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Review Paper:

The Pathogenicity of MERS-CoV, SARS-CoV and SARS-CoV-2: A Comparative Overview

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Abstract

The ongoing detrimental consequences of SARS-CoV-2 or COVID-19 are attributable to its remarkable pathogenesis and modes of transmission. Originating from a common ancestor of the previous coronavirus outbreaks, MERS-CoV and SARS-CoV-1, the former has been evolved in terms of its pathogenic mechanisms, routes of transmission and the extent of infection. The comprehensive evaluation of these modifications at the molecular level would reveal astonishing details about the extensive lethality of the current SARS-CoV-2 outbreak.

Further, these details can be utilized for the development of effective and specific treatment methods. This review elaborates the comparative assessment of the viral characteristics of coronaviruses: MERS-CoV, SARS-CoV-1 and SARS-CoV-2. With the comparative account, the study endeavours to leave a clear picture explaining the reason behind the extensive lethality of the current SARS-CoV-2 pandemic.

Keywords: SARS-CoV, MERS-CoV, Pathogenesis, Transmission, Infection.

Introduction

The past two decades of the 21st century have witnessed several malicious biological hazards that took the entire globe into an appalling situation including Ebola, Zika and Nipah viral outbreaks to name a few. However, they stood no match for the disastrous outbreak of severe acute respiratory syndrome-2 (SARS-CoV-2) or COVID-19 and its consequences.[34] Since its emergence in December 2019, the latter has resulted in a steep escalation in mortality rates. Expanding to the different parts of the world, it gained a status of the pandemic within no time due to its profound pathogenicity, transmission and resistance to the available therapeutic options.[54,65]

Though there were reports of outbreaks of other viruses from the same family, they were not as infectious as of the SARS-CoV-2. For example, four endemic human coronaviruses HCoV-229E, -NL63, -HKU1 and -OC43 were known to circulate in human blood yet causing no major casualties. It was reported that HCoV-229E and -OC43 accounted for 15–29% of respiratory pathogens with relatively reduced viral load which serves as a rough approximation.[15,76] The other two viruses HCoV-NL63 and -HKU1 were discovered only in 2004 and 2005 respectively, leaving negligible chances of a major outbreak due to their endemic nature.[15] But the health crisis began in 2003 when China reported the first of their epidemic kind, the SARS-CoV-1 or severe acute respiratory syndrome-1. This epidemic was responsible for the death of 919 people and 8422 cases, with the fatality rate of 11.0%.[76]

The zoonotic transmission of SARS-CoV-1 from December 2003 to January 2004 became a pavement for researches into the origin of this epidemic. Though it was declared as over in 2004 with no further cases detected, demonstration of SARS-CoV-like viruses found in bats revealed the chance of re-emergence of SARS in future.[44]

In support of this prediction, another epidemic coronavirus known as MERS-CoV (Middle East Respiratory Syndrome Coronavirus) was detected in the sputum of a deceased pneumonia male patient with renal failure in Saudi Arabia. The epidemic caused 858 deaths and 2494 cases with a fatality rate of 34.4% from 27 different countries.[76] The increased fatality rate was attributed to nosocomial infections and international travels that made it a global threat. In May 2015, South Korea reported the outbreak of MERS-CoV due to a returned individual from Middle East.[19] Besides a tremendous progression is made towards deciphering the biological features of SARS-CoV-1 and MERS-CoV at an unprecedented speed, a shocking and detrimental outbreak of COVID-19 has resulted in 387,155 deaths and 6,535,354 confirmed cases from 213 countries across the globe with an increasing death rate as of 6th June 2020.[71]

Although MERS-CoV and SARS-CoV-1 share several common and important features that are responsible for nosocomial transmission, preferential viral replication and viral immunopathology, SARS-CoV-2 stands with few uncommon characteristics that make it more malicious.[57] Though it has been isolated and the mechanisms of its pathogenicity and infectivity are deciphered, there is much room to know and highlight the viral mode of action, life cycle and pathogenicity.[17] This review focuses on the effective life cycle, severity, transmission modes, therapeutic options of SARS-CoV-2 to highlight its pathogenicity over the other two epidemic coronaviruses.

Animal Origin and Evolution

It becomes essential to note that two of the three viral outbreaks emerged from China and all the three shared the same zoonotic origin. China is said to be a homeland for diverse climates which bring about greater biodiversity. This allows bats and bat-borne viruses, most of them are ICTV coronavirus species, to grow in it making the country a hotspot for the viral growth. On the other hand, animals and meat products are extensively sold in Chinese wet markets which might have caused these viral outbreaks.[20]

Coronaviruses belong to the subfamily *Coronavirinae* in the family *Coronaviridae* and the order *Nidovirales.* The subfamily comprises four genera – α, β, γ and δ, based on their genomic constituents and phylogenetic relationships. α and β genera notably affect the mammals including humans whereas the other two affect birds. SARS-CoV and MERS-CoV are said to be highly pathogenic among the coronaviruses and can cause a severe acute respiratory syndrome in humans while the other 4 endemic viruses including HCoV-229E, -NL63, -OC43 and -HKU1 can only result in the development of mild upper respiratory disorders.

The origin of the SARS-CoV, MERS-CoV, HCoV-229E and -NL63 is expected to from bats whereas HKU1 and HCoV-OC43 are likely originated from rodents. Several studies conducted showed that bats are the origin of coronaviruses. But few of the clear examinations conducted at the molecular level revealed that the SARS-CoV-1 was found to be originated from both bats as well as palm civets.

Genome analysis of bats and palm civets revealed that a 29-nt sequence acts as a marker which is also expressed in humans as well[58] indicating the route of transmission of the virus to humans. However, a probe-based next-generation sequencing (NGS) showed that SARS-CoV-1 seems to have originated only from bats,[41] strongly supporting the idea of SARS originating from bats. Analysis of recombination has showed that civet SARS-CoV strain SZ3 was produced due to the recombination of WIV16 and Rf4092, the 2 existing bat strains revealing the role of palm civet as a reservoir as well as an intermediate host.[17]

Also, the presence of accessory proteins and other several gene products showed 89-90% genome similarity between bats and humans whereas phylogenetic evaluation proved the same.[58] In addition to palm civets, SARS-CoV-1 was also reported to be found in raccoon dogs of Chinese origin. The spike protein sequence SZ13 of raccoon dogs was found to be identical to SZ16 of palm civet.

Similarly, 2 other proteins, A030G and A031G are found to be identical to A022G indicating that raccoon dogs are also the potential reservoirs and intermediate hosts of SARS-CoV-1.[74] These studies insisted on the role of bats as primary hosts and other animals as intermediates. Apart from palm civets, bats were also found to be the potential reservoirs of MERS-CoV as well. A study found that 12 of the bat cells were susceptible to MERS-CoV infection based on which it was reported that the virus can replicate in the cells. The mRNA sequence analysis also revealed the presence of DPP4 or CD26, a receptor which is used by the MERS-CoV to enter the host cell.[38] Apart from bats, MERS-CoV is also reported to be originated from dromedary camels. Identification of prevalent MERS-CoV specific antibodies present in camels from the Middle East, Africa, Asia and detection of infections in camel serum showed the presence of virus from 30 years.

Genomic sequence of *Tylonycteris* bat HCoV-HKU4, *Pipistrellus* bat HCoV-HKU5 and MERS-CoV revealed that they are phylogenetically related.[17] Further, the respiratory sample analysis of patients, as well as camels affected with MERS-CoV revealed the presence of nearly identical genomes[52] indicating the role of dromedary camels as a potential reservoir and an intermediate host, though the original infection is said to be caused by bats.

In the vista, a coronavirus isolated from Malayan pangolin showed a 99% similarity with SARS-CoV-2, although it showed 96% similarity in case of bats. Five of the six amino acids from the receptor-binding domains (RBD) of both pangolin-CoV and SARS-CoV-2 are found to be the same. In support, the infected pangolins exhibited pathological symptoms like humans suffering from COVID-19 suggesting that they were a potent intermediate host between bat and humans. Studies on the S, N and ORF1a/1b genes suggested that SARS-CoV-2 was transmitted to humans by adapting evolutionary mechanisms. However, a comparative analysis of genetic data showed that SARS-CoV-2 originated from the recombination of pangolin-CoV and bat-CoV-RaTG13 virus,[48] yet again supporting the role of pangolin as a reservoir. But a contradictory theory suggests that laboratory manipulation of SARS-CoV-1 and MER-CoV resulted in the genesis of SARS-CoV-2.[41]

In addition, another study suggests the involvement of snake coronavirus in the production of recombinant SARS-CoV-2 alongside bat coronavirus. But the truth is yet to be revealed about these suggestions.[36] Though the MERS-CoV and SARS-CoV-1 had a definite primary host (bat) and several confirmed and potential intermediate hosts, SARS-CoV-2 was not found to be related with a definite host. The evolutionary mechanisms possessed by SARS-CoV-2 resulted in its effective transmission over the others. Hence, further studies are essential to confirm the role of intermediate hosts and to examine the manipulation of genetic recombination to control the outbreak of such a pandemic in future.[73]

Structural and Genomic Features

All the three epidemic coronaviruses share common features in terms of their structures and life cycles. Though one can notice few minute variations in case of their genomes, they ultimately lead to differences in the extension of

pathogenicity and transmission.[59] These variations have evolved in favour of the virus. Under electron microscopy, the virions generally appear as spherical shells with surface projections which are known as spike proteins, altogether creating an image like a solar corona. The single-stranded, positive-sense RNA is embedded inside the protein-coated envelope. This genome acts as a messenger (mRNA) with 5' cap and a 3' polyadenylated tail. Generally, it is believed to play three roles in case of all the three viruses; i) principal molecule for the completion of the infection cycle, ii) template for the process of replication and transcription and iii) packaged substrate in the newly formed viral particles.[66] In addition, it encodes the four structural proteins known as the spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins.

Though the structural proteins are the same, viruses differentiate from each other in terms of their accessory proteins as well as their nucleotide sequences. For example, SARS-CoV genome comprises a total of 29,727 nucleotides in length including the highest number of (11) ORF's (open reading frames) whereas the genome of MERS-CoV includes 30,119 nucleotides length coding for 5 accessory proteins encoded by ORF3, ORF4a, ORF4b, ORF5 and ORF8b. On the other hand, SARS-CoV-2 comprises 29,811 nucleotides with 6 accessory proteins encoded by ORF3a, ORF6, ORF7a, ORF7b and ORF8. These proteins might help the virus to evade the immune system to suppress the innate immune response.

The genome of the MERS-CoV comprises a 5'-terminal cap structure and a polyadenylate tail at the 3'-end. There is also a *rep* gene which includes 16 non-structural proteins (nsp1–16) at the 5'-end of the genome. The 3'-end of the genome contains structural proteins as well as accessory proteins.[59]

Unlike the other β-CoV's, MERS-CoV genome does not encode for hemagglutinin-esterase (HE), a viral envelope glycoprotein that facilitates the surface adsorption of virus and the host cell membrane. Instead, it uses another surface protein known as dipeptidyl peptidase-4 (DPP4) or cluster of differentiation 26 (CD26).[4] Apart from this, both the SARS viruses are known to share >80% similarity between them accounting for the same origin. The phylogenetic analysis also reveals that both the viruses are closely related than the MERS-CoV.[73] The ORF1b is said to be the largest gene in SARS-CoV-2, encoding pp1ab protein and 15 nsp's. However, few notable differences like an absence of 8a protein and variation in the number of amino acids in 8b and 3c proteins in SARS-CoV-2 can be noted.

As the spike (S) glycoprotein plays a significant role in the viral adsorption to the host cell, it is reported that the glycoprotein is modified via homologous recombination. Hence, the S glycoprotein SARS-CoV-2 has transformed into a mixture of SARS-CoV-1 and an unknown β-CoV. Along with SARS-CoV-1, SARS-CoV-2 too uses the Angiotensin-Converting Enzyme-2 (ACE-2) to bind to the host cell while a single N501T mutation in the SARS-CoV-2 might have significantly enhanced its binding affinity towards ACE2.[57] The receptor binding domain (RBD) and receptor-binding motif (RBM) of MERS-CoV and SARS-CoV greatly differ from each other in terms of their amino acid composition which leads to the differential binding process.[59]

The six regions of difference (RD) are present in the RNA of SARS-CoV-1 and 2 (RD1 to RD6) where RD1, RD2 and RD3 (448nt, 55nt and 278nt respectively) are responsible for the partial coding of ORF1a/b gene. RD4 and RD5 (315nt and 80nt respectively) are associated with the S gene, RD6 is of 214nt in size and is responsible for the partial coding of ORF7b and ORF8 genes. These RD's pose as potential markers for the identification of SARS-CoV-2 and may also aid in the development of new drugs.[73,75]

It is also reported that at the 5`-terminus, Pb1ab is the first ORF segment which encodes non-structural proteins with different sizes: 7073 aa (SARS-CoV-1), 7078 aa (MERS-COV) and 7096 aa (SARS-CoV-2). At 3`-terminus, the spike protein varies as 21493 aa (SARS-CoV-1), 1270 aa (MERS-CoV) and 1273 aa (SARS-CoV-2). Genetically, SARS-CoV-2 was found to be less similar to SARS-CoV-1 (about 79%) and MERS-CoV (about 50%).[45]

In addition to this, the proteomic analysis revealed that SARS-CoV-2 is different from human-derived SARS-CoV-1 in terms of two proteins ORF8 and ORF10. An aggregation motif derived from amino acid sequence 75-79 of the ORF8 obtained from SARS-CoV-1 was reported to trigger intracellular stress pathways along with the activation of NOD-like receptor family pyrin domain-containing-3 (NLRP3) inflammasomes. Thus, it becomes essential to evaluate the role of these two genes in SARS-CoV-2.

In addition, spike stalk S2 and N proteins in SARS-CoV-2 are highly conserved and share >90% identity with the bat-CoVs (bat-SL-CoVZC45 and bat-SL-CoVZXC21) and human-derived SARS-CoV-1. Along with the inhibition of gene products, the development of antiviral peptides can also be focussed with these studies.[73,75] The lethality of the SARS-CoV-2 can be assessed by the in-depth analysis of these variations supporting the development of new approaches to tackle the COVID-19.

Viral Progression in Host Cell

Life cycles of coronaviruses follow a similar outline which comprises the host cell-virus interaction, viral adhesion and replication.[45] All the viruses are known to interact through S protein with its complementary receptor on the surface of the host cells. The specificity of this interaction determines the tissue tropism and host range of the viruses that are the two important parameters of the viral adhesion.[3] Additionally, the complexities can be observed in terms of receptor binding, interaction and preferential replication in target cells. For example, SARS-CoV-1 uses ACE2 as one of the

main receptors and CD209L as an alternative with much lower affinity compared to the former.[31]

As ACE2 is expressed more in respiratory tract including alveolar cells, trachea, bronchi, serous glands of bronchi along with alveolar monocytes and macrophages, SARS-CoV-1 tend to enter and target these cells and replicate within them.[83]

Meanwhile, ACE2 also pretends to appear on the endothelial cells of arteries and veins, epithelial cells of renal tubules and kidneys, epithelial cells of the intestinal mucosa, cerebral neurons and immune cells like monocytes and macrophages. It provides a variety of cells to SARS-CoV-1. In case of MERS-CoV, the primary receptor for the binding is DPP4 or CD26.[76] This receptor is expressed notably on epithelial cells of kidney, alveoli, liver, prostate, small intestine and dendritic cells.

In addition, both SARS-CoV and MERS-CoV have the capability to infect immune cells including leucocytes, monocytes and macrophages, eventually leading to the disruption of the immune system.[83] The virus is also reported to deregulate the antiviral responses of T-cells due to its targeted approach towards them, as they possess high amounts of DPP4.

In a recent study, it was reported that MERS-CoV uses another alternative receptor known as GRP78. Through the flow cytometry and immunostaining methods, it was found that spike protein effectively binds with GRP78. It is reported to be highly conserved ER-residing chaperone which facilitates protein folding and assemblage. In addition, GRP78 is also reported to aid in the viral entry.[12] Another study revealed that the spike protein of MERS-CoV can induce adaptations in DPP4 from various backgrounds and can effectively invade the host cells.[39]

Compared to the other two viruses, SARS-CoV-2 uses TMPRSS as an alternative receptor to attach with the host cell. Like ACE2, TMPRSS2 also facilitates the viral entry to the cell. During this, it becomes essential for the spike protein to get cleaved and activated to facilitate the viral entry to the cell.[24] On the other hand, hemagglutinin esterases (HE) can also be found on the surface of some host cells which are the group of viral envelope glycoproteins that facilitate the viral adsorption.[4] It was reported that the CoV-hemagglutinin (CoV-HE) complex thus formed because of adsorption underwent remarkable modifications to facilitate the optimal binding of the SARS-CoV-2 into the host cell.

It is also reported that the plasticity of CoV-HE is attributed to the functional redundancy between spike protein and hemagglutinin component.[79] Therefore, it becomes evident that ACE2, TMPRSS2 and hemagglutinin also play an important role in the binding of the SARS-COV-2 to the host cell. However, these receptors and binding complexes can be targeted to develop novel antiviral drugs.

In case of a successful invasion, all coronaviruses show similar patterns of replication and translation inside the host cell. They use the host cell machinery to complete the replication. The corona viruses possess a non-segmented and positive-sense (+) RNA genome of varying length. They are reported to use their own RNA replicase enzymes to facilitate the replication. After the binding, adsorption and release of the viral genome, the life cycle of these viruses involves these steps: i) replication ii) translation iii) assemblage of the genome and peptides and vii) release of the progeny virus.

As the genome consists of at least six ORF's, the first ORF (ORF1a/1b) which has spread about two-third of the viral genome length encodes 16 nsps's. ORF1a and 1b comprise a frameshift sequence in between which produces two peptide chains known as pp1a and pp1b.[3]

Further, these polypeptides are processed by virally encoded chymotrypsin-like protease (3CLPro) or main protease (Mpro) and one or two papain-like protease into 16 nsp's. Subsequently, all the structural and accessory proteins are translated into a single guide RNA (sgRNA) of the viruses ORF10 and 11 which are present near the 3'-terminus and cover one-third of the genome encode for the four main structural proteins.[21] Apart from these, special structural and accessory proteins are produced like 3a/b protein, 4a/b protein and HE protein. These proteins are further responsible for the maintenance of the genome and viral replication.[9] In addition, a few abundant proteins are present in the membrane of the viruses.

The membrane (M) glycoprotein spans the membrane bilayer three times with a short NH_2-terminal domain projecting outside the virus and a long -COOH terminus behind inside the virion. The spike (S) protein belongs to the class of type-1 membrane glycoproteins which comprises the peplomers. Apart from binding, it aids the neutralisation of antibodies. The formation and composition of coronaviral membrane arise as a possible interaction between these envelope proteins whereas the synthesis of intracellular viral particles is facilitated by M protein.[45]

Further, the arrangement of N, E and M proteins is also different in these viruses. With these variations present, species-specific approaches at the molecular level can be used for the effective treatment.[22] The spike protein plays an important role in the life cycle of the virus. Several studies have been conducted to deduce the structure and function of the glycoprotein. Special attention should be given to the S protein as it is reported to possess several mechanisms to induce modifications with respect to its subunits and their respective receptor binding domains (RBD) and motifs (RBM). This ultimately results in the formation of modified binding complexes, facilitating effective binding and adhesion.[42] The preferential modifications in these domains provide the evidence for the evolution of SARS-CoV-2 in terms of its extensive pathogenesis.

Symptoms and Severity

Events followed in the life cycle depict the role of cellular receptors and their subsequent binding with the glycoproteins with the virus to form the binding complexes which further result in the viral infection.[25] In case of SARS-CoV-1, presence of ACE2 on different body cell initiates the aerosols, urine, sweat and stools of the patients to get infected with viral particles which are subsequently released into the surrounding environment and contaminate it.[26] Normally, SARS infected patients exhibit symptoms associated with pneumonia with rapid respiratory deterioration resulting in acute respiratory distress syndrome (ARDS) within the incubation period that lasts between 2-6 days or more.[43]

People with this condition also develop an increasing volume of fluid in their air sacs which results in difficulty in breathing. Due to the enhanced activated proinflammatory chemokine and cytokine secretion, atypical pneumonia with respiratory system failure can be seen.[59] Furthermore, neurological evaluation of few patients depicted the development of axonopathic polyneuropathy 3-4 weeks after the infection. Patients have also been reported with myopathy and rhabdomyolysis. Large artery ischemic stroke was also reported in few patients in case of critical illness.[63]

In case of MERS-CoV, presence of DPP4 or GRP78 receptors can lead to the development of acute and highly lethal pneumonia with renal dysfunction. The incubation period of the virus was found to be 6.4 days where a significant number of deaths occurred within 7 days.[68]

The other clinical symptoms include fever, chills, sore throat, cough, dyspnea, myalgia, chest pain, diarrhea, vomiting and abdominal cramps. In addition, it also exhibits the infiltration of macrophages and neutrophils and alveolar edema. The virus is reported to primarily affect the lungs followed by heart, liver, kidney and brain.[10] Severe symptoms observed in case of fatalities include pulmonary edema, damage of hyaline membrane, type-2 pneumocyte hyperplasia and lymphocytic intestinal pneumonia. It may also result in the development of neurological diseases.[2,3]

However, presence of some pre-existing medical conditions including diabetes, cancer, cardiovascular disease, chronic lung and kidney diseases often weakens the immune system of the patients, subsequently making them more likely to get affected.[7] The incubation period for SARS-CoV-2 is of 14 days while the onset of symptoms is within 4-5 days. SARS-CoV-2 infection would develop symptoms within 11.5 days in the infected person. Patients would witness similar clinical symptoms to pneumonia that are also observed in SARS-CoV patients.

Apart from these symptoms, excess of sputum production and muscle pain, disorientation, mucus fluid secretions in the nasal cavity, mucus containing blood stains from the lungs can be observed.[8,75] In some cases, abdominal distension and recurrent inclination to evacuate the bowels were also observed.[69] The patients admitted initially of heart palpitation and the chest tightness was also found to be infected, as most of the cardiovascular diseases possess high secretion of ACE2. It was also found that SARS-CoV-2 infected patients had at least most common disorder, either hypertension or the diabetes mellitus. Due to the possible adverse effects of drug-drug interaction, it is now recommended that such patients should be more careful and avoid contact with the infected person.[27,82]

Lately, patients with smell blindness i.e. anosmia and parageusia mean confusion of sense of taste were also seen. Like SARS-CoV-1 and MERS-CoV, neurological outcomes have described the possible presence of disease with skeletal muscle injury, acute cerebrovascular disease and impaired consciousness. However, studies are yet to focus on the issue to decipher the appropriate link.[35]

Transmission

Several serological studies conducted reveal that mild or asymptomatic MERS-CoV infections are difficult to assess due to their regular occurrence. Further analysis of human-to-human transmission cannot be performed with these cases due to their infrequent nature. Literature suggests that <50% of the infected people can transmit the disease further to healthy individuals they encounter with even in the early phase of the outbreak.[46] This indicates the prevalence of zoonotic transmission including camels and palm civets. However, unexpected breakouts of nosocomial origin tend to increase the human-to-human transmissions in a regular fashion.[70]

Recent outbreaks in South Korea and England are the remainders of the possible mayhem where travellers from the Middle East were responsible for it.[11,61] Studies suggested that the consumption of camel milk and a close encounter with camel urine are the possible ways of transmission.[28] It was also suggested that people consumed raw and uncooked meat along with vegetables would develop MERS-CoV symptoms.[51] The chief reason behind the transmission of the virus in humans is the result of exchanging aerosols between a healthy and an affected individual.[28]

In a study, MERS-CoV was evaluated for its transmission capabilities in two sets of climatic conditions. At the normal temperature (25^0 C), the virus exhibited high robustness and profound survivability. About 63.5% of microorganisms retained their infectiousness for 60 mins after aerosolization whereas in case of high temperature like that of Middle Eastern region (38^0C), viral decay was observed with a mere 4.7% survival rate over 60 min of the procedure.[55] This study indicated the role of temperature in the survival of the virus, even though it was not declared as a thermosensitive.

Though all the coronaviruses tend to be airborne pathogens, SARS-CoV-1 and SARS-CoV-2 show higher stability in the

air. Both the viruses possess similar transmission mechanisms and are more likely to spread in a community in close contact scenarios.[40] Fomites, touching the contaminated objects and body parts can equally transmit the disease along with airborne discharge and intake of the particles which is also route of transmission, where respiratory droplets or aerosols can be transmitted between individuals.[34] In case of MERS-CoV and SARS-CoV-1, viral shedding occurs only after the onset of symptoms, hence transmission occurs after the medical help. It is one of the notable factors where the progeny is released into the external environment, subsequently after the reproduction and particle assemblage in the host.[53]

However, in case of SARS-CoV-2, it was reported to spread even far before the occurrence of symptoms and possess similar half-lives (1.1-1.2 hrs) in aerosols. In this study, the artificial transmission of infection by airborne route was analysed *in vitro*, where the surface stability of both SARS-CoV-1 and SARS-COV-2 on different solid surfaces was analysed. The viability of virions was tested in aerosols, stainless steel, copper, plastic and cardboard. Even after the gap of 72 hrs, both SARS-CoV-1 and SARS-CoV-2 were found on these surfaces after initial applications with a negligible decrease in the viral load.

However, no viable SARS-COV-2 (after 4 hrs) and SARS-CoV-1 (after 8 hrs) were detected on copper surface indicating its anti-viral potential over the other solid surfaces. In case of aerosols, the virions were found viable up to 3 hrs with a negligible decrease in viral load. This study further sheds light on factors like minimum effective dose of the virus and survivability which might play a significant role in the treatment.[67] Another study revealed the extensive transmission of SARS-CoV-2 where two persons reported to recovered showed positive in clinical tests conducted a few days later.[37]

Meanwhile, the incubation period is also high compared to SARS-CoV-1, where it gets a significant amount of time to exhibit symptoms.[32] This escalates the chances of spreading the disease further to the people met without knowing about getting infected.[47,50]

In this aspect, the SARS-CoV-2 has truly become augmented causing more infection. Though the virus predominantly affects the children and aged due to ineffective innate immune response, it is observed with minimal effects on healthy young adults.[78] It is also reported that pregnant women are more vulnerable than any other age group, as they are more susceptible to respiratory infections and pneumonia.[30] A summary of epidemiology, origin and transmission, clinical features and viral characteristics has been given in table 1.

Treatment

Foundational aspects of pathogenesis are pre-requisite to improve the clinical status of the patients. It becomes essential to develop the novel therapeutic agents against these types of viruses. Several studies have reported the use of pharmacotherapy and immunotherapy to treat the infected individuals, though there are no confirmed reports of successful vaccination. In addition, few Chinese herbs are also reported to possess the antiviral effect on the virus, but they are yet to be cleared for clinical usage.[72]

Meanwhile, a study suggested the usage of various Indian medicinal plants against different stages of SARS-CoV-2 infections. The study also suggested the usage of AYUSH hospitals, where effective measures related to quarantine can be used to treat the patients.[56] In the vista, several countries are using drugs once used to treat malaria and influenza to treat SARS-CoV-2. These are the broad-spectrum antivirals that target the virus at different stages of its life cycle to inhibit the growth and development.

Although new therapeutic drugs are emerging, randomized controlled clinical trials need to be conducted to determine their efficacy and safety against human cells[64] while a few of them were also found effective against MERS-CoV and SARS-CoV. In contrast, the immunotherapy focuses on both human cells and the virus. Different therapies have been proposed to reduce the viral load via inhibiting the cellular signalling pathways; dysregulation of viral molecular pathways has also been targeted.[5]

Medical interventions including pharmacotherapeutics concentrate on the interaction between the host cell and virus. For example, MERS-CoV can be treated with drugs like chloroquine, ribavirin and nitazoxanide. Chloroquine impairs the glycosylation of ACE2 receptor, subsequently inhibiting the viral adsorption on the host cell. In addition, chloroquine also disintegrates the viral replication by increasing the intracellular pH levels.[14] Nitazoxanide also tends to inhibit the CoV-HE complex created by MERS-CoV upon binding to the host cell. It inhibits the hemagglutinin formation and protein implantation in plasma membrane. It may also initiate the IFN-1 production to reduce the hemagglutinin levels, thus preventing the viral adsorption.[13]

The other drug ribavirin affects the viral genome replication, thus preventing the viral growth. It acts as a purine nucleoside analog where its increased amounts hamper the viral replication in the host cell.[16]

As SRAS-CoV-1 and SARS-CoV-2 share common pathogenic features, the same therapeutic agents are used to treat both the diseases. Alongside chloroquine and nitazoxanide, hydroxychloroquine and arbidol are used to prevent the viral adsorption. Hydroxychloroquine is another analog of chloroquine which exhibits the same mode of action on the virus and is also used in combination with other drugs whereas arbidol inhibits the fusion of the viral envelope with endosome after endocytosis.[77,33]

In comparison with drugs affecting viral adsorption, a greater number of drugs deal with the inhibition of viral genome replication. Remdesivir and favipiravir block the activity of RNA polymerase to supress the replication process by causing mutations and chain termination. Remdesivir and favipiravir are chiefly used against SARS viruses and with the same mode of action, ribavirin is used to treat all three of the coronaviruses.[1,23]

In addition, few drugs like lopinavir and ritonavir inhibit the viral peptide synthesis. Both these drugs have been reported to affect the MERS-CoV and SARS viruses and they are given in combination. These drugs tend to inhibit the protease activity (3CLpro and Mpro) and hence the polypeptide production.[6,18]

Treatment with immunotherapy involves the treatment with monoclonal antibodies, interferons and protease inhibitors. This is due to predominance of immunopathology and little effect of antivirals. In case of MERS-CoV, these therapies are used at the final stage of the disease whereas combined pharmacotherapy and immunotherapies are used against SARS-CoV-1 and SARS-CoV-2. For example, triple combination of lopinavir/ritonavir, ribavirin and IFNb treatment is successfully used against SARS-CoV-2 patients which gave significant results.[29]

Table 1
Epidemiology, biological and clinical characteristics of the severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[59,65,73]

Categories	Characteristics	SARS-CoV-1	MERS-CoV	SARS-CoV-2
Epidemiology	Original Location	Guangdong, China	Jeddah, Saudi Arabia	Wuhan, China
	Number of Cases	8,422	2,494	6,535,354
	Number of Deaths	919	858	387,155
	Countries Affected	29	27	213
	Fatality Rate	11.0%	34.4%	2.3%
Origin and Transmission	Possible Natural Reservoir	Bats	Bats	Bats
	Possible Intermediate Host	Palm civets, Raccoon dogs	Dromedary camels	Pangolins
	Transmission	Respiratory droplets Close contact with patients Fecal-oral Aerosol	Respiratory droplets Close contact with patients, camels Ingestion of camel milk	Respiratory droplets Close contact with patients Possibly fecal-oral Possible aerosol
Clinical Features	Clinical Symptoms	Acute respiratory distress syndrome (ARDS), Fever, chills, sore throat, cough, myalgia, dyspnea, diarrhea.	Fever, chills, sore throat, cough, myalgia, dyspnea, diarrhea, abdominal cramps,	Excess sputum production, muscle pain, disorientation, mucus fluid secretions in nasal cavity, mucus with blood stains + SARS-CoV-1 symptoms
	Cells Affected	Respiratory tract, kidney, liver	Respiratory tract, intestinal tract, genitourinary tract, liver, kidney, neurons, monocyte; T-lymphocytes	Respiratory tract, intestinal tract, genitourinary tract, liver, kidney, neurons, monocyte; T-lymphocytes
	Presence of virus	Aerosols, urine, sweat, tools	Aerosols, urine, sweat, tools	Aerosols, urine, sweat, tools
Viral Characteristics	Type of Virus	RNA virus	RNA virus	RNA virus
	Species pathogen	β-coronavirus	β-coronavirus	β-coronavirus
	DNA length	29,727 nucleotides	30,119 nucleotides	29,811 nucleotides
	Predominant Receptor	ACE2	DPP4	ACE2
	Latency	2-6 days	2-10 days (6.4 avg.)	1-14 days (11.5 avg.)
	Contagious Period	10 days after onset of disease	Onset of virus isolation	Unknown
	Viral Replication Efficiency	High	Higher	Highest

Monoclonal antibodies (mAb's) are used to dysregulate the viral life cycle by prophylactic and therapeutic neutralization of the structural proteins of the virus. Both *in vitro* and *in vivo* studies proved that IgG antibodies have a profound effect against both MERS-CoV and SARS-CoV-1 viruses through the deactivation of spike protein. The cascade of reactions initiated by these mAb's result in blocking of the ACE2 receptor.[62]

Interferons (IFN's) include immunomodulators produced by the host cell in response to the specific pathogen targets. The IFN treatment is used against MERS-CoV, SARS-CoV-1 and SARS-COV-2 as well. IFN's are reported to reduce the viral loads in Vero E6 cells and primates. Though few studies reported their effect as equal to placebo, they still pose a better option with negative cytotoxic effects. Like drugs used in pharmacotherapy, protease inhibitors have also been used in immunotherapy. A non-peptide SARS-CoV-1 3CLpro inhibitor was reported to be produced from benzhydrylpiperazine which acts on the hydrophobic interaction with the protease.[80]

Similarly, a study evaluated the antiviral activity of 64 purified natural products against RNA helicase nsP13 and reported that infections induced by MERS-CoV, SARS-CoV-1 and SARS-CoV-2 can be regulated.[49] Known to be the most critical target of the therapeutic methods, the spike protein was found to be blocked by hydrolysed tannin present in Chinese and Turkish chestnuts. These peptides are beneficial in either way of inhibiting the viral activity as well as displaying negative cytotoxic effects.[81] Although several clinical studies have reported the beneficial factors related to medicines and immunotherapeutic products, the effect of social distancing and lockdown remains effective as equal to the treatment. One can avoid getting the disease with the proper usage of personal protective equipment and maintenance of public as well as personal hygiene.[60]

Conclusion

The unavailability of specific therapeutic agents and vaccines has aggravated the transmission of the SARS-CoV-2 or COVID-19 to become a global pandemic. The emergence of the virus has upheld the prediction made about future outbreaks of SARS-like virus during MERS-CoV and SARS-CoV-1 emergences. The predicted zoonotic origin and potential animal reservoirs can also be seen as a part of the current outbreak. Though the primary origin remains the same, the possible animal reservoirs have been shifted from wild animals to culinary farm animals, raising speculations about the modes of transmission. There is also a growing concern about the origin of the virus.

Several studies have indicated its existence for decades within some animals such as bats modified by evolutionary molecular mechanisms which in turn have eased the way for effective pathogenesis. Comparative genomic analysis reveals that the genome of the SARS-CoV-2 virus has undergone several modifications compared to the SARS-CoV-1 and MERS-CoV which ultimately resulted in the developments like changing in the binding pattern, usage of binding receptors, usage of replication machinery and production of essential proteins. Evaluation of proteomic features reveals the ability of SARS-CoV-2 to induce favourable changes on the host cell.

Compared to the SARS-CoV-1 and MERS-CoV, SARS-CoV-2 takes a greater amount of time to incubate in the host cell in the period of which the carrier might infect several other healthy individuals. The asymptomatic infection thus can result in further expansion of the pandemic. Meanwhile, the evolutionary aspects can also be seen in case of virion survival. SARS-CoV-2 possesses a higher rate of survival over the other two viruses. These factors collectively make the SARS-CoV-2 less sensitive to the available therapeutic methods and the same cause setbacks in the vaccine development process. In situations like this, a comprehensive approach including different social sectors battling SARS should be made. Known as 'One Health' approach, it aids to exchange the available data and advancements which might assist the mankind towards the betterment.

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References

1. Agostini M.L., Andres E.L., Sims A.C., Graham R.L., Sheahan T.P., Lu X., Smith E.C., Case J.B., Feng J.Y., Jordan R. and Ray A.S., Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease, *MBio*, **9(2)**, e00221-18 **(2018)**

2. Arabi Y.M., Harthi A., Hussein J., Bouchama A., Johani S., Hajeer A.H., Saeed B.T., Wahbi A., Saedy A., AlDabbagh T. and Okaili R., Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV), *Infection*, **43(4)**, 495-501 **(2015)**

3. Banerjee A., Baid K. and Mossman K., Molecular Pathogenesis of Middle East Respiratory Syndrome (MERS) Coronavirus, *Curr Clin Microbiol Rep*, **6(3),** 139-147 **(2019)**

4. Banerjee N. and Mukhopadhyay S., Viral glycoproteins: biological role and application in diagnosis, *Virus Disease*, **27(1)**, 1-11 **(2016)**

5. Barlow A., Landolf K.M., Barlow B., Yeung S.Y.A., Heavner J.J., Claassen C.W. and Heavner M.S., Review of emerging pharmacotherapy for the treatment of coronavirus disease 2019, *Pharmacotherapy*, **40(5)**, 416-437 **(2020)**

6. Cao B., Wang Y., Wen D., Liu W., Wang J., Fan G., Ruan L., Song B., Cai Y., Wei M. and Li X., A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19, *N Engl J Med*, **382(19)**, 1787-1799 **(2020)**

7. Centre for disease control and prevention, Middle East Respiratory Syndrome (MERS), Symptoms & Complications.

(Accessed from: https://www.cdc.gov/coronavirus/mers/about/symptoms.html) **(2020)**

8. Chen N., Zhou M., Dong X., Qu J., Gong F., Han Y., Qiu Y., Wang J., Liu Y., Wei Y. and Yu T., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, *Lancet*, **395(10223)**, 507-513 **(2020)**

9. Chen Y., Liu Q. and Guo D., Emerging coronaviruses: genome structure, replication and pathogenesis, *J Med Virol*, **92(4)**, 418-423 **(2020)**

10. Choi W.S., Kang C.I., Kim Y., Choi J.P., Joh J.S., Shin H.S., Kim G., Peck K.R., Chung D.R., Kim H.O. and Song S.H., Clinical presentation and outcomes of Middle East respiratory syndrome in the Republic of Korea, *Infect Chemother*, **48(2)**, 118-126 **(2016)**

11. Chowell G., Abdirizak F., Lee S., Lee J., Jung E., Nishiura H. and Viboud C., Transmission characteristics of MERS and SARS in the healthcare setting: a comparative study, *BMC Med*, **13(1)**, 210 **(2015)**

12**.** Chu H., Chan C.M., Zhang X., Wang Y., Yuan S., Zhou J., Au-Yeung R.K.H., Sze K.H., Yang D., Shuai H. and Hou Y., Middle East respiratory syndrome coronavirus and bat coronavirus HKU9 both can utilize GRP78 for attachment onto host cells, *J Biol Chem*, **293(30)**, 11709-11726 **(2018)**

13. Clerici M., Trabattoni D., Pacei M., Biasin M. and Rossignol J.F., The anti-infective Nitazoxanide shows strong immumodulating effects, *J Immunol*, **186**, 155.21 **(2011)**

14. Colson P., Rolain J.M., Lagier J.C., Brouqui P. and Raoult D., Chloroquine and hydroxychloroquine as available weapons to fight COVID-19, *Int J Antimicrob Agents*, **55(4)**, 105932 **(2020)**

15. Corman V.M., Muth D., Niemeyer D. and Drosten C., Hosts and sources of endemic human coronaviruses, Academic Press, London, 163 **(2018)**

16. Crotty S., Cameron C. and Andino R., Ribavirin's antiviral mechanism of action: lethal mutagenesis?, *J Mol Med*, **80(2)**, 86-95 **(2002)**

17. Cui J., Li F. and Shi Z.L., Origin and evolution of pathogenic coronaviruses, *Nat Rev Microbiol*, **17(3)**, 181-192 **(2019)**

18. De Wilde A.H., Jochmans D., Posthuma C.C., Zevenhoven-Dobbe J.C., Van Nieuwkoop S., Bestebroer T.M., Van den Hoogen B.G., Neyts J. and Snijder E.J., Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture, *Antimicrob Agents Chemother*, **58(8)**, 4875-4884 **(2014)**

19. De Wit E., Van Doremalen N., Falzarano D. and Munster V.J., SARS and MERS: recent insights into emerging coronaviruses, *Nat Rev Microbiol*, **14(8)**, 523 **(2016)**

20. Fan Y., Zhao K., Shi Z.L. and Zhou P., Bat Coronaviruses in China, *Viruses*, **11(3)**, 210 **(2019)**

21. Fehr A.R. and Perlman S., Coronaviruses: an overview of their replication and pathogenesis, In Coronaviruses, Humana Press, New York **(2015)**

22. Forni D., Cagliani R., Clerici M. and Sironi M., Molecular evolution of human coronavirus genomes, *Trends Microbiol*, **25(1)**, 35-48 **(2017)**

23. Furuta Y., Komeno T. and Nakamura T., Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase, *Proc Jpn Acad Ser B*, **93(7)**, 449-463 **(2017)**

24. Glowacka I., Bertram S., Müller M.A., Allen P., Soilleux E., Pfefferle S., Steffen I., Tsegaye T.S., He Y., Gnirss K. and Niemeyer D., Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response, *J Virol*, **85(9)**, 4122-4134 **(2011)**

25. Gralinski L.E. and Baric R.S., Molecular pathology of emerging coronavirus infections, *The Journal of Pathology*, **235(2)**, 185-195 **(2015)**

26. Groß S., Jahn C., Cushman S., Bär C. and Thum T., SARS-CoV-2 receptor ACE2-dependent implications on the cardiovascular system: From basic science to clinical implications, *J Mol Cel Cardiol*, **44**, 47-53 **(2020)**

27. Guan W.J., Ni Z.Y., Hu Y., Liang W.H., Ou C.Q., He J.X., Liu L., Shan H., Lei C.L., Hui D.S. and Du B., Clinical characteristics of coronavirus disease 2019 in China, *N Engl J Med*, **382(18)**, 1708-1720 **(2020)**

28. Han H.J., Yu H. and Yu X.J., Evidence for zoonotic origins of Middle East respiratory syndrome coronavirus, *J Gen Virol*, **97(2)**, 274-280 **(2016)**

29. Hung I.F.N., Lung K.C., Tso E.Y.K., Liu R., Chung T.W.H., Chu M.Y., Ng Y.Y., Lo J., Chan J., Tam A.R. and Shum H.P., Triple combination of interferon beta-1b, lopinavir–ritonavir and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial, *Lancet*, **395(10238)**, 1695-1704 **(2020)**

30. Jaimes J.A., Millet J.K., Stout A.E., André N.M. and Whittaker G.R., A Tale of Two Viruses: The Distinct Spike Glycoproteins of Feline Coronaviruses, *Viruses*, **12(1)**, 83 **(2020)**

31. Jia H.P., Look D.C., Shi L., Hickey M., Pewe L., Netland J., Farzan M., Wohlford-Lenane C., Perlman S. and McCray P.B., ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia, *J Virol*, **79(23)**, 14614-14621 **(2005)**

32. Jiang X., Rayner S. and Luo M.H., Does SARS-CoV-2 has a longer incubation period than SARS and MERS?, *J Med Virol*, **92(5)**, 476-478 **(2020)**

33. Kadam R.U. and Wilson I.A., Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol, Proc Natl Acad Sci, 206-214 **(2017)**

34. Kumari V.C., Patil S.M., Shirahatti P.S., Sujay S., Tejaswini M., Ranganath L.V., Jayanthi M.K. and Ramu R., The current status and perspective for the emerging pandemic: COVID-19, *Int J Pharm Pharm Sci*, **12(8)**, 1-10 **(2020)**

35. Kwong K.C.N.K., Mehta P.R., Shukla G. and Mehta A.R., COVID-19, SARS and MERS: A neurological perspective, *J Clin Neurosci*, **77**, 13-16 **(2020)**

36. Lam T.T.Y., Shum M.H.H., Zhu H.C., Tong Y.G., Ni X.B., Liao Y.S., Wei W., Cheung W.Y.M., Li W.J., Li L.F. and Leung G.M., Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China, *Nature*, **583(7815)**, 282-285 **(2020)**

37. Lan L., Xu D., Ye G., Xia C., Wang S., Li Y. and Xu H., Positive RT-PCR test results in patients recovered from COVID-19, *Jama*, **323(15)**, 1502-1503 **(2020)**

38. Lau S.K., Fan R.Y., Luk H.K., Zhu L., Fung J., Li K.S., Wong E.Y., Ahmed S.S., Chan J.F., Kok R.K. and Chan K.H., Replication of MERS and SARS coronaviruses in bat cells offers insights to their ancestral origins, *Emerg Microbes Infect*, **7(1)**, 1-11 **(2018)**

39. Letko M., Miazgowicz K., McMinn R., Seifert S.N., Sola I., Enjuanes L., Carmody A., Van Doremalen N. and Munster V., Adaptive evolution of MERS-CoV to species variation in DPP4, *Cell Rep*, **24(7)**, 1730-1737 **(2018)**

40. Lewis D., Is the coronavirus airborne? Experts can't agree, *Nature*, **580(7802)**, 175 **(2020)**

41. Li X., Zai J., Zhao Q., Nie Q., Li Y., Foley B.T. and Chaillon A., Evolutionary history, potential intermediate animal host and cross-species analyses of SARS-CoV-2, *J Med Virol*, **92(6)**, 602-611 **(2020)**

42. Luk H.K., Li X., Fung J., Lau S.K. and Woo P.C., Molecular epidemiology, evolution and phylogeny of SARS coronavirus, *Infect Genet Evol*, **71**, 21-30 **(2019)**

43. Meltzer M.I., Multiple contact dates and SARS incubation periods, *Emerg Infect Dis*, **10(2)**, 207 **(2004)**

44. Menachery V.D., Yount Jr B.L., Debbink K., Agnihothram S., Gralinski L.E., Plante J.A., Graham R.L., Scobey T., Ge X.Y., Donaldson E.F. and Randell S.H., A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence, *Nat Med*, **21(12)**, 1508 **(2015)**

45. Mousavizadeh L. and Ghasemi S., Genotype and phenotype of COVID-19: Their roles in pathogenesis, *J Microbiol Immunol Infect*, **S1684-1182(20),** 30082-7 **(2020)**

46. Müller M.A., Meyer B., Corman V.M., Al-Masri M., Turkestani A., Ritz D., Sieberg A., Aldabbagh S., Bosch B.J., Lattwein E. and Alhakeem R.F., Presence of Middle East respiratory syndrome coronavirus antibodies in Saudi Arabia: a nationwide, cross-sectional, serological study, *Lancet Infect Dis*, **15(5)**, 559-564 **(2015)**

47. Munster V.J., Koopmans M., Van Doremalen N., Van Riel D. and De Wit E., A novel coronavirus emerging in China-key questions for impact assessment, *N Engl J Med*, **382(8)**, 692-694 **(2020)**

48. Nadeem M.S., Zamzami M.A., Choudhry H., Murtaza B.N., Kazmi I., Ahmad H. and Shakoori A.R., Origin, potential therapeutic targets and treatment for coronavirus disease (COVID-19), *Pathogens*, **9(4)**, 307 **(2020)**

49. Nascimento Junior J.A.C., Santos A.M., Quintans-Júnior L.J., Walker C.I.B., Borges L.P. and Serafini M.R., SARS, MERS and SARS-CoV-2 (COVID-19) treatment: a patent review, *Expert Opin Ther Targets*, **30(8)**, 567-579 **(2020)**

50. Nuttall I. and Dye C., The SARS wake-up call, *Science*, **339(6125)**, 1287-1288 **(2013)**

51. Omrani A.S., Al-Tawfiq J.A. and Memish Z.A., Middle East respiratory syndrome coronavirus (MERS-CoV): animal to human interaction, *Pathog Glob Health*, **109(8)**, 354-362 **(2015)**

52. Paden C.R., Yusof M.F.B.M., Al Hammadi Z.M., Queen K., Tao Y., Eltahir Y.M., Elsayed E.A., Marzoug B.A., Bensalah O.K.A., Khalafalla A.I. and Al Mulla M., Zoonotic origin and transmission of Middle East respiratory syndrome coronavirus in the UAE, *Zoonoses and Public Health*, **65(3)**, 322-333 **(2018)**

53. Pan Y., Zhang D., Yang P., Poon L.L. and Wang Q., Viral load of SARS-CoV-2 in clinical samples, *Lancet Infect Dis*, **20(4)**, 411-412 **(2020)**

54. Patil S.M., Kumari V.C., Shirahatti P.S., Sujay S., Tejaswini M., Ranganath L.V., Jayanthi M.K. and Ramu R., COVID-19 infection: The prospects of pharmacotherapy, *Int J Health Allied Sci*, **9(5)**, 111-113 **(2020)**

55. Pyankov O.V., Bodnev S.A., Pyankova O.G. and Agranovski I.E., Survival of aerosolized coronavirus in the ambient air, *J Aerosol Sci*, **115**, 158-163 **(2018)**

56. Rastogi S., Pandey D.N. and Singh R.H., COVID-19 Pandemic: A pragmatic plan for Ayurveda Intervention, *J Ayurveda Integr Med*, **S0975-9476(20)**, 30019-X **(2020)**

57. Shereen M.A., Khan S., Kazmi A., Bashir N. and Siddique R., COVID-19 infection: Origin, transmission and characteristics of human coronaviruses, *J Adv Res*, **24**, 91-98 **(2020)**

58. Shi Z. and Hu Z., A review of studies on animal reservoirs of the SARS coronavirus, *Vir Res*, **133(1)**, 74-87 **(2008)**

59. Song Z., Xu Y., Bao L., Zhang L., Yu P., Qu Y., Zhu, H., Zhao W., Han Y. and Qin C., From SARS to MERS, thrusting coronaviruses into the spotlight, *Viruses*, **11(1)**, 59 **(2019)**

60. Taghrir M.H., Akbarialiabad H. and Marzaleh M.A., Efficacy of mass quarantine as leverage of health system governance during COVID-19 outbreak: a mini policy review, *Arch Iran Med*, **23(4)**, 65-267 **(2020)**

61. Thomas H.L., Zhao H., Green H.K., Boddington N.L., Carvalho C.F., Osman H.K., Sadler C., Zambon M., Bermingham A. and Pebody R.G., Enhanced MERS coronavirus surveillance of travelers from the Middle East to England, *Emerg Infect Dis*, **20(9)**, 562 **(2014)**

62. Totura A.L. and Bavari S., Broad-spectrum coronavirus antiviral drug discovery, *Expert Opin Drug Discover*, **14(4)**, 397-412 **(2019)**

63. Tsai L., Hsieh S. and Chang Y., Neurological manifestations in severe acute respiratory syndrome, *Acta Neurol Taiwan*, **14(3)**, 113 **(2005)**

64. Tu Y.F., Chien C.S., Yarmishyn A.A., Lin Y.Y., Luo Y.H., Lin Y.T., Lai W.Y., Yang D.M., Chou S.J., Yang Y.P. and Wang M.L., A review of SARS-CoV-2 and the ongoing clinical trials, *Int J Mol Sci*, **21(7)**, 2657 **(2020)**

65. Tu Y.F., Chien C.S., Yarmishyn A.A., Lin Y.Y., Luo Y.H., Lin Y.T., Lai W.Y., Yang D.M., Chou S.J., Yang Y.P. and Wang M.L., A review of SARS-CoV-2 and the ongoing clinical trials, *Int J Mol Sci*, **21(7)**, 2657 **(2020)**

66. Van Boheemen S., De Graaf M., Lauber C., Bestebroer T.M., Raj V.S., Zaki A.M., Osterhaus A.D., Haagmans B.L., Gorbalenya A.E., Snijder E.J. and Fouchier R.A., Genomic characterization of a newly discovered coronavirus associated with acute respiratory distress syndrome in humans, *MBio*, **3(6)**, e00473-12 **(2012)**

67. Van Doremalen N., Bushmaker T., Morris D.H., Holbrook M.G., Gamble A., Williamson B.N., Tamin A., Harcourt J.L., Thornburg N.J., Gerber S.I. and Lloyd-Smith J.O., Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1, *N Engl J Med*, **386(16)**, 1564-1567 **(2020)**

68. Virlogeux V., Park M., Wu J.T. and Cowling B.J., Association between severity of MERS-CoV infection and incubation period, *Emerg Infect Dis*, **22(3)**, 526 **(2016)**

69. Wei X.S., Wang X., Niu Y.R., Ye L.L., Peng W.B., Wang Z.H., Yang W.B., Yang B.H., Zhang J.C., Ma W.L. and Wang X.R., Clinical characteristics of SARS-CoV-2 infected pneumonia with diarrhea, *Clin Gastroenterol Hepatol*, **18(8)**, 1753-1759 **(2020)**

70. WHO, Middle East respiratory syndrome coronavirus (MERS-CoV): summary of current situation, literature update and risk assessment (No. WHO/MERS/RA/15.1), World Health Organization **(2015)**

71. WHO, Coronavirus (COVID-19) Situation report 137., (Accessed from: https://www.who.int/docs/default-source/sri-lanka-documents/20200605-covid-19-sitrep-137.pdf?sfvrsn=a13 df572_2) **(2020)**

72. Xie M. and Chen Q., Insight into 2019 novel coronavirus—an updated intrim review and lessons from SARS-CoV and MERS-CoV, *Int J Infect Dis*, **94**, 119–124 **(2020)**

73. Xu J., Zhao S., Teng T., Abdalla A.E., Zhu W., Xie L., Wang Y. and Guo X., Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV, *Viruses*, **12(2)**, 244 **(2020)**

74. Xu R.H., He J.F., Evans M.R., Peng G.W., Field H.E., Yu D.W., Lee C.K., Luo H.M., Lin W.S., Lin P. and Li L.H., Epidemiologic clues to SARS origin in China, *Emerg Infect Dis*, **10(6)**, 1030 **(2004)**

75. Xu X.W., Wu X.X., Jiang X.G., Xu K.J., Ying L.J., Ma C.L., Li S.B., Wang H.Y., Zhang S., Gao H.N. and Sheng J.F., Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series, *BMJ*, **368**, m606 **(2020)**

76. Yang Y., Peng F., Wang R., Guan K., Jiang T., Xu G., Sun J. and Chang C., The deadly coronaviruses: The 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China, *J Autoimmun*, **109**, 102434 **(2020)**

77. Yao X., Ye F., Zhang M., Cui C., Huang B., Niu P., Liu X., Zhao L., Dong E., Song C. and Zhan S., In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), *Clin Infect Dis*, **71(15)**, 732-739 **(2020)**

78. Yuki K., Fujiogi M. and Koutsogiannaki S., COVID-19 pathophysiology: A review, *Clin Immunol*, **215**, 108427 **(2020)**

79. Zeng Q., Langereis M.A., Van Vliet A.L., Huizinga E.G. and De Groot R.J., Structure of coronavirus hemagglutinin-esterase offers insight into corona and influenza virus evolution, Proc Natl Acad Sci U.S.A, 9065-9069 **(2008)**

80. Zhao Q., Weber E. and Yang H., Recent developments on coronavirus main protease/3C like protease inhibitors, *Recent Pat Antiinfect Drug Discov*, **8(2),** 150-156 **(2013)**

81. Zheng B.J., Guan Y., Hez M.L., Sun H., Du L., Zheng Y. and Tanner J.A., Synthetic peptides outside the spike protein heptad repeat regions as potent inhibitors of SARS-associated coronavirus, *Antivir Ther*, **10(3),** 393-403 **(2005)**

82. Zheng Y.Y., Ma Y.T., Zhang J.Y. and Xie X., COVID-19 and the cardiovascular system, *Nat Rev Cardiol*, **17(5)**, 259-260 **(2020)**

83. Zhou J., Chu H., Chan J.F.W. and Yuen K.Y., Middle East respiratory syndrome coronavirus infection: virus-host cell interactions and implications on pathogenesis, *Virol J*, **12(1)**, 218 **(2015)**.

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