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Review Article

A Comprehensive Study on COVID-19 Epidemiology, Anatomical Assemblage and Its Mechanism

Sameer Sharma*, Chourasiya R and Susha D
Department of Bioinformatics, BioNome Private Limited, Bangalore, India

***Corresponding author:** Sameer Sharma, Department of Bioinformatics, BioNome, Bangalore, India

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Abstract

The COVID-19, or also called SARS-CoV-2, which is causative agent of probably inevitable disease which is of big global public health problem. COVID-19 is a positive stranded RNA virus that is majorly found in wildlife & humans. And the outbreak of Novel Coronavirus is unleashing chaos across the world due to inadequate risk assessment with reference to insistence of problem. The COVID-19 pandemic has enrolled in a critical novel phase. When compared to MERS & SARS, SARS-CoV-2 has transmitted more rapidly, because of increased globalization and adaptation of Novel coronavirus. However, the recent outbreak of COVID-19 showing an immediate requirement for therapeutics targeting SARS-CoV-2. Here, we have discussed the different symptoms in COVID-19, SARS, MERS & common flu as well as structure of virus regarding its immune response and we are providing a brief about the Indian traditional plants as conceivable novel therapeutic pathways.

Keywords: COVID-19; SARS-CoV-2; Mechanism; MERS

Introduction

Coronavirus represents a wide group of viruses mainly affecting humans through zoonotic transmission. This is the 3rd instance of a Novel coronavirus after SARS in 2003 and MERS in 2012 [1,2]. The process of naming the SARS-CoV-2 or Novel coronavirus which emerged in Wuhan, China, in December 2019 [3]. Covid-19 has been labelled as public health emergency of International concern [4] and the epidemic curve are top of the layer [5]. Coronavirus is a large family of positive single stranded RNA viruses which native to the Nidovirales order. Coronaviruses are further divided into 4 classifications - alpha, beta, gamma and delta coronavirus [6]. Currently, it has been established that SARS-CoV-2 shares a genome sequence homology structure with bat coronavirus [7]. The distinguish factor is in the change in nucleotide of the spike protein and its receptor binding domain structures [8-10]. Nowadays they initiate the treatment which indulges the Lopinavir & Ritonavir drugs which primarily depends on the severity of illness. Indian medicinal plants or herbs are a momentous field for cure of various diseases [11] like Ayurveda & Siddha are still broadly used among the Indian population. In this review, the immunological influence and mechanism of SARS-CoV-2 infection in human host cells as well as the structure and disease targeted drugs. And we will also suggest that the Indian medicinal herbs would be a tremendous step to combat viruses like the SARS-CoV-2.

Coronavirus Analysis

Phylogenetic analysis or screening recommends that although Bats serve as the natural reservoir for SARS-CoV-2, there is another possibility of unidentified intermediate host that was commonly sold at seafood market in Wuhan before the outbreak [12]. Till now, 7 human Coronaviruses have confirmed which is named as Human coronavirus NL63 and Human coronavirus 229E, which native to the alpha-coronavirus genus whereas Human coronavirus OC43 (HCoV-OC43), Human coronavirus (HCoV-HKU1), SARS-CoV, SARS-CoV-2 and Middle East respiratory syndrome coronavirus (beta-coronavirus genus) [13]. Human coronavirus is principally complementary with the upper respiratory tract sickness scaling from mild to severe including common cold [14]. Investigation or analysis needs to be done to point out the exact source of illness or infection. According to WHO, on Feb 11th, 2020, officially named this viral infection called COVID-19 [15,16].

During the stages of infection from 2002 to 2003, 774 fatalities were recorded out of 7000+ infected populations across 37 countries [17]. And this was very closely similar to MERS-CoV at Saudi Arabia in 2012, which caused around 900 deaths among the 2495 known infected cases [18]. In SARS-CoV-2, the common symptoms noted in the infected peoples are cough, fever, dyspnea etc. [19].

Epidemiology (Table 1)

Mechanism for SARS-CoV and SARS-CoV-2

The infected ratio of the COVID-19 has been remarkable compared to SARs-CoV. One of the protein which is present in COVID-19, known as Nsp2 & 3 protein; mainly consists of mutation attached with the ability of the Coronavirus to be more infectious. Moreover, some proteins are very much different from COVID-19 proteins i.e. orf8 & orf10. These types of proteins are mostly easy to understand the living function of the particular protein structures. According to a study, a cleavage loci is observed in the COVID-19 virus (furin), which is not present in the SARS-CoV. So, this may be the dialectics behind the raised virulence of COVID-19 viruses [9].

The coronavirus especially, beta-coronaviruses go through with some processes to enroll into host cells and initiate the affecting host cells [9]. The main reason behind this mechanism is the Novel coronaviruses tether with the ACE2 receptor located in the alveoli of the lungs and respiratory tract [21]. The main mechanism behind the

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Table 1: Comparison of epidemiological characteristics between Common Flu, SARS, MERS and SARS-CoV-2.

Disease	Encounter of Disease	Symptoms	Conveyance of Disease	Incubation period	Treatment	References
Common Flu	Gradual	Runny nose, Sneezing, Sore throat, Mild fever, Headache	Human to Human	2 to 3 days after exposure	Illness can be treated by medication.	[20]
Severe Acute Respiratory Syndrome (SARS)	Sudden or immediate	Fever, Headache, Dry Cough, shortness of breathing, Muscle aches, Diarrhea	Human to Human	2 to 9 days after exposure	Pneumonia treating antibiotics, Breathing ventilator to deliver oxygen, Antiviral medicines	
Middle East Respiratory Syndrome (MERS)	Sudden or immediate	Nausea, Mild Fever, Diarrhea, Vomiting, Sneezing, Sore throat	Human to Human	5 to 9 days after exposure	Cure only for symptoms like Fluids replacement, Oxygen therapy	
Novel Coronavirus (COVID-19)	Sudden or immediate	Shortness of Breath, Fever, Dry Cough, Fatigue	Human to Human	2 to 14 days after exposure	No vaccines available. Symptoms can be cure.	

SARS-CoV is the protease cut the Spike protein into S1 & S2 domains, and that cleavage evokes a structural modification which initiate the S2 domain. And this whole process is followed by the enroll of FP into the membrane cells which promote the entry of the virus into cells. And it is also possible that Novel coronaviruses uses the same process or mechanism for enroll the viral cells into host cells.

According to this mechanism, if virus enroll into host cell, ACE2 will cleaved through ADAM17 into the extra membrane matrix and leads to alveoli bruises & increase the permeability [22]. And this might be done by the ACE2 which converts the angiostenin 1 to angiostenin II. Further, once the virus enters into proteins of the cell, the protein known as ORF3a is produced and cipher the calcium ion channels which is very much similar to SARS and Novel coronaviruses [22]. TRAF3 & ORF3a both are the responsible for the inflammasome complex which leads to the second signal like caspases inactivation, free radical productions and interleukins productions in Cytokines. In this mechanism, all these molecular pathways combined together which targeting the respiratory problems, a main symptoms of COVID-19. In viral infection mechanism, the main part is the interaction of viral cells with the host cell nucleases. And a study reveals that COVID-19 may use protease which is familiar to SARS-CoV like Plasmin and Furin in the cleavage of the S protein for enroll the virus into host cells.

In case of MERS (Middle East Respiratory Syndrome), the enrollment of MERS-CoV to the host cells through its type-1 transmembrane glycoprotein also known as S protein or spike protein. MERS can also enter the cells by auxiliary pathway *via* cell surface transmembrane protease. The host protease cleaves the Spike protein into 2 functional domains which is distinctive from each other, denoted as S1 subunit & S2 subunit and the transmembrane domains. The fusion of the membrane is conciliated through main structural changes which showed the fusion peptide resulting in the production of six=helix bundle. The depth of 6HB made up of triple stranded coiled like structure constructed by 3 Spike subunits which formed the trimmers. The main part of Life cycle of MERS is fusion with plasma membrane i.e. the fusion of spike protein to the membrane of the host for formation of double membrane vesicle in the host cells. The RNA of the virus undergoes multiplication process and initiate transcription followed by translation mechanism. After assembly and packaging of viral cells and lastly through exocytosis and MERS-CoV is released out of the host cells.

Role of Immune System in SARS-CoV-2

The human coronaviruses are generally very long around 30,000bp, positive-single stranded RNA viruses. Coronaviruses are like MERS & SARS are specifically adept at deceive immune response. In case of viral infection, host factors evoke the immune response against the viral cells. Mainly, T-cells, specifically $CD8^+$ and $CD4^+$ cells play a major antiviral role to delete the virus & to raise the risk of developing autoimmunity [23]. The $CD4^+$ T cells raise the amount of viral oriented antibodies by initiating the T cell dependent B cells. And $CD8^+$ T cells plays a critical role in clearing the coronaviruses in infected cells and evoking immune injury [24]. Moreover, it was also noted that T cell apoptosis was evoked by a novel BH3-like region presented in the C-terminal cytosolic domain of COVID-19 protein mediated by Bcl-xL [25]. From the scientific studies, it was confirmed that T cells respond to the S protein and other structural receptors like M and N proteins. It also noted that augmentation of SARS-CoV particularly neutralizing the antibodies requires $CD4^+$ T helper cells. Basically, these immunological studies expose that how compelling it is to figure out the basics of the immune responses in these viruses, so these immune cells can be proceed the viral attack with more specificity.

Anatomical Assemblage of SARS-CoV-2

The Novel Coronavirus or COVID-19 reside to the largest family of the RNA viruses and it is single stranded enveloped RNA virus with a 5'-cap structure and 3; -Poly-A tail [26,27]. The virus has main 4 structural proteins M (Membrane protein), N (Nucleocapsid protein), E (Envelope protein) and S (Spike protein) which regulates the function of these viral structures [25]. Only N and S proteins helps in the development of capsid and whole viral structure [28,29]. It has been noted that the SARS-CoV-2 and SARS-CoV have same kind of receptors mainly the receptor binding domain in the viral genome [30-32].

In case of SARS infection, the receptor binding motif of the Spike protein gets immediately bound to the ACE2 (Angiotension Converting Enzyme 2) in the host cells [33]. Angiotension Converting Enzyme 2 protein is expressed in the many organs of human body such as intestine, lungs, kidney and the main host cells of Coronavirus [34]. Moreover, no present study has confirmed that it will reduce the men's fertility but in Wuhan have observed that the disease can affect the development or production of sperm preceding to low sperm count [35].

It has been also observed that the receptor binding motif's of the Novel coronaviruses has a significant amino acid residue (Gln493) that helps the binding and fusion of Viral Spike protein with virus into the ACE2 protein of the human cells mainly the lung cells which results in respiratory illness in humans [34,30]. These data suggest that the receptors and its target basis of viral replication would be a

good step to find a cure for the SARS-CoV-2 disease.

Replication of Novel Coronavirus or SARS-CoV-19

The next process for the virus survival is its RNA replication and it is the most critical step done by the virus for its survival inside the host cells. ORFs or Open Reading Frame are used in this process of replication i.e. two polyproteins & a slippery sequence. Nsp proteins are present in the polyproteins which has a major role in replication but also attack the immune system of host during viral replication [36]. The mechanism of replication of COVID-19 is very similar to the SARS-CoV [37,31]. In replication, the genomic RNA contains a 5'end region that has the untranslated regions with the TRS (Transcription Regulation Sequence) present at the below region of the genome [38]. During the replication process inside the host, the Nucleocapsid protein of the virus attach to the genome while the Membrane protein is associated with the endoplasmic reticulum. Moreover, Nsp proteins assembled with the RNA into a helical twisted anatomy and buds into the Endoplasmic reticulum lumen. These mechanisms were discovered in the foregoing viruses and may have a significant role in SARA-CoV-2 [38,39]. In replication process, we evident that the intending Nsp proteins might enable in humans to develop a strategy which will be unable to continue the viral infection.

Current Diagnostic Approaches

At the time of MERS & SARS outbreaks effective diagnostic tools were used for exact investigation. Nowadays, it is necessary to develop a specific test for COVID-19 disease. According to CDC, they have recommended the collection of upper respiratory nasopharyngeal samples for the diagnostic tests [40]. The CDC detection tests targets the N region of and made up of 1 test for Beta coronaviruses and 2 unique probes for SARS-CoV-2. Once both got positive results, the sample is tested against specific COVID-19 RDRp [41]. Moreover, chest CT scans also have been used to detect and analyze the abnormalities present in the lung in SARS-CoV-2 infection [42-44]. But not in all cases may be perfectly detected with chest CT scans [45]. That is why it is necessary to do the molecular tests and check travel history as well. Hence, the diagnostic approaches of molecular treatment will help in analysis and curing COVID-19 effectively.

The broad majority of the drugs used for COVID-19 across the world comes under any of the following classification of drugs:

- Anti-viral drugs: The anti-viral drugs come under normally 3 mechanisms in the serine protease inhibition, virus-viral replication inhibition and ion-channel inhibition. Previous outbreaks of the viral infection such as SARS-CoV, Ebola Virus as well as MERS cured with this category of drugs [46].

- Anti-malarial drugs: These types of drugs are deleted gradually from the host remaining for the long time after intake. And disadvantage of anti-malarial drugs is that they develop resistance for any drugs comes under this category [47]. Chloroquine drug is an example of anti-malarial drug which has shown potential in the treatment of avian influenza [48] as well as they have anti-viral immune modulating properties.

- Anti-HIV drugs: These types of drugs based on their specific targets like retro-transcription, proteolytic processing, reverse transcription and viral cell fusion [49]. Lopinavir or Ritonavir is a protease inhibitor which is always go for the HIV virus. These drugs stop the production of viral proteins by damaging the proteolytic processing through copying its structure as a peptide cleaved by HIV protease [50,51].

Possible Prophylaxis Enactment (SARS-CoV-2)

Most of the health workers and doctors are exposed to the COVID-19 across the world. The current available prophylactic enactment is very constrained to rebate the infected peoples. So, in case of medication prophylaxis, vaccinations are important to excursion places where many diseases are endemic such as chloroquine treatment is initiated prophylactically a week before going to excursion areas where malaria is very prevalent. And nowadays anti-retroviral therapies are also coming in used prophylactically to cure the disease at liability to reduce HIV [52].

In case of Chloroquine & hydroxychloroquine as pre-exposure prophylaxis in contrast to SARS-CoV-19 by Yao et al. [53] hydroxychloroquine was more impressive and effective than chloroquine in reaching the half of the effective concentration (EC50). According to clinical trials of hydroxychloroquine and chloroquine, a study highlighted that use of high dosage leads to higher cellular accumulation & drown out the half life cycle. Based on all *in vitro* studies, researchers have arbitrated the prophylactic use of hydroxychloroquine and chloroquine on contrary to COVID-19.

However, the main objective of the prophylaxis is eluded if a drug will be use without knowing the scientific proofs or analysis, it leads to major hysteria like patients with arthritis, for the utilizing these drugs.

The above table shows the commercially accessible medicines used for the treatment of the many types of coronaviruses and the viral disease discussed in the above table indulges the SARS, RSV, MERS, ARVI & COVID-19 (Table 2).

- SARS: Severe Acute Respiratory Syndrome

Table 2: The types of coronaviruses and the viral disease discussed in the table indulges the SARS, RSV, MERS, ARVI & COVID-19.

Drug	Illness interprets	References
Chloroquine	SARS, COVID-19, MERS	[54]
Ritonavir/Lopinavir	SARS, MERS	[55]
Atazanavir	SARS, MERS	[47]
Capsid spike glycoprotein	Human coronavirus	[56]
Papain-like protease	SARS, human coronavirus	[24]
Remdesivir	COVID-19	[49]
Influenza drugs	MERS	[47]
Nebulization Inhalation therapy	COVID-19	[57]
Ruxolitinib	COVID-19	[58]
Azudivine	COVID-19	[59]
Oseltamivir	COVID-19	[13]
Cathepsin L.	SARS	[60]
Acyclovir	SARS, COVID-19	[61]

Table 3: Indian Medicinal plant for treating SARS-CoV-2 recommended by AYUSH [58].

Indian Medicinal plant	Types of Medical practice	Form of extract	Recommended usage	Effective against
Arsenicum album 30	Homeopathy	Tablet	Daily once in empty stomach (For 3 days)	COVID-19 & immune modulator
Andrographis paniculata	Siddha	Aqueous	Twice a day for 2 weeks	Fever & Cold
Eupatorium perfoliatum	Homeopathy	Tablet	Two drops in each nostril (twice a day)	Respiratory infection fever
Tinospora cordifolia	Ayurvedha	Aqueous	Twice a day for 2 weeks	Chronic fever
Kaba sura kudineer	Siddha	Tablet	Twice in a day	Fever, cough, sore throat, shortness of breath
Bignonia sempervirens	Homeopathy	Tablet	Two drops in each nostril (twice a day)	Asthma & respiratory symptoms
Adathodai Manapagu	Ayurvedha	Aqueous	Two drops in each nostril (twice a day)	Reduce lung inflammation viral infections

- RSV: Respiratory Syncytial Virus
- MERS: Middle East Respiratory Syndrome
- ARVI: Acute respiratory viral infections.
- Coronavirus Disease

Importance of Indian Medicinal Plants and Possible Effects on SARS-CoV-2

Indian herbs are considered to be oldest treatment in human history and its plays a significant role in accounting global health care needs [52]. Around 20,000 plant-based formulations used in folk cure in Indian traditional medicines [53]. The benefit of using these traditional plants in viral respiratory infections is to manage the immunity of human beings. Also, other studies on COVID-19 employing medicinal properties are rather less in India, a scientific research has exposed anti-mouse coronaviral activity (a surrogate of SARS-CoV) through the plants *Indigoera tinctoria*, *Vitex trifolia*, *Leucas aspera*, *Cassia alata*, *Clerodendruminerme gaertn* & *Evolvulus alsinoides* in Tamil Nadu [54].

The molecular process in which these medicinal plants target influenza virus may be studied to understand whether they target any molecule overlapping between SARS-CoV-2 & the influenza virus. Most importantly, many traditional herbs have exposed inhibitory activity against ACE, and these include *Coriandrum sativum* [55], *Cynara scolymus*, *Boerhaavia diffusa*, *Punica granatum Cassia occidentalis*. Among them, *Punica granatum Cassia occidentalis* exposed a competitive mode of action while the others were non-targeted inhibtors [56,57]. These type of plants needs to be studied further to investigate their original activity on the entry of SARS-CoV-2 into the host cells. Accordingly, it is necessary to explore the activity of these recommended traditional medicines on COVID-19 (Table 3) [58].

This board interprets the Indian Medicinal plants which is furnished by the AYUSH (The Ministry of Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homoeopathy), Govt. of India as a remedial approach for SARS-CoV-19.

COVID-19 - Pandemic Remonstrance

Novel coronaviruses have emerged as the deadliest pandemic threat throughout the world since its outbreak during December 2019. This a fact that Novel coronavirus is a viral disease that has been called to have the widest range of replication in its positive strand resulting in the rapid production of new progeny viral cells inside the living host cells. And it has also been noted that COVID-19 has a high mutation rate (change in structure) which leads to a barrier for analysis and therapeutic regimens (American Society for Microbiology, 2020). Because of the high rate of mutation, it has been difficult to understand the genomic structure or organization of the virus [59].

The structure of Novel coronavirus is not only the main factor that gives a massive challenge to research, survival in various environmental conditions and its ability to adapt make it impossible to find out the mode of survival. All the countries to continue to make efforts to diminish the human connection with facilitating nation as well as many steps have been started to ensure that the safety of the people such as social distancing & self-quarantine (Balachandar et al., 2020). And it is also has been reported that Asian countries are more susceptible to acquire this Novel coronavirus infection when compared to the other population [60]. Some instruction are the protective measures given by WHO [61].

Conclusion and Recommendation

Nowadays, SARS-CoV-2 has emerged as the most critical and deadly viral infection to be handled by the human population. According to World Health Organization, main concern among public health throughout the world and most of the nations have already taken precautionary measures against the COVID-19. This type of steps will help to reduce the exposure of COVID-19 cases in a given period of time. Currently, total confirmed cases across the world are more than 3,870,343 and deaths are 267,717; in which recovered rate is around 1,326,613 [62] as on 7th May 2020 and in India 53,045 cases according to ICMR, have been analyzed to be COVID-19 positive. Our review also suggests that the importance or usefulness of some medicinal plants that have been used for several years in the cure of infinite respiratory conditions.

The cases observed in many places of China & the outbreaks indulge large numbers of in USA, Germany, Spain & Italy. And the series of symptoms attached with COVID-19 array from difficulties in breathing & many more respiratory conditions to crucial conditions like kidney failures, SARS and even death. It has been also reported that older persons and peoples with pre-existing medical problems like heart disease, cancer and high blood pressures appears to be develop serious illness more often than others [26,63].

- Avoid touching eyes, mouth & nose when outside.
- Avoid gathering and traveling in crowded places.
- Wash hands completely using an alcohol-based hand sanitizer.

- Be updated about the COVID-19 virus.

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