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Evolution, pathophysiology and genetic modulation of novel Coronavirus

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Abstract

Recently, and after its emergence in Wuhan, China, the COVID-19 infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread in almost every country in the world. This infection has appeared as a subject of intensive debate and concern among most of the government's public health systems, researchers, and policymakers. The severity of this zoonotic disease upshot a pandemic situation, which has a long-term impact on the personal, behavioral, social, and economic, as well as on the political and state affairs. Variations in COVID-19 severity made the situation more critical to elucidate the genomics, and genetic pathways linked to susceptibility and transmission of SARS-Cov-2 infection. The current study aimed to shed some light on SARS-Cov-2 infection and COVID-19 introduction, as well as the evolutionary history, structure, pathophysiology, genetic modulation, diagnosis, and treatment, in order to provide insight into pandemic flinch, its emergence, and progression around the world. The current study also provides a summary of the near future possibility of developing the appropriate medication for COVID-19 treatment and management through the identification of new therapeutic target molecules, including vaccine development and appropriate preventive and control measures.

Keywords: COVID-19, Diagnosis, Genetic modulation, Pathogenesis, SARS-CoV-2

1. Introduction

By the end of 2019, in Wuhan Hubei Province, China, a bunch of pneumonia patients appeared with unknown cause; however, till March 23, 2020 across mainland China; around 80,000 laboratories confirmed this outbreak and the irregular human infections (Li *et al*., 2020). The scientists analyzed the sequence of this

new virus that has not been identified previously in any human subjects and reported that the unknown pneumonia is caused by a novel coronavirus (CoV), commonly termed as 2019-nCoV (Zhu *et al*., 2020). Later, on February 11, 2020, a standard format of Coronavirus Disease-2019 (COVID-19) has been announced by the World Health Organization (WHO), according to its nomenclature (WHO. 2020). On that specific day, the International Committee on Taxonomy of Viruses (ICTV) named this new coronavirus as SARS-CoV-2 (Gorbalenya *et al*., 2020). Earlier this new strain of novel coronavirus has not been identified in humans, and later this virus has been named on the basis of its visible structure under the microscope. Generally, the structure of a virus is composed of a core of genetic material mainly a single-stranded RNA (positive-sense) linked with a nucleoprotein within a capsid that contains a protein matrix, and this protein envelope carries club-shaped glycoprotein spikes, which give a crown appearance (Fang *et al*., 2020). Hence, in Latin the word corona refers to a crown.

Classification of coronaviruses is based mainly on their particular chemistry and mode of replication along with a halo or crown like appearance of the envelope glycoproteins. In humans, two serotypes of coronaviruses are observed including; OC43-like and 229E-like. Generally, multiplication of the viruses starts after entering the host cell where the uncoated genome undergoes transcription and translation. After that, a special nested set is formed by the mRNAs that shares a common 3′end, and then from the host cell membranes a new virion is formed through budding (Tyrrell and Myint, 1996). The SARS-CoV-2 virus is generally transmitted through the airborne droplets into the nasal mucosa where they locally replicate in the ciliated epithelium cells, thus initiating an inflammation and damage of the cells (Tyrrell and Myint, 1996). According to the previous studies, these coronaviruses multiply rapidly and grow in the epithelial cells of the respiratory tract. The damaged cells activate the inflammatory mediator's production through increasing the nasal secretion, and then cause swelling and local inflammation. These complications further obstruct the airway, increase the mucosal temperature and stimulate sneezing. The antibody titers in paired sera are used as basis for the laboratory diagnosis of the COVID-19 viruses. It is difficult to isolate the COVID-19 viruses, and currently nucleic acid hybridization tests such as polymerase chain reaction (PCR) are being manipulated. A significant threat to the human health is caused by these SARS-CoV-2 infections, as they are still speeding, and up till now no particular effective antiviral treatments such as vaccines or drugs are available (Mason, 2020). The main objectives of this review article are to summarize and review the systematic literatures dealing with the evolution, structure, pathogenesis, genetic modulation, diagnosis, and treatment of the novel coronaviruses (SARS-CoV-2).

2. Evolution

COVID-19 is a virus that is responsible for infection of the respiratory tract in the human body. This virus belongs to the family of Human Corona viruses (HCoVs), causing respiratory symptoms, such as common cold, bronchiolitis and pneumonia, with varying degrees of severity. COVID-19 name is attributed to the crown-like protein envelope that is present on its surface (Wiersinga *et al*., 2020; Ghosh *et al*., 2020).

Coronaviruses (CoVs) belong to the family *Coronaviridae*, subfamily *Orthocoronavirinae* and order Nidovirales. Coronaviruses (CoVs) can be categorized into 4 genera, involving α−/β−/γ−/δ-CoV. Generally, the α- and β-CoV are recognized to infect the mammals, whereas the γ- and δ-CoV are recorded to be bird's invaders. The SARS-CoV-2 belongs to β-coronavirus, which is an enveloped non-segmented positive-sense RNA virus (Zhu *et al*., 2020).

Up to date seven types of coronavirus have been discovered, including α-CoVs as HCoV-229E and HCoV-NL63, β-CoVs as HCoV-HKU1, and HCoV-OC43 that have mild pathogenicity, whereas β-CoVs such as SARS-CoV and MERS-CoV cause chronic

and severely fatal respiratory tract infections. SARS-CoV-2 is the newly discovered virus that causes severe respiratory tract infections. On the basis of genome sequencing analysis and evolutionary diagnosis of SARS-CoV-2, the virus is recorded to be 96.2 % identical to a bat CoV RaTG13, and 79.5 % identical to SARS-CoV. In fact, SARS-CoV has been isolated from bats during 2015- 2017, thus bats have been supposed as natural hosts of SARSCoV-2, and the virus might be transferred from them to humans through other unknown intermediate hosts. Moreover, a recent study revealed that SARS-CoV-2 could also use angiotensin-converting enzyme 2 (ACE2) to infect the humans, which is the same receptor as SARS-CoV (Zhou *et al*., 2020).

3. Structure

The diameter of the virus's structure is 120 nm having a double layer of lipids and a core of RNA genome. The envelope is made up of lipid bilayer and has a membrane, with anchored spike proteins structure. The RNA genome is bounded with a nucleocapsid protein (Paraiso *et al*., 2020), as shown in Fig. (1).

Several types of proteins are present in the viral structure that can be defined as:

S protein: The S protein is ~150KDa in size, and has a homotrimeric structure including S1 and S2 subunits. The S1 subunit plays a role as a receptor-binding domain, while the S2 subunit is responsible for forming the stalk of the spike. The function of both protein subunits is to help in binding of a virion to the host cell receptor. The protease found on the host cell is responsible for cleaving the S protein into segments, as the S protein is a kind of glycoprotein. The S-glycoprotein virion located on the surface of coronavirus is capable of attaching to the receptor ACE2, which is present on the surface of the human cells. This S protein is also responsible for lysis of the cell membrane, and enables the viral genome to be released into the cytoplasm, where it makes a copy of itself and replicates. As binding of SARS-CoV-2 spike (S) glycoprotein to the ACE2 receptor is the most important step for viral entry into the host cell, thus binding affinity of the virus-receptor is under intensive research through different techniques.

M protein: This is a membrane protein, which is responsible for providing the shape to the virion, and is in a dimeric form with a size of ~25 to 30 KDa.

E protein: The E protein is smaller in size up to ~8-12 KDa, and carries out an important function during infection. It causes the assembly and release of the virion from the host cell.

N protein: The N protein or nucleocapsid protein facilitates arrangement of the RNA genome into beads in a string arrangement. The N-terminal domain (NTD) and C-terminal domain (CTD) of the N protein are powerful enough to bind with the RNA, although their binding mechanisms are different (Astuti, 2020).

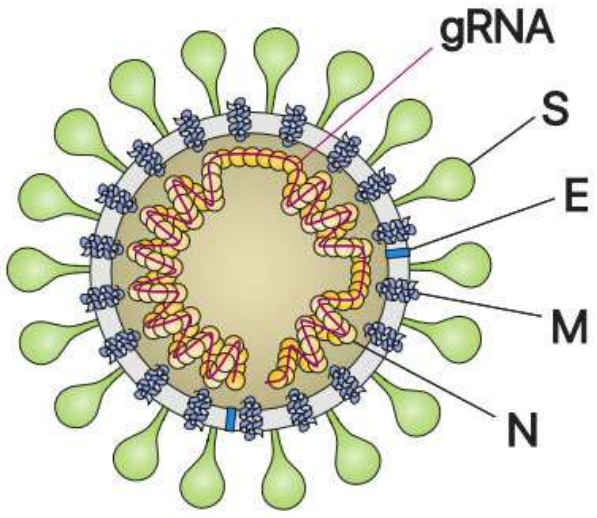

Fig. 1. Structure of SARS-CoV-2 virion (Kim *et al*., 2020)

Where; gRNA: Viral RNA genome, S: Spike protein, M: Membrane protein, N: Nucleocapsid protein

4. Pathophysiology

The causative agent of Coronavirus disease 2019 (COVID-19) is SARS-CoV-2 virus; however, very few information is available regarding the pathophysiology of COVID-19. On the basis of infected cells, the pathophysiology of COVID -19 can be divided into three distinct phases, which elaborate diverse clinical stages of the disease (Wu and McGoogan, 2020):

Phase 1

This is an asymptomatic phase that involves the initial 1st or 2nd days of infection, where viruses are transmitted from a person who does not show any infection symptoms. In this phase, the individuals are not ill and can perform their daily routines easily without the feeling of illness. The severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) is inhaled through the nasal cavity and then binds to the epithelial cells where replication of the virus starts. The key receptor of SARS-CoV and SARS-CoV2 is the angiotensin-converting enzyme 2 (ACE2), which is mainly attached to the cell membranes of cells in the lungs, intestines, kidneys, heart, and the arteries (Hoffmann *et al*., 2020).

Recent results of Hui *et al*., (2020) on SARS-CoV demonstrate that in the conducting airways the ciliated cells become infected. At this stage, the response of the innate immunity is inadequate and nasal swabs are used to detect the virus. Samples of patients with asymptomatic infections are considered positive after detection of the nucleic acid of SARS-CoV-2 through the reverse transcriptase-polymerase chain reaction (RT-PCR), although these patients do not show any apparent abnormalities in the chest images and/ or other clinical signs and symptoms (WHO. 2020). Clinical features of the asymptomatic and other types of COVID-19 infections are presented in Table (1). Although the burden of viruses might be low; however, the individuals are still become infected. For predicting the viral load; clinical course and succeeding infectivity, the RT-PCR is used for detecting the viral RNA. There should be standardized sample collection procedures, and the detection must be quick through throat swabs than nasal swabs. To control COVID-19, the primary detection of infected persons will be helpful in preventing the routes of transmission. As medical support is not followed during the asymptomatic infections; as there are no clear clinical signs in addition to lack of awareness, these contribute to the vast spread of COVID-19.

Table 1. Clinical features of the asymptomatic and other types of COVID-19 infections (WHO. 2020; Mason, 2020)

Distinct Phases	Clinical Symptoms	Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test for COVID-19
Phase 1 (Asymptomatic)	No chest imaging findings or other clinical symptoms	Positive
Phase 2 (Pulmonary)	Decreased oxygen levels, persistent cough and shortness of breath and blood clotting	Positive
Phase 3 (Hyper-inflammatory)	Hyper-activated immune system, acute respiratory distress syndrome (ARDS) hypoxia, bronchitis, pneumonia, respiratory failure, shock and other organ failures	Positive

Phase 2

The second phase is also known as the pulmonary phase, where propagation of the viruses starts from the upper airways and then they migrate down from the conducting airways to the respiratory tract. This viral infection strongly affects the human immune system leading to several primary respiratory symptoms, such as persistent cough, decreased oxygen levels, and shortness of breath. To clinically manifest the COVID-19 disease, there must be innate immune response markers existing along with the viruses (SARS-CoV-2) in the nasal swabs and the sputum. The clinical course may be followed by predicting the levels of cytokines and C-X-C motif chemokine 10 (CXCL10) (Tang *et al*., 2005), where CXCL10 is one of the most suitable disease markers in SARS. A recent study conducted by Chen *et al*., (2020) reported that in phase 2 there is a major issue with blood clots formation or blood clotting. In this phase, the disease is mainly limited to the upper and respiratory conducting airways that are mainly observed in almost 80 % of the infected patients, which can be treated at home by conventional symptomatic therapy like analgesic to reduce the pain (Wu and McGoogan, 2020).

Phase 3

Phase 3 is the most critical hyper inflammatory phase, where the immune system becomes hyper-activated leading to a cytokine storm, the body's own tissue is attacked and the heart, kidney, and other organs may be damaged as well. With advancement in the disease state, around 20 % of infected persons enter into phase 3 with developing symptoms of hypoxia, acute respiratory distress syndrome (ARDS), pulmonary infiltrates, and several other severe complications. Initially 2 % of the mortality has been recorded, which varies with the age and disease conditions (Wu and McGoogan, 2020). The alveolar type II cells existing in the lungs become infected by SARS-CoV-2 viruses that disturb the gas exchange system. The propagation of SARS-CoV within type II cells, cause the release of large number of viral particles leading thus to cell apoptosis and death (Qian *et al*., 2013).These viral particles release the self-replicating pulmonary toxins, which infect the type II cells that are the precursors of type I cells, as presence of the microvilli on type II cells better facilitates entry of the viruses. The pathological studies reported that both of the COVID-19 and SARS viruses show fibrosis, some multinucleated giant cells, abnormal wound healing, and fibrin rich hyaline membrane, with diffused alveolar damage, intense scarring and ARDS (Xu *et al*., 2020). Response of the acquired and innate immune is a must for quick recovery and regeneration of the epithelial cells. Several vulnerable groups especially the geriatric is mostly at risk due to the weak immune system, which reduces repair of the injured epithelium. Reduced clearance of the mucociliary is mainly recorded in elderly individuals, which increases spread of the viruses in the lungs, thus affecting the gas exchange unit (Ho *et al*., 2001). The dead cases due to COVID-19 have showed huge mucus secretions in both lungs, which differs from the Middle East respiratory syndrome (MERS) and SARS (Liu *et al*., 2020). Illness caused due to COVID-19 infection affect several organs and give rise to various symptoms, namely cough; sore throat, peritonitis, bronchitis, pneumonia, rhinorrhea, progressive demyelinating encephalitis, nasal obstruction, diarrhea, and gastroenteritis (Table 2). According to a previous study conducted by Cheng *et al*., (2020), it has been observed that either drug use and\or SARS-CoV-2 infection may cause mild lobular and portal activity; along with moderate microvascular steatosis, as noticed in the liver biopsy specimens. In the heart tissues, some mononuclear interstitial inflammatory infiltrates are also observed, demonstrating that SARS-CoV-2 may not personally impair the heart (Cheng *et al*., 2020). A previous research study of Shah and Dishop, (2014) suggests that children with weak immune system may get infected with CoV-NL63 virus (a species of coronavirus), which infect the upper respiratory tract and cause laryngotracheitis (croup).

In this phase 3, there is a rapid disease progression accompanied with other symptoms, including shock, respiratory failure, and other organ failures. Accordingly, there will be a need for mechanical ventilation along with Intensive care unit (ICU) monitoring treatments.

Table 2. Impact of SARS-CoV 2 at various organ levels (Robba *et al*., 2020)

Target Organs	SARS-CoV-2
Heart	Increased troponin level, thrombosis, cardiac injury and cardiac arrest.
Lung	Acute respiratory distress syndrome, pneumonia, hypo-hyper fused areas, hyperplasia of pneumocytes with patchy inflammatory cellular infiltration and thromboembolic event.
Kidney	Proteinuria, adverse drug reactions, hematuria, acute kidney injury (AKI) and thrombosis.
Liver	Increased ALT, AST, and GGT levels, decreased bilirubin levels, adverse drug reactions and acute liver injury.
Gastrointestinal tract (GIT)	Diarrhea, nausea, viral load found in the cytoplasm of epithelia of the rectum and duodenum, endothelial inflammation and guts dysbiosis.
Central nervous system (CNS)	Nausea, headache, vomiting, hemorrhage, thrombotic events, stroke and meningo-encephalitis.

5. Genetic modulation of COVID-19

Corona virus disease-19 (COVID-19) is now reported as a zoonotic viral disease, which is mainly caused by severe acute respiratory syndrome corona virus (SARS-CoV-2). The zoonotic SARS coronavirus (SCoV) originated from wild mammals in southern China; composed of single stranded RNA inside a lipid envelope. The genome of SARS-CoV-2 is fully sequenced, which encodes for non-structural proteins (NSPs) that form viral replicase transcriptase complex. This enzyme controls multiplication of the virus inside the human cells; along with other 4 structural proteins, known as spike (S); envelope (E), nucleocapsid (N), and membrane (M) protein. The genome size of SARS-CoV is 27.9 kb, while that for SARS-CoV-2 is of 26-32kb. SARS-CoV-2 has a positive single stranded RNA genome, which shows maximum genetic identity of 99 % with the corona virus of pangolins (ant eaters) (Zeng *et al*., 2020; Prompetchara *et al*., 2020). Based on their genetic sequences, there are previously reported 14 coronaviruses strains, which have been identified and divided into three major groups. The SARS-CoV is associated with Group II coronaviruses, the members that are mainly related to the human and bovine respiratory viruses

and the mouse hepatitis virus. The continuous tendency of Coronaviruses to undergo recombination and mutation increases the severity of their virulence. It has been also reported that there is variability in the severity of COVID-19 disease, and this may be attributed to the genetic variability in the response observed against this viral infection (Fehr and Perlman, 2015). Another reason for high virulence of SARS-CoV2 may be its affinity to ACE-2, as this virus expressed 10-20 folds more affinities to ACE-2 compared to SARS-CoV. For this reason, no vaccine has been developed till now that can efficiently provide long-term protection against the consequences of SARS-CoV-2 infections (Barrantes, 2020). Existence of an intermediate host that facilitates the zoonotic transmission of the COVID-19 from bats to human is still unknown. Furthermore, SARS-CoV2 transmission among humans through the aerosols is still a matter under investigation (Zhao *et al*., 2020). The extremely high transmissibility of SARS-CoV-2 and progression of disease may also be dependent on the human genetic factors; however, such factors are still largely unknown and under investigation. Despite of all these facts, the two key host factors of SARS-CoV-2, mainly ACE2 and TMPRSS2 have been investigated, to find out the SARS-CoV-2 unique genetic susceptibility recorded from ~ 81,000 human genomes across the different populations infected with coronavirus. The functional polymorphisms detected in ACE2 and trans-membrane protease, serine 2 (TMPRSS2) may lead to significantly different incidences and mortality rates among the COVID-19 patients (Hou *et al*., 2020). Recently, a study conducted by Asselta *et al*., (2020) suggests that TMPRSS2 variants and their resulting expressions may have more influence on the severity of COVID-19. The susceptibility and severity of COVID-19 have been found to be associated with genetic variability histocompatibility complex (MHC) and class I genes (human leukocyte antigen [HLA] A, B, and C). Furthermore, it has been also reported that specific HLA-B*46:01 gene product exhibits the lowest binding capacity to SARS CoV-2 virulent peptides, as the individuals infected with this allele may be more susceptible to COVID-19 disease. In contrast, the HLA-B*15:03 encoded protein has significant capacity to present the highly conserved SARS-CoV-2 peptides, which probably exist among all the commonly known human coronaviruses. This suggests that patients with this HLA genotype are probably more likely to develop immunity (Nguyen *et al*., 2020). Thus, for the management of SARS-CoV-2, systematic investigations should be intensified by the medical practitioners and scientific research communities, to study the functional polymorphisms in ACE2 and TMPRSS2 among the different populations. Such targeted studies could potentially pave the way for precision medicine/ drug development, discovery of efficient therapies, and personalized treatment strategies for COVID-19.

6. Diagnosis

Diagnosis of a disease is important in locations that have severe outbreaks, as identification of the patients will help in developing the public health measures and control the rate of outbreaks. Various types of diagnostic tools are available to identify COVID-19 infection including:

6.1. Routine laboratory tests

Changes in the various routine laboratory tests, such as muscle enzymes, lactate dehydrogenase (LDH), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), myoglobin, peripheral blood lymphocyte, and D-dimer, depict the severity of COVID-19 infection in particular cases. For example, in early stages of the ailment, the WBC count may be normal or low; however, the lymphocyte count decreases. In critical cases of COVID-19, an elevated troponin is observed. Most of the COVID-19 patients have elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), but normal procalcitonin. In case of severe patients, increased D-dimer and decreased peripheral blood and lymphocytes are observed. Similarly, elevated inflammatory factors are recorded in the severe and critically ill patients (Ibrahim *et al*., 2021).

6.2. Radiological imaging

Radiological examinations are also implied in early detection, control, and analysis of COVID-19. At the early stages of infection, there are usually no abnormal findings to be observed with the digital radiography (DR). For this purpose, computed tomography (CT) is recommended in cases of early analysis of subtle changes, which could not be detected with DR (Pan *et al*., 2020). Most of the chest CT observations include peripherally dispersed multifocal ground-glass opacities (GGOs) associated with patchy consolidations. The extent of COVID-19 disease progression depends upon the increase in numbers and density of GGOs in the chest CT (Zu *et al*., 2020).

6.3. Etiology assay

Reverse transcription PCR (RT-PCR) assay is widely used in the early diagnosis and monitoring of SARS-CoV-2 infections. To identify the RNA of COVID-19, samples of sputum, nasopharyngeal swabs, lower respiratory tract secretions, blood, and feces are collected, and then applied to Next Generation Sequencing (NGS). The specificity of RT-PCR assay has been recorded to be 59 to 78.2 % of the tested cases (Ai *et al*., 2020; Fang *et al*., 2020). The viral RNA can be detected in the early stages of clinical symptoms with this RT-PCR assay, even if negative CT findings have been recorded (Yang and Yan, 2020). The gene sequencing analysis is able to identify the SARS-CoV-2 RNA accurately. The major disadvantages of the RT-PCR assay are being very expensive and time consuming; accordingly, gene sequencing analysis is mostly recommended for research on the origin and types of SASR-CoV-2 (Feng *et al*., 2020).

6.4. Serological tests

The serological assays are based on detection of the antibodies that are produced in the patient's blood due to onset of the disease. The specific antibody IgM that is formed in response to COVID-19 infection is generally detected after 3 to 5 days of the disease onset, whereas detection of the IgG antibody requires a recovery period that is 4 times higher than that of the acute phase. Results of the recent study conducted by Li *et al*., (2020) that have been recorded in 397 cases, demonstrated that sensitivities of the specific IgM, specific IgG, and specific IgM^+ antibodies are 18.1 %, 6.0 %, and 64.5 %, respectively. The serological assays are quick, require 15 min. only to generate results, and could be used as rapid screening tests the in fields and in the laboratories.

7. Treatments of COVID-19

Up to date, there is no exact treatment for COVID-19, and the antibiotics have no effects against this viral infection, thus the scientists are still struggling to test for the possible treatments of such infections. The majority of cases with mild symptoms, including fever; body aches, coughing, sore throat, and breathing problems can be controlled by consuming counter medicine prescribed by the physicians, and such people will be easily recovered by treating themselves at home or by getting personal medical care. To fight COVID-19, many clinical trials are ongoing for developing and testing some already existing drugs to relieve the symptoms. To fight Ebola virus, an antiviral drug has developed named Remdesivir, which has been approved by the food and drug administration (FDA) to be used by the physicians for treating the hospitalized COVID-19 patients. According to the recent research studies carried out in U.S., remdesivir speeds up the recovery of patients suffering from the COVID-19 disease by 31 % faster. However, clinical trials on another drug termed Tocilizumab are in progress for treating the autoimmune conditions (Eastman *et al*., 2020).

A new drug named Corticosteroid dexamethasone has been approved by the U.S. National Institutes of Health for the severe COVID-19 patients, who require mechanical ventilation and/ or supplemental oxygen. Convalescent plasma therapy has been also recommended by the FDA for emergency use to treat the COVID-19 patients and to help them to build their immunity. To relieve the severe COVID-19 symptoms,

supportive care must be also provided that include bed rest, medication or cough syrup, and the use of pain relievers such as acetaminophen and ibuprofen (FDA. 2020).

Conclusion

Globally, one of the major risks to the healthcare workers and human populations is SARS-CoV-2 virus or COVID-19. Scientists are constantly working to develop a specific antiviral drugs or vaccines for controlling this fatal COVID-19. To reduce or control the infection rate of COVID-19, it is important to spread knowledge and to inform the people about ways of disease prevention. Moreover, additional researches should be performed to study the mode of replication; transmission, and pathogenesis of SARS-CoV-2 in humans. More skills are required to evaluate the toxicological effects of SARS-Cov-2 viruses on the human health.

Conflict of interest

The authors declare that no conflict of interests exists.

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Ethical approval

Non-applicable.

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