Journal of
Microbial & Biochemical Technology

OPEN ACCESS Freely available online

Review Article

Pandemic COVID-19 Emerging Global Concern: An Overview to Understand the Potential of Ca^{+2} in Pathogenesis and Advance Therapeutics Strategy on its Outbreak

Prem Raj Meena[1], Anjali Vashishth[2], Priyanka[1], Arvind P. Singh[1]*

[1]Department of Microbiology, School of LifeSciences, Central University of Rajasthan, Ajmer, India; [2]Department of Sport Biosciences, School of Sport Science, Central University of Rajasthan, Ajmer, India

ABSTRACT

The new public health crisis is threatening the world with the emerging and spread of coronavirus. In December 2019, a series of pneumonia and acute respiratory disease caused by novel corona virus SARS-CoV-2 had been appeared in china and spread out worldwide. World Health Organization (WHO) officially declared its name COVID-19 and 'pandemic' as a public health emergency in February 2020. Novel corona virus SARS-CoV-2 marked the third introduction of highly pathogenic and large-scale epidemic coronavirus into humans after SARS and MERS. As of till the end of June, a total of more than 1 crore confirmed cases were reported globally. USA, Brazil, Italy, India and Spain are leading affected countries, and around 5 lakh peoples have been died due to the global pandemic according to the WHO report. Meanwhile, several research groups studies suggested that it is likely the zoonotic origin of COVID-19 and person to person transmission has led the pandemic disease. Based on the published evidence, we systematically discussed and summarized the characteristics of novel corona virus SARS-CoV-2 and the role of receptor and protein in host-pathogen interaction. Evidence from previous studies suggests that knowledge regarding prevention and its treatment is still scarce. In this review, we have revealed the One-Health perspective and reservoir, biology of transmission, survival mechanism, and the potential role of Ca^{+2} ions in the pathogenesis mechanism of SARS-CoV-2, diagnosis characteristic symptoms, possible treatment and prevention in terms of One-Health from COVID-19. Along with this it also provides an essential insight into the control measures that would minimize the potential risk of disease transmission and will be helpful for vaccine development against the pandemic COVID-19.

Keywords: COVID-19;SARS-CoV-2; Novel coronavirus; HCoVs; One-Health; Zoonotic; Pathogenesis, Viral pneumonia; MERS-CoV; Chloroquine; Remdesivir

INTRODUCTION

Public health crisis is threatening the world with the emerging and spread of COVID-19. In December 2019, cluster of viral pneumonia cases was first observed in Wuhan, China (South China Seafood city food market, China), in January 2020 and it was suggested that the causative agent of pneumonia is a novel coronavirus (initially named "2019-nCoV" but changed to "SARS-CoV-2" by International Committee on Taxonomy of Viruses (ICTV)), which belonged to coronavirus family and subfamily orthocoronavirinae with the same lineage but with slight genetically distinct from the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). These were zoonotic in origin and linked with the respiratory, enteric, hepatic and neurological disease which associated to fatal illness in human [1-4]. The various outbreak of SARS-CoV in 2002 and the MERS-CoV in 2012, firstly demonstrated the transmission from animal to human and human to human. Recently the mystery of ongoing coronavirus health threats has emerged in China. Nevertheless, it is spreading rapidly in other countries that have attracted tremendous attention worldwide, and the World Health Organization (WHO) has already declared a health emergency and pandemic disease. On 12 January 2020, it was formally named Coronavirus Disease 2019 (COVID-2019) by the WHO [5,6]. A total of more than one crore (29 June 2020) cases of pneumonia have been registered worldwide, according

***Corresponding to**: Arvind P. Singh, Department of Microbiology, School of Life Sciences, Central University of Rajasthan, Ajmer, India, E-mail:prmeenacct@gmail.com

Received Date: February 26, 2020; **Accepted date:** June 10, 2020; **Published date:** June 17, 2020

Citation: Meena PR, Vashishth A, Priyanka, Singh AP (2020)Pandemic COVID-19 emerging global concern: An overview to understand the potential of Ca+2 in pathogenesis and advance therapeutics strategy on its outbreak. J Microb Biochem Technol. 12:433 doi: 10.35248/1948-5948.20.12.433

to WHO. Approximately five lakh people died as a result of this pandemic disease by the end of June 2020, the USA (1.2 lakh deaths) and Brazil (56109 deaths) was the nation most affected by this pandemic and the death occurred in Italy (more than 34000), Spain (27,000), France (approx. 28000).

Putative One-Health insights for the origin and evolution of "SARS-CoV-2"

Mutation and adaptation have driven co-evolution in coronaviruses and their host, including humans. Two human coronaviruses (HCoV) SARS and MERS were identified as a causative agent in humans in 2003, and these HCoVs were detected primarily from the bat as zoonotic sources. Based on different protein sequence coronaviruses (CoV) are divided into four genera α-/, β-/, δ-/, and γ-CoV. α-/, β-CoV can cause infection in mammalian while δ-/, γ-CoV tend to infect in birds. Based on the genome sequence of "SARS-CoV-2" is 96.2% identical to a bat CoV- RaTG13, whereas it shares 76% identity to SARS-CoV, that is why bat might be suspected as a natural host of nCoV-19 and could be transmitted from bat to human [7,8]. Based on phylogenetic analysis and specific protein residues, some studies also confirm that SARS-CoV-2 mainly linked to bat-SL-CoV-ZC45 and bat-SL-CoV-ZX21 [9], currently research devoted to the potential alternative host for SARS-CoV2 maybe such as snake, turtles, and pangolin [10]. Such findings have drawn attention, along with sequence identification, to the probable zoonotic roots of coronavirus. Infection with SARS-CoV-2 is potentially another vital example of the One-Health principle following SARS-CoV, MERS-CoV, and Ebola virus which overlaps human, animal, and environmental health [11]. Identifying the SARS-CoV-2 reservoir could be one of the milestones for monitoring, contaminating, and mitigating the animal outbreak.

Genome and critical virulence factors of SARS-CoV-2

The "SARS-CoV-2" genome is a non-segmented single-strand positive-sense (+ ss-RNA) with a 5'-cap structure and a 3'-poly-A tail with a genome size of at least 6-11 Open Reading Frames (ORF) [9,12,13]. There are 16 non-structural proteins (NSPs 1-16, except for γ-coronavirus due to lack of 1-NSP) that encode first ORFs (ORF 1a/b), which is 2/3 of the viral genome while remaining to encode structural proteins. For NSPs, genomic RNA directly translates polyprotein 1a/1ab (pp1a/pp1ab) and after translation, this protein forms Replication- Transcription Complex (RTC) in a double vesicular membrane (DMVs) [14]. The central four structural proteins Spike (S), Membrane (M), Envelope (E) and Nucleocapsid (N), and other accessory proteins that interfere with the immune response of the host, coded near 3'- N-terminus by some ORFs [2] (Figure 1). Among them, spike (S) protein plays the most crucial role in viral attachment, fusion, and invasion of the virus.Individually, each protein plays a minor role in the structure of virus particles, but also involved other aspects of the replication cycle. SgRNAs of CoVs [15] translates all accessory and structural proteins. Recent, study devoted that the mutation in NSP2 and NSP3 plays a role in the infection capability of different mechanisms of infection [16]. The Chinese scientist Thang et al. [17] performed a population genetic study of 103 SARS-CoV-2 genomes, classifying SARS-CoV-2 into two types L (70%) and S (30%), S-type L strains, and is more aggressive and pathogenic in nature.

Due to the existence of the RGD (Arg-Gly-Asp) motif, the S (spike) protein of SARS-CoV-2 differs from the normal coronavirus [18]. The primary function of this type's motif is to improve the binding capacity of SARS-CoV-2 to host lung cells, and this is perhaps the primary reason why novel coronavirus is more contagious within the lung cells than other respiratory syndrome viruses. Ca^{+2}, Mg^{+2}, and other ions play a vital role in binding in and pathogenesis mechanism of SARS-CoV-2.

Function of structural and non- structural proteins

Most of the function of 16-NSPs and 4-structural proteins have been reported already. Many of 16-NSPs play a vital role in CoVs replication, while structural protein plays a key role in pathogenesis [19]. The function of structural and non- structural proteins is summarized in Figure 1 and Table 1.

Mechanism of Transmission of COVID-19

A large number of persons have been identified in Wuhan, China-related to (South China, Seafood city food market, China) its suggested that its likely a zoonotic origin of COVID-19, and many research ongoing to the proof reservoir of COVID-19, but there are no consistent evidence of coronavirus reservoirs other than mammals and birds [35,36]. Based on the phylogenetic analysis and similar protein residues, some study also supports that SARS-CoV-2 mostly related to bat-SL-CoV-ZC45 and bat-SL-CoV-ZX21 [19]. Recent research also supports the possibility of alternative

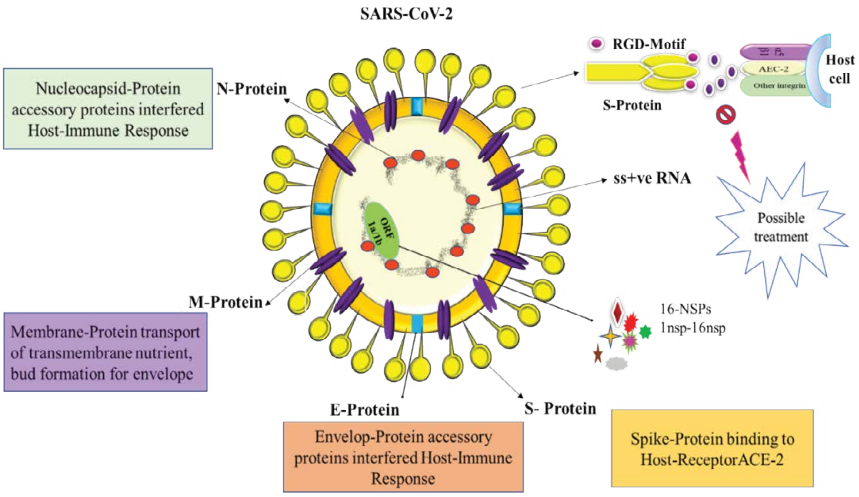

Figure 1: Schematic Model representation of SARS-CoV-2 with four main structural proteins (S-protein, M-protein, E-protein and N-protein) with their specific functions. Structure of S-protein shows the AEC-2 binding side and RGD-motif which bind to host cell receptor.

Table 1: Summarize of 16 Non-structural Proteins (NSP) in coronavirus and their function.

S. No	Non-structure Protein	Function	References
1	nsp1	Cellular mRNA Decay, Virus Replication and inhibition interferon (INF) signalling	[20]
2	nsp2	Virus Replication, RNA Helicase Activity, RNA Triphosphatase	[16,21]
3	nsp3	Shut off Cellular Proteins synthesis, promoting cytokine expression and host innate immune response	[16,22]
4	nsp4	Catalytic component of RNA Polymerase, Possess TATase Activity, Double-Membrane Vesicle (DMV)	[21,23]
5	nsp5	Main protease, chymotrypsin like protease, Proteolytic processing and IFN signalling	[24]
6	nsp6	Induce small spherical Vesicles, Limit autophagosome expansion,	[25,26]
7	nsp7	Specific RNA replication mechanism, Cofactor for nsp8 and nsp12	[27,28]
8	nsp8	Processivity factor of nsp7 and nsp12, primase activity	[29,30]
9	nsp9	ssDNA/RNA binding protein	[31]
10	nsp10	RNA synthesis	[31]
11	nsp11	Inhibit interferon beta induction	[32]
12	nsp12	RNA- dependent RNA polymerase	[26]
13	nsp13	Helicase activity	[26]
14	nsp14	RNA cap formation	[32]
15	nsp15	RNA endoribonuclease, Role in viral infection,	[33,34]
16	nsp16	S-adenosyl-L-methionine dependent RNA 2'-O MTase activity	[32]

hosts for SARS-CoV-2.Apart from different types of hosts, some factors even facilities SARS-CoV-2 to break cross species barriers, like a high mutation rate in RNA replication and adaptation of novel host. The mutation rate of SARS-CoV-2 is very high. It may be suggested that direct contact within termed the host animals and the consumption of wild animals was suspected to be the main route of SARS-CoV-2 transmission [19]. However, the transmission route and source remain a puzzle for the researcher.

Recent research shows the human to human transmission route of SARS-CoV-2, these studies data shows a person who has been visited Wuhan city market their family members also find infected by this virus [37,38]. According to WHO guideline person to person transmission occurred via direct contact or droplet spreading by the infected individual via coughing and sneezing. Likewise [39], has suggested the presence of this dangerous virus in fecal swab and blood that indicates the multiple transmission routes of infection. It's has been already shown that the transmission of SARS-CoV and MERS-CoV occurred through nosocomial transmission and considered airborne pathogens.

Host-pathogen interaction and Role of Ca^{+2} in Invasion and survival mechanism

A very important stage after transmission is the binding of coronavirus to host cell receptors. It is noteworthy that SARS-CoV-2 share the same cellular receptor with SARS-CoV genera. The spike protein of coronavirus from all four families, guides to coronavirus entry into the host cell [40]. Corona viruses entre into the host cell by a two-step process: first host cell receptor recognized for viral attachment and fuse viral and host cell membrane. The spike protein is present in two very different forms pre-fused (before fusion to host) and post-fused (after fusion to host cell). The pre-fused spike protein displays a homo-trimer structure with three receptor binding S1 receptor binding side and resting at the top of trimeric S2 [41-43]. The post-fusion structure is a coiled-coil structure with contained only S2 [44,45]. The virus invasion may have two pathways (a) the ACE-2 receptor (b) using the integrin receptor.Angiotensin-Converting Enzyme-2 (ACE-2) receptor presents the cell membrane of the cells of the lungs, heart, and kidney. ACE-2 is expressed by type I and type II alveolar epithelial cells. Among them, type II is shown more than 80% ACE-2 receptor. Men had a higher level of ACE-2 receptor rather than women. This enzyme considers as the main entry point for coronavirus [45,46]. SARS-CoV-2 can also fuse directly to the cell surface in the detection Beta-CoV receptor reveals that human cells expressing ACE-2 receptor have a crucial role to play in binding SARS-CoV-2, Spike (S) glycoprotein, and ACE-2 host receptor [47].

A 30 % difference in the S1 unit of S protein sequence between SARS-CoV and SARS-CoV-2. The RGD-motif of S protein, which is different in sequence from SARS-CoV and MERS-CoV, shows tightly binding to lung cells. It has long been known that SARS-CoV is primarily a respiratory disease, so it also needed protease from the respiratory tract such as trans-membrane protein serine-2 (TMPRSS-2) and HAT [48-51] (Figure 2). The TMPRSS-2 and HAT both activate the binding affinity of the S-protein cleavage trimer. Some studies support that the S-protein and ACE-2 increase the affinity 10 to 20-fold for SARS-CoV-2 [52,53]. After binding SARS-CoV-2 to host cell receptor, it required a serial activation of kinase and protease like activities for the internalization of the virus. The phagocytosis mechanism is complex, where the interconnected, and cross-activation of proteins take participates inside the cells. TMPRSS-2 and HAT cleaves pattern for S-fragments differ from each other; HAT cleaves S protein mainly at R667, where TMPRSS-2 cleaves at multiple sites, both cleavages enhance the cell-virus fusion [50]. The infection of the target cell by SARS-CoV-2 occurred due to S-pseudotypedvirions, which is less sensitive to cathepsin inhibitor when the target cell expresses TMPRSS-2 [50,51]. Pseudo virions are still producing by SARS-CoV-2; still, TMPRSS-2, rely on endosomal cathepsin for the entry. Meanwhile, other accessory proteins may be involved in viral binding and invasion, such as cathepsin [54] and clathrin (Figure 2), while potential molecules facilitated an uncertain membrane invasion of SARS-CoV-2 [53-55]. SARS-CoV-2 cell entry Depends on ACE-2 and TMPRSS2, and it is Blocked by a Clinically Proven Protease Inhibitor.

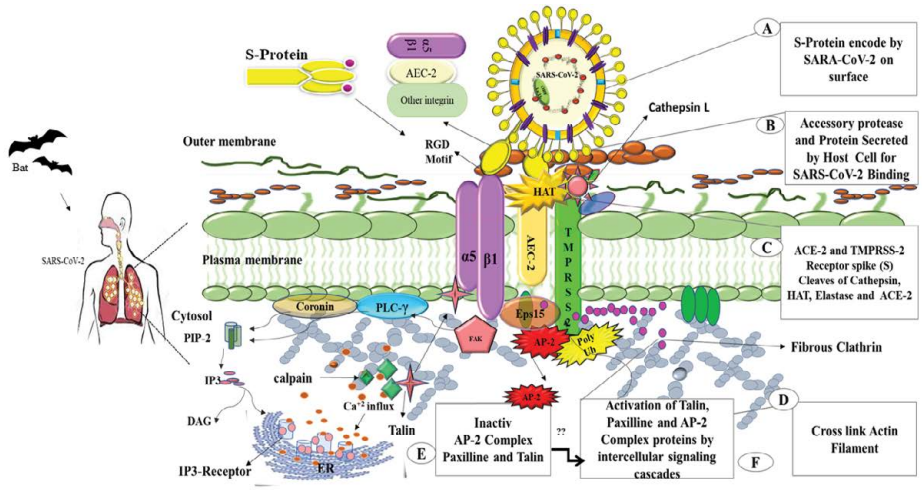

Figure 2: Schematic representation of the Transmission route of SARS-CoV-2 and Association of spike binding protein (S-protein) encodes by SARS-CoV-2 during host-pathogen interactions and Ca^{+2} role in pathogenesis mechanism: Possible origin from the bat of corona virus and transmission into a human. The bindingSARS-CoV-2 expressed spike (S-protein) protein that binds to the ACE-2 receptor that acts as a link to stimulate the TMPRSS-2 receptor to serve up a docking site to numerous kinases and protease, as AP-2 kinase. There is some other protease like HAT, cathepsin L and Elastase which also play a vital role in viral fusion and invasion. The ligand and receptor interaction stimulate AP-2 complex, TMPRSS-2 cleavage the S-protein which triggers the SARS-CoV-2 binding to the host cell.

Role of Ca^{+2} ion in invasion and host-pathogen interaction the SARS-CoV-2 spike protein (S-Protein) protein has RGD-motif which show highly binding and invasion capacity of SARAS-CoV-2. RGD-Motif bind to Integrin receptor α-subunit and β-subunit serve up a docking site to numerous kinases, as Focal adhesion kinase (FAK) for β-subunit and talin adaptor proteins. Phosphorylated FAK promote to phosphorylation of phospholipase C- γ (PLC-γ) that direct participate into generation and catalysis of inositol phosphate-3 (IP-3) via intermediated coronin after this IP3 diffused toward endoplasmic reticulum and bind at IP-3 receptor and present on E.R. Thus, this binding opens the Ca^{+2}ion channel and the Ca^{+2}ions influx inside cytosol and the increased concentration of Ca^{+2} ions inside cell which led to binding and invasion capacity of virus.

The lack of a complete understanding of the phagocytosis mechanism that is critical for SARS-CoV-2 to the host's which pathway involvement. A recent study shows that Ca^{+2} ions increase infectivity and entry into MERS-CoV and Rubella virus cells [56,57] because of the presence of negatively charged peptide on fusion protein (S-protein). Studies show that the spike protein of coronavirus has evolutionary changes and obtain some features for its adaptations in human host cells [18,58].

In our speculation, the RGD motif of the spike protein of SARS-CoV-2 may be bound to integrin receptor [59] of host cells that participate in host-pathogen interaction and leads to internalization. In some research article [56,57] it has been showing the involvement of Ca^{+2} ions play a significant role in which is several receptor-based events and initiates internalization of pathogenicity of the virus by altering the actin filaments and cytoskeleton arrangements through affecting the actions of several proteins [60]. When a virus binds an integrin receptor association (α5β1), a serial activation of kinase activates that contributes to the internalization is needed. The binding of virus or virus particle induce Ca^{+2} response inside the host cell that lead cellular response.The integrin α5-subunit and β1-subunit provide a docking site for various kinases, such as β-subunit Focal Adhesion Kinase (FAK) [61] and α-subunit Talin Adapter Proteins [62]. The tyrosine kinase FAK plays a vital role as a key mediator of the integrin signaling event controller. RGD motif of spike protein (S-Protein) interaction to integrin stimulates FAK tyrosine phosphorylation result's in FAK signaling activate, meanwhile at time stimulated FAK promotes phospholipase C-γ (PLC-γ) activities that directly participate in the generation and catalyzed of inositol triphosphate 3 (IP3) and Diacylglycerol (DAG).Thus, the PLC-γ activates coronin, found as an actin-binding protein within cytosol and thus further stimulation of PLC-γ these proteins proceed IP3 and this diffuse towards Endoplasmic reticulum (E.R.) and binds to inositol triphosphate-3 receptor (IP3R), present at E.R. this results in immobilization of Ca^{+2} into the cytosol [61,63]. Phagocytosis is a complex mechanism by interconnected and cross-activation of intracellular proteins. Moreover, in this complex mechanism, cytosolic proteins of the host also play a role in virus engulf, one of the best proteins talin, which a ubiquitous cytosolic protein that docks the α5-subunit of integrin and acts as a substrate for the Ca^{+2} activated protease, called calpain. Thus, an increase in Ca^{+2} concentration in host cells leads to re-armament or deform the actin filaments by binding on α-actin that provide an intact binding between actin filaments and help into the invasion of the virus into lung cells (Figure 2). So, this fact can be possible; the concentration of Ca^{+2} into lung cells also increases the binding and entry of SARS-CoV-2 inside the cell, and that plays a vital role in the pathogenicity of the virus. Nonetheless, if the concentration of Ca^{+2} ions in lung cells reduces, this may be a step towards reducing the degree of coronavirus infection.

After SARS-CoV-2 's invasion (Figure 3a), their formation of an early phagosome into the host cell, but it still remains unclear how SARS-CoV escape from the host immune system, it appears that the virus secretes Rab5, like protein that displays well on the phagosome, thus playing phagosome-lysosome fusion that helps to escape the immune system. One interesting phenomenon occurred, still, SARS-CoV secretes the pseudotypesvirion, which is less sensitive, and this led to the neutralization of the host antibody. This may be the main reason for the delay in the appearance of the symptoms of SARS-CoV-2, which are 4 to 14 days the incubation period of the virus. This effect was attributed to the release of the spike (S) fragments inside the body that lures antibodies and may be of great importance for the spread of the virus [50]. After immune compromise, the SARS-CoV-2 virus goes to replication, the viral RNA (+ve) released and uncoating, and translated into viral replicase polyproteins pp1a and 1b, which are cleaves into the small product by using viral proteinase. Negative strand

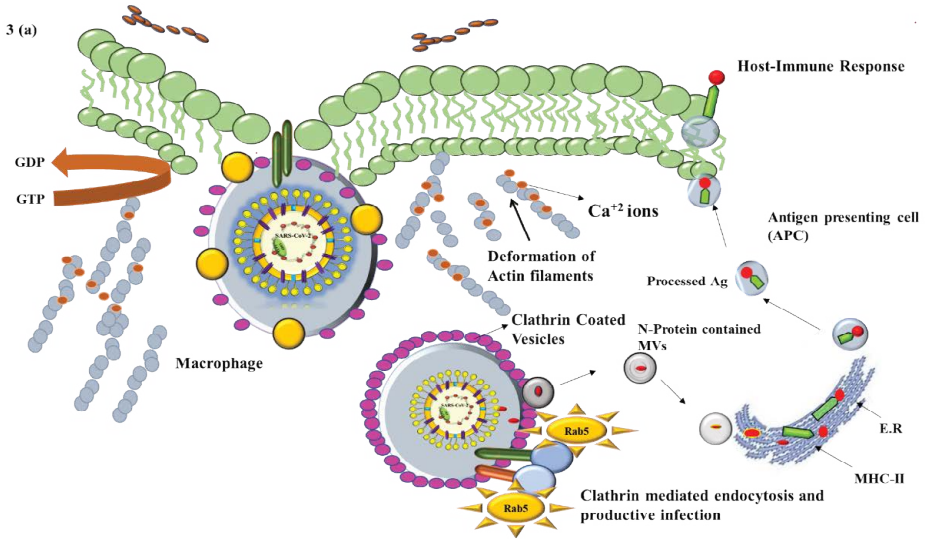

Figure 3a: Schematic representations of the clathrin mediated invagination, life cycle of SARS-CoV-2 and membrane vesicle organization Immune Response against SARS-CoV-2. SARS-CoV-2 membrane surface adhesions virulence factors like S-Protein and clathrin mediated, where S-protein is cleaved by the endosomal acid proteases (cathepsin L)105 to activate its fusion activity after invasion of the virus after invagination of SARS-CoV-2 some virulence protein expression in the early phagosome and use of origin of membrane vesicles (M.V.s) which are budding off from the early phagosome and present their peptides to Antigen Presenting Cell (APC) surface through MHC-II class protein pathway.

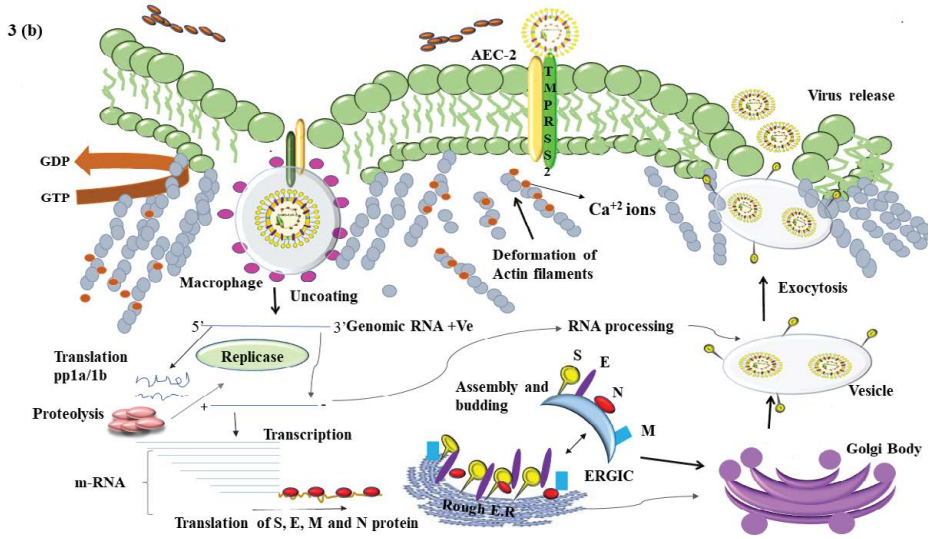

Figure 3b: After immune compromise the SARS-CoV-2 bacteria goes to replication, the viral RNS(+ve) released and uncoating, and translated into viral replicase polyproteins pp1a and 1b, which are cleaves into small product by using viral proteinase. Negative strand synthesized from some discourteous transcription and plus strand used a templet RNA for mRNA synthesis. Viral Nucleocapsid are assembled same time N protein in the cytoplasm is arranged onto virus RNA into ERGIC (Endoplasmic Reticulum-Golgi Intermediate Compartment). Then the virion is released from the cell through exocytosis mechanism. Virion are then released from cell through exocytosis mechanism. (where S-spike, N-Nucleocapsid, M-Membrane and E-Envelop proteins).

synthesized from some discourteous transcription and plus-strand used a templet RNA for mRNA synthesis. Viral Nucleocapsid are assembled same time N protein in the cytoplasm is arranged onto virus RNA into ERGIC (Endoplasmic Reticulum-Golgi Intermediate Compartment). Then the virion is released from the cell through exocytosis mechanism (Figure 3b) [64].

Clinical Characteristic and Diagnosis

The incubation period of COVID-19 is 4 to 14 days, and the most common symptoms in the patient are mild flu-like fever, cough, headache, shortness of breath, some gastrointestinal infection like dihedra, vomiting, and malaise [65]. SARS-CoV-2, firstly Diagnosis by the viral research institute in china, primary identification was made by classical Koch's postulates, and the morphology was observed by electron microscopy [66]. Real-time PCR (RT-PCR) used to detection of COVID-19 and further confirmation by Next-Generation sequencing. Moreover, Computerized tomography scans can also be used to detect infections with COVID-19; images display an abnormality in the chest [66,67]. Yet the chest image often shows a regular scan image of positive corona patients; for clarification, the presence of viral RNA in the patient body needs to be further tested. Recently, it has been seen every country used to rapid test kit, which is based on the Antibodies detection method.

Therapeutics strategy and prevention of COVID-19

At the present time, there are no specific drugs and definitive treatment against COVID-19 for potential therapy in human infection. All patients accept oxygen therapy and, the WHO

recommends extracorporeal membrane oxygenation (ECMO) with refractory hypoxemia [58]. For the critical condition, convalescent plasma therapy and immunoglobin G also used according to conditions being detected [68]; in 2014, WHO has recommended this convalescent plasma therapy against the Ebola virus.Based on previous experience combating SARS-CoV and MERS-CoV, some therapeutic strategy against COVID-19 can be used [19]. Antiviral drugs and corticosteroids (such as oseltamivir, peramivir, zanamivir, ganciclovir, acyclovir, and ribavirin) that were previously used for influenza virus in the clinical setting are invalid for COVID-19 [69,70]. Present time only broad-spectrum antiviral drugs (such as sofosbuvir, lopinavir/Ritonavir) and some antiviral like nucleoside (Remdesivir) or its analogs, and HIV-protease inhibitor is used for the treatment of COVID-19 [71-73].

Recently, chloroquine and hydroxychloroquine which has been used for several years to treat malaria and can prevent the replication of many viruses often used to treat COVID-19 [74-76]. In vitro, study reveal, a combination of Remdesivir and chloroquine effectively inhibits the SARS-CoV-2 that has recently emerged [18]. In addition, various vaccine strategies such as live attenuated, inactivated viruses, and vector-based, DNA vaccine have been developed but only tested in an animal model [77,78]. Nevertheless, the efficacy of these drugs still needs to be verified by clinical trials. One more sign that the demand for chloroquine, which is used to treat malaria for many years, increased now's days that indicate the possible link between SARS-CoV-2 and Plasmodium falciform protein sequence and pathogenesis. Data are not available, but it may be possible those patients who have already suffered from these known bacterial diseases can develop probably resistance against COVID-19, and this may be led to the developed vaccine against the corona virus. The RGD motif of spike protein and TMPSRSS-2 which plays an important role in binding to the host cell and the concentration of Ca^{+2} ions plays a major role in binding and invading the virus into the host cell if the receptor binding block is somehow reduced by any protease inhibitor and the concentration of Ca^{+2} ions inside the lung cells by some inhalation that may be a potential pre-therapy strategy for reducing the level of corona infection. ACE2 receptor binding to S-Protein can be blocked by monoclonal antibodies (such as Tocilizumab) [72,73]. Currently, there are numerous companies and research institute applied for clinical trial for the repurposing of existing drugs, for this the repurposing, randomized controlled treatment (RCT) being carried out to identify disease specific drugs [72]. Moreover, Indian traditional medicinal particles such as Ayurveda, Yoga and Unani, Siddha, Naturopathy & Homoeopathy (AYUSH) are considered as one of the oldest treatments in human history for successfully treatment of various diseases [72,79,80]. Indian herb also used for the preventive strategy against corona virus disease, for this The Ministry of AYUSH (Govt. of India) give focus on the preventive through modification in daily lifestyle for improving immunity [81]. According to Vellingiri et. al. there are various medicine plant recommended by AYUSH for fighting COVID-19 [72]. But it should be remembered still there is no efficient drug again SARS-CoV-2. Based on China's and other research data, the WHO released a guideline on how to prevent the pandemic COVID-19. The best majors now to control the source of infection early Diagnosis and effective treatment; isolation of patients also led to recovery. Recently, studies show, initial death COVID-19 outbreak occurred in older people, possibly due to a weak immune system that allows the rapid growth of viruses [82,83]. People should be aware of COVID-19 and avoid physical contact with a positive corona user, and avoid touching the wet substance such as fecal, urine, and cough droplet that will help regulate the spread of the infection. All countries release advisory to stop the spread of the pandemic disease, the passenger who has travel history from an infected country has been routinely checked. WHO gives some instruction to reduce the spread of COVID-19 which includes (i) wash your hand properly with the surfactant at least 20 sec, (ii) Avoid touching your face, (iii) Practice good respiratory hygiene, (iv) Maintain social distancing and avoiding crowded place and (v) Seek medical care early if you show symptoms [84].

CONCLUSION

SARS-CoV-2's intermittent emergency and epidemic reminds us that the CoV's of zoonosis are many global health threats. An effective vaccine against nCoV-19 urgently needs to be developed. The research should focus on strict preventive and control measures to reduce the potential risk of transmission of diseases. The study will rely on enforcing strict preventive and control measures that minimize the possible risk of disease transmission. Several pre-clinical data support that S-protein is considered a critical viral antigen for virulence, and this will lead to the development of new drugs against SARS-CoV-2 in the future. Moreover, in addition, this review will be supports understanding the role of the Ca^{+2} ions in SARS-CoV-2 pathogenesis and survival mechanism. In this study we revealed the potential role of Ca^{+2} and yet unknown, and these ions may play a role in raising the efficiency of SARS-CoV-2 binding or invasion into pulmonary cells.

Alternatively, plasma therapy can help to reduce the degree of COVID-19 infection. If we reduce the concentration of these ions inside the cell, this will help to lower the level of infection. This latest virus epidemic has threatened the worldwide economic, medical, and public health infrastructure. This study provided context to understanding the pathogenesis and survival mechanism of SARS-CoV-2 viral infection, diagnosis, possible treatment, and CoV prevention. Along with this, one-health's role in controlling such zoonotic pathogens is highlighted. We hope this research will be useful in combating infection with CoVs.

ACKNOWLEDGEMENTS

The author is thankful to other authors, and gratefully acknowledges to the Central University of Rajasthan, Ajmer India, we are also thankful to the Department of Science and Technology, Science and Engineering Research Board No. SB/YS/LS-98/2014 and EEQ/2017/000496), Government of India.

REFERENCES

1. Nishiura H, Jung SM, Linton NM, Kinoshita R, Yang Y, Hayashi K, et al. The extent of transmission of a novel corona virus in Wuhan, China. J Clin Med. 2020;9:330.
2. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic corona viruses. Nat Rev Microbiol. 2019; 17:181-192.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al.A novel coronavirus from patients with pneumonia in China. 2019. N Engl J Med. 2020;382:727-733..
4. Weiss SR, Leibowitz JL. Corona virus pathogenesis. Adv Vir Res. 2011;81:85-164.
5. Wang C, Horby PW, Hayden FG, Gao GF. A novel corona virus outbreak of global health concern. Lancet. 2020;395:470-473.

6. Yuen KS, Ye ZW, Fung SY, Chan CP, Jin DY. SARS-CoV-2 and COVID-19: The most important research questions. Cell Biosci. 2020;10:40.

7. Giovanetti M, Benvenuto D, Angeletti S, Ciccozzi M. The first two cases of 2019-nCoV in Italy: where they come from? J Med Virol. 2020;92:518-521.

8. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020; 395:565-574.

9. Chen Y, Liu Q, Guo D. Emerging corona viruses: genome structure, replication, and pathogenesis. J Med Virol. 2020;92:418-423.

10. Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J Med Virol. 2020;92:595-601.

11. Hemida MG. Middle East respiratory syndrome coronavirus and the one health concept. PeerJ. 2019;7:e7556.

12. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579:265-269.

13. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, et al. From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses. 2019;11:E59.

14. Sawicki SG, Sawicki DL, Siddell SG. A contemporary view of coronavirus transcription. J Virol. 2007;81:20-29.

15. Hussain S, Pan J, Chen Y, Yang Y, Xu J, Peng Y, et al. Identification of novel subgenomic RNAs and noncanonical transcription initiation signals of severe acute respiratory syndrome coronavirus. J Virol. 2005;79:5288-5295.

16. Angeletti S, Benvenuto D, Bianchi M, Giovanetti M, Pascarella S, Ciccozzi M. COVID-2019: The role of the nsp2 and nsp3 in its pathogenesis. J Med Virol.2020;92:584-588.

17. Tang X, Wu C, Li X, Song Y, Yao X, Wu X, et al. On the origin and continuing evolution of SARS-CoV-2. Natl Sci Rev. 2020;7:1012-1023.

18. Yan S, Sun H, Bu X, Wan G. An evolutionary RGD motif in the spike protein of SARS-CoV-2 may serve as a potential high-risk factor for virus infection?. Preprints. 2020.

19. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission, and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak–an update on the status. Mil Med Res. 2020;7:11.

20. Nakagawa K, Narayanan K, Wada M, Popov VL, Cajimat M, Baric RS, et al. The endonucleolytic RNA cleavage function of nsp1 of Middle East respiratory syndrome coronavirus promotes the production of infectious virus particles in specific human cell lines. J Virol. 2018;92:e01157-18.

21. Vasiljeva L, Merits A, Auvinen P, Kääriäinen L. Identification of a novel function of the Alpha virus Capping Apparatus RNA 5′-TRIPHOSPHATASE ACTIVITY OF Nsp2. J Bio Chem. 2000;275:17281-17287.

22. Montero H, Arias CF, Lopez S. Rotavirus nonstructural protein NSP3 is not required for viral protein synthesis. J Virol. 2006;80:9031-9038.

23. Tomar S, Hardy RW, Smith JL, Kuhn RJ. Catalytic core of alphavirus nonstructural protein nsP4 possesses terminal adenylyltransferase activity. J Virol. 2006;80:9962-9969.

24. Stobart CC, Sexton NR, Munjal H, Lu X, Molland KL,Tomar S, et al. Chimeric exchange of coronavirus nsp5 proteases (3CLpro) identifies common and divergent regulatory determinants of protease activity. J Virol., 2013;87:12611-12618.

25. Angelini MM, Akhlaghpour M, Neuman BW, Buchmeier MJ. Severe acute respiratory syndrome coronavirus nonstructural proteins 3, 4, and 6 induce double-membrane vesicles. mBio 2013;4:524-513.

26. Cottam EM, Whelband MC and Wileman T. Coronavirus NSP6 restricts autophagosome expansion. Autophagy. 2014;10:1426-1441.

27. Peti W, Johnson MA, Herrmann T, Neuman BW, Buchmeier MJ,Nelson M, et al. Structural genomics of the severe acute respiratory syndrome coronavirus: Nuclear magnetic resonance structure of the protein nsP7. J Virol. 2005;79:12905-12913.

28. Kirchdoerfer RN, Ward AB. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. Nat Commun. 2019;10:2342.

29. Xiao Y, Ma Q, Restle T, Shang W, Svergun DI, Ponnusamy R, et al. Nonstructural proteins 7 and 8 of feline coronavirus form a 2: 1 heterotrimer that exhibits primer-independent RNA polymerase activity. J Virol. 2012;86:4444-4454.

30. Su D, Lou Z, Sun F, Zhai Y, Yang H, Zhang R, et al. Dodecamer structure of severe acute respiratory syndrome coronavirus nonstructural protein nsp10. J Virol. 2006;80:7902-7908.

31. Egloff MP, Ferron F, Campanacci V, Longhi S, Rancurel C, Dutartre H, et al. The severe acute respiratory syndrome-coronavirus replicative protein nsp9 is a single-stranded RNA-binding subunit unique in the RNA virus world. Proc Natl Acad Sci U S A. 2004;101:3792-3796.

32. Shi X, Wang L, Li X, Zhang G, Guo J, Zhao D, et al. Endoribonuclease activities of porcine reproductive and respiratory syndrome virus nsp11 was essential for nsp11 to inhibit IFN-βinduction. Mol Immune.2011;48:1568-1572.

33. Chen Y, Cai H, Pan J, Xiang N, Tien P, Ahola T, et al. Functional screen reveals SARS coronavirus nonstructural protein nsp14 as a novel cap N7 methyltransferase. Proc Natl Acad Sci U S A. 2009;106:3484-3489.

34. Bhardwaj K, Palaninathan S, Alcantara JM, Yi LL, Guarino L, Sacchettini JC, et al. Structural and functional analyses of the severe acute respiratory syndrome coronavirus endoribonuclease Nsp15. J Biol Chem. 2008;283:3655-3664.

35. Bassetti M, Vena A and Giacobbe DR. The Novel Chinese Coronavirus (2019-nCoV) Infections: challenges for fighting the storm. Eur J Clin Invest. 2020;50:e13209.

36. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N E J Med. 2020;382:1708-1720.

37. Carlos WG, Dela Cruz CS, Cao B, Pasnick S, Jamil S. Novel wuhan (2019-nCoV) coronavirus. Am JResp Crit CareMed. 2020;201:7-8.

38. Wu P, Hao X, Lau EH, Wong JY, Leung KS, Wu JT, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. Eur Surveill. 2020;25:2000044.

39. Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. E Microb Infect. 2020;9:386-389.

40. Li F. Structure, function, and evolution of coronavirus spike proteins. Annu Rev Virol. 2016;3:237-261.

41. Walls AC, Tortorici MA, Bosch BJ, Frenz B, Rottier PJ, DiMaio F, et al. Cryo-electron microscopy structure of a coronavirus spike glycoprotein trimer. Nature. 2016;531:114-117.

42. Kirchdoerfer RN, Cottrell CA, Wang N, Pallesen J, Yassine HM, Turner HL, et al. Pre-fusion structure of a human coronavirus spike protein. Nature. 2016;531:118-121.

43. Yuan Y, Cao D, Zhang Y, Ma J, Qi J, Wang Q, et al. Cryo-EM structures of MERS-CoV and SARS-CoV spike glycoproteins reveal the dynamic receptor binding domains. Nat Commun. 2017;10:15092.

44. Walls AC, Tortorici MA, Snijder J, Xiong X, Bosch BJ, Rey FA, et al. Tectonic conformational changes of a coronavirus spike glycoprotein promote membrane fusion. Proc Natl Acad Sci U S A. 2017;114:11157-11162.

45. Li F, Berardi M, Li W.H., Farzan M, Dormitzer PR, Harrison SC. Conformational states of the severe acute respiratory syndrome coronavirus spike protein ectodomain. J Virol. 2006;80:6794-6800.

46. Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein.Viruses. 2012;4:1011-1033.

47. Wan Y, Shang J, Graham R, Baric R.S., Li F. Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. J Virol.2020,94:e00127-20.

48. Shulla A, Heald-Sargent T, Subramanya G, Zhao J, Perlman S, Gallagher T. A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. JVirol. 2011;85:873-882.

49. Kam YW, Okumura Y, Kido H, Ng LF, Bruzzone R, Altmeyer R. Cleavage of the SARS coronavirus spike glycoprotein by airway proteases enhances virus entry into human bronchial epithelial cells in vitro. PLoS One. 2009;4:e7870.

50. Glowacka I, Bertram S, Müller MA, Allen P, Soilleux E, Pfefferle S, et al. 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. 2011;85:4122-4134.

51. Bertram S, Glowacka I, Müller MA, Lavender H, Gnirss K, Nehlmeier I, et al. Cleavage and activation of the severe acute respiratory syndrome coronavirus spike protein by human airway trypsin-like protease. J Virol. 2011;85:13363-13372.

52. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat Microbio. 2020;5:562-569.

53. Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog.2011;14:e1007236.

54. Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc Nat Acad Sci. 2005;102:11876-11881.

55. Millet JK, Whittaker GR. Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. Virus Res. 2015;202:120-134.

56. Mathieu D, Felix AR, Margaret K. Rubella virus: First calcium-requiring viral fusion protein. PLoS Pathog.2014;10:004530.

57. Straus MR, Tang T, Lai AL, Flegel A, Bidon M, Freed JH, et al. Ca2+ ions promote fusion of Middle East Respiratory Syndrome coronavirus with host cells and increase infectivity. J Virol. 2020;94:e00426-20.

58. Sigrist CJ, Bridge A, Le Mercier P. A potential role for integrins in host cell entry by SARS-CoV-2. 2020, Antiviral Res.2020;177:104759.

59. Millard M, Odde S, Neamati N. Integrin targeted therapeutics. Theranostic. 2011;1:154-188.

60. Fox JE, Goll DE, Reynolds CC, Phillips DR. Identification of two proteins (actin-binding protein and P235) that are hydrolyzed by endogenous Ca2+-dependent protease during platelet aggregation. J Bio Chem. 25;260:1060-1066.

61. Trimble WS, Grinstein S. T.B. or not T.B.: Calcium regulation in mycobacterial survival. Cell. 2007;130:12-14.

62. Lawson C, Schlaepfer D. Integrin adhesions: Who's on first? What's on second?. Cell Adh Migr. 2012;6:302-306.

63. Poutanen SM, Low DE, Henry B, Finkelstein S, Rose D et al. Identification of severe acute respiratory syndrome in Canada. N Engl J Med. 2003;348:1995-2005.

64. Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009;7:226-236.

65. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan China: The mystery and the miracle. J Med Virol. 2020;92:401-402.

66. Sun P, Lu X, Xu C, Sun W, PanB. Understanding of COVID-19 based on current evidence. J Med Virol. 2020;92:548-551.

67. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. NEngl J Med. 2020;382:929-936.

68. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis. 2020;20:398-400..

69. Li H, Wang YM, Xu JY, Cao B. Potential antiviral therapeutics for 2019 Novel Coronavirus. Ch J Tub Resp Dis. 2020;43:E002.

70. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. 2020;323:1406-1407.

71. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). Biosci Trends. 2020;14:69-71.

72. Vellingiri B, Jayaramayya K, Iyer M, Narayanasamy A, Govindasamy V, Giridharan B, et al. COVID-19: A promising cure for the global panic. Sci Total Env. 2020;725:138277.

73. Paital B, Das K, Parida SK. Inter nation social lockdown versus medical care against COVID-19, a mild environmental insight with special reference to India. Sci Tot Envi. 2020;728:138914.

74. Aguiar AC, Murce E, Cortopassi WA, Pimentel AS, Almeida MM, et al. Chloroquine analogs as antimalarial candidates with potent in vitro and in vivo activity. Int J Parasitol Drugs Drug Resist. 2018;8:459-464.

75. Savarino A, Boelaert JR, Cassone A, Majori, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. Lancet Infect Dis. 2003;3:722-727.

76. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. J Virol. 2005;2:69.

77. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. Nat Rev Microbiol. 2013;11:836-848.

78. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: Recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14:523-534.

79. Ravishankar B, Shukla VJ. Indian systems of medicine: A brief profile. Afr J Tradit Complement Altern Med. 2007;4:319-337.

80. Gomathi M, Padmapriya S, Balachandar V. Drug studies on Rett syndrome: From bench to bedside. J Auti Dev Disor. 2020;1-25.

81. https://pib.gov.in/PressReleasePage.aspx?PRID=1600895

82. Wang W, Tang J, Wei F. Updated understanding of the outbreak of 2019 novel coronavirus (2019-nCoV) in Wuhan, China. JMed Virol. 2020;92:441-447.

83. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. NEngl J Med. 2020;382:1199-1207.

84. https://www.who.int/publications/i/item/clinical-management-of-covid-19