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Review Article

Coronavirus Disease 2019 (COVID-19): The Pandemic Challenge

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Abstract

Coronavirus disease 2019 (COVID-19) was emerged in seafood market in Wuhan, China on 31 December 2019. Till, 31 May 2020 WHO reported that more than 5,900,000 people have affected with this virus and more than 367,000 have passed away. this virus has spread to almost all over the world (in more than 200 countries/territories). At the moment, this virus fits best the Darwin Theory of the "survival of fittest", proliferating happily in almost every environment and affecting people of all ages, though frequency varies (depending upon depends upon age or immune system of the infected person). The COVID-19 is a beta-CoV which belongs to sub-genus Sarbeco-virus. Its genome consists on a single stranded RNA which nucleoproteins envelop surround it. Its genomic material is approximately 29 kb long and is arranged in 5UTR-replicase-spike(S)-Envelop(E)-Membrane(M)-Nucleocapside(N)-3UTR order and SEMN encode structural protein. This virus has showed upto 98% homology with bat derived coronavirus and comparatively less similarity with SARS-CoV, BatCoV RatG13 and MERS-CoV, however the original source of COVID-19 is still under investigation. Evidence suggests initial transmission from animal to person and later person to person via contact, droplet or airways. Scientists are working to develop new therapeutic treatment. Previously available drugs Kaletra, nelfinavir, pitavastatin, perampanel and praziquantel were observed as trial candidates against COVID-19. Furthermore, FDA approved antiviral drugs including penciclovir, chloroquine, nalfamusta etc. for the treatment of COVID-19's infections. Currently, different broad-spectrum antiviral drugs such as remdesivir, lopinavir and Ritonavir have showed excellent antiviral effect against COVID-19. To date, there is no approved treatment or vaccine for the treatment of COVID-19 infections and WHO has announced the development of vaccine for the treatment of COVID-19 may take upto 18 month. The development of new antiviral drug for COVID-19 is an urgent need so that human can fight against this virus and future pandemic could be handled. Taken that into account, wearing mask, social distancing, quick timely diagnosing of all the possibly affected cases of COVID-19, isolating them from the public areas and keeping them in quarantine is the only possible solution. New quick diagnostic procedures and preventive strategies may help in fighting the epidemic and pandemic infection of this virus until COVID-19 vaccine is available.

Keywords: *COVID-19; Coronavirus; Epidemiology; nCoV-19; Pandemic; SARS-CoV-2*

Abbreviations

CoV: Coronavirus; COVID-19: Coronavirus Disease 2019; nCoV-19: Novel Coronavirus 2019; SARS-CoV-2: Sever Acute Respiratory Syndrome Coronavirus-2; BatCoV: Corona Virus of Bat Origin; PBUH: Peace Be Upon Him

Introduction

Coronavirus have crown-like spikes on their surface. Therefore, they are known as coronavirus (CoV). These viruses belong to the family Coronaviridae and order Nidovirales. Coronaviruses are well known for their infections in vertebrates including birds, reptiles and mammals [1,2]. To date, seven coronaviruses have been reported. These viruses have long history and descriptions but in short, human coronavirus 229E (HCoV-229E) and (HCoV-OC43) were reported in 1960s, sever acute respiratory syndrome coronavirus-1 (SARS-CoV-1) was reported in 2003, (HCoV-NL63) in 2004, (HCoV-HKU1 in 2005, Middle East Respiratory Syndrome coronavirus (MERS-CoV) emerged in 2012 and the seventh one, COVID-19 is emerging today with rapid proliferative rate [3-5].

With the outbreak of the 2019 novel coronavirus (2019-nCoV) infections in the city of province Hubei (Wuhan) China, from 31 December 2019, it rapidly started spreading in other areas and countries [6]. On 11 February 2020, the World Health Organization (WHO) announced a new name for 2019 novel coronavirus (2019-nCoV): coronavirus disease (COVID-19) and the International Committee on Taxonomy of Virus also renamed the 2019-nCoV to sever acute respiratory syndrome coronavirus (SARS-CoV-2) [7]. To date, COVID-19 has affected more than 5,900,000 patients in more than 200 countries/territories including Pakistan and led to 567,000 death worldwide as data of 31 May 2020. In this way, this virus has become one of the major and sever global health concern (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200531-covid-19-sitrep-132.pdf?sfvrsn=d9c2eaef_2). Keeping in mind, the health of global population and rapid proliferation of COVID-19, the WHO has announced the 6th world emergency on January 30, 2020 [8].

Epidemiology

Based on the results of CoV outbreak in china and then all around the world, the incidence of COVID-19 is increasing with exponential rate as WHO situation report also indicating (Figure 1) and still there are chances of upto eight-fold increase in infection rate [9,10]. Current incubation period of COVID-19 ranging between 2.1 - 11.1 days with the mean of 6.4 and it have potential asymptomatic transmission [11]. The situation of COVID-19 incidence is increasing with proliferative rate and still COVID-19 has great potential to spread further (Figure 1). Although there is decline in corona cases in mainland China but it is increasing its numbers in other countries at a very fast rate as WHO report indicated (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200531-covid-19-sitrep-132.pdf?sfvrsn=d9c2eaef_2).

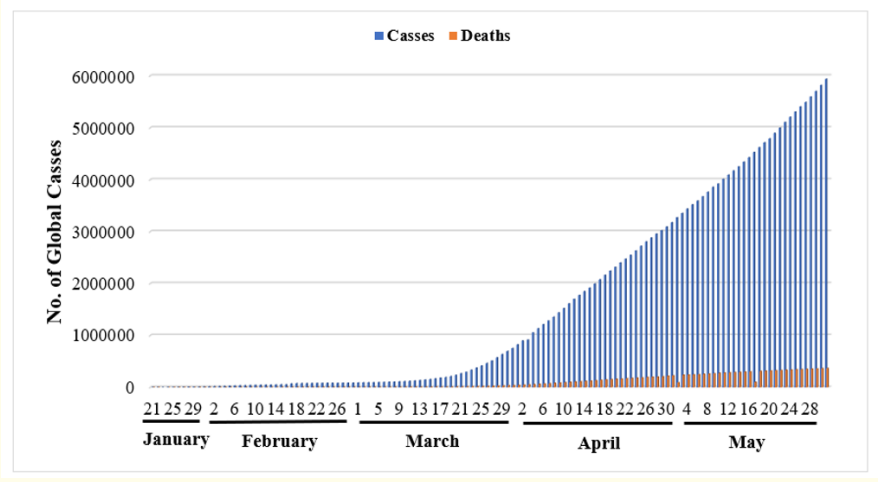

Figure 1: *Daily accumulative cases of laboratory-confirmed cases of COVID-19 as of 31 May, 2020 based on WHO situation reports.*

To date more than 200 countries/territories have reported confirmed COVID-19 cases. These countries include mainland China, Pakistan, India, Iran, Japan, Bangladesh, Russia, Thailand, Germany, USA, UK, Canada, Italy, Finland, Sweden, Cambodia, Madagascar, Australia, Malaysia, Singapore, Philippines, Viet Nam, New Zealand, Brunei Darussalam, Mongolia, Fiji, Papua New Guinea, Spain, France, Switzerland, Netherland, Austria, Belgium, Norway, Poland, Indonesia, Bhutan *etc*. USA is at top with 1,716,078 cases and 101,567 deaths. Total 5,900,000 cases have been reported worldwide with 367,000 death. (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200531-covid-19-sitrep-132.pdf?sfvrsn=d9c2eaef_2).

Origin

Many studies have indicated that wild animals and bats are the natural reservoirs and play fundamental role in transmitting different viruses like Ebola, Nipah and Coronaviruses [12]. COVID-19 is the seventh among the family of known corona viruses. COVID-19 is a beta-CoV which have 70% genetic similarity to SARS-CoV. Many researchers have reported that COVID-19 is also originated from bats like SARS-CoV and MERS-CoV. But there is little controversy about idea and it should be confirmed whether this pneumonia can transfer directly to human OR through intermediate host [13-15].

Advanced research and complete genome sequence revealed that the COVID-19 have 96% similarity with a bat's coronavirus (Figure 4); this means that COVID-19 belongs to bat [14,15]. Wu D., *et al*. [16] reported that bat may be the natural reservoir while minks may be the intermediate host. Other studies have indicated that intermediate hosts may have multiple hosts [17]. To save humanity from these fatal viruses, it is necessary to identify that original reservoir so that these can be prevented [15].

Pathogenicity and symptoms of COVID-19

The S protein of CoV is a structural protein and form spikes, plays important role in entry into the host cell [3]. The virus binds to the receptors with the help of these spike [18]. The CoV make direct contact with the host cell's plasma membrane while entering into the host cell [19]. A critical proteolytic cleavage event occurs at the CoV's S protein on S20 position mediate the membrane fusion and viral infection [20]. In addition, the clathrin dependent and independent endocytosis also play role in the virus entry into the host cell [21].

As soon as virus enter the cell, it releases its RNA in the host's cytoplasm which will be translated in two polyproteins (Figure 3C) and structural proteins, following this step the viral genome will start replication [22]. The recently formed glycoprotein will be inserted into the endoplasmic reticulum or Golgi's membrane and combination of genomic RNA and nucleocapsid protein will form nucleocapsid. After that, the virus will start germination in the endoplasmic reticulum Golgi intermediate compartment (ERGIC). Finally, the virus containing vesicle will fuse with host plasma membrane and release the virus [18].

The symptoms of COVID-19 appear after approximately 5.2 days of incubation period [23]. After the appearance of symptoms COVID-19 take 6 - 41 days to take patient to death. This period has variation because coronavirus highly depends on patient's age and immune system. This period was shorter in the patient having age more than 70 years and was longer in the patient of less than 70 years [24]. The most common symptoms which have been observed in COVID-19's patients are fever, cough, fatigue, sputum production, headache, diarrhea, hemoptysis, lymphopenia, grand-glass opacities, dyspnea and sever pneumonia [4,24-26].

Chest CT scan results reveled that this virus greatly induce severe pneumonia, RNAaemia, acute respiratory distress, acute cardiac injury, and ground-glass opacities and these abnormalities ultimately lead to death (Figure 2). It should be noted that the symptoms of COVID-19 are similar to beta coronavirus which was identified earlier [4]. But, COVID seems to be more severe as it targets the lower airway as evident of upper respiratory distress and chest radiograph of COVID-19 patients revealed that it also produces infiltrate in the upper lobe of the lungs which increase the dyspnea and hypoxemia [27].

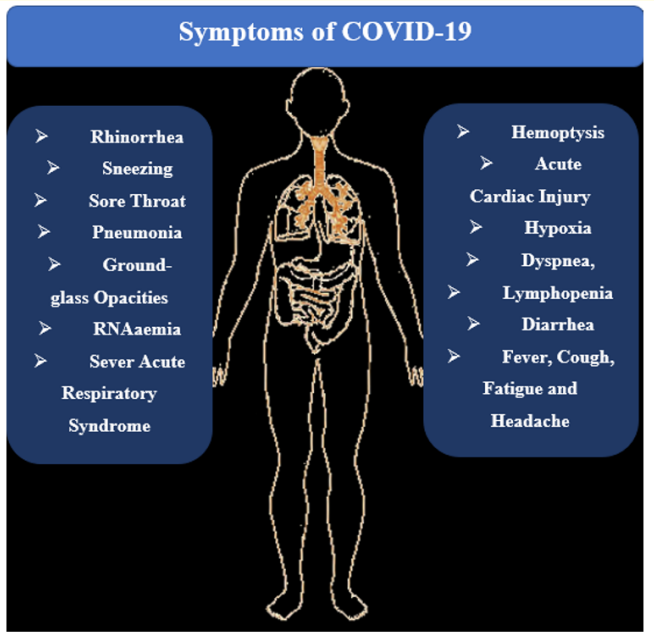

Figure 2: *Different Symptoms which has been observed like Ground-glass opacities, acute cardiac injury etc. COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhea, sneezing, and sore throat. And intestinal disorder like diarrhea which was observed in other CoVs patients.*

Genome and structure of COVID-19

The COVID-19 is a beta-CoV which belong to subgenus Sarbeco-virus. Its genome consists on a single stranded RNA which nucleoproteins envelop surround it. Its genomic material is approx. 29kb long and is arranged in 5UTR-replicase-spike(S)-Envelop(E)-Membrane(M)-Nucleocapside(N)-3UTR order and SEMN encode structural protein (Figure 3A and 3B). Phylogenetic-analysis of COVID-19's complete genome sequence showed that COVID-19 is more closely related to the bats origin CoVs such as Bat-sl-CoVZC45 and Bat-sl-CoVZXC21 (approximately 98% homology). But this virus showed less similarity with SARS-CoV, BatCoV RatG13 and with MERS-CoV. A phylogenetic tree was constructed from the complete genome sequence of different CoVs taken from NCBI, using MEGA-X software following neighbor joining tree method (Figure 4).

The genetic material of COVID-19 contains six functional open reading frames (ORFs) and which consist on ORF1a/b, S, E, M, N and many accessory genes are also present like ORF8 (Figure 3C). Two Replicase polyproteins *i.e.* pp1a and pp1ab would be proteolytically cleaved into the 16 non-structural proteins (nsps). These proteins are responsible for transcription and replication of the COVID-19. ORF3b also encode another novel protein whose function is unknown. ORF8 seems to encode a secreted protein with the involvement of alpha-helix and six stranded beta sheets which have unknown functional domain [28].

The S gene of COVID-19 which encode for structural protein is much less similar with the previously known CoVs. Furthermore, the spike protein encoded by S gene of COVID-19 is much longer than the spike protein of SARS-CoV [14,29]. The spike protein consists of two domains (S1 and S2), both of these domains paly important role in determine the host parasite reaction and mode of transmission. The S2 subunit of COVID-19 is 99% identical with SARS-CoV and is highly conserved [30]. The C-terminal of S1 bear the receptor binding protein

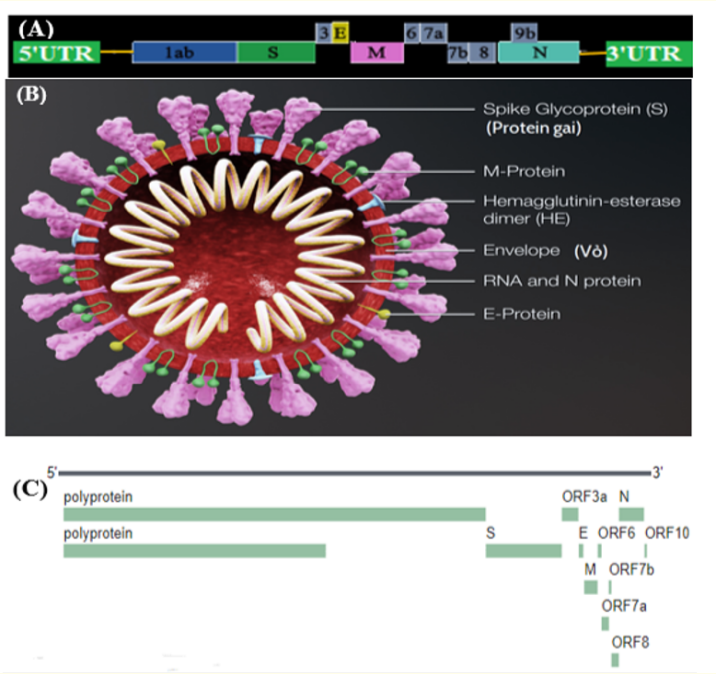

Figure 3: *Genomic organisation and structure of COVID-19. (A). COVID-19 consist on 5 untranslated region (5 UTR) including 5 leader strains, open reading frame (ORF) 1a/b, envelope, membrane and nucleoprotein, accessory proteins like ORF 3,6, 7a, 7b, 8 and 9b. 3 untranslated regions (3 UTR) are also present. (B). COVID-19 consist of single-strand positive sense RNA which is surounded by nucleocapsid protein in the core and four protein are present on the encellope namely: Spike protein, Envelope protein and Membrane protein. (C). Six iopen reding frames (ORFs) are present and severall accesory genes like S, E, M, N, and polyproteins pp1a and pp1ab.*

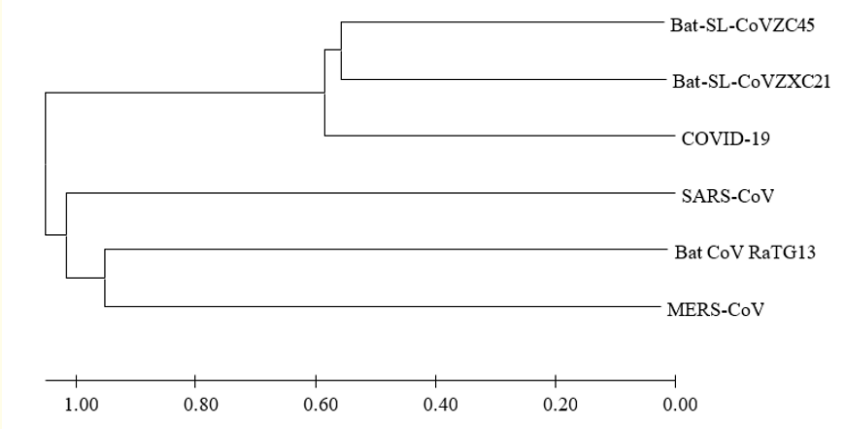

Figure 4: *The genetic variability of COVID-19. The phylogenetic tree was constructed based on the complete genome sequences of COVID-19 and previously available CoVs following neighbor-joining tree method by using MEGA-X software.*

which is responsible for the contact with host cell receptors. Recent studies have indicated that S1 domain of COVID-19 has binding sites, similar with SARS-CoV [30,31]. Recently, Zhou P., *et al*. [14] and Zhao S., *et al*. [9] have reported that COVID-19 use the ACE2 receptor for entry into the ACE2 expressing cells; just like SARS-CoV and much of these are type II alveolar cells. That's why further studies are the need of hour to understand whether ACE2 targeting drugs are a possible solution of COVID-19 infection or COVID-19 become resistant to them.

Transmission

The people infected from COVID-19 in Wuhan, China had history of visiting the sea food market of few days before. This suggests that COVID-19 might have transmitted from initially from animal-to-human. In just a few days, large number of people infected with COVID-19, with no history of visiting the sea food market, proved human-to-human transfer of COVID-19, later suggested either virus mutation or adaptation [30-32].

At the moment, this virus fits best the Darwin Theory of the "survival of fittest", proliferating happily in almost every environment and affecting people of all ages, though frequency varies. Many researchers have reported that this virus transmit through three primary ways; person-to-person contact, aerosol transmission and by touch [33,34]. There also evidence that this can transmit by droplet. When an infected person sneezes or coughs, virus containing droplet can spread to many feet away, to the surface or on to the person present nearby. There also possibilities of ocular surface transmission [30]. Shaking hands with infected person, touching infected objects, frequent touching of nose or face can also lead to COVID-19 infection [31].

Diagnosis and treatment

Diagnosis of CoVs is not required in all the self-limited infection, as most of the patients have clear symptoms of CoVs. Still, it is necessary to identify the infectious agent particularly in epidemic outbreak. Previously, COVID-19 has not been observed in human history that's why no vaccine or treatment is available for the treatment of COVID-19's infection. The number of new corona cases are increasing with proliferative rate, even after the implementation of global emergency. Therefore, diagnosing all the possible cases of COVID-19 as soon as possible and isolating them from the public areas and keeping them in quarantine is the need of hour. New diagnostic procedure and strategies including multiplex nucleic acid amplification and microarray-based assays may help in fighting the epidemic and pandemic infection [35,36]. COVID-19 nucleic acids can be detected in the sample like nasopharyngeal swabs, lower respiratory tract infections etc [37].

Till 31 May 2020 there is no approved treatment or vaccine for the treatment of COVID-19 infections and WHO has announced the development of vaccine for the treatment of COVID-19 may take upto 18 month. It is very challenging task to develop a safe and stable vaccine for this viral infection as the development of a new drug is always a very long process. In this sudden pandemic scenario, the scientists were unable to develop a new vaccine by using traditional methods. A previous study showed that an anti-HIV drug which is known as Kaletra have excellent therapeutic effect on SARS and MERS but its activity against COVID-19 is still under investigations [38,39]. In previous SARS-CoV epidemic, a report from Hong Kong told that the patients treated with Kaletra (400 mg ritonavir and 100 mg lopinavir) for 14 days in combination with ribavirin as initial therapy were recovered while the patients who didn't received Kaletra therapy were died [40]. Hence, National Health Commission of the China recommended "Kaletra" for the treatment of Wuhan pneumonia. Among other options, one is the screening of previously available antiviral drugs in the market and check their activity against COVI-19. In this scenario, one drug, nelfinavir has potential against COVID-19's infection. Additionally, pitavastatin, perampanel and praziquantel were observed to be moderate candidates against COVID-19 [41]. Furthermore, other FDA approved antiviral drugs including penciclovir, chloroquine, nalfamusta etc. are also being characterized for the treatment of COVID-19's infections.

Recent studies have indicated that remdesivir and chloroquine showed excellent results using *in vitro* assay [42]. Chloroquine has the ability to actively inhibit the viral particle by binding with its receptors before its entry into the cell [43]. Furthermore, many studies also

reported chloroquine as versatile bioactive agent against many other viruses like rabies virus, poliovirus, HIV, hepatitis A and C virus, Dengue and Ebola virus etc [44]. Recently, another study on COVID-19 infections reported that chloroquine (EC_{50} = 1.13 µM; CC_{50} > 100 µM, SI > 88.50) potently blocked virus infection at low-micromolar concentration and showed high SI and may be characterized for human use against COVID-19 [42]. The chloroquine is a derivative of thymoquinone (TQ), which is the component of the Black Seed (*Nigella sativa*/ Kalonji seed). The Prophet Muhammad (PBUH) told 1400 years ago that, "the black seed can heal every disease, except death" [45]. The Prophet further announce that "The one who sent down the disease sent down the remedy and for each disease, Allah Almighty has given a cure". Now it's our duty to seek out those remedies and use them with skill and kindness [46].

Preventions and further recommendations

Preventions and management of the coronavirus pandemic and epidemic are summarized in figure 5. Since most of the CoV are of animal origin including COVID-19. Therefore, movement of wild animals to human population and sale should be banned. Hilal/restricted food should be adopted worldwide to avoid any future pandemic or zoonotic disease. Facilities should be enhanced and more research should be done for the early recognition of cause and drug development. All the international routes should be closed immediately to prevent the spread of infection in other counties and all over the world and frequent hand washing should be a practice [47]. One health approach should be adopted, so that no human can infect from any animal in future.

Prevention	Rapid Response	Reducing Viral Transmission	Treatment
❖ Close Wild Animals' Market ❖ Promote Hilal Food ❖ One Health Approach ❖ Restricted Public Movement ❖ Proper Hygiene	❖ Early Detection and Diagnosis ❖ Proper Information Transfer ❖ Rapid Mobilization of Healthcare Personnel ❖ Isolate Contagious Patient	❖ Check Mechanism of Transmission ❖ Aggressive Quarantining ❖ Proper Sanitizing ❖ Minimize Person to Person Contact	❖ Vaccine Development ❖ Other Anti-viral Drug Development ❖ Supportive Care Measures ❖ Improving Healthcare Facilities

Figure 5: *Key to control future CoVs pandemic. Based on the results of COVID-19 and previously known CoVs's pandemics.*

New techniques are the need of hour to prevent the further spread of epidemic like treatment efficiency, better diagnostic procedure, determine transmission pattern, isolating contagious patients and batter quarantine strategy. There should be strict control in medical institutions and research center. So, that no infection can emerge from these sites. There should be no more movement of people towards the infected area and proper on time information should be given to the people. The health system should also be strong enough to handle any epidemic situation. Wearing masks and social distancing should be mandatory and penalties should be implemented in case of not following preventive measures by general public. Artificial intelligence should be adopted for batter integration of information and conduct comprehensive research and analyze public health risks. Use of internet, social media and electronic media must provide correct knowledge to public for prevention and provision of online and quick consultation to guide patient seeking medical advice [8,47,48].

Conclusion

The COVID-19 was reported in Wuhan, China. The patients reported with CoV had history of visiting Hunan seafood market where live bats, snakes, raccoon, dogs, palm civets and many other animals sold. This virus started spreading to other areas of the China and world and now, more than 200 countries/territories has been affected with COVID-19. The original source of COVID-19 is still under controversy but phylogenetic analysis of complete genome sequence of COVID-19 which was found in Wuhan and from other Bat-derived CoV suggest that this virus is also has Bat origin. Still, no promising treatment has been developed for the cure of COVID-19 and researchers are still working to develop an efficient antiviral drug for COVID-19 treatment and strategies to prevent spread of this virus. Currently, different broad-spectrum antiviral drugs which are available in market are being characterize for the development of new therapeutic treatment for COVID-19. Remdesivir, Lopinavir and Ritonavir have showed excellent antiviral effect against COVID-19. The development of new antiviral drug for COVID-19 is an urgent need so that human can fight against this virus and future pandemic could be handled. Wild animal markets must be closed and restricted food must be a routine. Recently chloroquine emerging as permissible treatment for coronavirus disease. Chloroquine is a derivative thymoquinone which is a component of black seeds (*N. Sativa*/ Kalonji seeds) and Prophet Muhammad 1400 years ago told us that "the black seed can heal every disease, except death".

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Competing Interest

Authors have no competing interest.

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