Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 5 Issue 2 February 2021

Review Article

Therapeutic Strategies for Novel Corona Virus Disease (COVID-19): A Comprehensive Review

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Received: December 08, 2020

Published: January 11, 2021

Abstract

A newly emerged Human Coronavirus (HCoV) was reported in month of Dec 19 in Wuhan city of China (COVID-19). Due to high virulence ability and resistance of corona virus, several studies were carried out to screen existing drugs like antiviral, anti-malarial and anti-tubercular as potential targets for the treatment of disease. Therefore, its essential to develop an effective treatment strategy to control the virus spread and prevent the disease. In this review Here, we have reported the novel approaches and strategies that were used to treat and prevent COVID infection. Although it seems that antiviral drugs, antiprotozoal, antibacterial drug, an anti-malarial drug, and immunosuppressive drug are effective in improving clinical manifestation, there is no definite treatment protocol. Lymphocytopenia, excessive inflammation, and cytokine storm followed by acute respiratory distress syndrome are still unresolved issues that making the disease more severe. Various herbal drugs derived from Indian traditional medicines, Chinese herbals medicine/traditional Chinese medicine (CHM/TCM) were used to prevent the progression of disease.

Keywords: COVID-19; SARS-CoV-2; World Health Organization (WHO)

Introduction

The first case of newly emerged Human Corona virus (HCoV) was reported in month of Dec 2019 in Wuhan city of China (COVID-19) [1]. On 12th January 2020 World Health Organization (WHO) declares COVID-19 is a pandemic and caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a non-segmented RNA virus and mainly identified in the broncho-alveolar secretions, sputum and saliva [2]. The virus belongs to the family *Coronaviridae* and genus *Betacoronavirus* which is interrelated to severe acute respiratory syndrome coronavirus (SARS-CoV) and (ME RS-CoV) [3,4].

The various symptoms of COVID-19 are chest congestion, fever, respiratory distress, myalgia, fatigue loss of appetite, shortness of breath, cough and headache, the 1st case of COVID-19 in India was reported on 30 Jan 2020 in Kerala and as on December 2020 more the 95 Lakhs peoples were suffered from the diseases with more than 1 lakh of deaths [5,6].

Critics of the specific Coronavirus CSS idea have guaranteed that "cytokine storm has basically no definition" [7] and that there is absolute "no proof that will Coronavirus will provoke cytokine storm" in the patient [8]. Cytokine storm is a clinical aggregate of immune dysregulation recognized by perpetuated service of lymphocytes

and macrophages that leads to secretion of large quantities of cytokines which causes systemic swelling and multi-organ failure with high mortality.

Interleukin-6 and COVID-Cytokines storm

In early scientific studies another mediator in COVID-19 is elevated level of interleukins-6 (IL-6) [7,8]. In COVID-cytokines storm numerous inflammatory cytokines like IL-1, IL-10, and tumor necrosis factor(TNF)-α are raised approximately 2-100 times above normal levels, whereas IL-6 shows much higher concentration as compared to other interleukins. Some studies reported that marked elevation in serum IL-6 levels in the 100-10, 000 pg/mL range in patients with serious disease [9-11]. These markedly elevated IL-6 levels in COVID-CSS are similar in magnitude to serious CAR T-cell CRS [19] and higher than other hyper-IL-6 syndromes such as metacentric cattleman disease, where IL-6 is elevated but typically <100 pg/mL [12]. HLH is said to encompass a varied spectrum of "hyper ferritinemia hyper-inflammatory syndromes with a common terminal pathway but with different pathogenetic roots" [13].

IL-6 is difficult disks immune dysregulation plus respiratory failing within COVID-CSS will be quickly accumulating. Raised serum IL-6 will be linked with lymphopenia, reduced lymphocyte cytotoxicity and endothelial service. These types of defense defects may become partially renewed simply by therapy with IL-6 blockade with tocilizumab [14,15]. Study related to IL-6 pointed out that concentration of IL-6 > 80 pg/mL and C-reactive proteins concentration > 97 mg/L is very predictive and is associated with respiratory system failure [9].

Life cycle of COVID-19

The life cycle of COVID-19 begins in host cells once it reaches to lungs and binds to the type-II pneumocytes of the alveoli using its spike proteins (S protein) to the cellular receptor Angiotensin converting enzyme-2 (ACE-2). After binding to the receptor conformational changes in the S protein facilitates viral envelope fusion with the cell membrane through the endosomal pathway. Following fusion with host cells, virus injects its positive single stranded RNA (+ssRNA) into host cell which then translates into viral replicase poly proteins pp1a and 1ab and results in to cleavage to small products by viral proteinases. The polymerase produces a series of sub-genomic mRNAs by discontinuous transcription and finally translated into relevant viral proteins. Host RNA dependent RNA polymerase converts the viral RNA into new virions genome. Viral proteins and genome RNA are subsequently assembled into virions in the endoplasmic reticulum and Golgi apparatus and then transported via vesicles and released out of the cell (Figure 2).

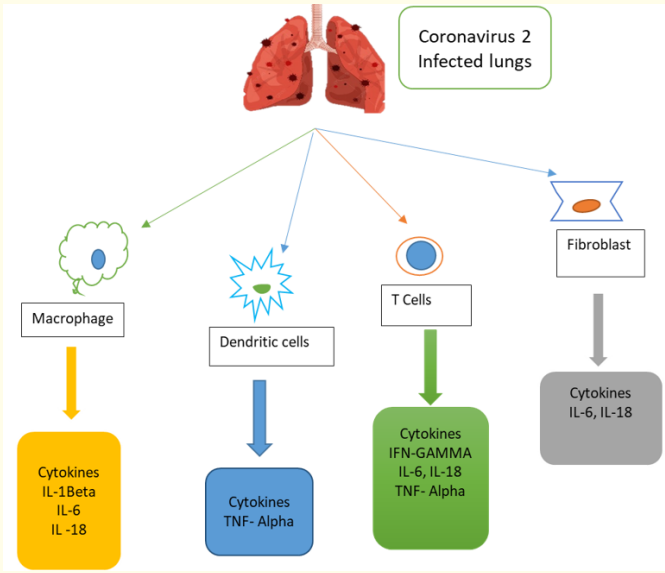

Figure 1: Inter-relation of various mediators in COVID-19.

Healthy person gets infected when they come in contact with infected person. Once at the surface, the virus reaches to alveolar type-2-pneumocytes where it attaches with spike protein with ACE2 receptor of type-2 cells. Following fusion with host cells, virus injects its positive single stranded RNA (+ssRNA) into host cell. Host cells, ribosome's translates the viral into large viral proteins which is further chopped into smaller proteins and used to make the structural proteins of progeny virions. Host RNA dependent RNA polymerase converts the viral RNA into new virions genome. Progeny virus after completing the life cycle burst the host cells, starts infection into nearby cells. In severely infected patients, virus also affects the vital organs like kidney and heart.

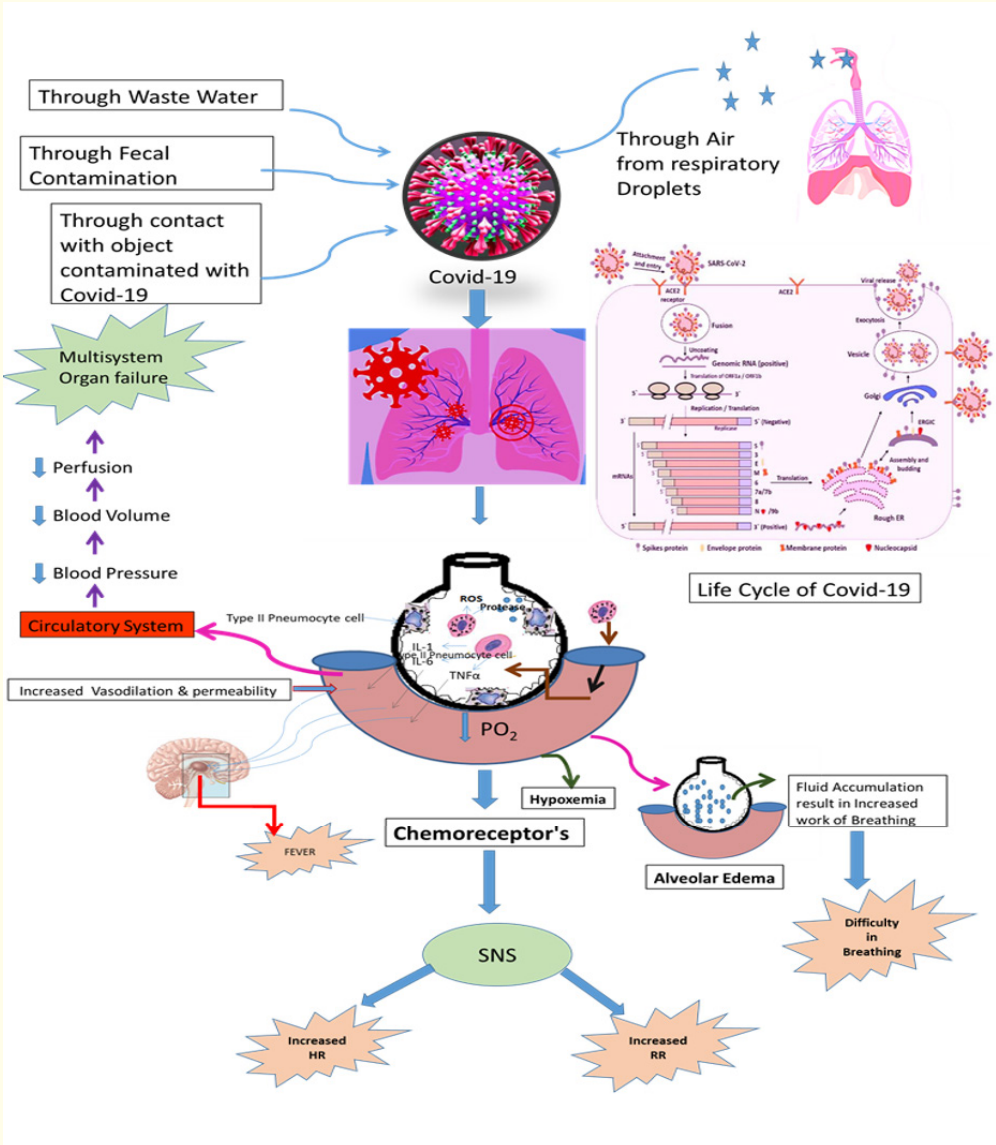

Figure 2: Life cycle of COVID-19.

To date there is no effective medicine available for the treatment of COVID-19 hence in this review we focused on repurposing of drugs used in traditional Chinese and Indian as well as allopathic system of medicine (Figure 3) which may be used alone or in combination to get maximum advantage of therapy.

Treatment strategies for COVID-19

Antibacterial drug

Teicoplanin

It is a semisynthetic glycopeptide antibiotic used to treat serious infections caused by gram-positive bacteria. This drug showed

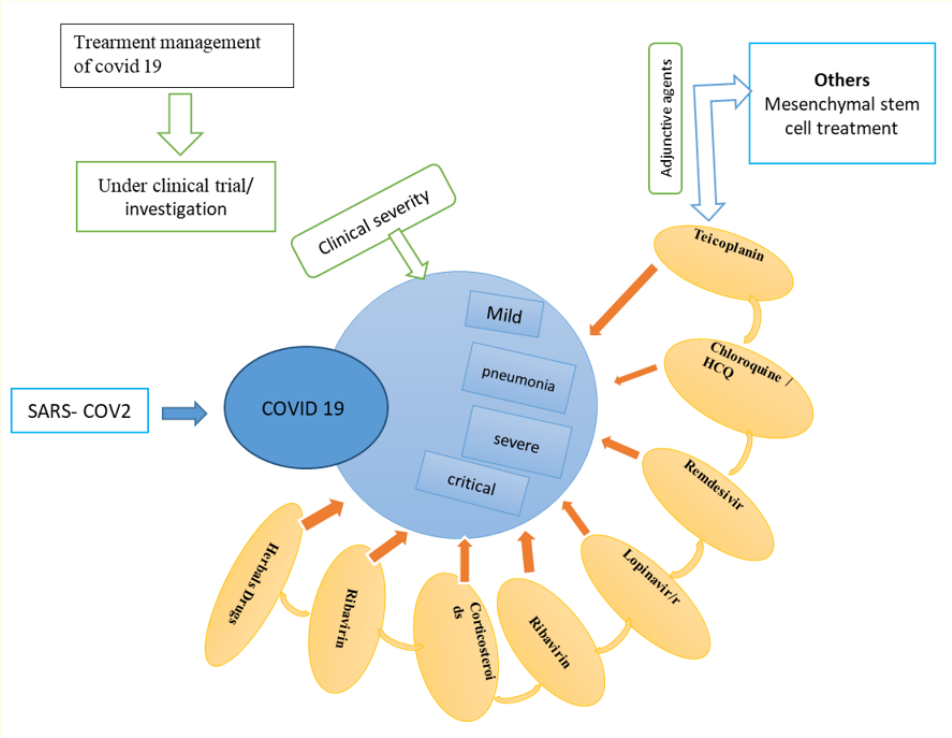

Figure 3: Drugs in treatment of COVID-19.

prominent effect when taken at a dose of 400mg once a day to treat infection associated with corona virus [16]. It acts by inhibiting spike viral protein by cathepsin L which is responsible for the release of genomic viral RNA [17].

Antiprotozoal drug

Chloroquine/hydroxyl chloroquine

Chloroquine acts by inhibiting the virus at the entry-level to the host cell while if it already inside the cell then it prevents the replication of the virus by changing the acidic pH of DNA replication and its organelles. Some researchers found that hydroxyl chloroquine is more safer as compared to chloroquine and showed better results in covid 19 by decreasing the cytokines storm and reducing the inflammatory response. it has an inhibitory effect by interfering with the glycosylation of the angiotensin-converting enzyme 2 [18,19]. It decreases the proinflammatory cytokines production against covid 19 [19].

Antiviral drugs

Remdesivir

Remdesivir was identified by the Gilead Sciences for the treatment of hepatitis C, is a broad-spectrum antiviral drug it shows effective results against SARS COV pandemic disease in 2003 which is likely matched with SARS COV2. This drug is repurposed for the emergency use in the treatment of COVID after approval from US food and Drug Administration for 19 [20]. It showed prominent results in clinical study and found 31 percent effective as compared to other drugs. The recovery time of this drug is 11 days vs. 15 days in the placebo and reducing mortality [17,21].

Lopinavir/ritonavir

Lopinavir is the most common antiviral drug used to treat various types of infectious diseases it is broad-spectrum antiviral drug. Recent studies showed its effectiveness against SARS COV2. It

showed inhibitory activity against the main protease and prevents the entry of virus into host cell. ritonavir has greater binding efficiency. Recent study showed that lopinavir and remdesvir but not ritonavir prevented the SARS COV2 replication [22]. It is recommended that this drug decreases the viral load which is responsible for the discontinuation of antiviral properties. The recommended dose of lopinavir and ritonavir is 400 and 100 mg for the duration of 6 to 15 days respectively [23,24].

Ribavirin

It is a guanosine analog and possess broad-spectrum antiviral activity, it prevents the inosine monophosphate dehydrogenase, thus removing the guanosine from the cell. It is also an inhibitor of RNA synthesis [24,25]. It was given intravenously 8mg/kg every 8 hours for 14 days for achieving effective and better outcomes. Ribavirin gives better results when given in combination with lopinavir/ritonavir for the treatment of covid 19 [23,26,27].

Herbals drugs

Herbal drugs proven to be most effective for reducing the symptoms of COVID-19 [28]. They play a vital role in boosting immune response to fight against various types of diseases. Which is mainly due to specific immunomodulation is to be understood because of local and systemic interventions for treatment of various diseases [29]. Herbal medicines will serves as an alternative to allopathic medicines due to lower adverse effect and wide margin of safety. In China, the National Health Commission has announced that herbal medicines will be used together with western medicine to achieve better results for the treatment of COVID-19 [30]. Unani system of medicines employees use of plant and related product derived from it and effective against treatment of various diseases which are presented by Arabs and Persians in India [32]. The various unani preparation used for treatment of COVID-19 to boost immunity were depicted in table 1**.**

Biological name and family	Unani name	Part used	Method of use in Unani medicine	Active ingredients	Mechanism of action	Ref.
Cydonia oblonga Mill., Rosaceae	Behidana	Berries	Decoction for oral use	Hydroxycinnamic derivatives	Anti-oxidant	[33]
Ziziphus jujube Mill.,	Unnab	Fruit	Decoction for oral use	Betulinic acid	Anti-proliferative on some influenza viruses, anti-inflammatory	[34]
Cordia dichotoma G. Forst., Boraginaceae	Sapistan	Fruit	Decoction for oral use	Hydroquinones, terpenoids, steroids, flavonoids	Anti-microbial, antioxidant, antiulcer on gastric mucosa	[35]

Table 1: Commonly used Unani medicines in treatment of COVID-19.

Homeopathic medicines

It was introduced as an alternative system of medicine by German scientist Samuel Hahnemann in (1755-1843) more than 200 years ago [36,37]. Homeopathic medicines are widely used to treat viral infections and bacterial infections. In India, AYUSH approved homeopathic medicines for the treatment of coronavirus on January 30, 2020. Arsenic album 30 showed prominent effects against COVID 19. It is obtained from the metal arsenic which is given in empty stomach for a duration of 3 days which may be responsible for boosting the natural defense mechanism of body [28,38].

Chinese herbals medicine/traditional chinese medicine (CHM/TCM)

CHM are widely used to treat SARS-CoV-2 in China. The Institute of Pharmacology of the Academy of Sciences has identified 30

CHM drugs. China used its first medical treatment using CHM at Jinyintan Hospital on 26 January 2020 [31]. Some of the common medicinal plants used in TCM were depicted in table 2 and 3.

Severity	Pattern Identification	Composition of herbal formula	Ref
Mild	Seasonal epidemic invading the exterior-defense	Lonicerae Flos, Platycodonis Radix, Forsythiae fructus, Menthae Herba, Schizonepetae spica, Lophatheri Herba, Glycine Semen preparatum, Phragmitis Rhizoma, Arctii Semen Cyperi Rhizoma, Citrireticulatae Pericarpium, Perillae folium,Glycyrrhizae Radix et Rhizoma, Bupleuri Radix, Saposhnikoviae Radix, Cinnamomi ramulus, Osterici seu notopterygii Radix et Rhizoma	[39]
Moderate	Dampness-heat blocking the lung	Ephedrae Herba, Glycyrrhizae Radix et Rhizoma, Armeniacae Semen amarum, Gypsum fibrosum, Amomi Fructus rotundus, Coicis Semen, Magnoliae Cortex, Pinelliae Rhizoma praeparatum, Talcum, Helwingiae Medulla, Stachyuri Medulla, Lophatheri Herba Citri Reticulatae Pericarpium, Magnoliae Cortex, Atractylodis Rhizoma, Glycyrrhizae Radix et Rhizoma, Pinelliae Rhizoma, Agastachis Herba, Amomi tsao-ko Fructus	[39]
Severe	Heat toxin blocking the lung Intense heat toxin with blockage of bowel Qi and dysphagia	Gypsum fibrosum, Armeniacae Semen amarum, Rhei Radix et Rhizoma, Trichosanthis fructus, Scutellariae Radix, Talcum, Artemisiae scopariae Herba, Fritillariae cirrhosae Bulbus, Acori tatarinowii Rhizoma,Akebiae caulis, Forsythiae fructus, Agastachis Herba,Amomi fructus Rotundus, Belamcandae Rhizoma,Menthae Herba. Rhei Radix et Rhizoma (Enema using herbal decoction)	[39]

Table 2: Chinese herbal medicines for COVID-19.

TCM Material	Mechanism of action	Ref
Plant-derived phenolic compounds and root extract of *Isatis Indigotica*	Inhibit the cleavage activity of SARS-3CLpro enzyme	[40]
Water extract of *Houttuynia cordata*	Inhibit the viral SARS-3CLpro activity Block viral RNA-dependent RNA polymerase activity (RdRp) Immunomodulation	[41]
Chinese Rhubarb extracts	Inhibit SARS-3CLpro activity	[42]
Quercetin and TSL-1 from *Toona sinensis* Roem	Inhibit the cellular entry of SARS-CoV	[43]
Emodin derived from genus *Rheum* and *Polygonum*	Inhibit interaction of SARS-CoV Spike protein and ACE2. Inhibit the 3a ion channel of coronavirus SARS-CoV and HCoV-OC43	[44,45]
Kaempferol derivatives	Inhibit 3a ion channel of coronavirus	[46]
Baicalin from *Scutellaria baicalensis*	Inhibit Angiotensin-converting enzyme (ACE)	[47,48]
Saikosaponins	Prevent the early stage of HCoV-22E9 infection, including viral attachment and Penetration	[49]

Table 3: Traditional Chinese Medicine for COVID-19.

Conclusion

This review provides valuable information regarding the various drugs used in Ayurveda, Unani, Homeopathy as well as in Chinese traditional medicine for the prevention and treatment of COVID-19. It focused on repurposing of drugs and possible mechanism of action in treatment of COVID-19 which may be useful for the researcher who wants to explore the hidden potential of these drugs for further research and development in the treatment of SARS CoV-2 for the treatment of COVID-19.

Conflict of Interest

None.

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