Acta Scientific Biotechnology

Volume 2 Issue 4 July 2021

Review Article

The Use of Ayurvedic Herbs as an Alternative Treatment for Covid-19 - A Review

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Received: May 29, 2021

Published: June 30, 2021

Abstract

Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory disease caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2). It was first identified in December 2019, in the city of Wuhan, Hubei, China. Within 3 months, the virus had spread globally. The World Health Organization (WHO) declared it a global pandemic on March 11, 2020. The number of people diagnosed with COVID-19 globally surpassed the 167,848,565 mark on May 26, 2021. Currently, there are 14,975,588 Active cases in worldwide infected with the disease with 3,227,188 deaths. As of date, there are no cures for the disease in modern western medicine. There has been some literature reporting successful treatment of COVID-19 using traditional Chinese medicine as well as some poorly documented used of Indian Ayurvedic herbs.

Significance

- This review provides an update on the rapidly evolving global pandemic as well as the current drugs being used as well as alternative Ayurvedic medicines available and their potential as well as limitations in the treatment of COVID-19.
- The Ayurvedic herb concoction Kabasura Kudineer has been used as a treatment for COVID-19 and reports indicate success.

Keywords: COVID-19; Corona Viruses; Ayurveda; Kabasura Kudineer

Introduction

Coronavirus disease (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The coronaviruses are a family of viruses that are enveloped positive stranded RNA viruses in the order of Nidovirales. Most coronaviruses infect animals, (i.e. bats, birds and mammals), which act as an intermediate host reservoir. However, they may sometimes change host and infect humans causing respiratory illnesses ranging from the common cold to more severe diseases such as Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) and most recently, the Coronavirus disease (COVID-19) [1].

History

Four corona viruses, namely OC43, NL63, 229E and HKU1 have been known to infect humans and have been in circulation in the human population and are known to cause mild respiratory dis-

eases. In the past decade, there have been two incidences of animal betacorona virus crossover to humans. These incidences resulted in severe respiratory disease [2,3]. The first incidence was in the years 2002 - 2003, a new β coronavirus originating in bats crossed over to human beings. It was transmitted via the Civet Cats as intermediary hosts in the Guangdong province China [4]. The virus was designated severe acute respiratory syndrome corona virus and infected over 8000 people with a mortality rate of about 10%. In 2012, another coronavirus the Middle East respiratory syndrome corona virus (MERS-CoV) also of bat origin with the camel as an intermediate host emerged with around 2500 cases with a mortality rate of 34%.

Epidemiology of COVID-19

Currently, there are over 167,638,686 confirmed cases of COVID-19 globally the disease has involved into a pandemic affecting 191 countries and regions. At the time of writing, the Johns Hopkins Coronavirus Resource Centre reports the maximum number of cases are in the USA (33,165,820), followed by India and Brazil with 26,948,874 and 16,194,209 cases respectively [5]. The mortality rate of COVID-19 has varied from country to country depending on various parameters such as the number of people tested, population demographics, factual reporting as well as healthcare delivery [6]. Global mortality as a direct result of COVID-19 or related complications currently stands at 3,481,615, with the USA reporting the highest number of deaths at 590,925, followed by Brazil (452,031) and India (307,231) with case-fatality ratios (CFR) of 1.8%, 2.8% and 1.1% respectively (Figure 1). Mexico has the highest CFR at 9.2% despite having less than 1 million confirmed cases (2,399,790) [5].

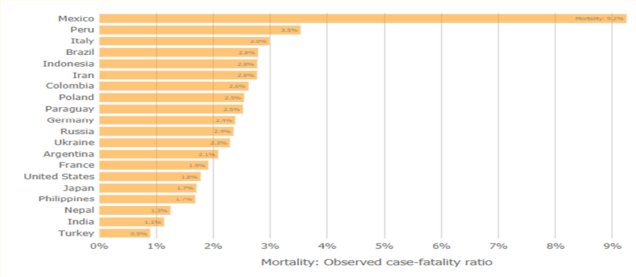

Figure 1: Mortality: Observed case-fatality ratio. Adapted from [8], (Accessed 26/05/21).

The CDC reports that the COVID-19 case counts are underestimated (CLSS. 2019) this is because only a fraction of the actual infections are diagnosed and reported. In Europe and the USA, seroprevalence studies have shown that the rate of prior exposure to SARS-CoV-2 is up to 10 higher than the reported cases this is after taking into account false negatives and positives [7]. Initial reports from the CDC indicated that the highest fatality rates among patients with COVID-19 in the USA were among persons aged ≥ 65 years with the highest percentage outcomes (27%) among those aged ≥ 85 years. Low fatality rates were reported among individuals aged 20 - 54 years and no fatalities among persons aged ≤ 19 years [8].

COVID-19 origin and spread

Genetic analyses studies by Li., *et al*. 2020 showed that the SARS-CoV-2 virus was more similar to the BetaCoV/bat/Yunnan/RaTG13/2013 virus than to the virus isolated from the pangolins, which were previously thought to be its origin. However, the Guangdong pangolin coronaviruses have a higher amino acid identity (97.4%) with SARS-CoV-2 than the bat coronavirus RaTG13 (89.2%) in the Receptor Binding Domain (RBD) [9-11]. In the rest of the genome, the RaTG13 possess a higher amino acid sequence identity with SARS-CoV-2 than the pangolin coronaviruses. Additionally, phylogenetic analysis on the same sites of the RBP indicated that RaTG13 is more closely related to the SAR-CoV-2 than to the pangolin coronaviruses [12,13]. This evidence suggests that the pangolins may have been an intermediate host in the SARS-CoV-2 crossover transmission to humans.

Within 28 days of the outbreak, the novel coronavirus was identified. The first mode of disease transmission of the novel coronavirus has not been identified. However, an analysis of the initial cluster of infections suggested that infected persons had a common point of exposure, a seafood market in Wuhan, Hubei Province China [14]. In addition to providing different types of animals for human consumption, this market also sells live animals including bats, snakes and poultry [15]. It has been suggested that this is the possible point of zoonotic transmission [16].

SARS-CoV-2 rapidly spread from a regional outbreak to a global pandemic in just a few months. Global research efforts have focused on developing effective vaccines against the virus and its disease COVID-19. However, some of the basic epidemiological parameters, such as the exponential epidemic growth rate and the

basic reproductive number, R0, across geographic areas remain to be determined. A recent study however, suggests an R0 of approximately at 5.7 [17].

The WHO reports that SARS-CoV-2 human to human transmission is principally through direct contact and by small droplets produced when infected individuals cough. However, there have been reported cases of acquired respiratory viruses in transplant patients [18]. Possible intrauterine transfer has been reported, characterized by abnormal IgM and IgG and cytokine test results in an infant born via caesarean section to a COVID-19 positive mother. The elevated levels of the IgM antibody suggest that the neonate was infected in utero, as IgM antibodies are not transferred to the fetus via the placenta [6]. However, transmission of SARS-CoV-2 via blood transfusion, organ transplantation, trans placental and perinatal routes, requires further investigations for confirmation. It is uncertain the precise interval during which an individual infected with SARS-CoV-2 can transmit the infection. Studies have shown that the potential to transmit the virus may be prior to the development of symptoms. Additionally, the infectivity of the virus is highest early in the course of the illness and the risk of transmission reduces thereafter. Reports suggest that transmission is unlikely after 7 to 10 days of illness [19-21]. SARS-CoV-2 may remain viable and in an infectious state in aerosols for hours. The half-life of the virus has been reported as 1.1 hours in aerosols, 5.6 hours on stainless steel and 6.8 hours on plastic [22,23].

The transmission of SARS-CoV-2 from asymptomatic infected individuals is well documented [24-26]. A study conducted in a long term care facility recorded a SARS-CoV-2 outbreak. Infectious viral cultures were made from RT-PCR positive upper respiratory tract specimens in asymptomatic patients at the facility as early as six days before the onset of symptoms. These findings suggest that the levels and duration of the viral RNA in the upper respiratory tract of asymptomatic patients are similar to those of symptomatic patients. However, the extent to which the transmission occurs from asymptomatic patients as well as its contribution to the pandemic are not documented.

Virology and pathogenesis

The coronaviruses are a large group of viruses classified in the order Nidovirales, the family - *Coronaviridae*, subfamily - *Orthocoronavirinae*, genus- *Betacoronavirus* and the subgenus *Sarbecovirus* [27]. They are enveloped, non-segmented positive-sense RNA viruses and have large genomes and can contain up to 33.5 kilobase (kb) genomes. The SARS-CoV-2 virion is approximately 50 - 200 nm in diameter [28]. Structurally, Coronaviruses contain four structural proteins. These are the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, all of which are encoded within the 3′ end of the viral genome [28]. The SARS-CoV-2 viruses evolved into two major types, the L and S types. The S type is the more ancient of the two and the L type has been shown to be more aggressive and was prevalent in the early stages of the outbreak in Wuhan [29].

The Angiotensin-converting enzyme 2 (ACE2) is an enzyme attached to the cell membranes of cells located in the lungs, arteries, heart, kidney, and intestines. It has been identified as a functional receptor for coronaviruses including SARS-CoV-2 by utilizing a novel metallocarboxyl peptidase angiotensin receptor (ACE) 2 to gain entry into human cells [30,31]. SARS-CoV-2 infection is achieved by the binding of the S1 unit of the viral S protein to the host ACE2 cellular receptor. During viral entry, the spike proteins (S) located on the envelope of the SARS-CoV-2 are cleaved into S1 and S2 subunits. The S2 subunit does not interact with the ACE2 receptor. It however, contains the functional elements that are required for virion membrane fusion [31]. The S1 subunit contains the RBD and binds to the peptidase domain (PD) of the ACE2 receptor to gain entry into the host cell [31,32]. The RBD of SARS-CoV-2 and SARS-CoV have high similarity. However, five of the six critical amino acid residues (AA) in the RBD were different between SARS-CoV and SARS-CoV-2 (Figure 2) [33]. A 3D structural analysis was performed and indicated that the spike of SARS-CoV-2 has a higher binding affinity to the ACE2 receptor that that of SARS-CoV [33]. The high affinity of SARS-CoV-2 for the ACE2 receptor may contribute to the high levels of transmissibility of the virus between humans. However, additional investigative studies are required to confirm this.

Clinical manifestations

COVID-19 causes flu-like symptoms including fever, fatigue and a dry cough. The incubation period ranges from two to fourteen days. This is the time between infection and the onset of symptoms. Most infected people show symptoms within five to six days. However, in some cases, infected people may be asymptomatic [1].

According to the WHO, signs of infection include fever, fatigue, and a dry cough, shortness of breath and breathing difficulties. In

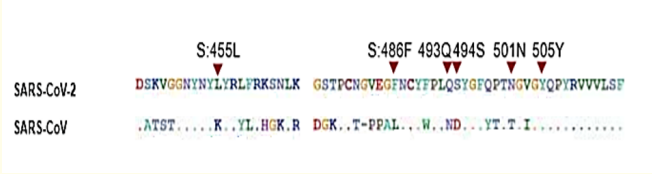

Figure 2: Conservation of 6 critical amino acid residues in the spike (S) protein. The critical active sites are Y442, L472, N479, D480, T487, and Y491 in SARS-CoV, and they correspond to L455, F486, Q493, S494, N501, and Y505 in SARS-CoV-2 (marked with inverted triangles), respectively. Adapted from [40].

severe cases, the disease can lead to pneumonia, multiple organ failure and death [5]. Other symptoms such as tiredness, aches, runny nose and sore throat may also prevail. Patients at higher risk may develop severe secondary complications such as cardiovascular disease, chronic respiratory disease and hypertension (Table 1).

Severity	Symptoms	Percentage	Onset
Mild Infection	Fever, difficulty breathing, fatigue	80.9%	Day 1 - 14
Severe Infections	Respiratory distress syndrome	13.8%	Day 15 - 30
Critical Infection	Respiratory failure, septic shock and multi-organ failure	4.7%	May vary
Fatal Infection	Cerebrovascular disease	2%	May vary

Table 1: Symptoms of COVID -19 in patients according to severity in the patient populations.

Source: Wang., *et al*. 2020 [37].

Diagnosis of SARS-CoV-2

As of October 2020, the Centers for Disease Control (CDC) recommend the following guidelines for the testing of COVID-19 caused by the SARS-CoV-2. These recommendations have been developed based on information that is currently known about COVID-19 and are subject to change as additional information becomes available.

Nucleic acid or antigen testing

Assays for viral testing include those that detect for SARS-CoV-2 nucleic acid or antigen. Viral (nucleic acid or antigen) tests investigate nasopharyngeal or oropharyngeal aspirates, washes or swabs specimen. In addition, bronchoalveolar lavage, tracheal aspirates, sputum and serum samples can also be used to determine whether an infection with SARS-CoV-2, the virus that causes COVID-19, is present. A quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) can be performed [34].

Viral tests are recommended to diagnose acute infection of both symptomatic and asymptomatic individuals, to guide contact tracing, treatment options, and isolation requirements some tests are point-of-care tests, meaning results may be available at the testing site in less than an hour. Other tests must be sent to a laboratory, a process that may take at least 1 - 2 days.

Antibody testing

Currently, there are no FDA approved antibody tests for the diagnosis of SARS-CoV-2 infection. The CDC does not recommend using antibody testing as the sole basis for diagnosis of acute infection. This is because antibody tests cannot determine current infection with the SARS-CoV-2, but rather previous infection by federal government.

However, serologic assays may be used to support clinical assessment of persons who present late in their illnesses in some instances. It is advisable to use these in conjunction with viral detection tests. If there is suspicion of a post-infectious syndrome caused by SARS-CoV-2 infection (e.g., Multisystem Inflammatory Syndrome in Children; MIS-C), serologic assays may be employed.

Control and prevention of COVID-19 infection

There are a number of restrictions put in place by the World Health Organization on a personal as well as environmental level to minimize the spread of COVID-19 [1]. Some of these include the consistent and correct use of personal protective equipment (PPE) to help reduce the spread of pathogens. In addition, there have been a number of publications that provide training on the effective use of PPE, appropriate hand hygiene as well as human conduct [1].

At the personal level, the WHO encourages frequent and consistent hand washing with soap, rubbing hands together for at least

20 seconds. Alternatively, an alcohol based sanitizer of at least 70% alcohol can be used [1]. By the first week of April, the WHO recommended that individuals aged 2 and older should wear masks to cover the nose and mouth in public settings. At the hospital level, patients showing symptoms of COVID-19 are to be isolated private quarantine rooms and anyone they might have come into contact with should be placed in quarantine for a period of 14 days after the exposure has ended according to the Guidance on Management of Coronavirus Disease 2019. Additionally, hospital staff to minimize the exchange of equipment between patients. Consistent and adequate sterilization of all equipment undergoing transportation from patient to patient to be employed religiously as well as the correct disposal of used PPE. The guidelines also encourage healthcare workers identify a specialized team to deal with COVID-19 patients to limit the spread of infection in the health institutions.

Current treatment and medication

SARS-CoV-2 therapeutic targets

As mentioned earlier, SARS-CoV-2 infection is achieved via the binding of the S1 unit of the viral receptor protein ACE2. The S1–S2 subunits of the S protein contains a furin-like cleavage site which is activated by furin, a cellular protease [35]. In addition to playing a role in the activation of the S protein, furin also aids in cell membrane fusion and intercellular spreading [36]. The furin activation of the subunits enables the interaction between the S protein and the ACE2 receptor and the consequent downregulation of ACE2. Thus, the ACE2 receptor holds great potential a therapeutic target against SARS-CoV-2. There have been a number of suggestions proposed to block viral entry into the cells. These include, administration of recombinant Human ACE2 (rhACE2) which acts as a competitive interceptor of SARS-CoV-2 resulting a reduction of cell penetration against viral infection [37].

Studies have indicated that the SARS-CoV, MERS-CoV as well as the influenza virus employ host cell proteases for activation of their envelope glycoproteins [38]. The transmembrane protease/serine subfamily member 2 (TMPRSS2) mediates viral host cell entry via S protein priming [36]. The serine protease inhibitor Camostat Mesylate which is active against TMPRSS2 has been found to partially block SARS-CoV-2 driven entry into the human epithelial cell line CaCo2. The addition of the inhibitor E-64d which inhibits CatB/L resulted in full inhibition [36]. This indicated that SARS-CoV-2 could use both CatB/L as well as TMPRSS2 for S protein priming in these cell lines.

SARS-CoV-2 experimental drugs

There are currently no clinically proven treatments for COVID-19, prevention and quarantine are the most widespread way to stop the fast spreading of the virus. There have been several strategies that have been employed to treat COVID-2019 patients, these include, the use of a wide range of antivirals such as Ritonavir, Favipiravir (T-705), Lopinavir (protease inhibitor used to treat HIV) [15], remdesivir (Newly discovered antiviral drug), Ribavirin and oseltamivir (Used in China to treat COVID-19) [9,13].

Additionally, the antimalarial Chloroquine, and the biologic response modifier, Interferon have also been used in the management of COVID-19 [38]. Oxygen therapy as well as broad-spectrum antibiotics against secondary bacterial and co-infections, steroids and fluid management [39]. Several clinical studies have used convalescent plasma to help aid in recovery avoiding severe adverse reactions [39].

Research efforts for the COVID-19 drug discovery process can be grouped into three classifications. Firstly, the repurposing of currently used antivirals through trial and error at the clinical level. This is majorly advantageous because the metabolic profiles of the applied drugs are well understood as are the required dosage, as well as side effects. However, the functional efficacy of these drugs from one viral family to another and may be low [40]. Secondly, the development of novel drugs through the study of the molecular and pathological characteristics of the COVID-19. Although this process may lead to high selectivity and efficacy for SARS-CoV-2, the process has been long and time consuming and have been dependent on the elucidation of the molecular mechanisms of SARS-CoV-2 infection as well its genomic organization [15]. It is however worthy to note that the SARS-CoV and MERS-CoV outbreaks provided a backbone which informed the discovery of potential and high confidence therapeutic targets against SARS-CoV-2. This leads to the third classification, which is based on high-throughput *in-silico* screening drug discovery to identify therapeutic agents against SARS-CoV-2 via understanding of their mode of action [41].

There have been traditional medicines that have been used worldwide and have gained importance in fighting infections. Some of these medicines have proven significant against various respiratory illnesses such as A H1N1 Influenza, A H7N9 Influenza, and SARS-CoV [31]. These medicines may also be developed and applied in the treatment of COVID-19. Some of the traditional Indian Ayurvedic medicines are reviewed in the following section.

Current alternative drugs in use

There is evidence for the use of medicinal plants as drugs for various affiliations including viral infections throughout human civilization [42]. There have been a number of studies that have chronicled the use of traditional Chinese medicine against COVID-19 [40,43]. Traditional Chinese medicine was extensively used to treat COVID-19 in the early days of the epidemic and there are a number of studies that report success [43,44].

There have been reports of the use of Ayurvedic medicines to treat COVID-19. One such is of a patient treated with two Ayurvedic herbs, namely, Sudarsana Churna during the stage of high fever classified as Jwara. Treatment was administered from day 1 to day 13. The other reported drug used was Vidaryadi Ghritam. This was administered after the fever had subsided, a period referred to as Jwara mukti. Treatment was administered between days 14 and 30. The study reports that there was a quick resolution of symptoms in the patient. Additionally, there was no progression of the disease to a severe stage. No adverse reactions were recorded [45]. However, this study is limited to one patient and only two herbs. There are a large number of Ayurvedic herbs currently in use for various types of viral respiratory diseases which may prove to be effective for COVID-19. The mode of action of the herbs used has been reported as follows; Sudarsana Churna alleviates fevers and aids in breathing. Vidaryadi Ghritam cures loss of taste and stimulates digestion [45].

The Practitioners of Siddha medicine have recently published a guideline for the use of Ayurveda in the treatment of COVID-19 [46]. In their guidelines, the Siddha Practitioners suggest an Ayurvedic drug known as Kabasura Kudineer for COVID-19 treatment. Kabasura Kudineer is an herbal concoction, comprising dry ingredients of ginger, pippali, clove, cirukancori root, mulli root, Kadukkai Ajwain and other ingredients which can be found in table 2. It is pale brown in colour and reported to bitter in taste.

Dosage

The recommended dosage of the Kabasura Kudineer herbal concoction is 25 - 50 cm^3 twice daily or as directed by the Siddha physician. The concoction is made by adding 5 - 10 grams of the Kabasura Kudineer in 300 cm^3 of water. This is then boiled and reduced to 50 cm^3 on a low flame. A teaspoon of honey may be added. This is then administered twice a day for 6 - 12 weeks [46]. Other anti-viral used for the treatment of COVID-19 proposed by the Guidelines for Siddha Practitioners include, Kaba Sura Kudineer, Nilavembu Kudineer and Pavala Parpam.

Sl. No	Botanical Name	Plant part
1	*Zingiber officinale* Rosc	Rhizome
2	*Piper longum* L.	Fruit
3	*Syzygiumaromaticum* (L.) Merr and L. M. Perry	Flower bud
4	*Tragiainvolucrata* L.	Root
5	*Anacyclus pyrethrum* (L.) Lag.	Root
6	*Hygrophila auriculata* (Schum.) Heine	Root
7	*Terminalia chebula* Retz.	Pericarp
8	*Justicia adhatoda* L.	Leaf
9	*Plectranthus amboinicus* (Lour) Spreng	Leaf
10	*Saussurea costus* (Falc.) Lipsch.	Root
11	*Tinospora sinensis* (Lour) Merr.	Stem
12	*Premna herbacea* Roxb. (Official substitute)	Root
13	*Andrographis paniculata* (Burm.f.) Nees	Whole plant
14	*Cissampelos pareira* L.	Root
15	*Cyperus rotundus* L.	Rhizome

Table 2: Ingredients of Kabasura Kudineer ayurvedic concoction. Source: Guidelines for Siddha Practitioners for COVID-19 [49].

Discussion

There is a need to perform more clinical studies on these Ayurvedic herbs as treatments for COVID-19 to develop a standard treatment protocol. The current administration of the herbs in the treatment of COVID-19 are not well documented, there are no side effects or adverse reactions recorded and neither is there statistical evidence of successfully treated patients. Additionally, the Guidelines for Siddha Practitioners does not give clinical information about patients who have been treated with these herbs, their presentation, course of the disease, dietary requirements whilst on the treatment or at which stages of the infection the various herbs may be have increased efficacy. Additionally, the mode of actions of the Ayurvedic herbs have not been reported.

Conclusion

There are currently no available medicines and established protocols to treat COVID-19. However, there has been a reported case of successful treatment using alternative medicines such as the Ayurvedic herb concoctions Sudarsana Churna and Vidaryadi Ghritam. Although the use of these two drugs prevented deterioration of the disease into a more critical condition, more clinical studies are required establish a treatment protocol. We also examined the use of the Ayurvedic herb concoction Kabasura Kudineer as proposed by the Guidelines for Siddha Practitioners with reports of successful treatment of COVID-19. Studies to establish treatment protocols as well as the mode of action of the herbs as well as special diet will need to be undertaken to make inferences on the efficacy of the herbs in treating COVID-19.

Conflict of Interest

The authors declare no conflict of interest.

Funding

Not applicable

Availability of Data and Materials

All data generated or analyzed in this study are included in this published article.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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