COVID-19 Pandemic: Evidences from Clinical Studies

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Abstract

The public health crisis is started with emergence of new coronavirus on 11 February 2020 which triggered as coronavirus disease-2019 (COVID-19) pandemics. The causative agent in COVID-19 is made up of positively wrapped single-stranded RNA viruses ~ 30 kb in size. The epidemiology, clinical features, pathophysiology, and mode of transmission have been documented well in many studies, with additional clinical trials are running for several antiviral agents. The spreading potential of COVID-19 is faster than its two previous families, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). Apart from clinical manifestation, comorbid status is playing key role for prevalence of COVID-19 infection and mortalities. The comorbid effects associated with COVID-19 are diabetes, cardiovascular, digestive, hepatitis-B, cerebrovascular, hypertension, liver injury, coronary heart disease, cancer, rheumatoid arthritis, and neurological impairment. Antimalarial drugs (chloroquine and hydroxychloroquine), remdesivir, Tocilizumab, clopinavir/ritonavir, convalescent plasma therapy, spike protein-angiotensin-converting enzyme 2 (ACE2) inhibitors, human monoclonal antibodies, mRNA-1273, mesenchymal stem cells, Indian and Chinese traditional medicine, small molecules antioxidant, natural products and dietary supplements, high doses of vitamin-E, -C, -D, minerals, flavonoids,and IFN-beta are therapeutic intervention running to develop treatment against COVID-19. Although clinical usage of these therapeutic agents against COVID-19 is well documented, cytokine storms, absence of appropriate animal model have limited its therapeutic use. This review explores the clinical information currently available on COVID-19 on the mechanisms of infection, prevention, management, comorbid status, and current drug treatment options.

Keywords: COVID-19; SARS-CV-2; Comorbid condition; Antimalarial drugs; Remdesivir

Abbreviation

WHO: World Health Organization; CNS: Central nervous system; CVD: cardiovascular disease; MAS: Macrophage activation system; CT-Computed tomography; SARS: Severe acute respiratory syndrome; MERS-CoV: Middle East respiratory syndrome coronavirus; COVID- 19:Coronavirus disease-2019; 2019-nCoV: Novel 2019 coronavirus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TMPRSS2-: Transmembrane protease serine 2;

ACE2: Angiotensinconverting enzyme 2; RDRP-RNA-polymerase RNA-dependent; IBD: Inflammatory bowel disease (IBD); IFPMA: International Federation of Pharmaceutical Manufacturers; DCVMN: Developing Countries Vaccine Manufacturers' Network; OP: Oropharyngeal; RCTs: Randomized controlled trials; ARDS: Acute respiratory distress syndromeDepression, anxiety and stress scale (DASS); CDC:Centers for Disease Control and Prevention; ssRNA: Single-stranded ribonucleic acid; DASS; Depression, anxiety, and stress scale; IES-R: Impact of Event Scale-Revise

Introduction

COVID-19 is a global public health emergency originating from Wuhan city (30 January 2020, Hubei province), China, and has been rapidly transmitted to over 200 countries around the world [1-3]. The World Health Organization (WHO) confirmed the first case reported a month later on 31 December 2020 [4]. Collaborative efforts and clinical solidarity studies are underway worldwide to detect new viruses that cause rapidly spreading diseases, SARS-CoV-2 (denomination 2019- nCoV) and to monitor and develop new therapies with a proven safety profile to prevent outbreak [5-8]. Coronavirus is positive sense and single strand RNA enveloped by outer three structural proteins, i.e. membrane (M), spike (S) and envelope (E) [9]. The members of the family Coronaviridae infect an extensive collection of animals. The total amount of RNA present inside the virus varies between 26–32 kb. Family coronavirids are categorized into subfamily alpha, beta, gamma, and delta coronaviruses that are present in animals and humans. Betacoronavirus may cause severe respiratory illness for other SARS and MERS endemics [10-12]. In humans, they have caused mild respiratory infections such as the common cold and cough. Clinical manifestations associated with COVID-19 are fever, cough, indigestion, and pneumonia [13]. Acute respiratory distress syndrome (ARDS) is the main factor of respiratory failure and severe mortality. The similarity in terms of viral load between asymptomatic and symptomatic patients contributes to the onset of symptoms as super-spreaders [14]. The most common preexisting comorbidities are diabetes, cardiovascular disease (CVD), digestion, cerebrospinal, hypertension, hepatitis-2, cancer, rheumatoid arthritis and neurological debility (Table 1) [15]. Current clinical studies confirm that COVID-19 infection is not confined to respiratory tract but also invading other organ such as central nervous system (CNS) producing neurological impairment [16]. However, retrospective clinical, laboratory, and computed tomography studies have suggested vertical intrauterine transmission of COVID-19 in from infected pregnant women to fetus [17]. Currently limited data on vertical transmission from mother to fetus, no evidence of intrauterine transmission [9,18]. Due to the COVID-19 infection, there is a possibility of developing the congenital disease in the fetus. Further, the prevalence of COVID-19 and severe disease associated with sex and smoking correlate with high expression of the ACE2 receptor [19- 22]. Some studies, however, recommend that active cigarette smoking is not connected with COVID-19 disease severity [23]. However, Brake et al suggested that smoking increased the binding of the ACE2 receptor to COVID-19 and more mortality in the Chinese city of Wuhan, where men have a high rate of smoking [24-26]. Clinical trials are running into protective and curative effect of antiviral agents such as antimalarial drugs (chloroquine and sister molecule hydroxychloroquine), remdesivir, Lopinavir/ritonavir,Favipiravir, Ribavirin, angiotensin convertin enzyme (ACE2) blockers, Tocilizumab, Sarilumab,convalescent plasma therapy, Human monoclonal antibody, mRNA-1273 vaccine, mesenchymal stem cells, traditional Chinese medicine, indian traditional medicine, natural products and dietary supplements, vitamins, immunoenhancers such as IFN-alpha and zinc and many others sumarised in table-2. Chloroquine phosphate has shown efficient in treating COVID-19 infection with acceptable safety standards in multicenter clinical trials [27]. Immunotargeting of epitopes provide new paradigm of therapy against coronavirus. Nearly, 120 epitopes present on B and T cells, determined by considering high similarity between SARS-CoV-2 and SARS-CoV [28]. Immune system hyperactivity may occur in COVID-19 patient that may be the leading cause of hyperinflammation (cytokine storm nomenclature) and macrophage activation syndrome (MAS). MAS is most often outside the lung and is an activation of the intravascular coagulation cascade for overweight fever, lymph enlargement, hepatosplenomegaly, anaemia, cytopenius, liver function disorders, and inflammation [29]

Hyperinflammation therapy is the critical need to decrease mortalities [30]. Hyperinflammatory syndrome is a secondary hemophagocytic lymphohistiocytosis (SHLH), characterized by malignant hypercytosis and MAS with multiorgan failure [31]. Current theory deals on the progress of new therapies, including antivirals and vaccines with proven safety profiles.

Plant	Molecules	Research outcomes	Reference
Nigella Sativa	Nigellidine and α- Hederin	Potential treatment to COVID1-9 and further needed to explore clinical trial.	[135]
Digitalis purpurea	Digitoxigenin	Inhibitors of COVID-19 based on energy of interaction between molecules and target protein.	[136]
Tinospora cordifolia (giloy)	Polysaccharide G1-4A, Cordifolioside A and Syringing	Earlier reports on immunomodulatory effect (MAPK, cAMP, PI3K-AKT, NF-kB, interleukin, and TNF).	[137]
Aloe barbadensis miller	Aloeride	Interaction of viral enzyme and envelope. Clinical trial necessary to confirm activity.	[138, 139]
Curcuma longa	Demethoxycurcumin	Potential inhibitor of COVID-19 causing virus	[140]
Withania somnifera	Withanone	Prophylaxis (Antiviral, immune enhancing and vascular integrity) and management (Pyrexia, anti-inflammatory, protecting alveoli).	[141, 142]
Zingiber officinale	6-Gingerol	Better pharmacokinetic and highest binding affinities with enzyme of COVID-19.	[140]
Ocimum sanctum	Apigenin, Baicalein, Chrysin, Luteolin, Scutellarein, Tangeritin, Wogonin and 6-Hydroxyflavone	Targeting RdRp enzyme of SARS-CoV.	[143]
Cannabis sativa	Cannabidiol	Prevent infection with SARS-CoV-2. Alter the expression of ACE2 and TMPRSS2.	[144]
Withania somnifera	Withanolide D and Withaferin A	Good binding affinity and best ADME properties and potential inhibitors against COVID-19 Main Protease,	[145]
Piper nigrum	Piperine	Enhance immune system as a prophylactic measure against COVID-19.	[146]

Table: 1: Potential role of natural plant-based product against COVID-19 infections.

Comorbid condition	Patients (N) and Country	Key points and correlation of patients with COVID-19 with comorbid effect	references
Cancer	(N=1035) Kirkland, WA, USA	30th-day mortality COVID-19 cancer patients were elevated and associated with general risk factors. Long-term follow-up is needed to better understand the effect of COVID-19 on outcomes in cancer patients.	[119]
Diabetes	(N=16,003) for 33 studies	COVID-19 diabetic patients have twice the mortality and severity rate than non-diabetics.	[147]
Hepatitis B	(N=1,099)	The study confirms that COVID-19 patients are more likely to be infected with hepatitis B. More severity of cases is reported in patients with hepatitis B.	[148]

Comorbid condition	Patients (N) and Country	Key points and correlation of patients with COVID-19 with comorbid effect	references
CVD	Wuhan, China	CVD is an important risk factor for rapid progression and an unfavorable prognosis for COVID-19. To prevent rapid degeneration more intensive care should be under taken in patients with CVD.	[115]
Digestive	(N=91), Wuhan, China.	Gastrointestinal symptoms during this disease and continue to release viruses in the stool, despite respiratory samples being negative.	[149]
Neurological impairment	(N=214), Wuhan, China	Neurological symptoms were observed in 36.4% of patients with COVID-19 and common in patients with severe infection (45.5%) based on their respiratory status, which included acute cerebrovascular events, impaired consciousness and injury.	[150]
Chronic kidney disease	(N=51) patients with a mean age of 64 ± 15 years, 57% men. Madrid, Spain	Mortality rate of COVID-19 patients are higher in Chronic kidney disease.	[151]
Liver injury	(N=41), Wuhan, China.	Progressive respiratory failure and massive alveolar degenerations is fatal for COVID-19 infection and more mortality (3%).	[152]
Rheumatoid arthritis	(N=231) Ankara	COVID-19 resembling rheumatic diseases, the possible reasons for why children are affected less severely.	[153]
Smoking	(N=1099) Paris, France	Smoking persons are higher risk of COVID-19 infections.	[26]

Table 2: Comorbid statuses on COVID-19 infection summarized.

This review summarizes the COVID-19 hypothesis background, pathogenesis, method of transmission, comorbid status, current treatment, and clinical studies of cytokine storms.

Historical Background

The corona viruses (CoVs) were first identified in 1930 [32] in domesticated chickens called avian infectious bronchitis virus (IBV), and first human coronaviruses (HCoV) were identified by Tyrr and Bynoe named B814 in late 1960 However, they were unable to grow in tissue culture. Further, Hamre and Procknow were able to grow this virus in tissue culture called 229E and lipid containing coat of this virus majorly involved for infection in human. Meantime McIntosh et al were successfully grow in organ culture and given the name “OC”. Furthermore, electron microscopy on fluids from organ cultures infected with B814 demonstrates that B814 resembled like infectious bronchitis virus (IBV) of chicken. Other virus such as 229E and OC also showed similar morphology [33].

Further, in 2001, Canadian scientist observed flu like symptoms in 500 patients, among 17 to18 were infected with Corona virus confirmed by virological analyses through PCR. Until, 2002, corona virus was treated as simple and nonfatal to human. In 2002-2003, evidence suggests that corona virus transmitted in human via civet cat, and 8422 people suffered from this virus with 11% mortality rate. Lately, this virus identified as severe acute respiratory syndrome (SARS) virus [34]. Next, in 2003, several countries such as USA, Hong Kong, Singapore, Thailand, Vietnam and Taiwan have reported that more than 100 patients die due to SARS. Another study of Hong Kong was confirmed 50 patients of SARS while 30 of them were confirmed as corona virus infected [35]. In 2004, World health organization (WHO) and centers for disease control and prevention (CDCP) announced as state emergency. Recent, in 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) bat origin emerged in Saudi Arabia with camel as intermediate host and reports were presented 2494 infected patients and 858 deaths [36-39]. In December 2019, cases of unknown etiology of pneumonia first reported in Wuhan, Hubei Province of china caused by a corona virus, named 2019 novel corona virus (2019-nCoV). Further, WHO gave the name COVID-19" on 11 February 2020 [40].

Epidemiology, Characteristic, Pathogenesis, and Transmission of COVID-19

Epidemiology

COVID-19 was originated in animal market of Wuhan city, Hubei Province of China and represented a major transporter hub for virus with unknow etiology of pneumonia [PMC7166041]. COVID-19 cases were first confirmed in Haunan seafood market by etiological investigation of respiratory samples of patients. Without delaying, China notified the outbreak to WHO and COVID-19 outbreak was declared as public health emergency of international concern on Jan30, 2020 [41]. Furthermore, sequencing results evident that COVID-19 has >95% homology with bat coronavirus and >70% similarity with the SARS-CoV. Nonetheless, environmental sample from Haunan market also tested COVID-19 positive, implying that virus originated from Haunan market [42]. While Chinese government thinking and how to curb the outbreak, withing short period of time number of corona case increases exponentially without having any exposure to Haunan Market, confirming that virus transmission human to human occurring. The first fatal case was reported in 11th January 2020 [1,5]. Moreover, immense migration of people during Chinese New Year celebration put world on high risk for epidemic. Subsequently, the infection move rapidly from China and enclasp Thailand, Japan and South Korea [43]. Cases of COVID-19 reported in healthcare workers on 20th January 2020. Soon after, on 23rd Jan 2020, Wuhan was lockdown [44] and extended to other cities of China to curb the human to human transmission [45].Seeing the seriousness of COVID-19 many country including India put screening mechanisms to identify the symptomatic people returning from china and placed them in quarantine if they are suspected for COVID-19 [46]. Meanwhile, WHO worked with International Air Transport Association (IATA) and issued guideline for cabin crew and airport worker for preventive measure. Immediately it was apparent that the infection could be transmitted by asymptomatic people and before onset of symptoms. Therefore, several countries evacuated their citizen from Wuhan through special flights and returning from china, placed all people symptomatic in isolation for 14 days and tested for COVID-19. Cases continue to increase exponentially and several studies reported an epidemic doubling time of 1.8 day [47]. 12th Feb 2020, china issued guideline for confirmed cases and include patient for molecular test such as RT-PCR (reverse transcriptase-polymerase chain reaction) but clinical, radiological and epidemiological features of COVID-19 outbreak leading to increase up to 15000 in single day(https://www.who.int/emergencies/ diseases/novel-coronavirus-2019/situation-reports).This virus is a very contagious and spread all over world in short time [1,4,48]. Around 6,354,624 cases of COVID-19 and 376796 deaths have been reported till June 01,202 (https://www.worldometers.info/coronavirus). Virus was replicated in ciliated epithelium that caused cellular damage at infection site. According to a study reported in 2019, Angiotensin converting enzyme 2 (ACE.2), a membrane receptor exopeptidase used by corona virus in entry to human cells [49-51]. Virus transmission routes were represented in Figure 1.

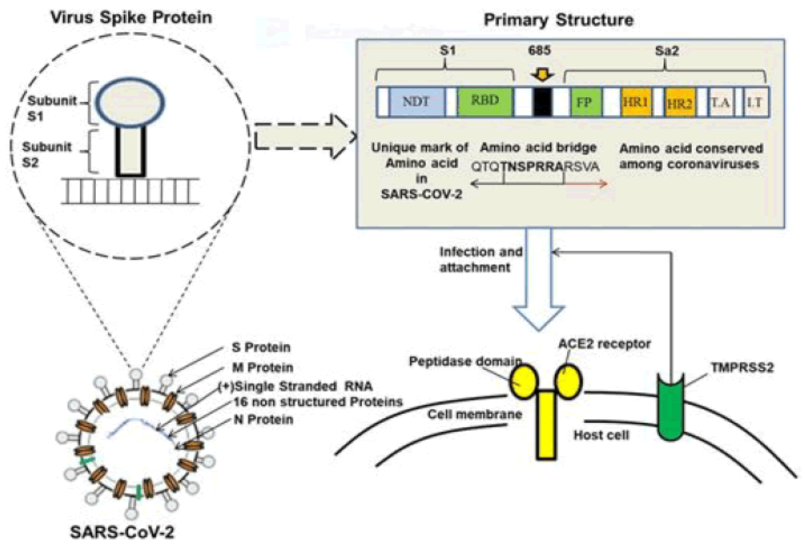

Figure 1: Systematic structure, spike prorein and its domain,host cellular attachement receptor(ACE2) and the cellular proteases (TMPRSS2) for SARS-CoV-2 activation.

Figure 1: Representative photomicrograph of histopathological features in pulmonary necropsies.

Characteristic of COVID-19

COVID-19 is an enveloped non-segmented positive-sense-singlestranded RNA virus (+ssRNA) and its diameter approximately 60-140nm with crown shaped appearance [52-55]. The corona family classified into four genera of CoVs, namely alpha-, beta-, gamma- and delta-coronavirus. Among them, alpha- and beta-CoV are able to infect mammals, while gamma- and delta-CoV tend to infect birds [54]. Currently, seven human CoVs (HCoVs) are identified to infect the human. These are HCoV-OC43, and HCoV-HKU1 (beta-CoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alpha-CoVs). Other human CoVs such as SARS-CoV, SARS-CoV-2, and MERS-CoV (beta-CoVs of the B and C lineage). COVID-19 showed 94.6 % amino acid similarities with SARS-COV and its genome has 96% homology with SARS-like coronavirus (Bat-CoV (RaTG13) [56].This suggest that COVID-19 belongs to beta-CoVs family and its RNA genome contains 29891 nucleotides, encoding for 9860 amino acids. Evidence showed 2% of the human population are healthy carriers of a CoV and these viruses are responsible for about 5% to 10% of acute respiratory infections [55]. Its genome encode has four major structural proteins; (1) the nucleocapsid protein (N), (2) the spike protein (S), (3) envelop protein (E), and (4) membrane glycoprotein (M) [56]. Spike is composed of a Transmembrane trimetric glycoprotein protruding from the viral surface, which determines the diversity of corona viruses and host tropism. Spike comprises two functional subunits; S1 subunit is responsible for binding to the host cell receptor and S2 subunit is for the fusion of the viral and cellular membranes [57].

Pathogenesis and transmission of COVID-19

The COVID-19 infection could be asymptomatic or symptomatic and asymptomatic infections pay more attention how to control the spreading of virus. The symptoms of COVID-19 infection appear approximately 5.2 day of incubation. The COVID-19 symptoms to death range vary between 6 to 41 days with a median of 14 days. However, this range depends on the age of the patient and the underlying diseases. [41]. The most common clinical manifestation at onset of COVID-19 infections includes fever, cough, fatigue, dyspnea, headache, hemoptysis, diarrhea, lymphopenia, and radiographic evidence of pneumonia. Besides, acute respiratory distress syndrome

(ARDS), RNAaemia, acute cardiac and Kidney injury were also reported [5, 58,59]. Currently, several countries normally using chest CT scan in the identification of asymptomatic infections [60]. Most of the symptoms of COVID-19 like SARS-CoV and MERS-CoV infections. Although clinical manifestation of COVID-19 poorly understood, hence studied on SARS-CoV and MERS-CoV provides us a lot of clinical pathogenic information which can help in recognition of COVID-19 [61]. Ocular infection of COVID-19 is not studied well but reports indicated that virus can cause ocular infection in various wild animals [62]. Case studies on women suggested that there is no evidence transplacental transmission of COVID-19 [63]. Clinical manifestation of COVID-19 in children are different than adult, even though they show milder disease and low death rate than adult [64]. However, some studies suggested they need more attention [65]. Nonetheless, frontline health worker (Otolaryngologists) are on major risk of COVID-19 infection [66]. The report suggests that airborne droplets require caution for healthcare professionals who treat COVID-19 and need safety and handling while maintaining a distance greater than 2 meters [9,67,68]. However, still global scientific community are behind to understand the exact molecular pathophysiology of COVID-19 and might study on animal and clinical trial offer promising avenue for treatment of COVID-19.

It is evidence that COVID-19 has potential to hijack the human angiotensin- converting enzyme-2 (ACE-2) receptor to infect the humans, as like SARS-CoV. ACE-2 is a type-1 integral membrane glycoprotein that mainly expressed in lung, heart, kidney, and intestine [9]. ACE-2 is a master regulator of RAS by converting angiotensin (Ang) I and II into Ang 1-9 and Ang1-7, respectively [69]. Full length ACE2 contains N-terminal peptidase domain (PD) and a C terminal Collectrin-like domain (CLD) that ends with a single transmembrane helix and a ~40-residue intracellular segment [70]. Studies on SARSCoV, demonstrated that S protein (spike glycoprotein) on CoV surface exist in a metastable pre-fusion confirmation, mediates receptor recognition and membrane fusion (Figure 1). Infection triggers the cleavage of trimeric S proteins into S1 and S2 subunits, receptor binding domain (RBD) of S1 directly binds to the peptidase domain (PD) of ACE-2, and S2 subunits facilitate the membrane fusion [70]. In the whole process of virus entry into cells, the spike protein (S) of virus must prime by the protease called TMPRSS2 [71]. Recent finding showed S protein of COVID-19 has higher affinity than SARS-CoV in binding to ACE-2 receptor [72]. Once virus enters into host cells, uncoats the genome and followed by the transcription and translational process. Cytoplasmic membrane is a major site for COVID-19 genome replication and transcription. The COVID-19 replicase complex consists of a maximum of 16 viral subunits and various cellular proteins. Besides, it also has RNA-dependent RNA polymerase, RNA helicase which are common to RNA viruses; however, it has unique machinery which is not common to RNA viruses such as putative sequence-specific endoribonuclease, 3′ -to-5′ exoribonuclease, 2′ - O- ribose methyltransferase, ADP ribose 1′ -phosphatase, and cyclic phosphodiesterase activities. Finally, the viral genomic RNA packed into mature particle at the Endoplasmic-Golgi intermediate complex and transported to the cell surface for their released via exocytosis [73].

Current pharmacological treatment status for COVID-19

Today, entire world has been suffering from a challenge against COVID-19. Till date, 27,997,526 corona virus cases have been reported, out of which 907,029 patients died all over the world and 1,960,472 patients recovered. Unfortunately, no drug or vaccine has yet been approved to treat human against COVID19. Several options can be envisaged to control or prevent emerging infections of COVID-19, including vaccines, monoclonal antibodies, interferon therapies and small-molecule drugs. Initial analyses of genomic sequences from COVID-19 indicate that the catalytic sites of the four COVID-19 enzymes share a high level of sequence similarity to the corresponding SARS and MERS enzymes [36]. Although there are no specific targeted therapies for COVID-19 patients, there are some potential therapeutic candidates in development for COVID-19 based on clinical trials (Figure 2).

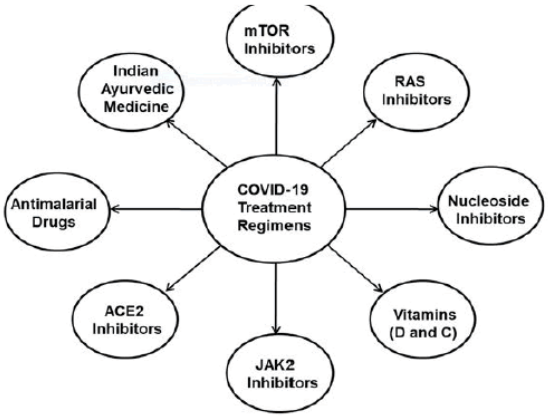

Figure 2: General existing therapeutic regimen against SARS- CoV-2 infection.

Figure 2: Representative photomicrograph of histopathological features in pulmonary necropsies.

Antiviral drugs

Remdesivir: Remdesivir, a nucleotide prodrug, originally developed to control the Ebola virus [74] that subsequently demonstrates its efficacy in inhibiting corona viruses such as SARSCoV and MERS-CoV in vitro [75]. Treatment with intravenous remdesivir successfully improved the clinical state of the first U.S. COVID-19 patient [76] .Remdesivir is now being tested in several clinical trials designed to evaluate its efficacy and safety for the treatment of COVID-19. The treatment of remdesivir to critically ill patients reduced the mortality rate. Additionally, it was also tested in combination with chloroquine and found to be effective against COVID-19. However, efficacy of the drug to treat COVID-19 patients need to be further explored.

lopinavir/ritonavir: lopinavir/ritonavir (lpv-r), a nucleoside analogue, is a human immunodeficiency virus (hiv)-specific protease inhibitor that serves as first-line therapy for hiv [77]. lpv-r has been reported to have in vitro inhibitory activity against sars-cov [78], and combination therapy of lpv-r and ribavirin provided favorable results in treating patients with sars [78]. triple combination therapy with lpv-r, ribavirin and ifn-α has shown clinical effectiveness for mers [79]. monotherapy with lpv-r did not provide protection against covid-19 patients [80]. however, combination of lpv-r and arbidol improves the pulmonary computed tomography images [81]. collectively, the combination therapy of lpv-r and other antiviral agents in early stages of covid-19 infection might be promising strategy for treating covid-19.

favipiravir: favipiravir also known as avigan is actually approved to treat influenza in japan and china and is under investigation for use in covid-19. it interferes with viral genome replication. clinical trial in wuhan based on conventional therapy demonstrated that favipiravir has higher efficacy than arbidol in terms of the 7-day recovery rate and duration of symptom attenuation in patients with moderate covid-19 infection [82].

ribavirin: ribavirin is an approved nucleoside analogue used to treat sars-cov patients [83, 84]. this drug shows significant effect in combination with a nucleotide analogue sofosbuvir which is under clinical trial. the wide availability and low cost of ribavirin support its use for the treatment of covid-19 infection.

Antimalarial drugs

Chloroquine and hydroxychloroquine: Chloroquine (CQ) and hydroxychloroquine (HCQ) are the class of quinoline derivatives and widely used to treat malaria caused by Plasmodium vivax, P. malariae, and P. ovale. It is obtained from cinchona bark and also used to treat autoimmune disease apart from malaria. CQ and HCQ, a less toxic derivative of CQ, has antiviral activity against SARS-CoV and also demonstrated anti-SARS-CoV-2 activity . CQ and HCQ can attenuate “cytokine storms” by decreasing cytokine production due to its immunomodulatory effects, which is high in COVID-19 infection [5]. The combination of CQ/HCQ with Remdesivir or second generation macrolide such as Azithromycin produces beneficial effects against COVID-19 infection [37,85]. However, there is a report of increased ventricular arrhythmias and decreased survival rate of patients infected with COVID-19 after the treatment with CQ/HCQ either alone or in combination with macrolide [86]. A number of clinical trials are underway to evaluate the efficacy of CQ/HCQ against COVID-19. CQ/ HCQ are promising approach to treat COVID-19 due to its low cost and easy availability. The studies and clinical trials on this drug are going on and needs a further research.

Convalescent Plasma Therapy

The plasma from infected people who have recovered from disease is called convalescent plasma. Patients who have recovered from COVID-19 possess antibodies to fight against infection. Plasma therapy provides a great degree of protection for recipients affected by the emerging virus [87]. This therapy is considered to be helpful for those patients with COVID-19 who does not respond to other treatments. Recently, the efficacy of convalescent plasma in controlling SARS-CoV-2 has been reported by Chinese researchers [88]. While convalescent plasma therapy is promising, it is not safe as a treatment option for COVID-19. Thus, the safety and efficacy of use of convalescent plasma to treat COVID-19 in clinical trials require more research.

Spike Protein-Angiotensin Converting enzyme 2 blockers:

Angiotensin converting enzyme 2 (ACE2), negative regulator of the renin angiotensin system (RAS), is widely expressed in lung tissue, blood vessels, intestine, heart, liver, kidney and brain. ACE2 is also a functional receptor of SARS-CoV [89] and SARS-CoV-2 [8]. The spike protein of SARS-CoV and SARS-CoV-2 binds to the host ACE2 receptor and then enters target cells. Thus, blocking spike protein binding to ACE2 might offer some protection against SARS-CoV-2 infection. RAS and ACE2 inhibitors are widely used to treat cardiovascular disease. The selective ACE2 inhibitor DX600 might show beneficial results against SARS-CoV-2 infections [90]. In a report, circulating ACE2 protein when administered intravenously produced significant blockade of initial stages of SARS-CoV-2 viral entry and infections by preventing the binding of viral spike protein onto host cell surface ACE2. However, there has been no definite evidence on whether taking ACE2 inhibitors is effective for COVID-19 infected patients.

Human monoclonal antibody against COVID-19

Monoclonal antibodies are currently used for diagnostic and therapeutic purposes. FDA has approved numerous monoclonal antibodies to treat diseases such as cancer and autoimmune disorders. Several monoclonal antibodies such as bevacizumab, tocilizumab, and meplazumab are used to treat SARS-CoV-2 infections.

Tocilizumab and sarilumab: Tocilizumab (TCZ) is a monoclonal antibody against IL-6 receptors and used in autoimmune diseases such as rheumatoid arthritis and multiple myloma [91]. IL-6 is involved in the activation of various immunological and inflammatory mediators, which are responsible for respiratory collapse observed in SARS-CoV-2 infected patients. COVID-19 disease severity depends on the increase in pro-inflammatory factors, suggesting that increase in cytokine IL-6 is involved in the development of COVID-19. Thus, TCZ has been hypothesized to suppress the inflammation in patients infected with SARS-CoV-2. Several clinical trials for TCZ have been approved for COVID-19, and the National Health and Family Planning Commission of China has approved the treatment with TCZ in patients with elevated IL-6 level. Another IL-6 receptor monoclonal antibody Sarilumab is under clinical trials for SARS-CoV-2. Like TCZ, it is also used in the treatment of rheumatoid arthritis and it suppresses the IL6 receptor mediated inflammation [92]. According to a report from Regeneron Pharmaceuticals, a phase Ⅱ/III clinical trial for sarilumab has been conducted to assess its therapeutic effects in patients with severe COVID-19 infection. The potential therapeutic role of Sarilumab in COVID- 19 needs to be further confirmed in clinical conditions.

Bevacizumab: Bevacizumab is a monoclonal anti-vascular endothelial growth factor (VEGF) antibody that competes with VEGF receptors on the surface of endothelial cells for VEGF binding, and thus inhibiting the effects caused by binding VEGF to its receptors. Previous reports have shown that plasma VEGF levels markedly increase in patients with Acute respiratory distress syndrome (ARDS) [93]. ARDS is a common complication in patients suffering from COVID-19 and bevacizumab might be a potential anti-ARDS therapeutic approach to treat the disease. Bevacizumab is therefore likely to be a promising therapy against COVID-19.

Vaccines for COVID-1

Currently, there is no vaccine available specific for COVID-19 infection. Most of the institutes and pharmaceutical companies areworking on a SARS-CoV-2 vaccine. One such vaccine is mRNA-1273, which is developed by scientists of National Institute of Allergy and Infectious Disease along with Moderna. This vaccine delivers the antigen into human cells to elicit SARSCoV-2-specific neutralizing antibodies thereby protecting against COVID-19 infection. mRNA-1273 was the first vaccine to be tested in a clinical trial against COVID-19. Similar type mRNA vaccine BNT162 was developed by BioNTech and Pfizer company to treat COVID-19 infection, which is under the clinical trials. Another, newly developed, potentially effective vaccine is PittCoVacc developed by University of Pittsburgh School of Medicine scientists [94]. PittCoVacc generates SARSCoV-2 specific antibodies by using its spike protein. This vaccine tends to be safer due to use of microneedle array technique. Several other vaccines are under development process.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent stromal cells, isolated from different mesenchymal tissues. MSCs have ability to differentiate into variety of cell types. The mechanisms by which MSCs exert their therapeutic effects include immuno-regulation. In case of COVID-19, a number of inflammatory factors that release cytokines are being produced by the immune system. MSCs have shown to prevent the release of cytokines by the immune system and thereby participate in endogenous repair by reparative properties of the stem cells. MSCs also increases the regulatory T cells, and decreases proinflammatory factors such as IL-6 and TNF-α [95,96]. A recent case study was reported in China on COVID-19 infected female patient in which 21 days treatment with umbilical cord MSCs provides effective results [97]. In another study at Beijing You An Hospital, treatment with MSC transplantation significantly improved immune function levels without obvious adverse effects in 7 patients with COVID-19 [98]. Thus, MSC therapy might be one of the most promising treatment options for COVID-19.

Traditional Chinese medicine (TCM) to treat COVID-19

The Chinese government is heavily promoting traditional medicines as treatments for COVID-19. In China, senior government officials and the state media are pushing a range of traditional Chinese medicines as being effective at alleviating symptoms and reducing deaths. Several traditional Chinese medicines have been recommended by the National Health Commission of China (NHCC) for the prevention and treatment of COVID-19 [99]. These traditional medicines have antiinflammatory activity and beneficial immunomodulatory effects for the prevention of viral infections including SARS-CoV. A published important report demonstrates that glycyrrhizin, an active constituent of liquorice root which is the most frequently used Chinese herb, potently inhibited the replication of SARS virus [100]. There are several Chinese herbs formulated in medicine provide beneficial effects in treating patients with COVID-19. According to the latest edition of Guideline, several multiple component Chinese herbal products are recommended as a preventive measure [34]. For the patients in the medical observation period, Huo Xiang Zheng Qi Shui, Lian Hua Qing Wen Capsule, Shu Feng Jie Du Capsule and Jin Hua Qing Gan Granule should be used. In the clinical treatment period, patient should be administered with Qing Fei Pai Du Tang, Xi Yan Ping Injection, Xue Bi Jing injection, Re Du Ning Injection, Tan Re Qing Injection, Xing Nao Jing Injection. Additionally, in critical situation Shen Fu Injection, Sheng Mai Injection, Shen Mai Injection, Su He Xiang Pill and An Gong Niu Huang Pill should be administered.

Indian traditional medicine as a treatment of COVID-19

In India, the treatment with modern medicine co-exists with indigenous systems of medicine, such as Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homeopath. which are extensively used all over the world [101]. In response to the COVID-19 crisis, the Indian government released a set of guidelines, developed based on the opinion of 16 eminent vaidyas, entitled “Ayurveda’s immunity boosting measures for self-care during the COVID-19 crisis”, and made them available to the public (https://www.ayush.gov.in/docs/123. pdf). These guidelines listed ten measures that were aimed at boosting immunity against infection. Recommendation by Ministry of AYUSH, Government of India involved drinking warm water throughout the day and using spices such as turmeric, cumin, garlic and coriander in cooking. Ayurvedic treatment are also recommended such as consuming chyavanprash, drinking kadha, golden milk, applying coconut or sesame oil in nostrils and rinsing mouth with these oils. The relevance of ayurvedic treatment to psychological and immune function during the COVID-19 outbreak requires direct experimental testing. The further development of such explanatory models could clarify the usefulness of “traditional” medical practices during disease outbreaks, and could facilitate a more synergistic interaction between traditional and modern medicine [101].

Natural products and dietary supplements

Our daily diet is rich in lots of vitamins, minerals, carbohydrates, proteins, fats, and lipids. It plays an important role in maintaining the body’s homeostasis and build up immunity. Various biological active natural products are also a part of our diet and they exert multiple therapeutic effects such as anticancer, antioxidant, anti-inflammatory, anti-diabetic, antibacterial, antiviral and antifungal. Since ancient times humans has been dependent on medicinal plants for the treatment of various ailments. Active compounds obtained from these plants are widely used as a remedy for numerous maladies. Among them widely used natural products are curcumin from turmeric, quercetin from onion, withaferin A from Ashwagandha. Curcumin inhibited the pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α level and decrease the cytokine storm in Ebola virus infected experimental models [102]. Furthermore, curcumin via its protease inhibitor activity also inhibited the SARS-CoV replication and supposed to be effective against SARS-CoV-2 infections. Ministry of AYUSH also recommended turmeric in daily diet as a treatment measure against COVID-19. Quercetin, widely present in red onions is a plant flavonol having pharmaceutical effects against inflammation. It also possesses antiviral activity and inhibited the SARS-CoV entry into the host cells. The other natural product withaferin A is isolated from Ashwagandha (Withania 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 [103], which may show plausible effects against COVID-19.

Vitamins

Several clinical nutritionists have also recommended consuming adequate amounts of Vitamin C and D. Vitamin C is water soluble and found in citrus fruits. Vitamin C is widely known as an antioxidant and inhibits aging induced oxidative stress. It is also involved in the process of wound healing. Vitamin C is considered as strong immune booster, prevent from common cold and protects from wide array of microbial infections [104]. Thus, vitamin C might have a promising role to treat COVID-19 patients having lung damage. Vitamin D is associated with the regulation of bone metabolism. Increasing evidence show that vitamin D deficiency is associated with increased autoimmunity as well as in an increased susceptibility to infection [105]. Vitamin D has an important role in modulating immunological functions and reduces the risk of respiratory tract infections due to COVID-19. Vitamin D induces antimicrobial peptides which in turn reduce the rate of replication. Several clinical trials of vitamin D in patients with COVID-19 are underway.

Effect of Immuno-enhancers on COVID-19

Interferons (IFNs)

Interferons consist of families of numerous type Ⅰ species (IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω) and one type Ⅱ species (IFN-γ) [106]. It has been reported that Type Ⅰ IFNs have antiviral activity against SARS-CoV-2 infection [107,108]. They interfere with viral replication and spread by secretion of cytokines which activate the adaptive immunity. In China, administration of 5 million U of IFNα in combination with ribavirin by vapor inhalation twice a day has been recommended as a treatment measure against COVID-19 infection [39]. Clinical trials have been performed to evaluate the effect of combination of lopinavir/ritonavir and IFNα2b or a combination of lopinavir/ritonavir with ribavirin and IFNβ1b on COVID-19 infected patients. IFNβ1 might be a safe and easy treatment measure against COVID-19 in the early stages of infection.

Zinc as a treatment option for COVID-19

Zinc, an essential micronutrient for human health, plays a key role in the immune system. It is physiologically important for the synthesis of enzymes in the body, and also plays a role in protein synthesis, wound healing and cell division. Zinc deficiency causes several immune dysfunctions and loss of taste. Interestingly, there are numerous reports showing the loss of sense of smell and taste in the early stages of COVID-19 infected people [109, 110]. Furthermore, zinc acts as an inhibitor of various other RNA viruses such as SARSCoV and also inhibits the replication of corona virus [111]. First clinical trial of intravenous zinc in COVID-19 patients is underway in Australia. Furthermore, several clinical trials of the combination of zinc and other candidates such as HCQ in patients with COVID-19 are underway.

Prevalence of Comorbidity and its effect on COVID-19

The presence of comorbidities has been one of the factors that is constantly found in all cases of COVID-19 deaths worldwide (Table 2). The mortality rate was found to be higher in severe cases of COVID-19. It was found to be higher in older patients with comorbidities such as hypertension (HTN), chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), cerebrovascular disorders and cardiovascular disease (CVD) [112, 113]. Huang et al reported the first instance of presence of comorbidity in 27 COVID-19 patients (66%) in a cohort of 41 patients (median age=49 years; 73% men) who had exposure to animal markets in China during COVID-19 outbreak [5]. Another cohort study showed that 32% of the COVID-19 patients had underlying comorbidities of which 20% had diabetes and 15% had hypertension [114]. A epidemiological study on 99 COVID-19 patients also reported that 40% had cardiovascular and cerebrovascular disease [115]. Another study also found HTN, T2DM, CVD and cerebrovascular diseases being the most common comorbidities in their cohort of patients with SARS-CoV-2 [116]. Zhou et al. conducted a retrospective study on 191 COVID-19 subjects and confirmed that 48% had pre-existing comorbidities in which 30 % had diabetes mellitus and 8% had coronary heart disease [7]. Additionally, non-survivors were reported to have an escalated rate of co-morbidities in comparison to survivors [117]. T2DM, HTN and coronary heart disease (CHD) are the common comorbidities in non-survivors. Acute heart failure (23%) and acute cardiac injury (17%) are most common secondary outcomes in COVID-19 patients when compared to primary outcomes such as (59%), respiratory failure (54%), ARDS (31%), and acute kidney injury (15%) [7]. These secondary outcomes were found to be higher in non-survivors when compared to survivors Moreover, routine laboratory parameters or nonspecific biomarkers such as alanine transaminase (ALT), lactate dehydrogenase (LDH), cardiac troponin I (cTnI), ferritin and interleukin-6 (IL-6) were elevated in SARSCoV- 2 infection [117]. However, estimation of biomarkers is not adequate in diagnosing myocardial injury in SARS-CoV-2 infections, further clinical studies should be addressed based on multimodal approach for the diagnosis of extent of cardiac complications. Similarly, COVID-19 patients with cardiovascular disease (CVD) as the co-morbidity showed higher mortality rate [118]. Apart from above mentioned reasons, myocardial injury was found to be the main cause of death in SARS-CoV-2 infection with higher circulating levels of cytokine interleukin (IL-6) and serum levels of C-reactive protein (hsCRP). Cancer as comorbidity has also been investigated in COVID - 19 [119]. [109]. A study in cohort of 1590 patients in COVID-19 demonstrated the higher risk of 1% for COVID-19 and a high risk of severe events of 39% in cancer patients when compared with those without (0.29 % and 8%). Severe events included either admission to the intensive care unit undergoing invasive ventilation or death [15]. Although, the recent communication also doubts the adequacy of the evidence for a concluding the association between COVID-19 and cancer. In this context, it should be emphasized that the observed frequency of comorbidities may also reflect transmission dynamic within particular age groups, identification of cases or test practices adopted by the hospital during the early stages of the epidemic. Paradoxically, the percentage of patients with kidney disease and malignancy such as comorbidity was relatively low [119]. COVID-19 can also cause damage to other organs such as the heart, liver, and kidneys, as well as to organ systems such as the blood and the immune system [5,120,121]. Patients finally die from multiple organ failure, shock, ARDS, heart failure, arrhythmias and kidney failure [114,122].

Conclusion and Future Directions

COVID-19 infection spreading continuously all over world and current treatment is yet to undefined due to unknown pathophysiology, mode of transmission and absence of appropriated animal model. However, recently it has been reported that golden Syrian hamster resemble COVID-19 with low mortality and promising tool for investigating transmission, pathogenesis, treatment and vaccination against SARS-CoV-2 [123]. This review focuses on the history of COVID-19, clinical characterization, comorbid effects and information on current therapeutic arrangements. Clinical studies of previously known antiviral molecules and natural herbal medicines are required to detect COVID-19 treatment. Molecular investigations have suggested that the antiviral potential of bioactive therapies targeted at SARS-CoV2-polymerase RdRp reveals an central function in the fight against COVID-19 [124]. The library of compounds studied as 6- shogaol, 6-gingerol, β-sitosterol, piperidine, apigenin, piperine, quercetin, α-bisabolol have immune boosting properties to prevent COVID-19 infection [125]. While there are many small molecule antioxidants, vitamins, minerals, natural products and supplements that have been proposed as alternative treatments for COVID-19, most of them do not validate or lack adequate evidence or multicenter clinical trials in research studies or methodology. Unfortunately, COVID-19 is considered an incurable outbreak; however, scientists are strictly involved in preventing medical intervention. Under the leadership of WHO, solidarity clinical trials were launched to occupied international patients around the world to activate R&D blueprints and accelerate diagnostics, vaccines and therapeutics. In all countries below the 35 degree southern hemisphere, people with low mortality receive enough sunlight to maintain adequate vitamin D [126-128]. The populationbased study confirmed that vitamin C and D high doses supplements could combate the risk of viral infection and death. Super-spreaders have been reported during the SARS and MERS epidemics. Although the transmission rate of COVID-19 patient currently is 2.2, the number of cases increases rapidly worldwide. However, children are not considered super-spreaders and can go back to school [129]. With the advancement of diagnostic techniques, potential super-spreaders with asymptomatic cases have been discovered [130]. Currently no anti-COVID-19 vaccine or preventive treatment undergoes all clinical trials, but some adjunct therapists work (Table 1).The design and trends of the technology expansion platforms evaluated as nucleic acid (DNA and RNA), virus-associated particles, amino acids, peptides, replicating and non-replicating viral vectors, recombinant proteins, live attenuated viruses and inactivated viruses are approaches to treatment developed against COVID-19. Novel lipid nano-particles (LNP) encapsulated mRNA, mRNA-1273 which express S-protein of SARSCoV- 2, provides durability, stability and stimulate strong immune response [131,132]. However, other vaccines such as adenovirus type 5 (Ad5) vector that expresses SARS-CoV S-protein (Ad5-nCoV), DNA plasmid encoding S-protein delivered by enhanced electroporation (INO-4800), DCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs (LV-SMENP-DC), and a APCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins (Pathogen specific aAPC) are in clinical phase I and II from lead developers. Ad5-nCoV is genetically engineered vaccine candidate with defect in replication. INO-4800 and its sister candidate INO-4700 are DNA vaccine matched with SARS-CoV-2 and MERS-CoV S-protein DNA [133,134]. Finally, strong international level involvement of vaccine developers, regulators, policymakers, workers, and government bodies will be necessary to ensure that a promising late stage vaccine candidate can be developed. We collectively urge to gather the technical, financial, and scientific support necessary to successfully address the COVID-19 pandemic through the Global Immunization Program and provide a strong foundation in the future to fight any pandemic.

Conflict of Interest

None.

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