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# 1. Therapeutic Management for Covid-19: A Pandemic Disease

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## 1.1 Introduction:

The world has seen the onset of a pandemic of a new infectious disease from December 2019. This has been formally named as the Corona Virus Infectious Disease (COVID)-19 by a consensus group of WHO experts. Numerous clusters of patients started to surface in Wuhan, Hubei Province, China in mid-December 2019. They presented with features of a viral respiratory illness with complaints off ever, cough, headache and breathlessness. Some of the patients had evidence of respiratory failure, shock, acute respiratory distress syndrome (ARDS) and sepsis. The current global pandemic due to the highly contagious COVID-19 infection is rapidly spreading in many countries with a high number of deaths. Many communities and countries have enforced restrictions, permitting only essential activities. Health systems around the globe are currently preparing to manage the surge of the influx of critically ill patients. During this phase, care providers, administrators, and policymakers work in concert to understand and combat this deadly pandemic. The current knowledge about COVID-19 is limited but rapidly evolving. During this outbreak, the medical community used evidence gleaned from past outbreaks of SARS-CoV and MERS-CoV to predictCOVID-19's behavior, clinical presentation and treatment. In addition, corona viruses are known to cause signs and symptoms of multi-organ system damage, many of which are subtle and can go unnoticed by trained medical professionals.

Furthermore, frontline healthcare personnel lack a comprehensive review of the numerous clinical pulmonary and extra-pulmonary manifestations of deadly corona viruses making self-education time consuming. SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2 is a newly emerging human infectious corona virus, originated in Wuhan, China, and has been spreading rapidly in China and other countries since December 2019.

The World Health Organization (WHO) also declared a global emergency on January 31st due to increasing concerns over its fast spread, and on March 11th the disease was recognized as a pandemic. Since the bases for pathogenesis of this virus and its proliferation is unclear, there is still no vaccine or definitive treatment against it. Thus, medications used against SARS-CoV-2 are mainly based on their effectiveness on earlier strains of corona virus, SARS-CoV and MERS-CoV. Therefore, the immediate introduction of potential COVID-19 treatments can be essential and salvaging. In this article, new potential COVID-19 therapies are briefly reviewed.

### 1.1.1 Prevention of COVID-19 Entry and Its Transmission:

WHO Director General constitutes a Public Health Emergency of International Concern for the outbreak of COVID-19, recommends the options to prevent the disease in new areas and possible reduction in human-to-human transmission to curtail its further spread that can be achieved by the strict quarantine, which involves the movement restriction or separation from the rest of the population with sustained and intense hygiene measures.

Avoiding mass gatherings in enclosed spaces, maintaining the distance of at least 1 meter from any person with respiratory symptoms (e.g., coughing, sneezing); wearing a medical mask for an adequate level of protection combined with hand hygiene frequently by using an alcohol-based hand rub or soap is recommended.

The people who develop respiratory complications during quarantine period should be specially treated and managed as a suspected case of COVID-19 and further tests should be required to confirm whether positive or negative. The front-line healthcare personnel must use the personal protective equipment (PPE) includes N95 or FFP2 standard masks, gowns, gloves, eye protection shields to protect themselves, patients, and others when providing the care.

### 1.1.2 Diagnostic Criteria:

The viral research institution in China has conducted preliminary identification of the SARS-CoV-2 through the classical Koch's postulates and observing its morphology through electron microscopy. So far, the golden clinical diagnosis method of COVID-19 is nucleic acid detection in the nasal and throat swab sampling or other respiratory tract samplings by real-time PCR and further confirmed by next-generation sequencing.

### 1.1.3 Rapid Diagnostic Tests:

In 2nd or 3rd week of illness, various antibodies have been detected in the convalescent serum of the donors. Serological assays to detection of SARS-CoV-2 are in the process of development. They need to undergo clinical trials and the regulatory review process. These assays will help to understand the epidemiology of the disease and detection of asymptomatic infection in a given population. Rapid diagnostic test kits have been recently developed in 4-6 weeks' time. They can detect the SARS-CoV-2 in few hours and can be used as screening tests in certain hot-spot areas of the epidemic. Various commercial and research labs like Bosch and Abbott have launched the rapid diagnostic tests.

These molecular cartridge-based assays have an accuracy of 95% for detection of infection (nasal/throat swabs) and meet various quality control standards as per WHO. They can be used at various points of patient care and no transportation of samples is required. However, the test results by these rapid diagnostic kits need to be confirmed by RT-PCR for SARS-CoV-2.

## 1.2 The Current Update and Possible Treatment Options for Management of Covid-19:

### 1.2.1 Renin Angiotensin System (RAS) Inhibitors in SARS-CoV-2 Patients:

RAS and ACE2 inhibitors are widely used in treating patients with hypertension. As described earlier ACE2 is the target receptor for SARSCoV-2 and is highly expressed in epithelial cells in the oral mucosa. Additionally, this protein is widely expressed in immune reactive cells such as macrophages, lungs, blood vessels and intestine. Clinical findings suggest that circulating ACE2 levels were significantly increased in diabetic and cardiovascular patients; however, this protein is aberrantly expressed with ACE inhibitors Lisinopril alone. But the ACE2 activity is not altered correspondingly, while cardiacACE2 mRNA expression was increased with RAS receptor inhibitor Losartan. Combination of Losartan and Lisinopril did not affect theACE2 activity compared with Losartan alone, but on other side, ACE2mRNA was highly expressed with Losartan alone. Thus, there is a lack of correlation between up and down expression of ACE2 mRNA with ACE2 activity. However, there is a debate on the use of RAS and ACE inhibitors in SARS-CoV-2 pneumonia infections and few clinical trials are going on for the usage of Losartan among patients who have not previously administered with RAS inhibitors and are either hospitalized or not hospitalized. The selective ACE2 inhibitor DX600 might show beneficial results inSARS-CoV-2 infections; however, its clinical significance in COVID19has not evaluated. Further, in one promising study, circulating recombinant human soluble ACE2 protein upon intravenous administration produced significant blockade of initial stages of SARS-CoV-2viral entry and infections by preventing the binding of viral spike protein onto cell host cell surface ACE2 receptors.

### 1.2.2 Anti-Malarial Drugs Inhibit the SARS-CoV-2 Infections:

Chloroquine and Hydroxychloroquine are the class of Quinoline derivatives and widely used to treat malaria caused by *Plasmodiumvivax, P. malaria*, and *P. ovule*. It is the active constituent of the bark of Cinchona (*Cinchona of ficinalis*) plant. Apart from malaria, Chloroquine and Hydroxychloroquine can be used to treat amoebiasis and other autoimmune disorders such as rheumatoid arthritis and lupus erythematosus syndrome. Chloroquine and its derivative Hydroxychloroquine inhibit the hem polymerase in malarial trophozoites, resisting the conversion of heme to hemozoin. Plasmodium species continue to accumulate toxic heme, killing the parasite and exhibits anti-malarial activity. Whereas the antiviral activity of Chloroquine is exerted by diffusing into the host cells and accumulating in endosomes, lysosomes and Galgi complexes, where it is converted into protonated form, then this moiety is deposited in organelles and further involve in raising the surrounding pHs The raised pH in endosomes and lysosomes prevent viral fusion and inhibits the viral entry by endocytosis into the cells.

ACE2 is the target receptor for SARS-CoV and SARS-CoV-2 for viral fusion, however, Chloroquine does not affect the ACE2 levels but down regulated the terminal glycosylation of ACE2. Insufficient glycosylation of ACE2 offers inefficiency to bind with SARS-CoV-2 viral spike proteins and inhibits viral fusion. In the field of nano medicine, Chloroquine/Hydroxychloroquine has been used extensively to understand the mechanism of nano particles uptake into cells. It was used as inhibitor of nano particles uptake via endocytosis pathway. Similar kind of viral particle entry through endocytosis route is proposed to be inhibited by Chloroquine. The combination of Chloroquine or its derivative Hydroxychloroquine with drugs like Remdesivir or Azithromycin demonstrated to produce beneficial effects against this novel virus. However, its use in SARS-CoV-2 therapy has not been approved by US FDA and there are multiple clinical trials going on to evaluate the efficacy of Chloroquine/Hydroxychloroquine. Apart from therapeutic benefits, Chloroquine exerts various side effects such as fever, chills, loss of appetite, blurred vision and insomnia. Additionally, few reports indicated that Chloroquine exerts proarrhythmic effects by increasing the QT interval in the ECG patterns and decreasing the heart rate.

This drug cannot be indicated for the patients who suffer from retinopathy and porphyries. Based on the promising evidences, Chloroquine may become suitable drug for SARS-CoV-2 disease. Further, to improve the efficacy, Hydroxychloroquine may be used in place of Chloroquine.

There were reports suggested the superior antiviral effects of Hydroxychloroquine compared to Chloroquine with better safety profiles. Further, the combinational approach along with other antiviral drugs may be designed to evaluate the efficacy. Other anti-malarial drugs such as Artesunate and Artemisone found to be effective against human cytomegalo viruses, but effect of these compounds on SARS-CoV-2 needs to be evaluated.

Moreover, the severe inflammatory cytokine storm observed in multiple organs may be curtailed by Chloroquine due to its immuneomodulatory effects.

### 1.2.3 Antibacterial and Anthelmintic Drugs:

Azithromycin is a renowned antibacterial drug belongs to the class of microcline antibiotics. It shows antibacterial activity by binding to bacterial 50s ribosomal subunit and represses the protein synthesis. It is commonly used in the treatment of pneumonia, sinusitis, Lyme disease, skin infections and sexually transmitted diseases. Apart from antibacterial activity, Azithromycin has antiviral activity observed in bronchial epithelial cells infected with rhinovirus, where it increased the production of interferon-stimulated genes. Additionally, its anti-viral activity was reported against Zika virus in human glialcells, where it prevented the virus induced alterations in fetal brain. Also, the combination of Hydroxychloroquine and Azithromycin was found to be effective in SARS-CoV-2 associated pneumonia, where this combination significantly decreased the virus load and involved in the elimination of virus. Energetic based modeling suggests that this drug combination might show the effect on SARS-CoV-2 spike-ACE2complex. Recently Pfizer has reported the necessary data of Azithromycin for SARS-CoV-2 clinical trials. Another anti-biotic and anti-tuberculosis drug Carrimycin being tested to treat theSARS-CoV-2 patients, currently, it is under clinical trials, however, its safety and efficacy need to be established in COVID-19 patients.

The fluoroquinolone antibacterial drug Ciprofloxacin is used to treat respiratory tract infections. Apart from its antibacterial activity, it can reduce the replication of polyoma BK virus. Ciprofloxacin reduced the viral load with $IC_{50}$ value (50% virus inhibitory concentration) of 216.67 ± 16.7 µg/ml, whereas, Coumermyc in showed the $IC_{50}$ value of 10.6 ± 3.9 µg/ml. The amino glycoside antibiotics including Neomycin, Kasugamycin, and Streptomycin inhibited herpes simplex, influenza A and Zika virus replication by up regulating the interferon stimulated genes (ISGs). The polyether antibiotic CP-44161 is recommended to treat varicella-zoster virus infections and also it inhibited the proliferation of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). However, these antibiotics were not tested onSARS-CoV-2.The US-FDA approved anthelmintic drug Niclosamide is also explored as an anticancer, antibacterial and antiviral agent. Also, it was found to be effective as a protease inhibitor in shedding the SARS-CoV and MERS-CoV replication and viral antigen synthesis was suppressed by Niclosamide at 1.56 µ M. It might be a good pharmacological agent to treat SARS-CoV-2 infections as well and studies may be designed to evaluate the same in vitro and clinical conditions.

The FDA approved ant parasitic drug Ivermectin is widely used as an essential medicine to treat lymphatic filariasis, strongyloidiasis, ascariasis, head lice, scabies, and river blindness etc. Ivermectin was tested for its repurposing anti-viral activity against SARS-CoV-2, where it has own excellent antiviral activity. The in vitro results suggest that Ivermect in reduced viral RNA load>5000 fold with 5 µ M concentration at 48 h. It might be a good repurposing drug in treatingSARS-CoV-2 infections and further studies are required for this specific use.

### 1.2.4 Antiviral Drugs:

An American biotechnology company Gilead Sciences developed the antiviral drug Remdesivir (GS-5734) against Ebola virus. Remdesivir exerts broad-spectrum antiviral activity and showed beneficial results in SARS-CoV and MERS-CoV induced respiratory infections. It has been recommended to administer to SARS-CoV-2 infected patients in United States of America, Europe, and Japan, where physicians found the beneficial results. But it is not yet approved by the drug regulators for treating the patients who are suffering from SARS-CoV-2.Remdesivir is a pro drug and is metabolized to its active form GS-441524, which is a nucleotide analogue inhibitor of RNA-dependent RNA polymerases. It interferes with the viral RNA polymerase activity and further inhibits the viral exoribonuclease involved in proofreading and ultimately causes the deprivation of viral RNA production. Remdesivir was tested in clinical isolates of SARS-CoV-2*in vitro*, where it exhibited significant antiviral activity. Further, it was also tested in combination with Chloroquine and found to be effective against COVID-19.

However, the data available is limited on Remdesivir and further studies need to be conducted to prove its essential role in treating COVID-19 along with its drug-drug interactions and contraindications. Oseltamivir is recommended to treat and prevention of Influenza A and Influenza B viruses. It belongs to the class of neuraminidase inhibitors and acts as a competitive inhibitor of neuraminidase enzyme present in influenza virus and prevents the respiratory tract infections. This enzyme involved in the cleavage of the silica acid which is an important component of glycoprotein's presents on the surface of human cells and helps new visions to exit the cells.

The therapeutic potential of Oseltamivir on SARS-CoV-2 infections needs to be evaluated. Few of the combinational drugs such as ASC09F and Ritonavirare being evaluated together with Oseltamivir, these are under the clinical trials now. Corona viruses are associated with different types of proteases such as main protease (Mpro) also known as three chymotryps in-like protease(3CLpro), papa in-like proteases (PL pro) and transmembrane protease, serine 2 (TMPRSS2). Mpro involved in viral replication and plays a pivotal role in processing the polyproteins, which are translated from its RNA. Among all, pyridine-containing α-ketoamide compound 13b inhibited the SARS-CoV-2 Mpro with IC50 value of$0.67 \pm 0.18$ μ M and showed improved safety and lung tropism as well as suitable for inhalational route of administration. In another hand, the virtual screening for approved drugs using 3D model of SARS-CoV-2 Mpro with the help of the crystal structure of SARS-CoV, which is having almost 96% similarity. They proposed and considered nearly 16 candidates and among Ledipasvirand Velpatasvir are attractive and might be effective in treating COVID-19 with minimal side effects. Apart from these, Remdesivir, Saquinavir and Darunavir, as well as flavones and coumarone derivatives were found to be effective againstSARS-CoV-2 Mpro.

Another SARS-CoV-2 protease PL pro plays an important role in viral replication and survival, which mainly involved in cleaving the viral polyproteins, compounds isolated from Alpinia officinarum and ginger having SARSCoV-2 PL pro inhibitory activity confirmed by molecular docking studies. Also, virtual docking studies support that Chloroquine and form sterol also found to be effective against SARS-CoV-2 PL pro. In contrast to others, Bagherzadeh et al. proposed that dual protease Mproand PL pro inhibitors Valaganciclovir, Nelfinavir, Merimepodib, Remdesivir, Inarigivir, Taribavirine and TAS106-106 are suitable inCOVID-19 therapy, among all Remdesivir and Inarigivir showed highest binding affinity. Cam stat maculate is TMPRSS2 inhibitor, is involved in proteolysis processing of spike proteins and it suppressed theSARS-2-S-driven fusion into Caco-2 and Vero-TMPRSS2 cells and might be effective in COVID-19 therapy. Other protease inhibitors include Lopinavir and Ritonavir were found to be effective in SARS-CoV infections and also these drugs are currently under the clinical trials for testing the efficacy and safety against SARS-CoV-2. Investigators performed an open-label randomized trial at Wuhan hospital, China.

They have given the treatment to adult SARS-CoV-2 patients with oral Lopinavir and Ritonavir (400and100 mg, respectively) twice daily for 14 days. They found that Lopinavirand Ritonavir combination was significantly effective againstSARS-CoV-2. However, further studies are needed to draw a clearconclusion on the usage of the combination of Lopinavir and Ritonavirin SARS-CoV-2.

The nucleoside analogue Ribavirin has extensive activity against DNA and RNA viruses and it is used to treat SARS-CoV patients. The exact antiviral mechanism of Ribavirin has been studied for decades and it is still unclear. Ribavirin usage is associated the major side effect of anemia which is found in 27-59% of patients. The importance of Ribavirin for fighting against SARS-CoV-2 was evaluated in combination with protease inhibitors and corticosteroids. This drug has been showing significant results with so fosbuvir and this combination is under the clinical trials (NCT01497366).The nucleotide analogue Sofosbuvir is used to treat hepatitis C and it is recommended in combination with Ribavirin, Velpatasvir, and Voxilaprevir.

Molecular docking studies of RNA dependent RNA polymerase model suggest that Sofosbuvir in combination with Ribavirin and Remdesivir could exhibit possible therapeutic effects in SARSCoV-2. Basically, Sofosbuvir is a pro drug, which converts into active metabolite GS-461203 (2′-deoxy-2′-α-fluoro-β-C-methyluridine-5′-triphosphate) and serve as a defective substrate for the non-structural protein 5B (NS5B) of RNA dependent RNA polymerase and further inhibits RNA synthesis.

Sofosbuvir and other combinations will be tested in the view of adverse effects such as purities, upper respiratory tract infections, and lymphopenia. The short-term anticoagulant, antiviral and antibacterial drug Nafamost maculate inhibits Spike protein induced membrane fusion in MERS-CoV and also researchers suggested that using Nafamost at alone or with combination of antiviral drugs could be a safe approach in treating COVID-19.

### 1.2.5 Effect of Interferon's on SARS-Cov-2:

The 166 amino acid sequence of Interferon alfacon-1 is produced by recombinant DNA technology, which is the class of non-naturally occurring type-I interferon. Interferon alfacon-1 acts as anticancer and antiviral agent. The therapeutic effect of Interferon alfacon-1 was observed in leukemia, melanoma, HIV/AIDS related Kaposi's sarcoma, and hepatitis C. It is also found to be effective in SARS-CoV and also tested in SARS-CoV-2 in combination with corticosteroids. Interferon alfacon-1 shows antiviral activity by binding to interferon receptors type 1 including IFNAR1 and IFNAR2c. Further, it initiates the demonization and activates the Janus kinas 1 (Jak1) and tyrosine kinas 2 (Tyk2) phosphorylation.

The signal transducers and activators of transcription 1 and 2 (STAT1 and STAT2) bind to the phosphorylated IFNAR and initiate the expression of immuneomodulatory and antiviral protein expression including protein kinas R (PKR) and 2′-5′ oligoadenylate syntheses (2′-5′ OAS). Additional clinical studies are required to approve this drug for SARSCoV-2 therapy.

There are multiple reports on the antiviral activity of IFN-α and IFN-β, and combinations of IFN-α/β, IFN-β 1a and IFN-γ against SARS-CoV and these agents might be also effective againstSARS-CoV-2 too, which need to be evaluated in suitable studies.

## 1.3 Therapeutic Importance's of Amniotic Fluid Cells and Convalescent Plasma in SARS-CoV-2 ARDS Infections:

Amniotic fluid cells are the possible source of stem cells for clinical purposes such as fetal therapies and regenerative medicine, where they proliferate rapidly can differentiate into different cells. The human amniotic fluid is approved by US-FDA for tissue injury and also used to treat inflammatory and fibrotic diseases. The researchers from the University of Utah tested the nebulizer and/or intravenous purified amniotic fluid in SARS-CoV-2 patients, where it reduced the respiratory inflammatory responses observed with this novel pandemic virus. Recently they received the approvals from regulatory bodies to perform the clinical trials (NCT04319731).

### 1.3.1 Monoclonal Antibodies to Treat SARS-CoV-2 Infection:

Monoclonal antibodies are currently used for diagnostic and therapeutic purposes. Various monoclonal antibodies are approved by USFDA to treat cancer and autoimmune disorders. Additionally, few of monoclonal antibodies are tried to treat SARS-CoV-2 infections such as Bevacizumab (NCT04305106), Tocilizumab (NCT04317092), and Meplazumab (NCT04275245) etc. The SARS-CoV- specific human monoclonal antibody, CR 3022, which has the ability to bind with SARS-CoV-2 RBD (KD of 6.3 n M). CR3022epitope was not overlapped with the ACE2 binding site within SARSCoV-2 RBD. This novel monoclonal antibody might be effective clinically for treating SARS-CoV-2 associated pneumonia. Human-to-human transmission of SARS-CoV-2 is possible due to interaction of spike protein with human ACE2; thus, spike protein is the main target for antibody-mediated neutralization. Various neutralizing monoclonal antibodies are tested against SARS-CoV including 80R, CR 3014, CR3022, m396, B1, 201, 68, 1F8, and 5E9, these antibodies might play an important therapeutic role in SARS-CoV-2 infections. Collectively, spike proteins, ACE2 and their interactions are the main targets for developing new therapeutic monoclonal antibodies for treating SARS-CoV-2 infections.

Tocilizumab is used in autoimmune diseases such as rheumatoid arthritis and multiple myeloma and it is a human recombinant IL-6receptor (IL-6R) antibody. It is associated with major side effects such as allergy, liver toxicity and hyperlipidaemia. IL-6 is involved in the activation of various immunological and inflammatory mediators, which are responsible for respiratory collapse observed inSARS-CoV-2 infected patients. Tocilizumab is under phase II clinical trials and tested for SARS-CoV-2 induced pneumonia (NCT04317092).Another IL-6R monoclonal antibody Sarilumab is under clinical trials for SARS-CoV-2 (NCT04315298). It is widely used in the treatment of rheumatoid arthritis and it suppresses the IL6R mediated inflammation.

Cytokine storm is responsible for the pneumonia condition in SARS-CoV-2 infected patients. Clinical trials on Sarilumab and Remdesivir have been initiated to test the therapeutic efficacy against SARS-CoV-2. The potential therapeutic role of Sarilumab in COVID-19 need to be further confirmed in clinical conditions.

### 1.3.2 Natural Products and Dietary Supplements:

Our diet contains a lot of vitamins, minerals, carbohydrates, proteins, fats, and lipids and they play an important role in maintaining the homeostasis in our body and play important role in maintaining the immunity. Additionally, our diet contains various biological active natural products and they exert multiple pharmacological properties such as anticancer, antioxidant, anti-inflammatory, anti-diabetic, antibacterial, antiviral and antifungal properties etc. The battery of pro inflammatory cytokines is responsible for the cytokine storm, which is involved in manifestation of severe acute lung injury this is the main cause for SARS-CoV-2 induced morbidity and mortality. The active constituent of turmeric, Cur cumin exhibits wider pharmacological activities such as anti-bacterial, antiviral, anticancer, anti-diabetic properties. Cur cumin inhibited pro-inflammatory cytokines IL-1β, IL-6, and TNF-α level and suppressed the cytokine storm in Ebola virus infected experimental models.

Additionally, Cur cumin also inhibited the SARS-CoV replication and the effective concentration ($EC_{50}$ value) was found to be around 10μ M and also acted as a protease inhibitor. Thus, it might be effective against SARS-CoV-2 infections, where intravenous (I.V.) route of administration in suitable formulation form may enhance the better bioavailability. Similarly, a thorough search across all the natural products needs to be evaluated for their direct antiviral effects and their potential role in controlling severe inflammatory responses observed in COVID-19 induced pneumonia.

The Indian traditional plant Neem (Azadirachta indica) and its parts such as leaves, seeds, flowers, barks and routes are widely using in various diseases. Ancient people believe that it is a Sarva roga nivarini (the cure for all diseases). Methanolic extract of neem leaves exhibited antiviral activity against HSV-1 infections by glycoprotein mediated viral fusion. Nimbolide is an active constituent of Neem tree explored as a pharmacological modulator in treating various diseases such as cancer, diabetes, and inflammatory diseases. TNF-α is apheliotropic cytokine involved in activation of various signaling cascade and this cytokine might be playing role in respiratory failure associated with COVID-19 mediated pneumonia. Nimbolide is found to be TNF-α inhibitor and also suppresses the nuclear translocation of p65 NF-κ Band HDAC-3 and inhibited the cytokine storm observed in ARDS experimental model. Thus, it might show beneficial effects in SARSCoV-2 infections by direct antiviral activity or indirect supportive therapy by controlling the inflammatory cytokine storm. This natural product may have clinical significance in inflammation associated with viral diseases.

The other natural product with a ferine A is isolated from Ashwagandha (With ania somnifera) and widely used to treat various diseases such as cancer, fibrosis, and inflammatory disorders. It has shown the antiviral activity against Herpes Simplex virus 1 and 2, which may show plausible effects against COVID-19.Andrographolide is a diterpenoid isolated from Andrographis paniculata, which has been employed in treating various diseases such as cancer and inflammatory diseases. Apart from anti-inflammatory activity, andrographolide exhibits immuneomodulatory effect by increasing the level of cytotoxic T-cells, NK cells, phagocyte cells.

### 1.3.3 Vaccines for Corona Viruses:

The epidemics of SARS (2003), MERS (2012) and the recent SARS-2 (2019) has generated a lot of interest in the preventive strategies like the drug chemoprophylaxis for health care individuals and close contacts of index patients of the COVID-19. The role of drugs has been discussed in a separate section. After the SARS epidemic in 2003, various researchers all over world got in the effort of developing a candidate vaccine for the same. There are about 43 vaccines that have been developed. However, most of them are in the pre-clinical phase. They are yet to undergo phase 1 randomized trials in humans.

These vaccines are DNA, inactivated, live attenuated vaccines (LAV), viral vector based (non-replicating) protein sub-unit vaccines and other 6 unknown vaccine types.37 One of the RNA based vaccines (LNP-encapsulated mRNA) has been made available for the phase 1 clinical trial in humans. This vaccine has been developed by collaborative effort of scientists at NIAID/NIH and a biotechnology company (Moderna Therapeutics) in USA.

The clinical trial began in mid-March 2020 and has already enrolled few patients in Seattle, USA (NCT04283461). It will study the efficacy and adverse reactions of the candidate vaccine in 45 adult volunteers from 18 to 55 years of age. Another vaccine that has gone in phase 1 clinical trial is a non-replicating viral vector vaccine (ChiCTR2000030906). It has been bioengineered by using an adenovirus vector (type 5) at Beijing Institute of Biotechnology and Can Sino Biological Inc. It uses the same platform as was used for developing a vaccine for Ebola virus. However, this is just the beginning and it will take 12-18 months for the trial to complete and have the data to interpret for antibody response and long-term efficacy.

### 1.3.4 Host Immune Responses:

An understanding of the various host cell immune responses evoked by the corona viruses may help us to develop effective drugs and vaccines for this infection. Various researchers have studied the T-cell immune response to SARS-CoV in the past. Recently with the evolution of the SARS-CoV-2 or COVID-19 epidemic in China a resurgence of interest in the immune mechanisms has been generated. An innate immune response evoked by the macrophage activation leads to a T-cell mediated response. The macrophages present CoV antigens to the T-cell subsets (Th 17) which lead to a massive release of various cytokines like IL-1, IL-6, IL-8, IL-21, TNF-b and MCP-1. This is responsible for the immune amplification. These cytokines and chemokines are responsible for recruitment of lymphocytes and other leukocytes to the site of inflammation. This immune amplification is partly responsible for the tissue damage in the respiratory alveoli, bronchioles, pulmonary interstitial walls etc. The increased expression of the inflammatory mediators has a down regulatory effect on NK cells and CD8 cells, which are important for the lymphocytes to clear the virus. Binding of the S-protein to various host cell receptors like ACE2 and DPP4R enables the viral RNA to gain entry in the host cell cytoplasm. Various toll like receptors (TLR) like TLR-3, TLR-4 are important to either evade the immune response or recognition of S-protein. The S-protein recognition leads to activation of pro-inflammatory cytokines.

### 1.3.5 Conclusion:

The current COVID-19 pandemic is the third major global illness due to a novel corona virus. Understanding COVID-19 along with the other known novel corona viruses places the newest corona virus in context. We presented the similarities and differences in pathogenesis, manifestations, and outcomes with respect to a spectrum of extra-pulmonary organ systems. Increasing knowledge about COVID-19literature will aid in earlier recognition and more effective therapy. Corona virus infections have led to few epidemics and a new pandemic in last 2 decades. The infections vary in clinical manifestations from self-limiting viral respiratory tract infections or gastroenteritis to severe form like the SARS-CoV-1, MERS and the recent SARS-CoV-2 infections. These have led to a significant morbidity and mortality and a global economic crisis. Newer developments in therapeutics, preventive therapy in the form of chemoprophylaxis and vaccines are underway. Newer information about the molecular mechanisms, clinical manifestations, epidemiological pattern and preventive public measures is available each week in all the scientific or medical journals. In addition, lot of input is being provided by electronic and print media for public awareness.

Only few articles published in the initial phase of COVID-19epidemic have been cited to maintain brevity of the article. It will not be appropriate if a little note is not made about the unsung heroes of this pandemic. The world's 'new heroes' are the medical workers. The doctors, nurses, paramedical staff and other healthcare workers who are directly or indirectly involved with patient care in isolation wards and critical care areas. They risk their own lives, knowing that there are no effective drugs or vaccines available at present.

### 1.3.6 Future Perspective:

Over the past 50 years, in the pre-SARS era, many different CoV shave been identified that caused a wide variety of human and veterinary diseases. In particular, the human CoV were found to cause mild respiratory diseases. In November 2002, SARS-CoV infection was emerged in Guangdong Province of China, identified to be fatal resulting in ARDS, which became a pandemic in 37 countries with over8000 reported cases and 800 deaths. This deadly SARS virus was found to be originated from horseshoe bats that transmitted to pangolins before reaching humans. At that time no specific drugs or vaccines were available and only preventive measures were implemented to limit the transmission rate by maintaining social distance, quarantine, travel restrictions, patient isolation. In 2012, another zoon tic CoV were identified from Saudi Arabia postulated to have originated from the dromedary camels which infected 2494 people and 858 deaths were reported, in late December 2019, a recent global outbreak, a novel CoV strain has been evolved which is linked to a seafood market in Wuhan, Hubei Province, China with the symptoms varying from mild respiratory illness and pneumonia in most of the patients, to fatal consequences that progresses to ARDS by the induction of a pro-inflammatory cytokine storm. As of 8 April 2020, approximately 1.43million cases of COVID-19 have been confirmed worldwide, and this pandemic is rapidly escalating all around the globe and most of the countries implemented the most restrictive mass quarantines that led to severe global socioeconomic disruption which has become the greatest concern of WHO. As of now, there are no specific approved drugs for treating SARS-CoV-2 and currently, physicians are using the repurposing drugs such as Chloroquine/Hydroxychloroquine, Remdesivir, Tocilizumab, Azithromycin, Dexamethasone, and Acetaminophenetc. They are showing plausible results, however more studies are required for specific use against SARS-CoV-2. Moreover, immune boosters such as Vitamin C, Zinc and other natural products are suggested in preventing the viral infections. Additionally, scientists are developing the new antiviral drugs and vaccines, and few are under the clinical trials. Apart from traditional drug therapy, medical practitioners are transfusing the convalescent plasma to rescue the critically ill patients with successful outcome in viral load reduction; Also, MSCs were effective for treatment with encouraging improvement with fewer side effects. Thus, there is a lot of scope to develop antiviral drugs and vaccines against SARS-CoV-2; there is a need for vigorous effort on the vaccine development and exploration of potential antiviral treatment regimens. Simultaneously, the primary and intermediate host and mechanism of its cross-species spread and human interface needs to be investigated.

Owing to the fact that new CoV viruses will continue to evolve on the basis of their ability to undergo frequent recombination's of their genomes, mutations, the propensity to infect multiple species and the increasing human-animal interface, the strict legislations should be made to prohibit the consumption and farming of terrestrial wild animals to prevent the future outbreaks.

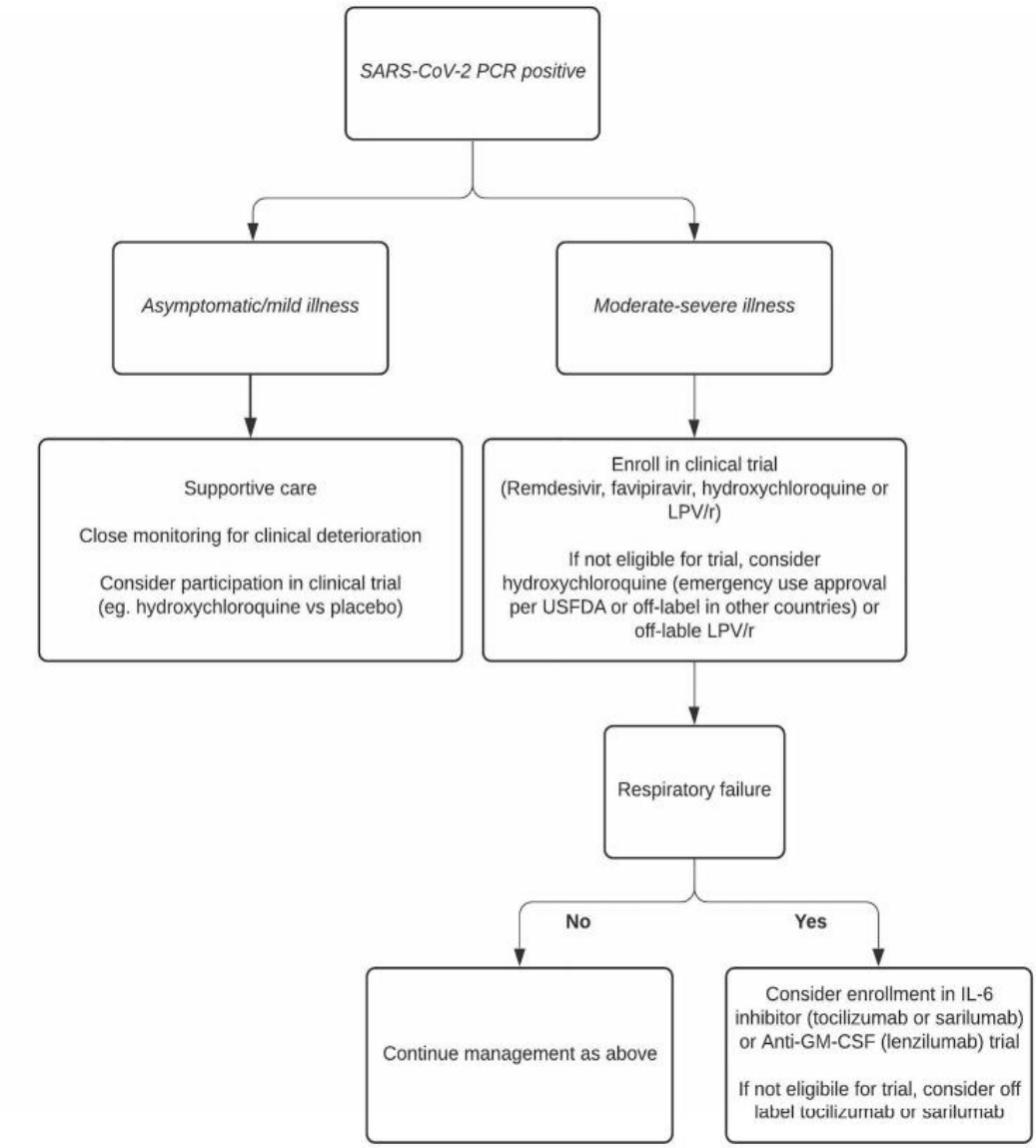


**Figure 1.1: Hypothetical Algorithm for Treatment of Corona virus Disease 2019**