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Review Article

OVERVIEW OF CLINICAL RESEARCH AND ITS APPLICATIONS IN DRUG DISCOVERY AND MANAGEMENT OF COVID-19 IN INDIA

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Abstract:

COVID-19 is a disease caused by SARS-CoV-2 that can trigger what scientists call a respiratory tract infection. It can affect your upper respiratory tract (sinuses, nose, and throat) or lower respiratory tract (lungs and windpipe). The clinical demonstration of SARS-CoV-2-infected patients ranged from mild non-specific symptoms to severe pneumonia with organ function destruction. In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started presenting to local hospitals with severe pneumonia of unknown cause. Research on COVID-19 from Alternative and Complementary Medicines are being carried out in many countries. In Ayurveda, the majority of the trials are related to ayurvedic drugs or drug combinations. The recommended formulations, some have undergone scientific investigations, such as AYUSH, Arsenica Album, Chyawanprash, Kabasur Kudineer, Guduchi, Ghanavati, Nilavembu Kudineer, for their possible preventive or therapeutic impact. One of the potential treatment strategies is the discovery of drugs by targeting essential proteins in viral life cycle. Main Protease become an attractive drug target, since it plays a pivotal role in mediating viral transcription and replication. According to the data published by FDA's Coronavirus Treatment Acceleration Program (CTAP), as on 31 December 2020 there were 595+ drug development programs in planning stages, 400+ trials reviewed by FDA, 8 treatments currently authorised for emergency use and 1 treatment approved for COVID 19.

KEYWORDS: COVID-19, SARS-CoV-2, Clinical research, AYUSH, Drug discovery process

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INTRODUCTION:

A corona virus is a kind of common virus that causes an infection in your nose, sinuses, or upper throat. The most coronaviruses are not dangerous. The coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), is rapidly spreading from its origin in Wuhan City of Hubei Province of China to the rest of the world [1]. Till 06 February 2020 around 28,276 confirmed cases of COVID-19 and 565 deaths have been reported. India has reported 29 cases till date. Fortunately, so far, children have been infrequently affected with no deaths. But the future course of this virus is unknown. [2,3] SARS-CoV-2 is one of seven types of coronaviruses, including the ones that cause severe diseases like Middle East Respiratory Syndrome (MERS) and Sudden Acute Respiratory Syndrome (SARS). The other coronaviruses cause most of the colds that affect us during the year but are not a serious threat for otherwise healthy people. [4]

History:

On 31 December 2019, the World Health Organization (WHO) was formally notified about a cluster of cases of pneumonia in Wuhan City, home to 11 million people and the cultural and economic hub of central China. By 5 January 2020, 59 cases were known and none had been fatal. [5] Ten days later, WHO was aware of 282 confirmed cases, of which four were in Japan, Thailand and South Korea. [6] There had been six deaths in Wuhan, 51 people were severely unwell and 12 were in a critical condition. The virus responsible was isolated on 7 January 2020 and its genomes shared on 12 January 2020. The cause of the severe acute respiratory syndrome (SARS) that became known as COVID-19 was a novel coronavirus, SARS-CoV-2. The rest is history, albeit history that is constantly being rewritten: as of 12 May 2020, 82,591 new cases of COVID-19 worldwide were being confirmed daily and the death rate was over 4200 per day. [7]

In India, The first cases of COVID-19 in India were reported on 30 January 2020 in three towns of Kerala, among three Indian medical students who had returned from Wuhan, the epicentre of the pandemic. [8] Lockdowns were announced in Kerala on 23 March, and in the rest of the country on 25 March. [9,10]

Origin and Spread of COVID-19

In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started presenting to local hospitals with severe pneumonia of unknown cause. Many of the initial

cases had a common exposure to the Huanan wholesale seafood market that also traded live animals. The surveillance system was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On 31 December 2019, China notified the outbreak to the World Health Organization and on 01 January the Huanan Sea food market was closed. On 07 January 2020 the virus was identified as a coronavirus that had >95% homology with the bat coronavirus and > 70% similarity with the SARS-CoV-2. Environmental samples from the Huanan Sea food market also tested positive, signifying that the virus originated from there [4,11]. The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring [12]. The first fatal case was reported on 11 January 2020. The massive migration of Chinese during the Chinese New Year fuelled the epidemic. Cases in other provinces of China, other countries (Japan, Thailand and South Korea in quick succession) were reported in people who were returning from Wuhan. Transmission to healthcare workers caring for patients was described on 20 January 2020. By 23 January, the 11 million population of Wuhan was placed under lock down with restrictions of entry and exit from the region. Soon this lock down was extended to other cities of Hubei province. Cases of COVID-19 in countries outside China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries [13]. Airports in different countries including India put in screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19. Soon it was apparent that the infection could be transmitted from asymptomatic people and also before onset of symptoms. Therefore, countries including India who evacuated their citizens from Wuhan through special flights or had travellers returning from China, placed all people symptomatic or otherwise in isolation for 14 d and tested them for the virus.

Cases continued to increase exponentially and modelling studies reported an epidemic doubling time of 1.8 days [14]. In fact, on the 12th of February, China changed its definition of confirmed cases to include patients with negative/ pending molecular tests but with clinical, radiological and epidemiological features of COVID-19 leading to an increase in cases by 15,000 in a single day [15]. As of 05 March 2020 96,000, cases worldwide (80,000 in China) and 87 other countries and 1 international conveyance (696, in the cruise ship Diamond Princess parked off the coast of Japan) have been reported [16]. It is important

to note that while the number of new cases has reduced in China lately, they have increased exponentially in other countries including South Korea, Italy and Iran. Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries) have died [16]. India, which had reported only 3 cases till 2 March 2020, has also seen a sudden spurt in cases. By 5 March 2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an Indian who travelled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined. [17]

These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects. [4]

Symptoms:

The symptoms of COVID-19 infection appear after a growth period of approximately 6 to 7 days. [18] The period from the onset of COVID-19 symptoms to death ranged from 6 to 45 days with a median of 14 days. [19] This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients > 70-years old compared with those under the age of 70. [19] The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, dyspnoea, diarrhoea, and lymphopenia. [19-22] Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAemia, acute respiratory distress syndrome, acute

cardiac injury, and incidence of ground-glass opacities that led to death. [21] In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs [23] that likely induced both systemic and localized immune response that led to increased inflammation. Regrettably, treatment of some cases with interferon inhalation showed no clinical effect and instead appeared to worsen the condition by progressing pulmonary opacities. [23]

It is important to note that there are similarities in the symptoms between COVID-19 and earlier beta coronavirus such as fever, dyspnoea, dry cough, and bilateral ground-glass opacities on chest CT scans. [21] However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat. [24,25]

In addition, based on results from chest radiographs upon admission, some of the cases show an infiltrate in the upper lobe of the lung that is associated with increasing dyspnoea with hypoxemia. [26] Importantly, whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhoea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress. Therefore, it is important to test faecal and urine samples to exclude a potential alternative route of transmission, specifically through health care workers, patients etc. [24,25] Therefore, development of methods to identify the various modes of transmission such as faecal and urine samples are urgently warranted in order to develop strategies to inhibit and/or minimize transmission and to develop therapeutics to control the disease. [27]

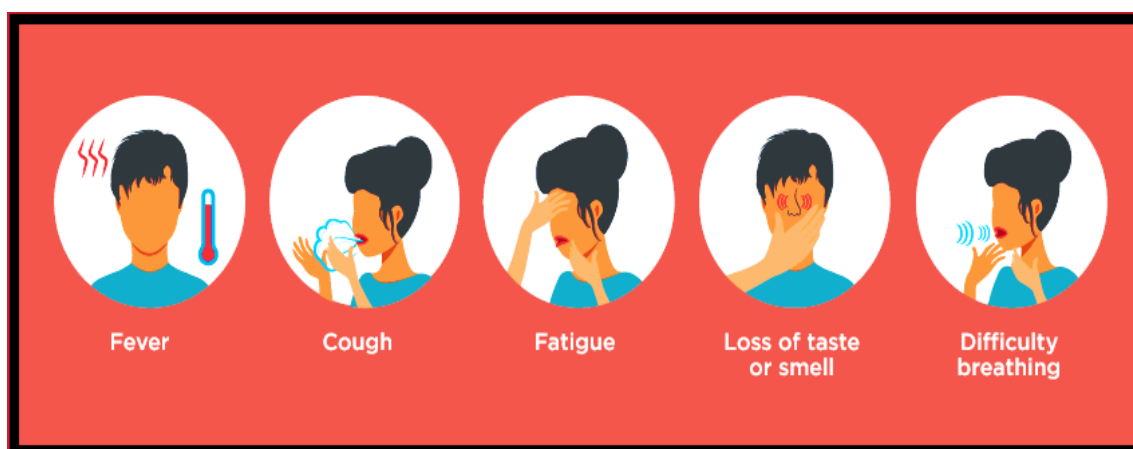


Fig 1: Symptoms of COVID-19

Epidemiology:

Current available evidence for COVID-19 suggests that the causative virus (SARS-CoV-2) has a zoonotic source closely related to bat-origin SARS-like coronavirus. It is an enveloped RNA beta coronavirus related to the severe acute respiratory syndrome (SARS) virus, and the virus has been shown to use the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry.

The persons infected by the novel coronavirus are the main source of infection. Direct person-to-person transmission occurs through close contact, mainly through respiratory droplets that are released when the infected person coughs, sneezes, or talks. [28-31]

The median incubation period is 5.1 days (range 2–14 days). The precise interval during which an individual with COVID-19 is infectious is uncertain. As per the current evidence, the period of infectivity starts 2 days prior to onset of symptoms and lasts up to 8 days. The extent and role played by pre-clinical/asymptomatic infections in transmission still remain under investigation.

The clinical manifestations of SARS-CoV-2-infected patients ranged from mild non-specific symptoms to severe pneumonia with organ function damage. The clinical manifestations of COVID-19 virus infection include asymptomatic infection, mild upper respiratory symptoms, severe viral pneumonia with respiratory failure, and even death. The progression from prodromes (fatigue, headache, usually fever, and cough) to severe pneumonia, acute respiratory distress syndrome (ARDS) requiring oxygen support, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) and is most commonly seen in the second week following onset of symptoms of a viral infection.[28] Many patients infected with SARS-CoV-2, especially for severe patients, had complications including ARDS, shock, acute cardiac injury, acute renal injury, and secondary infection. Therefore, severe patients or intensive care unit (ICU) patients have a relatively higher mortality. [32]

The kinetics of viral replication in the respiratory tract has not been well characterized, but this relatively slow progression provides a potential time window and opportunity for antiviral therapies to influence the course of the disease.

Clinical Features of COVID-19:

Clinical features of hospitalized COVID-19 patients have been described in China, Singapore and South Korea. [33,34-37] The prominent clinical manifestations have included fever, cough, fatigue,

myalgia, dyspnoea, and radiographic evidence of pneumonia. Shock, acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury, and deaths were reported in severe cases. [33,36,38,39] Early reports indicated that the infection occurs in clusters within groups in close contact, and that severe disease was more common in the elderly, men, and those with comorbidities. [36] The epidemiologic and clinical features of COVID-19 disease in the United States are beginning to be elucidated, specifically in critically ill patients. [38] Additional information is needed to help clinicians understand the characteristics of this disease. In this case series, we examine the clinical features, epidemiology, and outcomes of 105 hospitalized patients from three university-affiliated hospitals in Seattle, Washington. The characteristics associated with severe versus non-severe clinical courses are described. [40]

Clinical Trials of COVID-19:

Common laboratory findings of COVID-19 include lymphopenia, thrombocytopenia, and leukopenia, respectively. [41,42,43-45] Other abnormal laboratory finding included elevations in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum ferritin, and interleukin-6 (IL6) in Chen's research study. [46] Many patients also had increased levels of D-dimer, lactate dehydrogenase (LDH), creatine kinase (CK), prolonged prothrombin time, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). [41,42,43-47] The typical imaging features of chest computed tomography (CT) for novel coronavirus pneumonia (NCP) included ground-glass opacity, bilateral patchy shadows, and subsegmental areas of consolidation, sometimes with a rounded morphology and a peripheral lung distribution. [42,43-45,48,49] Abnormalities in chest X-ray vary, but typically reveal bilateral multi-focal opacities. Imaging may be normal early in infection and can be abnormal in the absence of symptoms. [50]

Management of Person with COVID-19 infection:

COVID-19 disease does not have any approved treatment. However, an array of drugs approved for other indications, as well as multiple investigational agents, are being studied for the treatment of COVID-19 in several hundred clinical trials around the globe. [51]

Some drugs and vaccines have been accessed through Emergency Use Authorization, expanded access programs, or compassionate use mechanisms. Favipiravir and Remdesivir are among the antiviral agents that have been given authorization by the Drugs

Controller General of India (DCGI), India for its emergency use in COVID-19 patients. [52]

Drug Discovery on COVID-19 In AYUSH

People are turning to alternative treatments for cure or prevention because there is no promising medication accessible. Research on COVID-19 from Alternative and Complementary Medicines are being carried out in many countries. [53] Countries including India, China, and South Korea, have issued guidelines on traditional medicines for the prevention and management of COVID-19. [54] Several initiatives have been launched to support ongoing research in the Traditional, Integrative, Complementary and Alternative Medicine (TICAM) to utilize available traditional knowledge in an integrated manner. [55,56] Ayurveda, Yoga, Naturopathy, Unani, Siddha, an Pandemic Homeopathy (abbreviated as AYUSH) [57] are five alternative and complementary therapies prevalent in India that are widely used in COVID-19 management. At inception of the pandemic, ministry of AYUSH issued advice based on an advisory panel

of AYUSH experts and primitive evidence that recommended the use of some herbs and measures to enhance immunity. [58] In this advice, traditional herbs and measures, which have already been in use for decades for various ailments like fever, cough, and respiratory distress, and as a non-specific immunity enhancer, possessing anti-viral, anti-bacterial and anti-microbial properties, were recommended. [59] Among recommended formulations, some have undergone scientific investigations, such as AYUSH, Chyawanprash, Guduchi Ghanavati, Arsenica Album, Kabasur Kudineer, Nilavembu Kudineer, for their possible preventive or therapeutic impact. [60] Some trials on AYUSH interventions are already completed and published [61-64] or in press. Findings of such studies need to be appraised and summarized carefully through syntheses of evidence to determine the strength of the evidence. Further, it is time for AYUSH health policy makers to examine and revise the guidelines recommended for COVID-19 using an evidence-based tactic, involving the best research existing till date. [65]

Table No 1: Management of COVID-19 Infection

Clinical Severity	Symptoms	Formulations	Dose
Management of COVID-19 infection	Fever with Body ache, Headache	Nagaradi Kashaya	20ml twice a day or as directed by Ayurveda Physician
	Cough	Sitopaladi Churna with Honey	2g thrice daily with Honey or as directed by Ayurveda physician
	Sore throat, Loss of taste	Vyoshadi vati	Chew 1-2 pills as required or as directed by Ayurveda physician
	Hypoxia	Vasavaleha	10g with warm water or as directed by Ayurveda Physician
	Fatigue	Chyawanprasha	10g with warm water/ milk once a day
	Diarrhoea	Kutaja Ghana Vati	500mg-1g thrice daily or as directed by Ayurveda physician
	Breathlessness	Kanakasava	10ml with equal amount of water twice a day or as directed by Ayurveda physician

Drug discovery for COVID-19:

Many institutions and researchers worldwide are involved in finding pharmacological interventions to COVID-19 at the earliest. [66] A remarkable achievement has been seen on this path through the development of vaccines in a short span of time. Nevertheless, considering the urgent requirement of precise therapeutics to fight this pandemic and the obvious limitations of vaccine use, the need for antiviral agents, anti-inflammatory agents or monoclonal antibodies to fight this pandemic still exists. According to the data published by FDA's Coronavirus Treatment Acceleration Program (CTAP), as on 31 December 2020 there were 595+ drug development programs in planning stages, 400+ trials reviewed by FDA, 8 treatments currently authorised for emergency use and 1 treatment approved for COVID 19. [67]

One of the first clinical candidates that has received attention is remdesivir, a pre-existing drug candidate developed by Gilead Sciences as part of an antiviral development effort, with initial results against Ebola virus (EBOV) reported in 2015. [68] It was recently authorized for compassionate use and has now entered controlled clinical trials. Like all other therapeutic approaches for patients with COVID-19, remdesivir was not developed specifically to treat COVID-19, and here we review its discovery and mode of action. [69] And the scale of the humanitarian and economic impact of the COVID-19 pandemic is driving evaluation of next-generation vaccine technology platforms through novel paradigms to accelerate development, and the first COVID-19 vaccine candidate entered human clinical testing with unprecedented rapidity on 16 March 2020.

In Ayurveda, the majority of the trials are related to ayurvedic drugs or drug combinations. This is a welcome finding. Ayurveda is a traditional medicine system of India which, as per experts, could not be developed as science because of being neglected at various levels [70]. In the current situation where, aggressive efforts are needed to find something which may help against COVID 19, drugs from the indigenous system must be explored against the COVID 19. It seems that the Ministry of AYUSH is making reasonable efforts to encourage researchers to explore these products for COVID 19. This is a good sign of future integration between allopathic and AYUSH system, as the practitioners from both streams are working together for the first time. Many ayurvedic preparations like Amalaki (*Emblica officinalis*), Ashwagandha (*Withania somnifera*), Guduchi (*Tinospora cordifolia*) etc. are known to have immunomodulation properties and all these

preparations are being explored in these trials and as these preparations are used since years for many diseases, has proved record of safety [71,72].

CONCLUSIONS:

After SARS-CoV and MERS-CoV, SARS-CoV-2 is now causing a pandemic of infectious respiratory disease, with a much wider and more significant impact on global healthcare and economy. Facing with this severe and urgent situation, the sprint to find effective treatments has been dramatically accelerated. One of the potential treatment strategies is the discovery of drugs by targeting essential proteins in viral life cycle. Main Protease become an attractive drug target, since it plays a pivotal role in mediating viral replication and transcription. Via virtual and experimental screenings, a series of drug candidates have been reported to date. Some of these agents were repurposed drugs, which previously designed for other applications with approved drug ability. They showed good performance in *in vitro* anti-SARS-CoV-2 study and could rapidly enter further clinical trials. Other agents were *ab initio* designed drugs based on 3-dimensional structure of Main Protease, and these compounds demonstrated the advantage of more potent inhibition and specificity toward Main Protease.

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