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Review Article

Current Potential Antiviral Agents for Coronavirus Disease 2019 (COVID-19) Therapy

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first discovered in Wuhan, Hubei Province, China. SARS-CoV-2 infects the respiratory tract, which causes coronavirus disease 2019 (COVID-19). Various studies have been conducted to find effective therapies. However, there is still no specific treatment or therapy for COVID-19. This literature review, summarizes some recent research on several potential antiviral agents, both drugs that are commonly used in the medical world such as ivermectin, to medicine from herbal plantsand some drugs that are in the process of clinical trials such asremdesivir, lopinavir/ritonavir, Interferon β, ribavirin, convalescent plasma, and monoclonal antibodiesfor COVID-19 therapy.

Keywords : SARS-CoV-2, COVID-19, Antiviral Agents, Potential therapy

INTRODUCTION

In December 2019, the novel Betacoronavirus or 2019 novel coronavirus (2019-nCoV) was first discovered in Wuhan, Hubei Province, China.[1] Currently, 2019-nCov has been officially named by the International Committee on Taxonomy Virus (ICTV) as a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] SARS-CoV-2 infects the respiratory tract which causes coronavirus disease 2019 (COVID-19).[1] Based on the results of the SARS-CoV-2 genome analysis, this virus is suspected to be a recombinant coronavirus originating from bats and unidentified coronaviruses.[2] As of July 6, 2020, from 188 countries, there were 11.409.805 positive confirmed cases of COVID-19 with mortality rates of 533.684 cases or case fatality rate (CFR) of 4.6%.[3]

Various studies have been conducted to find effective therapies and found several drugs that have the potential to overcome SARS-CoV-2 infections such as interferonalpha (IFN-α), lopinavir / ritonavir (LPV / r), ribavirin (RBV), chloroquine phosphate (CLQ / CQ), remdesivir and umifenovir (arbidol).[2] However, there is still no specific treatment or therapy for COVID-19. This literature review summarizes some of the recent research on several potential antiviral agents for COVID-19 therapy.

SOME POTENTIAL ANTIVIRAL AGENTS

Ivermectin

Ivermectin is a broad-spectrum anti-parasitic drug that has been widely used in medicine.[4] From the results of in vitro study, Ivermectin is known to inhibit the replication of several viruses, including human immunodeficiency virus (HIV-1), dengue virus (DENV), and Venezuelan equine encephalitis virus (VEEV).[5]

Caly L *et al*. 5 showed that Ivermectin could also inhibit the replication of the SARS-CoV-2 virus in Vero / hSLAM cells by 93% in 24 hours, and 99.8% in 48 hours. The Food and Drug Administration (FDA) has approved the use of Ivermectin to treat parasitic diseases because it has proven to be safe for humans.[6] However, Ivermectin has not been clinically tested, especially for COVID-19 disease. Thus, further research is needed.

Human recombinant soluble ACE2 (hrsACE2)

Human recombinant soluble ACE2 (hrsACE2) is a drug that is currently in the process of clinical trials for COVID-19 therapy. From the results of in vitro study, hrsACE2 inhibit SARS-CoV-2 infection on cells significantly.[7]

To enter the host cells, the glycoprotein in the SARS-CoV-2 envelope spike must bind to the cellular receptor, such as angiotensin-converting enzyme 2 (ACE2).[8] Within the cell, SARS-CoV-2 will synthesize proteins that are needed to form new virions, which will appear on the cell surface.[8] By inhibiting the interaction between ACE2 and the SARS-CoV-2 envelope spike, hrsACE2 may prevent the virus's entry into the cell to prevent its replication.[7]

Zinc (Zn)

Zinc is an essential micronutrient for humans and physiologically needed in the body's immune system to fend off viral infections.[9] From the results of in vitro study, Zn can inhibit the replication of several viruses, such as rhinovirus, coxsackievirus B3, hepatitis C, hepatitis E, to SARS-CoV.[9–12]

Zn has an antiviral effect on SARS-CoV through an RNA-dependent RNA polymerase (RdRp) inhibitory pathway, which prevents viral replication.[13] There has been no research regarding the antiviral effect of Zn, specifically on SARS-CoV-2, both in vitro or in vivo. Nevertheless, Zn is believed to be beneficial for COVID-19 patients. Currently, there is an ongoing clinical trial to find out the benefits or potential of Zn as a candidate for COVID-19 therapy.[14]

Echinacea

Echinacea is an herbal medicine that is known to reduce symptoms due to respiratory tract infections. Echinacea is also known to have an immunomodulatory effect; hence it is quite popular to be used as a health supplement that may increase immunity against infectious diseases.[15]

Hudson J *et al*[17] concluded that in vitro, *Echinacea purpurea* extract was sensitive to herpes simplex virus, respiratory syncytial virus, rhinovirus, and all avian influenza virus strains. Echinacea purpurea extract was proven to be able to inactivate SARS-CoV and MERS-CoV in infected cell cultures.[18] Therefore, it is anticipated that *Echinacea purpurea* extract is effective against all strains of Coronavirus and can be effective prophylaxis for SARS-CoV-2.[17] The study has not undergone a peer-review process. However, the results can serve as an indication for further research.

3 chymotrypsin-like proteases (3CLpro) inhibitors

3CLpro is an enzyme that plays a vital role in coronavirus replication, including MERS-CoV and SARS-CoV.[2] Cinanserin, is known to contain serotonin receptor antagonists or 3CLpro inhibitors which can inhibit 3CLpro, hence preventing the replication of SARS-CoV.[2] Some in vitro studies also showed that flavonoids in herbal plants could inhibit hepatitis C virus, MERS-CoV, and SARS-CoV replication through the inhibitory effect of 3CLpro.[18,19] Some of these flavonoids include, herbacetine, quercetin, and helichrysetin, rhoifolin and pectolinorin.[20]

Remdesivir

Remdesivir is a broad-spectrum antiviral drug that is used to treat RNA viruses. This drug is able to inhibit RNA-dependent RNA polymerase (RdRP) in RNA viruses, including MERS / SARS-CoV.[21] In vitro study showed that this drug can effectively inhibit SARS-CoV-2.[21] Some clinical trial results that have been published, show remdesivir is a promising drug as a therapeutic choice for COVID-19 patients.[22] Although the clinical trial process have not been completed, U.S. The Food and Drug Administration (FDA) has allowed remdesivir to be used to treat COVID-19 patients.[23]

Lopinavir/ritonavir (LPV/r)

LPV/r was originally a combination drug to treat human immunodeficiency virus (HIV) infections, but now it is also use as one of the treatment options for SARS-CoV-2 infection.[24] Cao *et al* conducted an undisclosed clinical trial on 199 subjects to assess the effectiveness of LPV / r compared to standard services in COVID-19 patients.[25] As a result, there was no significant difference in the time for clinical improvement and in the 28-day mortality assessment, a lower number was found in the LPV / r group.[25] Treatment with LPV / r also did not reduce RNA viral load or duration of viral load detection compared with standard supportive care. In addition, SARS-CoV-2 RNA was still detected in 40.7% of patients in the lopinavir / ritonavir group at the end of the trial on day 28.[25] The results of this study require further study in order to determine whether treatment with LPV / r given at Certain disease stages can reduce some complications in COVID-19 patients.

Combination of Lopinavir / ritonavir (LPV / r), Interferon β-1b (IFN β-1b), and Ribavirin (RBV)

Hung *et al* conducted an undisclosed clinical trial in 127 subjects, with 86 of them randomly were treated with a combination of LPV / r, IFN β-1b, and RBV, while 41 subjects were included in the control group.[26] As a result, the combination group had a significantly shorter average clinical improvement time from the first day of treatment, to the nasopharyngeal swab being negative (7 days) compared to the control group (12 days).[26] LPV / r combination therapy, IFN β-1b, and RBV are proven to be safe and superior when compared to the combination of LPV / r alone in reducing viral load, alleviating symptoms, to shortening the duration of treatment of patients with mild symptoms of COVID-19.[26]

Convalescent Plasma

Convalescent plasma transfusion is a common modalities to treat infectious diseases. The effectiveness of convalescent plasma as a potential therapy was first discovered through clinical trials during the Spanish flu pandemic in 1918–1920.[27,28] Convalescent plasma from patients who have recovered from COVID-19 patients is known to have a therapeutic effect because it has antibodies to SARS-CoV-2.[28] From several studies in critical COVID-19 patients, all patients experienced clinical improvement.[28] Although the current study of convalescent plasma administration in COVID-19 patients is still limited, the FDA approves this therapy especially in critical COVID-19 patients.[29] Plasma donors were given by patients who had confirmed positive SARS-CoV-2, had been declared cured (negative on SARS-CoV-2 detection) and were symptom free for 14 days. Patients and donors must also had a match blood cross-match.[28]

Monoclonal antibodies

Monoclonal antibodies are a potential therapy for dealing with SARS-CoV-2 infection.[30] Some monoclonal antibodies such as CR3022, CR3014, 47D11, B38 and H4 identified by ELISA, have the potential to neutralize SARS-CoV-2 by inhibiting the interaction of protein S1 protein subunits against ACE2 receptors and inhibit virus replication.[30,31] Further research is needed to better understand the role of monoclonal antibodies as one of the potential therapies for COVID-19.

CONCLUSION

Until this point, COVID-19 cases around the world continue to increase. Without specific management found for COVID-19, preventive and protective measures have become the best option. The existence of potential drugs that could become COVID-19 therapy raises the probability of finding specific therapies.

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