dosage range for the herb Glycyrrhizae Radix et Rhizoma ranged from 3 to 60 g, which maybe related to the nature of the herb itself. The herb Glycyrrhizae Radix et Rhizoma has been the most commonly used adjuvant in most herbal medicine formulae in assisting herbal interactions. Studies have reported that the herb itself contains antiviral and anti-inflammatory qualities [54-56]. Glycyrrhizae Radix et Rhizoma possesses beneficial effects in respiratory diseases by nourishing Qi, resolving phlegm, and reducing cough [57]. Based on the currently available evidence, this herb has also been proposed as a novel immunomodulatory drug for COVID-19 [58]. Hence, the recommended dosage of the Glycyrrhizae Radix et Rhizoma highly depends on the role of herbs play in each herbal formula.

**Others**

Recently, the antiviral effects of Black Seed Oil (BSO) from *Nigella sativa* was investigated using Murine Cytomegalovirus (MCMV) as model organism, the results showed that BSO exhibited a striking antiviral effect against the viral infection, with increased innate immunity [59]. Polyphenols and proanthocyanidins extracted from the bark of *Hamamelis virginiana* alongside two new hydrolysable tannins (Shephagenins A and B), Hippophaenin A and Strictinin extracted from the leaf of *Shepherdia argentea*, showed remarkable inhibitory effects on Herpes Simplex Virus 1 (HSV-1) [60] and Human Immunodeficiency Virus 1 (HIV-1) reverse transcriptase (RT) [61]. The inhibitory effect of the *Shepherdia argentea* leaf extract on HIV-1 RT was enacted by tannins [61]. The antiviral potential of essential oils from *Melaleuca alternifolia* and eucalyptus exhibited a high level of antiviral activity against HSV-1 and HSV-2 in viral suspension tests [62]. The activities of anti-herpes components could be the result of terpinen-4-ol [63]. It was found that essential oil obtained from *Santolina insularis* had direct antiviral effects on both HSV-1 and HSV-2 [64] with drastic inhibition of cell-to-cell transmission [65]. Sandalwood oil [*Santalum album* L.] showed a dose dependent effect against HSV-1 but not HSV-2 with no reported cytotoxicity [66].

Polysaccharides extracted from the leaf of *Rhizophora apiculata* (RAP) and the bark of *Rhizophora mucronata* (RMP) were subjected to laboratory analysis using in vitro cell culture system [67, 68]. Both RAP and RMP protected Meta Trader 4 (MT-4) cells from HIV-induced cytopathogenicity and blocked the expression of HIV P24 antigens (viral capsid protein) preventing the virus binding to the cell and the formation of syncytia upon co-cultivation of MOLT-4 cells (T-cells lines originally derived from a patient with T-cell acute lymphoblastic leukemia in relapse multitreated) and MOLT-4/HIV-1IIIB cells [66]. Reference [69] found that Aloe Polymannose (AP), a mannose Biological Response modifier (BRM) purified from *Aloe barbadensis* (Miller plant) enhanced concentrations of anti- Chorionic Villus Biopsy 3 (CVB3) antibodies. Their research showed that AP can effectively boost human immune system to produce antibodies against capsid protein epitopes of a non-enveloped Picornavirus. Therefore, there is a huge possibility of BRM (AP) enhancing antibody production and concentration within the human body against other enteroviruses and poliovirus strains attenuated for vaccine production [69].

Also, biflavonoids (Amentoflavone, Agathisflavone, Robustaflavone, Rhusflavanone and Succedaneflavanone) extracted from two medicinal plants (*Rhus succedanea* and *Garcinia multiflora*), showed promising antiviral activities against Influenza (type A and B), Para-Influenza (type 3), Respiratory Syncytial virus (RSV), Adenovirus (type 5 and measles) and herpes viruses (HSV-1, HSV-2, Human cytomegalovirus [HCMV] and varicella zoster virus [VZV]) [70]. Amentoflavone and robustaflavone demonstrated significant antiviral activities against HSV-1 and HSV-2 [66]. Morin, extracted from *Maclura cochinchinensis* had high antiviral activities against HSV-2 [71].

**Synthetic drug treatment options for COVID-19**

Currently, there are no approved drug(s) or clinical therapy for the treatment of human coronavirus infection. The race against time in delivering effective treatment to hospitalized patients has given an edge to drug repurposing efforts, with a focus on agents having already known pharmacokinetic and pharmacodynamics profile, and manufacturing insights by pharmaceutical companies. Searchlights are being beamed on the following drugs.

**Chloroquine and hydroxychloroquine**

Chloroquine and hydroxychloroquine, which have been used for many years in malaria and chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus have antiviral activity with various mechanisms. They are used for prophylaxis against COVID-19 in many countries [72, 73]. In an in vitro study, chloroquine inhibited SARS-CoV-2. In addition to its immunoregulatory and anti-inflammatory effects, it has been reported to increase endosomal pH and prevent SARS-CoV cellular receptor glycosylation, thereby preventing the viral infection [74]. According to computer simulations, it is estimated that hydroxychloroquine and chloroquine bind to the Uridine diphosphate-N-



DOI : 10.2016-19146535/ ; DOI Link :: http://doi-ds.org/doilink/10.2020-85722646/

acetylglucosamine-2 epimerase active area that catalyzes the rate-limiting step in the sialic acid biosynthesis. Thus they can interfere with terminal glycosylation of proteins in the golgi apparatus [75].

It has been demonstrated that hydroxychloroquine blocks the macrophages 1 (M1) polarization which is the inflammatory macrophage subtype [76]. Eight to ten days after the symptoms start in COVID-19, conversion to the inflammatory M1 macrophage subtype occurs against the humoral immune response to the SARS-CoV-2 S protein [75].

According to many studies, chloroquine and hydroxychloroquine improve glycemic control in treatment-resistant diabetic patients by repairing pancreatic β function [77]. They provide the increase in insulin active form by inhibiting the enzymatic degradation of insulin via elevating the intracellular pH. Besides reducing proinflammatory cytokines, especially Tumor necrosis factor alpha (TNF-α) and Interleukin 6 (IL-6), they reduce insulin resistance [72]. Therefore, in the COVID-19 patients who use antidiabetic medication, the dose adjustment of oral antidiabetic drugs or insulin should be done well while prescribing the chloroquine/hydroxychloroquine [18].

Data is limited for the use of chloroquine and hydroxychloroquine in COVID-19 and larger studies are needed. According to Chinese reports, chloroquine successfully treated 100 COVID-19 patients with improved radiological findings and increased viral clearance [78].

In the non-randomized 80 patients' clinical cohort, hydroxychloroquine and azithromycin combination reduced viral load in COVID-19 patients, and relieved clinical symptoms in most patients [79]. Moreover, in Wuhan, any of the 80 lupus patients receiving chronic hydroxychloroquine treatment have not been observed to develop COVID-19 infection. Subsequently, 62 patients with mild COVID-19 signs and symptoms were randomly treated with standard of care or 200 mg hydroxychloroquine twice daily for 5 days alongside the standard of care. In 80.67% of the participants using hydroxychloroquine, COVID-19 pneumonia findings were repaired in CT scanning in the control group, this rate remained at 50.8%. While exacerbation of disease was not developed in any patient in the hydroxychloroquine group in 12.9% of the control group patients, were disease was aggravated [75, 80].

The median effective concentration (EC50) value of hydroxychloroquine was found lower compared to chloroquine [81]. Chloroquine dosage is 500 mg orally 1 or 2 times a day [82]. According to pharmacokinetic modeling studies, for COVID-19 treatment, hydroxychloroquine should be used as 200 mg twice a day, after the loading dose of 400 mg twice a day [83].

Chloroquine and hydroxychloroquine are well tolerated drugs. But they can cause rare and serious side effects such as QTc prolongation (the interval from the beginning of the QRS complex to the end of the T wave on an electrocardiogram representing ventricular depolarization and repolarization and indicating the time during which ventricular contraction and subsequent relaxation occurs), arrhythmia, hypoglycemia, neuropsychiatric effects, and retinopathy [83, 84]. Therefore, their use in high doses should be avoided [85].

**Remdesivir**

Remdesivir is a monophosphate prodrug which metabolizes to active C-adenosine nucleoside triphosphate analogue. Remdesivir is a viral replication inhibitor. It is effective on upper respiratory infection, especially at earlier phases. Remdesivir's RNA base adenosine-like structure provides the strong inhibition of viral RNA polymerase. Remdesivir is taken into RNA strands by the virus and causes chain termination [85]. The first clinical use of remdesivir has been in the treatment of Ebola [86]. Due to its broad spectrum, it is promising for the treatment of COVID-19. Remdesivir has shown in vitro activity against many coronaviruses, including SARS-CoV-2 [87]. Safety and pharmacokinetics of remdesivir have been investigated in single and multiple doses in phase 1 clinical trials. It was well tolerated in intravenous infusions between 3 mg and 225 mg, liver and kidney toxicity did not develop. The treatment dose is 200 mg single loading dose followed by 100 mg daily infusion. Successful results have been reported in the treatment of COVID-19 [83].

**Lopinavir/ritonavir**

These agents were developed to inhibit the protease of HIV responsible for the cleavage of a long protein chain during the assembly of new viruses. Lopinavir can be formulized with protease inhibitor ritonavir which decreases the metabolization of lopinavir by inhibiting cytochrome (CYT) P4503A enzyme. It was established to be active *in vitro* against the severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV-1) during the 2003 outbreak [88]. The combination has been said to work in marmosets infected with the Middle East respiratory syndrome (MERS) coronavirus [89]. It is applied in COVID-19 at a dose of 400 mg / 100 mg up to 14 days twice a day [90]. The outcome of clinical trials on the use of this combination for the treatment of COVID-19 patients has been of mixed fortunes, hence, more studies need to be conducted.

**Nitazoxanide**

Nitazoxanide has demonstrated potent *in vitro* activity against SARS CoV-2, with an EC50 at 48 hours of 2.12 μM in Vero E6 cells [74]. This potent activity is consistent with EC50 values for nitazoxanide and its active metabolite, tizoxanide, against MERS-CoV in Rhesus Monkey Kidney Epithelial cells (LLC-MK2 cells) where EC50 values of 0.92 and 0.83 μM have been demonstrated, respectively [91]. Nitazoxanide displays broad spectrum *in vitro* antiviral activity against influenza, respiratory syncytial virus, parainfluenza, rotavirus, and norovirus amongst others in addition to coronaviruses. This broad spectrum antiviral activity is believed to be due to the fact that the mechanism of action is based on interference with host regulated pathways involved in viral replication rather than virus-specific pathways [91].

Due to its broad-spectrum antiviral activity, nitazoxanide is being investigated for the management of influenza and other acute respiratory infections. Positive results were demonstrated in a phase 2/3 study for the outpatient management of influenza, where a dose of 600 mg by mouth twice a day (BID) of nitazoxanide was associated with a day improvement [92]. Three phase 3 randomized controlled trials in uncomplicated influenza have since been completed, although results are unavailable. Nitazoxanide failed to reduce the duration of hospitalization or the time to symptom alleviation in a



DOI : 10.2016-19146535/ ; DOI Link :: http://doi-ds.org/doilink/10.2020-85722646/

phase 2 randomized controlled trial in patients with severe acute respiratory illnesses requiring hospitalization, predominantly caused by respiratory viruses [93]. While the *in vitro* activity of nitazoxanide against SARS CoV-2 is encouraging, more data are clearly needed to determine its role in the management of COVID-19.

**Tocilizumab**

Tocilizumab is a humanized monoclonal antibody that inhibits both membrane-bound and soluble IL-6 receptors. IL-6, which is secreted by monocytes and macrophages, is one of the main drivers of immunologic response and symptoms in patients with cytokine-release syndrome (CRS). While tocilizumab was first approved by the Food and Drug Administration (FDA) in 2010 for the treatment of rheumatoid arthritis, it has gained traction in recent years for treatment of patients with CRS following chimeric antigen receptor T-cell (CAR T) therapy as a corticosteroid-sparing agent [94]. Indeed, it received FDA-approval for severe or life-threatening CAR T-associated CRS in 2017 due to its efficacy and safety profile. While criteria for grading CRS severity varies by cancer center, it has been proposed to administer tocilizumab to CRS patients with any of the following; oxygen requirement < 40 %, hypotension responsive to fluids or a low dose of a single vasoactive agent, or Grade 2 organ toxicity as defined by the Common Terminology Criteria for Adverse Events [95]. IL-6 antagonism may make a patient more susceptible to bacterial infection and has been associated with neutropenia and thrombocytopenia in patients receiving chronic therapy with tocilizumab for giant cell arteritis or rheumatoid arthritis. In a case series of 53 adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia, Grade 3 CRS or higher was associated with increased risk of subsequent infection but it was unclear whether tocilizumab or corticosteroid use promoted this risk [96]. There were no reported adverse events in the 60 tocilizumab-treated patients submitted to the FDA for the CRS indication, which recommends a maximum of 4 doses for treatment [97].

**Corticosteroids**

Similar to other severe respiratory tract infections, there is significant interest and controversy surrounding the role of corticosteroids for the management of severe pneumonia due to coronaviruses. The potential benefit of these agents to blunt the inflammatory cascade seen in severe disease needs to be carefully weighed against the concerns for secondary infections, adverse events, and other complications of corticosteroid therapy. The data assessing the role of corticosteroids as adjunctive care for severe coronavirus (SARS-CoV-1, MERS-CoV, and SARS-CoV-2) pneumonia are difficult to interpret. Given the retrospective observational nature of these analyses, there is significant confounding by indication that is difficult to control or correct for in addition to limited sample sizes. Patients who receive corticosteroids have a higher severity of illness, and are more likely to require invasive interventions and be receiving intensive care. Additionally, there is significant heterogeneity with regards to timing of corticosteroid initiation which can significantly impact disease progression and likelihood of response. All these features lead to patients who receive steroids being at increased risk for poor outcomes. Additionally, there is great variation in agent and dosage used which can impact both safety and efficacy. Therefore, any therapeutic decisions based on the literature for corticosteroids need to keep these considerations in mind [98].

**Ribavirin and Interferon**

Ribavirin is the guanosine analogue that inhibits the viral RNA dependent RNA polimerase. Its effects on other coronaviruses have suggested its use in the treatment of COVID-19. In the *in vitro* study, it was found that ribavirin inhibits SARS-CoV replication at high concentrations. It must be known that ribavirin leads to hematological toxicity in a dose dependent manner [83]. The doses required for antiviral activity against SARS range from 1.2 g to 2.4 g by mouth every 8 hours, which are associated with excessive toxicity to patients [99]. Researchers evaluated the *in vitro* activity of ribavirin against SARS-CoV-2 and found an EC50 of 109.5 μM, which was over 100 times less potent than remdesivir [74]. The risk of hematologic toxicity at high doses likely outweighs potential clinical benefit, and therefore ribavirin was not considered a viable candidate for further investigation by the World Health Organization research and development plan for SARS-CoV-2 given lack of *in vitro* efficacy, toxicity profile, and poor outcomes.

Interferon-α (IFN-α) which is the broad-spectrum antiviral agent is approved for viral hepatitis treatment. Interferon-α is used in the treatment of COVID-19 with vapor inhalation at a dosage of 5 million units twice a day. It is used for 10 days alone or combined with ribavirin (500 mg 2-3 times a day) or with lopinavir/ritonavir (400 mg/100 mg) [85]. Interferon-β (IFN-β) has been developed to treat chronic obstructive pulmonary disease. It restores the lung damage and has the ability to fight the viral infection. The reduction in IFN-β formation is related to the predisposition to the severe respiratory diseases as a result of viral infections. Immune system suppresses IFN-β formation in SARS-CoV-2 infection. In the United Kingdom, IFN-β trial use has been approved in COVID-19 patients. Similar to IFN-α and IFN-β can be inhaled by self-administration of patients [85].

**Oseltamivir and baloxavir**

Given their antiviral activity against influenza, considerable attention has been paid to oseltamivir, and to a lesser degree baloxavir, as potential treatment options for COVID-19. This was exacerbated by the initial report from researchers in Wuhan where patients managed with COVID-19 received oseltamivir in addition to broad spectrum antimicrobials [23]. It is important to note that use of oseltamivir was not as targeted therapy of SARS CoV-2, but rather driven by the lack of a knowledge of the causative pathogen at the time of treatment and the desire to empirically treat influenza. The authors do not suggest the use of oseltamivir for COVID-19 in that publication, and there are no data that suggest *in vitro* activity of oseltamivir against SARS CoV-2. In fact, the only data assessing oseltamivir activity against coronaviruses demonstrated it to be ineffective at inhibiting SARS CoV-1, even at a concentration of 10,000 μM/L [99]. Coronaviruses do not utilize neuraminidase and thus there is no enzyme to be inhibited by oseltamivir. This would hold true for zanamivir, peramivir, or any other neuraminidase inhibitor agents. Similarly, neither a defined mechanism nor *in vitro* data have suggested that baloxavir would demonstrate activity against SARS CoV-2



DOI : 10.2016-19146535/ ; DOI Link :: http://doi-ds.org/doilink/10.2020-85722646/

or other coronaviruses. Therefore, given the critical need for these agents in the management of influenza and concern for drug shortages with oseltamivir, these agents should be avoided in patients with COVID-19 once influenza has been ruled out.

**Umifenovir (Arbidol)**

It is a promising antiviral agent that targets the Spike protein / ACE2 interaction and has a unique mechanism of action that inhibits membrane fusion of the viral envelope [100]. It is an approved influenza drug in Russia and China. In vitro activity against SARS-CoV led to its use in COVID-19. It is being tried against COVID-19 with 200 mg orally every 8 hours [83]. It is known to reduce mortality rates in COVID-19 patients [87].

**Favipiravir**

Favipiravir is the first agent approved for influenza virus in February 2020 [85]. It is an RNA dependent RNA polymerase inhibitor for the RNA viruses such as SARS-CoV-2. Favipiravir also has shown an effect against SARS-CoV-2 *in vitro* [91]. In February 2020, favipiravir pre-clinical trials were conducted in 80 patients in China. Side effects were detected less compared to lopinavir / ritonavir [101]. Clinical researches are still in progress [83].

**Competing Interests**

The author declares that there is no competing interest.

**Statement**

The manuscript has been read and approved by the author, that the requirements for authorship as stated earlier in this document have been met, and that the author believes that the manuscript represents honest work.

## 3. CONCLUSION

The COVID-19 pandemic represents the gravest global public health threat seen since the 1918 influenza outbreak and has rapidly become a global healthcare emergency. COVID-19 develops more severely in patients with comorbidities such as hypertension, diabetes and cancer. Currently, there are no specific therapeutic agents for this disease, due to its broad clinical spectrum. At the moment, prevention by physical intervention can help limit the rate of transmission, and mortality within human populations worldwide. In order to significantly reduce or totally eradicate the deleterious effects of COVID-19 infections around the world, available antiviral drugs and clinical therapy options such as umifenovir, ribavirin, Oseltamivir, favipiravir, chloroquine/hydroxychloroquine, tocilizumab, remdesivir, lopinavir-ritonavir, and nitazoxanide are tested against SARS-CoV-2. Moreover, some natural herbal compounds have demonstrated encouraging anti-viral properties, hence can be considered a promising alternative approach in the treatment of covid-19. Pre-clinical evaluations and clinical trials of some of the proposed herbal remedies and synthetic therapies/drugs itemized in this review should be considered, and treatment recommendations made by medical experts. In addition, until the vaccine and specific antiviral therapy against SARS-CoV-2 are developed, the available management options are being tried to recover the COVID-19 cases with mild clinical symptoms.

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