Potential of pharmacological and herbal for COVID-19: a narrative review

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Abstract: The pandemic coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an unprecedented challenge to identify effective drugs in the prevention and treatment process. At present, there is no proven therapy for this disease, although therapeutic approaches continue to be carried out using traditional medicines (herbal) and pharmacological therapy. Information about SARS-CoV-2 virology has rapidly developing and scientists try to provide a number of potential drugs. Remdesivir has strong *in vitro* activity against SARS-CoV-2. Several potential drugs are currently underway in a clinical trial. Chloroquine, hydroxychloroquine, and oseltamivir have not been proven to have efficacy, and the benefits of corticosteroids are still diverse. Current clinical evidence does not support the termination of angiotensin converting enzyme 2 (ACE2) inhibitors or angiotensin receptor blockers, coagulation therapy in patients with COVID-19 concomitant with comorbidities.

Keywords: COVID-19, herbal, pharmacology, therapy

Introduction

Coronavirus is one of a large family of viruses that can be found in humans as well as animals. The first report of a SARS-CoV-2 virus infection patient that was able to attract world attention occurred at the end of December 2019 in Wuhan, China. On February 11, 2020, the International Taxonomy Institute named this virus "Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2)" as the official name for this type of virus, previously known as 2019-nCoV [1].

SARS-CoV type 2 is belonged to virus family that caused SARS and MERS. SARS-CoV-2 binds to the ACE2 receptor on lung cells through the receptor binding domain, then enters the cell and multiply, causing clinical symptoms found in infectious patients such as fever, cough, flu, and loss smell. The SARS-CoV-2 virus is mostly transmitted by coughing or sneezing during close physical contact. Asymptomatic, pre-symptomatic, and symptomatic carriers can transfer infection [2].

Pathophysiology

Coronavirus is found in humans and other mammals as a single-stranded RNA virus in dogs, cats, chickens, cows, pigs, and birds. Coronavirus causes disorders of the lungs, gastrointestinal tract, and nervous system. SARS-CoV type 2 is a third-generation coronavirus that has spread extensively in the last two decades, causing severe sickness in people [3]. SARS-CoV pandemic, began in China in 2002-2003 and was the first coronavirus to cause serious illness [4], while MERS was first reported in the Arabian Peninsula in 2012 [5]. The coronavirus may adapt and infect new hosts through recombination processes and genetic variety. In addition to the bat, new research reveals that humans get infected through a pangolin intermediate host [7,8].

Pathogenesis

At the beginning of infection, the SARS-CoV-2 targets several human cells through viral S protein that binds to the ACE2 [9], whereas protease 2 transmembrane serine protease (TMPRSS2) promotes viral absorption by cleaving ACE2. ACE2 and TMPRSS2 are expressed especially in type II alveolar epithelial cells in the respiratory tract [10,11].

Severe lymphopenia can develop in COVID-19 patients when the SARS-CoV-2 attacks and destroys T cells. Furthermore, an inflammatory viral response that includes may harm lymphopoiesis while also increasing lymphocyte apoptosis. It has been suggested that ACE2 receptor upregulation from ACE inhibitors

and angiotensin receptor blocking drugs increases susceptibility to SARS-CoV-2 infection; however, a large cohort research comprising 4480 COVID-19 patients in Denmark discovered no link between the two drug classes and the risk of infection or mortality in the hospital [12,13].

In severe COVID-19 patients, the incidence of severity of coagulation activation and blood clotting factors was found. This is evidenced by a study in China, showing that 71% of the 183 people who died due to COVID-19 were found to have intravascular coagulation diffusion, a condition of impaired blood flow characterized by excessive blood clotting, causing blockage (thrombus) in the blood vessels in various organs in the human body [14].

Transmission

Droplets released when speaking face-to-face, coughing, or sneezing are the most prevalent mechanisms of transmission, according to epidemiological statistics. Transmission is more likely when spend more time with an infected individual (within 1-2 meters for at least 15 minutes) and spend less time with symptomatic persons, but brief exposure to asymptomatic contact has a lower risk [16]. Another mode of transmission is through surface contact by touching a virus-infected object's surface. However, the significance of this transmission is difficult to assess.

Viruses can also be detected 3 to 4 days after inoculation on impermeable surfaces [17]. Virus contamination is also found in several hospital treatment rooms; however, it is estimated that the number of viruses detected on the surface of these objects decreases rapidly within 48 to 72 hours due to routine disinfection [18]. The presence of the virus on the surface of objects strengthens the potential for virus transmission through door handles, eating utensils, and droplets through close direct face-to-face contact is still the main factor in the process of spreading the virus.

Symptoms and Signs

Common symptoms that occur in COVID-19 patients are cough, fever, shortness of breath, myalgia, and fatigue [19,20]. Changes in the sense of smell or taste appear to be common finding in patients with mild/moderate disease; these symptoms sometimes appear before other COVID-19 symptoms [21]. As for the presentation of the severity of COVID-19 patients,

around 80% were with mild disease, 14% with severe disease, and 5% with critical illness.

Some COVID-19 patients will show no symptoms, although the exact proportions are not clear. Limited evidence from several countries suggests that up to 12% of SARS-CoV-2 transmission can occur through asymptomatic individuals [22]. It is likely to be higher in some places such as nursing homes [23]. Auscultation of the chest may reveal inflammation of the airways, rales (crepitus), and/or bronchial breathing in a patient with pneumonia or respiratory distress. Auscultation should be reserved for those who are important for decision making. Patients with respiratory distress may experience tachycardia, tachypnea, or cyanosis that accompanies hypoxia (23).

Doctors assessing COVID-19 patients should be aware of a phenomenon called "silent hypoxia", which is a lowered drop in oxygen saturation and triggers acute respiratory failure without any obvious respiratory symptoms. Only a minority of patients have other organ dysfunction, which means that after the initial phase of acute damage, traditional methods of recognizing further damage (e.g. NEWS2 score) cannot help predict patients with respiratory failure [24]. Although most patients with COVID-19 in the community will have mild disease, caution is needed when having respiratory symptoms and signs in patients with suspected COVID-19.

Supportive Therapy

Currently, the available therapeutic strategy for treating SARS-COV-2 infection is supportive and transmission prevention. There are four possible strategies to be applied: (i) consume of nutritious foods to boost immunity; (ii) use of masks and face shields; (iii) use of essential oils as air disinfectants to stop aerosol transmission; and (iv) use disinfectant [25].

Many plant and substances are known to have antiviral and immunomodulatory properties such as Aloe vera, astragalus, ganoderma, ginseng, curcumin, cinnamaldehyde, allicin, and piperin [26]. This activity is based on selective stimulation of cytokines, activation of lymphocytes, increasing the number of natural killer cells and increasing the activity of macrophages. Several natural products, such as baicalein and baicalin, have also been proven to suppress SARS-CoV-2 [27]. The herbal remedy Lian Hua Qing wen may suppress SARS-CoV-2 replication and reduce pro-inflammatory cytokine (Table 1) [28].

Table 1. Herbals that have the potential as antivirus for corona

Herbals	Compound/extract	Testing Model	Mechanism of action	References
Lianhuaqingwen	*Forsythia suspensa* (Thunb.) Vahl (Weeping forsythia	Vero E6 model with SARS-COV-2 infection	Inactivation of SARS-CoV-2 replication, reduces production of pro-inflammatory cytokines and affects the morphology of virus cell particles.	[28,30]
	Ephedra sinica Stapf (Chinese ephedra;			
	Lonicera japonica Thunb. (Japanese honeysuckle;			
	Isatis indigotica Fortune			
	Mentha haplocalyx Briq.			
	Dryopteris crassirhizoma Nakai (Thickstemmed wood fern)			
	Rhodiola rosea L. (Golden root)			
	Gypsum Fibrosum (Gypsum)			
	Pogostemon cablin (Blanco) Benth. (Patchouli)			
	Rheum palmatum L. (Chinese rhubarb)			
	Houttuynia cordata Thunb. (Fish mint)			
	Glycyrrhiza uralensis Fisch. (Liquorice)			
	Armeniaca sibirica (L.) Lam. (Siberian apricot)			
Rhizoma cibotii (Rhizome of Scythian Lamb)	Extract *Rhizoma cibotii*	Vero cell model with SARS-CoV-1 infection	Inhibits the replication of the SARS-CoV-1 virus	

It is also suggested that inhaling essential oil vapor increases the suppression of airborne germs and viruses. *Citrus bergamia, Eucalyptus globulus, Pelargonium graveolens, Cinnamomum zeylanicum* leaf oil, and *Cymbopogon flexuosus* are some of the essential oil vapors that have been shown to have anti-influenza viral activity. [29]. Using essential oils to disinfect the air without risking human health could be an efficient way to halt the spread of COVID-19. However, the minimum essential oil concentration required to reduce SARS-CoV-2 should be investigated further. To enhance the immune system and defend the body from COVID-19, a combination of immunomodulatory foods and herbs is recommended. Other scientific investigations or clinical trials must, however, validate these findings.

Potential candidates for pharmacological therapy of COVID-19

At this time, there is no known anti-viral drug that has been proven to work for COVID-19. Several clinical trials are undergoing such as remdesivir, favipiravir, plasma convalescent, hyper-immune immunoglobulin, dexamethasone, statins, tocilizumab, sarilumab, anakinra, ruxolitinib, heparin, and antifibrotics. At various phases of the disease and in different manifestations of the disease, the use of those medications is likely to have varied qualities. Viral suppression is likely to be most effective at the outset of infection, whereas immunomodulatory drugs and anticoagulants can help reduce disease development and thromboembolic consequences in hospitalized patients [18].

The majority of antiviral medications presently being tested on COVID-19 patients were initially created to combat the influenza virus, HIV, Ebola, or SARS/MERS [31]. When compared to standard therapy, the protease inhibitor lopinavir-ritonavir had no effect in 199 hospitalized adult patients with severe COVID-19 [32]. Meanwhile, the use of ribavirin, favipiravir, and remdesivir, which block viral replication, these drugs seem to show the most promising results [31,33].

Patients who were given remdesivir had a faster recovery time than those who were given a placebo (11 vs 15 days) [33].

During the 1918 flu pandemic, plasma therapy from individuals who had recovered from viral illness was first recorded. The first reports of five severely sick COVID-19 patients who were administered convalescent plasma shown improved clinically outcome [34]. In a clinical trial involving 103 Chinese patients with severe COVID-19, no significant differences in clinical improvement were found between those assigned to conventional plasma vs standard therapy at 28 days (51.9% vs. 43.1%). Alternatively, blood plasma-derived hyper-immune globulin and monoclonal antibodies targeting the SARS-CoV-2 virus are presently being studied [35].

Another promising therapy strategy is monoclonal antibodies that target inflammatory mediators such as IFN-γ, IL-1, IL-6 to avoid organ damage in COVID-19 patients [36]. Tocilizumab and sarilumab, an IL-6 inhibitor, are a good option for COVID-19 patients. Tyrosine kinase inhibitors (such as imatinib) are still being researched for their ability to reduce pulmonary blood vessel leakage in COVID-19 patients.

In trials, corticosteroids have had inconsistent results when used to treat viral pneumonia and acute respiratory distress syndrome (ARDS). In the RECOVERY Trial, 2104 individuals with COVID-19 who received 6 mg of dexamethasone daily for 10 days versus 4321 patients who received standard therapy were proven to survive longer [37]. according to a retrospective cohort investigation, methylprednisolone therapy reduced the risk of mortality in 201 patients with COVID-19 pneumonia and ARDS in Wuhan, China [38]. The use of corticosteroids in individuals with a shorter duration of symptoms and who do not require supplementary oxygen, on the other hand, has shown to be ineffective [18].

Subcutaneous low molecular weight heparin for thromboembolic prevention should be given to almost all COVID-19 patients who are hospitalized. Currently, there are over 300 clinical therapeutic trials in progress. There is presently no solid evidence that any medicine can improve outcomes based on randomized clinical studies (Table 2).

Conclusion

COVID-19 patients commonly experience fever, dry cough, and shortness of breath. Lymphopenia and increased lactate dehydrogenase are two frequent radiographic and laboratory findings. Sepsis and rapid respiratory failure can define COVID-19 symptoms, including asymptomatic carriers and fulminant/severe illness. Around 20% of COVID-19 hospitalized patients have severe symptoms that intensive care, and more than 75% of COVID-19 hospitalized patients require supplementary oxygen treatment. In people who need supplemental oxygen, dexamethasone medication reduces 28-day mortality, while the use of remdesivir reduces the time it takes to recover from 15 to 11 days (release from hospital or no need for extra oxygen). The use of convalescent plasma did not decrease recovery time in a randomized study of 103 individuals with COVID-19. Antiviral treatment, immune modulators, and anticoagulants are now being tested. In the United States, the case-fatality rate varies substantially with age, ranging from 0.3 deaths per 1000 cases in patients aged 5 to 17 years to 304.9 deaths per 1,000 cases in patients 85 years and older. Case fatality of patients hospitalized to the

Table 2. Several potential drugs that are still in the clinical trial for COVID 19

Drug	Use
Remdesivir	Patient MERS CoV and Ebola
Lopinavir/ritonavir	50% decreased MERS CoV activity
Ribavirin	Patients with MERS CoV infection
Oseltamivir/Tamiflu	Patients with influenza
Chloroquine/hydroxychloroquine + Azithromycin	Malaria, lupus, arthritis
Convalescent plasma therapy	Patients with influenza
ChAdOx1 nCoV-19 vaccine	COVID-19 clinical trials
Vitamin C	CITRIS-ALI trial

intensive care unit (ICU) can reach 40%. At least 120 vaccines against SARS-CoV-2 are in the works. Face masks, social distancing, and contact tracking are the key strategies of controlling transmission until a viable vaccine is available. Monoclonal antibodies and hyper-immune globulin are two other techniques that can be employed to stop the virus from spreading.

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Declaration of interest

The authors declare no conflict of interests in the journal publication of this article.

Author contribution

ST constructed the study design. ST and TAR performed and analyzed the article. TAR prepared the first draft manuscript and ST revised the final version of the paper. ST and TAR have read the final manuscript.

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