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Covid-19 Drug Targets and Therapeutics: A Review

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Abstract: COVID-19 is a disease triggered by SARS-CoV-2 virus that was discovered in Wuhan City, China, in December 2019. Today, this virus has spread over the globe, and is expanding faster in the United States, Brazil, India, and Russia than in China, where the epidemic started. As with other coronaviruses, this may trigger respiratory tract infections in patients with mild to severe illnesses such as pneumonia and acute respiratory distress syndrome. Currently, there are no effective drugs, therapies, or procedures. However, empirical therapy is used to manage and save lives. Furthermore, earlier treatments including chloroquine, hydroxychloroquine, remdesivir, lopinavir/ritonavir, and favipiravir were advised to help fight COVID-19. Additionally, various molecular methods and in silico procedures have been evaluated for virus targeting. The study assessed all alternative medicines, including immunotherapy, cellular therapy, peptides and peptidomimetics, ketone-based covalent inhibitors, adjuvant medicines, multi-target coronavirus protein targets, Mpro inhibitors, the heme oxygenase mechanism, nano-drug, and Chinese medicine. This study concludes that the above drug targets and therapeutics are distinct and function differently in the battle against COVID-19 viruses. Rather than a single antiviral, a mixture of antivirals with distinct modes of action could be more efficient, while not overlooking their adverse effects.

Keywords: COVID-19, Medications, SARS-CoV-2, Treatments, Virus, Antiviral

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Introduction

Coronaviruses are a large family of viruses that affect a wide variety of species and can trigger moderate to extreme respiratory infections in humans. COVID-19, formerly known as the 2019 Novel Coronavirus (2019-nCoV) respiratory disease, is caused by a novel coronavirus, the SARS-CoV-2 virus, which was identified in December 2019 in the Chinese city of Wuhan in the province of Hubei. COVID-19 was formally

named in February 2020 by the World Health Organization (WHO). COVID-19 is a beta coronavirus that can induce anything from a simple/common cold to extreme acute respiratory syndrome (SARS) induced by SARS-CoV, which was identified in 2002, and MERS-CoV (MERS) syndrome, which was identified in 2012. According to the WHO-China Joint Coronavirus Disease 2019 report (COVID-19), this is a zoonotic

virus, and based on existing data, bats seem to be the COVID-19 virus reservoir (El-Din Abu-Rahma *et al.*, 2020; Novikov *et al.*, 2020; Tian *et al.*, 2021).

Virus characteristics and clinical manifestations:

SARS-CoV-2 is in the Nidovirales order and the Coronaviridae family. The family is classified into two subfamilies, Coronavirinae and Torovirinae, with the subfamily Coronavirinae subdivided into four genera: (a) Alpha coronavirus; (b) Beta coronavirus; (c) Gamma coronavirus; and (d) Delta coronavirus. SARS-CoV-2 is a novel Beta coronavirus that infects humans. It is a positive-sense ssRNA virus with an enveloped nucleocapsid. The SARS-CoV-2 genome was phylogenetically analysed and shown to be strongly linked (88 per cent identity) to two bat-derived SARS-like coronaviruses obtained in eastern China in 2018 (bat-SL-CoVZC45 and bat-SL-CoVZXC21) but genetically distinct from SARS-CoV and MERS-CoV. Further evaluation of the SARS-CoV-2, RaTG13, and SARS-CoV genome sequences reported that the virus is more closely linked to BatCoV RaTG13, a bat coronavirus previously observed in *Rhinolophus affinis* from Yunnan Province, with 96.2 per cent of total genome sequence identity. A research discovered that no signs of recombination between SARS-CoV-2 and other bat-borne viruses such as BatCoV RaTG13, SARS-CoV, or SARSr-CoVs was observed in the genome of SARS-CoV-2. Taken together, these observations indicate that bats might have been the virus's initial host (Harapan *et al.*, 2020).

Like other coronaviruses, SARS-CoV-2 contains genetic material within the surface of the spike proteins that assist in the formation of the human cell, accompanied by gene fusion and delivery to the host cell. Latest findings suggest that SARS-CoV-2 spikes, like the virus that caused the 2002 SARS outbreak, bind to ACE2 receptors on the surface of human cells. The novel virus has the potential to trigger respiratory tract infections in patients ranging from mild to fatal, including pneumonia and acute respiratory distress syndrome (ARDS). Numerous patients suffer from

moderate to extreme respiratory problems that resolve with supportive care and do not need further medication. Serious health effects from COVID-19 are more likely to arise in geriatric and comorbid patients with diabetes or coronary artery disease, persistent respiratory syndrome, cancer, or other chronic diseases. After 2-14 days, fever, toxicity, shortness of breath, respiratory problems, excessive chest discomfort or strain, sudden distress or inability to arouse, or blue lips or facial blueness manifest (based on MERS COV virus data). COVID-19 is often linked with behavioural and neurological events in children and adults, including delirium or encephalopathy, turmoil, stroke, meningoencephalitis, impairments in smell and taste perception, fear, depression, and sleeping disturbances. Unfortunately, COVID19 patients reported three distinct types of extra-pulmonary complications: liver damage, fulminant myocarditis, and acute kidney injury (Baig *et al.*, 2020; Das *et al.*, 2020; Aly *et al.*, 2021; Wang and Guan, 2021).

Drug Targets and Potential Treatments:

Due to the high level of similarities between SARS-CoV-2 and SARS-CoV, prior work on SARS antiviral development is extremely beneficial and expedient. SARS-CoV-2 utilizes a spike protein that attaches to its host's ACE2 cell-surface receptor. As the viral RNA attaches to the host ribosome, two polyproteins required for the formation of new mature virions are formed. Each of these polyproteins are cleaved proteolytically by the coronavirus key proteinase (3CLpro) and a papain-like protease (PLpro). Additionally, all CoVs contain an RNA-dependent polymerase RNA (RdRp) that is responsible for replicating the RNA genome. Almost all of these proteins could be used to combat SARS-CoV-2. The potential danger of the virus infecting animal reservoirs and the risk of the virus reappearing from pathogens associated with the epidemic/pandemic CoV necessitate a strong commitment to testing for effective antiviral drugs. In this regard, efforts in medicinal chemistry to develop novel antiviral therapies for

SARS-CoV and MERS-CoV may be extremely beneficial in identifying potential SARS-CoV-2 therapies. One theoretically very promising approach is the synthesis of a broad variety of antivirals directed against massive viral proteases shared by all coronaviruses in order to offer robust and multifaceted therapeutic solutions for some potentially fatal respiratory conditions (Ghosh *et al.*, 2020; Gil *et al.*, 2020; Lotfi *et al.*, 2020; Shagufta and Ahmad, 2021).

The advent of extremely contagious diseases such as COVID-19 necessitates the rapid identification of several therapeutic options. Within a limited time span, reprocessing experiments using computerised drugs can provide therapeutic alternatives. We could complete the drug screening in 4-5 days using an acceptable HVS methodology and sufficient CPUs, GPUs, and other cutting-edge hardware. Given the relatively broad size of the SARS-CoV-2 antagonists, the screening time for other therapeutic objectives with smaller ligands could be even shorter. The discovery of drugs for the treatment of other diseases in order to treat a new disease is a significant benefit of repurposing medicines (Borcherding *et al.*, 2020; Hatada *et al.*, 2020; Sivasankarapillai *et al.*, 2020; Xu *et al.*, 2020; Ojha *et al.*, 2021; Wang and Guan, 2021; Wu *et al.*, 2021).

COVID-19 pathogenesis results in a diverse array of clinical manifestations that are based on specific host and viral responses. As a result, stage-specific interventions can be selected to maximize patient recovery and survival. Early therapeutic approaches should emphasize the virus's or host virus's role in the virus's life cycle. Oftentimes, early methods are intended to preserve the RAS equilibrium by inducing ACE2 signaling (Tripathi *et al.*, 2021).

Therapy:

The medical therapies available for COVID-19 are divided into the following categories: immunotherapy, cellular therapy, antivirals and

other drugs, peptides and peptidomimetics, ketone-based covalent inhibitors, adjuvant drugs, targeting multitarget coronaviral proteins, Mpro inhibitors, heme-heme oxygenase, nanodrug, and Chinese medicine (Klouda and Stone, 2020; Kucukoglu, Faydali and Bul, 2020; Savosina *et al.*, 2021; Shagufta and Ahmad, 2021; Wu *et al.*, 2021).

Cellular therapy:

Mesenchymal stem cells and Natural killer cells:

MSCs can help in the prevention of cytokine storm syndrome, ARDS, and acute lung damage in patients with chronic COVID-19 infections, making them an encouraging treatment option. According to some researchers, NK cells may exhibit antiviral efficacy against SARS-CoV, herpes simplex virus type 1 (HSV-1), cytomegalovirus, and HIV through ADCC mediators. CYNK-001, an allogeneic, commercially available NK cell therapy derived from navel cord blood, was developed in Sorrento and Cellularity as a novel therapy method for COVID-19 therapy and prevention (Kucukoglu *et al.*, 2020).

Immunotherapy:

Immunoglobulins- Intravenous gamma globulin has been commonly used in Singapore to treat patients with SARS, but one-third of critically ill patients have developed venous thromboembolism, including lung embolism (Kucukoglu *et al.*, 2020).

Interferons- As part of the congenital immune response to viral infections, IFN included in Type I IFNs grows very quickly and prevents coronavirus transcription in both animals and humans. Additionally, they help both innate and adaptive immune responses in response to viral infections. IFN- effectively inhibited SARS-CoV replication *in vitro*. Type I interferons in combination with IFN- have also been shown to inhibit SARS-CoV replication *in vitro* (Kucukoglu *et al.*, 2020).

Convalescent plasma therapy- Antiviral antibodies, IgG, IgA, IgM, IgE, and IgD, can be obtained from recovering patients and used effectively to treat

patients with viral infections using convalescent plasma. Additionally, passive immunization of convalescent plasma from individuals with SARS-CoV infection can be beneficial. This therapeutic protocol was evaluated for its feasibility, safety, and clinical efficacy in critically ill MERS patients and was found to possess immunotherapy ability. Similarly, recovering SARS patients were beneficial for convalescent plasma treatment of other SARS patients. If available, convalescent plasma therapy against COVID-19 will normally be used in critically ill patients (Kucukoglu *et al.*, 2020).

Monoclonal antibody- Based on the generation of monoclonal antibodies, the SARS-CoV-2 outbreak can be averted. Numerous experiments have shown that monoclonal antibodies directed against the SARS-CoV spike protein can inhibit the virus's entrance into host cells. Tocilizumab is a monoclonal antibody against the interleukin 6 (IL 6) receptor. This agent can be used against COVID-19 in patients with severe and extensive lung disease who have elevated IL-6 levels. Thus, the viral-induced cytokine storm has the potential to terminate the systemic inflammatory response. Bevacizumab is a humanized monoclonal antibody that inhibits the development of vascular endothelial cells (VEGF). It may decrease the amount of VEGF produced as a result of hypoxia, severe inflammation, and hyper-regulation of the affected respiratory tract. These symptoms can help prevent edema in patients with COVID-19 pneumonia (Fakhouri *et al.*, 2020; Kucukoglu *et al.*, 2020).

Covalent Inhibitors Based on Ketones:

SARS 3CLpro inhibitors with high potency were discovered in two classes: acyloxy methyl ketones and hydroxymethyl ketones. SARS CoV-1 was highly inhibited in 3CLpro and antiviral experiments by hydroxymethyl ketone derivative 4. Additionally, four are excellent candidates for further development as coronavirus therapy due to their adequate solubility, plasma stability, and

low in vitro and in vivo clearance (Hoffman *et al.*, 2020).

Uses of RNA-dependent RNA polymerase (RdRp) inhibitors:

Numerous viruses' diversity is commonly attributed to their rapidly evolving RNA genomes, which allow infection to persist against host cell resistance. The RNA-dependent RNA polymerase is a potent enzyme found within the RNA infection genome that aids in the synthesis of RNA by catalysing the growth of phosphodiester bonds between RNA templates. As a result, RdRp is an important therapeutic target in RNA virus diseases, including SARS-CoV-2. Nucleoside inhibitors (NIs) bind structurally to the RdRp protein in the enzyme active site, while non-nucleoside inhibitors (NNIs) bind to the RdRp protein in allosteric sites. Through testing these inhibitors, more comprehensive guidelines for developing effective anti-RNA drugs can be made, and they may theoretically be used for COVID-19 therapy due to the current public health emergency (Shagufta and Ahmad, 2021; Tian *et al.*, 2021).

Use of peptides and peptidomimetics:

Rapid, successful, and cost-effective solutions are needed. The first line of protection and the lessons learnt from such techniques are repurposing and immunotherapy (including passive and active immunization), all of which aid in the effective design and manufacture of peptide-based therapeutics. Lessons learned from previous coronavirus pandemics, such as SARS-CoV (2003), have been applied to the current pandemic. Comprehensive structural studies of the surface viral spike (S) protein and the host entry receptor ACE2 have been performed in order to develop peptide-based therapeutics. Additional experiments are currently being conducted in animal models and laboratory settings. Due to their improved stability and bioavailability, synthetically modified peptides, peptidomimetics, are extremely radical. At various stages, various

peptidomimetics targeting S-Protein and ACE 2 are being created (Vanpatten *et al.*, 2020).

Adjuvant drug (inhibitors interacting in Neuropilin-1):

Neuropilin-1 (NRP1) is a multifunctional protein found on the cell membrane that has an effect on the physiological functions and conditions of the human body, for which special molecules have been developed over the last two decades to suppress and control certain functions, but are still being developed today. Thus, the role of NRP1 in the infectious COVID-19 process becomes more critical, and by limiting these functions to COVID-19, a disease of less effect on the human body may be created, assisting the immune system and altering COVID-19's natural history as currently understood (Vique-Sánchez, 2021).

Multitarget coronaviral protein blockers:

CoViTris2020 and ChloViD2020, two antioxidant polyhydroxy 1, 3, 4-oxadiazole substances, are the first coronaviral protein blockers of exceptionally high potencies (reach about 65 and 304 times, for CoViTris2020, and 20 and 93 times, for ChloViD2020, more potent than remdesivir and favipiravir, respectively). These two 2,5-disubstituted-1,3,4-oxadiazoles have been computationally screened for their anticoronaviral-2 bioactivities (using a newly developed robust *in vitro* test against COVID-19) and biologically screened for their anticoronaviral-2 bioactivities (Rabie, 2021).

Mpro inhibitors:

For virus replication, structural and non-structural proteins derived from the polyprotein produced by translation of the virus's genomic RNA are required. The main protease (Mpro) converts polyproteins into structural and non-structural proteins. Three antivirals, ritonavir, nelfinavir, and saquinavir, were predicted to be the most potent Mpro inhibitors. Additionally, pralmorelin, iodixanol, and iotrolan were identified through systemic screening. Given the restrictions on iodixanol and iotrolan, structural changes could

result in more stable and healthy antivirals. About twenty molecules interact positively with the Mpro target protein. They are typically classified into four classes depending on the scaffold structure: substituted pyrazoles, cyclic amides, pyrrolidine-based compounds, and a variety of derivatives. These can be used to identify clinically useful therapeutic agents for COVID-19 as possible molecules or as leads for additional drug development (Khan *et al.*, 2018; Alnajjar *et al.*, 2020; Chellapandi and Saranya, 2020; El-Din Abuo-Rahma *et al.*, 2020; Hatada *et al.*, 2020; Joshi *et al.*, 2020; Amin *et al.*, 2021; Kanhed *et al.*, 2021; Shagufta and Ahmad, 2021).

Heme-Heme Oxygenase System inhibitors:

COVID-19 patients with ARDS also have a critical underlying disorder, including pneumonia injury and hemolysis. Heme is a movement of the prothesis that is needed for the operation of a wide variety of hema-proteins, including haemoglobin and cytochromes. However, free heme derived from damage promotes the expression of adhesive molecules, leukocyte activation, vascular permeability, platelet activation, supplementary activation, thrombosis, and fibrosis. The anti-inflammatory enzyme heme oxygenase produces biliverdin/bilirubin, iron/ferrite, and carbon monoxide (HO). As a result, we hypothesise that although free heme contributes to several of the inflammatory phenomena observed in critically ill patients with COVID-19, inducing HO-1 or leveraging heme can provide safety. Not only does HO-activity degrade poisonous heme, but it also has significant anti-oxidant and anti-inflammatory properties for their effector molecules (Wagener *et al.*, 2020).

Nano drugs:

The applications of nano chemistry can be summarized in terms of specific nanomaterials such as (i) polymeric, (ii) self-assembling proteins, (iii) inorganic, and (iv) peptide-based. Additionally, there is considerable interest in biosensors based on NPs, which are critical tools for detecting individuals infected with pathogens.

Conventional methods of diagnosis focus on nucleic acid recognition and have a number of disadvantages, including (i) poor specificity and laborious experimental procedures, (ii) a lengthy time interval between sample collection and data processing, (iii) a high risk of false-negative results, and (iv) a lack of accuracy resulting in incorrect assessments of patients with other viral infections. Certain experiments have shown that nanotechnology-based approaches can inflict significant harm and may also impair lung function at respiratory sites. When it comes to NPs and associated therapies, we must consider four major pathobiological factors: oxidative stress, genotoxicity, inflammation, and fibrosis (Sivasankarapillai *et al.*, 2020).

Pharmacological and clinical therapeutic agents:

Favipiravir:

In 2014, Japan approved favipiravir as an oral antiviral drug for influenza infection (T-705 or Avigan). Additionally, it is used to treat Ebola-related diseases. It inhibits the virus's transcription and replication directly by disintegrating nascent vRNA (viral ribonucleic acid). Additionally, it prevents toxic material from being introduced into the vRNA replication and transcription domains (Sreekanth Reddy and Lai, 2021).

Chloroquine (CQ):

Chloroquine is used for malaria prophylaxis and treatment, but is also used off-label in the treatment of various rheumatic diseases, as well as the prevention of Zika virus infection in extraintestinal amebiasis and chloroquine prophylaxis. According to the US Food and Drug Administration's Emergency Usage Regulations (EUA), the unchanged dose for COVID-19 is 1 g on day one and 500 mg once daily for 4-7 days, based on clinical evaluation. The dosage trend for this medication is 1 g on day one (Klouta and Stone, 2020; Zou *et al.*, 2020).

Hydroxychloroquine (HCQ):

Aminoquinoline is a derivative of hydroxychloroquine (HCQ). The drug is used for the treatment of uncomplicated malaria as well as prophylaxis. This medication is also used for the treatment of rheumatoid arthritis, chronic lupus erythematosus discoides, and systemic lupus erythematosus. In the paediatric age range, developmental idiopathic arthritis, discoid arthritis, and systemic lupus erythematosus are treated. In India and a few other countries, this medication is used to treat COVID 19 patients (Klouta and Stone, 2020; Song and Fields, 2020; Zou *et al.*, 2020).

Combination of HCQ with azithromycin:

22 COVID-19-positive patients were given 600 mg HCQ daily in conjunction with azithromycin, and azithromycin was added to the treatment depending on their clinics. On day 6, a significant reduction in viral load was observed in comparison to controls. They concluded that hydroxychloroquine treatment significantly reduced the viral load in COVID-19 patients and synergized with azithromycin. Researchers are studying the efficacy of this combination in several countries, with or without the use of other drugs.

Remdesivir:

Remdesivir or GS-5734, a drug used to treat Ebola fever and coronavirus infections, was used in the research as an adenosine triphosphate analogue. Remdesivir inhibits the replication of the viral enzyme RNA-dependent RNA polymerase. On 1 May 2020, the Food and Drug Administration (FDA) approved the EUA for emergency care use in COVID-19 patients hospitalized, based on preclinical data and preliminary clinical data on rapid retrieval. When incorporated into embryonic viral RNA chains, this inhibits the viral life cycle at several points, resulting in an early termination in the post-viral process. By incorporating active triphosphate into the viral RNA, interfere with RNA-dependent polymerase and inhibit replication and exoribonuclease

proofreading and function. Clinical findings indicate that positive results with little or no adverse symptoms or deaths have been observed in patients. This treatment has been approved by the US Food and Drug Administration for emergency use of COVID-19 patients and has also been proposed as a new solution by a number of national healthcare organisations (Kouznetsov, 2020; Kucukoglu, *et al.*, 2020; Liang *et al.*, 2020; Reza *et al.*, 2020).

Lopinavir-ritonavir:

Abbott commercialized this combination in 2000 under the brand name Kaletra; both lopinavir and low-dose ritonavir inhibitors are antiretroviral proteases that work synergistically to treat HIV infection. Ritonavir blocks the metabolism of lopinavir, prolonging its half-life and antiviral effectiveness. The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend ritonavir-boosted combination therapies as first-line treatment for HCV genotype 1a/b and four therapy-naïve patients with or without cirrhosis (Magro, 2020).

Ribavirin:

Initially approved for the treatment of acute respiratory syncytial virus (RSV) infection in children, ribavirin is a Guanosine precursor discovered in 1972 by Witkowski and colleagues. It has a broad spectrum of anti-RNA/DNA viral activity and is used to deter infection from viruses such as Lassa fever, influenza A, influenza B, and others. It was later tested for hepatitis C virus infections and found to be effective in the treatment of chronic hepatitis C infections when combined with interferon-alpha. It functions by incorporating and inhibiting viral RNA, resulting in viral genome mutations and inhibiting normal viral replication. Additionally, the activity of RNA-dependent polymerase is inhibited (Magro, 2020).

Danoprevir:

Danoprevir is an inhibitor of HCV N53 protease approved in China for non-cirrhotic genotype 1b,

in combination with other medications (Magro, 2020).

Arbidol:

Arbidol is an antiviral agent derived from an indole derivative that has been approved for the prophylaxis and treatment of influenza and other viral respiratory infections in Russia and China. This drug prevents the virus from fusing with the cell membrane, which is a necessary step in cell entry. Additionally, it inhibits hepatitis virus entry and replication *in vitro*. Arbidol and its mesylate arbidol showed antiviral activity against SARS-CoV by inhibiting virus replication in cell cultures. Arbidol has been tested alone or in combination with other COVID-19 antivirals, and several beneficial effects have been discovered (Magro, 2020).

Neuraminidase inhibitors:

Oseltamivir, zanamivir, and peramivir are antivirals that block the release of viral particles from the hosts and suppress the viral neuraminidase enzyme. These compounds are prescribed for influenza as neuraminidase inhibitors. Inhibitors of neuraminidase are used in MERS-CoV infection as an observational therapy. Also, oseltamivir has been published for use with or without COVID-19 antibiotics and corticosteroids on covid patients (Magro, 2020).

Anti-cancer drug:

A number of non-cancer drugs, as well as antiviral and anti-inflammatory medications, can potentially be reused in the treatment of COVID 19. These agents are currently being investigated for their ability to blunt the hyper-inflammatory response induced by COVID-19. With cytotoxic agents such as etoposides and methotrexate, or immune modulators such as BTK inhibitors or imatinib, there is a chance of destroying the humoral and cellular immune systems, thus leading to secondary infections and complications. The recent research compared the differential susceptibilities of cancer patients and found that patients with haematological malignancies have

an increased infectious resistance compared to patients with strong malignancies. Future clinical trials, either single-arm or randomised controlled trials, would be beneficial in determining the effectiveness of anti-cancer medications in COVID-19 patients (Borcherding *et al.*, 2020).

Chinese medicine:

In the area of COVID 19 disease prevention and treatment, active compounds found in Chinese medicines such as glycyrrhizin, hesperetin, baicalin, and quercetin are considered critical. *In vitro* inhibitors of SARS virus transcription can include glycyrrhizin, the active ingredient in liquorice roots used in Chinese medicine. Recently, it was discovered that glycyrrhizin binds to the ACE2 receptor. It has been shown to be clinically successful against the SARS virus in clinical trials using large doses of glycyrrhizin. Additionally, glycyrrhizin can inhibit the transcription of the SRAS-associated virus *in vitro*.

Other drugs:

In addition to these medicines, Ivermectin and Nitazoxanide have also been found to be promising medicines to treat patients with COVID-19 (Magro, 2020).

Therapeutic pathways to mitigate inflammatory responses triggered by SARS-CoV-2:

Potential therapeutic strategies for reducing the inflammatory responses induced by SARS-CoV-2 include FcR inactivation. At the moment, there is no specific SARS-CoV-2 treatment available. As a result, it is important to identify successful antiviral agents to combat the virus. A fascinating target for drug design is the coronavirus (CoV) main protease (Mpro, also known as 3CLpro), which plays a critical role in viral replication and transcription. SARS-CoV-2, a newly discovered virus that induces fatal inflammatory responses and acute lung injury, is reportedly untreatable with antiviral medication. Numerous SARS-CoV-mediated inflammation pathways exist, based on correlations in the inflammatory responses to COVID-19 and SARS-CoV (Butowt *et al.*, 2020; Lee

and Choi, 2021)

This RNA virus exhibits a strong affinity for porphyrins. The cell invades the enzyme-2 (ACE-2) receptor transforming angiotensin and binds to hemoproteins, resulting in a severe systemic inflammatory response, most notably in areas with elevated ACE-2 levels, such as the heart, lungs, and kidneys, and ultimately systemic disease. The inflammatory response manifested by increased cytokine levels and reactive oxygen species inhibits heme oxygenase (HO-1), resulting in the loss of subsequent cytoprotection. Some infectious diseases, such as HIV, Ebola, SARS/MERS, and human immunodeficiency virus have shown this phenomenon. Numerous medications of early scientific potential have been studied. Patient obesity, a chronic infectious condition characterized by a simple cytokine overload, is disproportionately impacted by this disease. Cytochrome P450 (CYP) enzymes (primarily CYP2D6) are responsible for the metabolism of the most commonly used COVID-19 medications. Genetic polymorphisms in CYP2D6, HO-1, ACE, and ACE-2 further complicate matters. Upregulation of HO-1 can aid in the treatment/prevention of cytokine storms. Currently, care should focus on increasing heme oxygenase activity and administering antiviral drugs. That will be the last silver bullet for vaccine production (Tripathi *et al.*, 2021).

In addition to these medications, there are also encouraging findings in unregulated trials of several other biologic, chemical and conventional medicines.

This study concludes that the above-mentioned medication objective and alternative therapies have various effects in combating COVID-19. However, the use of single drugs might not be effective enough to contain this lethal virus; thus, it may be more efficient to use combined antivirals with various mechanisms of action, while not underestimating their adverse effects. Further clinical trials should urgently be carried out to evaluate the promising pharmacotherapy

agents and to determine the best way to prevent the spread of this infection and to lessen the risks of the next disease epidemic.

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