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COVID-19: Invasion, pathogenesis and possible cure – A review

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ABSTRACT

Today, Coronavirus disease (COVID-19) which is believed to be transmitted from bats to humans where the people of Wuhan city, China exposed to the wet animal market is an important international public health anxiety (Xiong et al., 2020). Although, several measures were undertaken to treat the diseases by various medical advancements and by a variety of treatment procedures, still the mortality is higher. Hence, social distancing has been implemented to control the current outburst of this pandemic which spreads through human to human transmission. As a consequence, there is a need to completely understand the route of invasions of the virus into the humans and the target receptors besides the other factors leading to the disease. Several vaccines and drugs have been developed with its own pros and cons. Many are still under the various phase of R&D and clinical trials. Here we highlight the possible entry molecules, pathogenesis, symptomatology, probable cure and the recently developed vaccines for the existing pandemic due to the COVID-19.

1. Introduction

A sequence of severe atypical respiratory ailment happened in Wuhan, China during December 2019 which eventually spanned to other cities as well (Xiong et al., 2020). Soon after, researchers concluded that the ailment is due to the novel coronavirus. This new coronavirus was similar to SARS-CoV which resulted in the outbreak of SARS during 2002–2003 (Ksiazek et al., 2020). Hence, the World health Organisation (WHO) named the disease due to this virus as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2/ 2019-nCoV/ COVID - 19). This virus is a member ofBeta coronaviruses like SARS and MERS (Chan et al., 2015; Elfiky et al., 2017; Shereen et al., 2020). The outburst of COVID-19 was believed to start from animals, in particular from Bats in the seafood market in Wuhan, China (Wang et al., 2020a). Subsequently, it was documented that social human to human spread played a vital part in the outbreak as it became deadly, pandemic and impacted enormous people across the globe (Wang et al., 2020a). Nevertheless, this has become a major threat and based on the data from WHO, a total of 216 countries were affected with 217,558,771 confirmed cases and 4, 517,240 deaths by COVID-19. It is also reported that 5,272,630,490 vaccine doses are administered as on 01.09.2021 (https://covid19.who.int/). Scientists all over the world are still involved in active research day and night to find a preventive as well as curative vaccine/medicine for COVID-19. In spite of these tremendous efforts towards the containment of the contagious disease, no unique and specific drug has been advised for the cure of COVID-19 till date though treatment has been given with already developed medicines.

SARS-CoV-2 initially attacks the respiratory system and can be diagnosed through the symptoms like fever, vomiting, headache, dizziness, general weakness, diarrhoea etc. (Memish et al., 2013; Shi et al., 2020). As days progressing, these symptoms become heterogenous towards the development of ARDS and the disease could lead to mortality with the mounting number of patients surrender globally. These death rates are predicted to be higher in elder population than in the case of young individuals (Qiu et al., 2020; Lu et al., 2020; Zhou et al., 2020). The elderly patients are reported to have a higher mortality rate due to high case fatality rate and symptomatic infection rate (Leung, 2020; Seung-Ji and Jung, 2020). Hu et al. have observed that age also affects the time from hospitalization to death and viral clearance (Hu et al., 2020).

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Presently, due to the prevailing third wave of this pandemic across the world, however, Japan has entered into the fourth wave according to the report from WHO (https://www.who.int/countries/jpn/), despite efficient vaccination procured from different pharma industry, the medical team is still struggling to diagnose precisely and contain this outbreak as there is no targeted therapy available. Nevertheless, there are several diagonistic kits and methods available at present such as rapid kit test approved by FDA and EMA for the diagnosis of COVID-19, CRISPR/Cas-based systems, biosensors and ddPCR. A major reason may be due to the faster mutation of the COVID-19 virus and varying degree of symptoms which eventually lead to the diagnosis problems. Besides wide antimicrobial agents, quite a few anti-malarial drugs have been utilized to treat the infected persons like that of azithromycin, lopinavir-ritonavir, chloroquine, remdesivir, hydroxychloroquine, etc., (Cao et al., 2020; Gautret et al., 2020). So far none of these drugs have been found to be an appropriate drug for COVID-19 and hence further therapies are underway and are being tested under clinical trials. As a consequence, many countries have adopted lockdown and social distancing in order to control the spread of the deadly virus. Vaccines developed by Moderna Inc, Pfizer and BioNTech, Johnson & Johnson and AstraZeneca have been developed and approved for use since Mid 2020 (Maria and Wonodi, 2021) (https://www.prevention.com/health/a35118263/astrazeneca-vs-pfizer-vs-moderna-covid-19-vaccine/). Several other potential vaccines are in preclinical development by academic institutions, pharmaceutical companies, and government agencies. Therefore, a thorough interpretation of the invasive mechanism of this virus has become an urgent need, which in turn will develop a clear focus in identifying the potential target site and produce an effective antiviral drug for COVID-19 specifically. Based on the above points, in this review we focus on the path of invasion and pathogenesis to identify the precise target sites and propose the possible remedial path ways focusing on the investigation of the possible drugs and vaccines proving a great efficacy against COVID-19 infection.

2. Structure of SARS- CoV 2

The enveloped coronaviruses (CoVs) are a versatile family of positive-sense RNA viruses that are scattered commonly among animal species. They are of full genome size ~ 30 kilobases in length and ranging from 40 nm to 200 nm in diameter and infect several species and often in pleomorphic form. (Channappanavar et al., 2014). These are classified into four major categories according to their genomic structure as α, β, γ, and δ wherein the α and β CoVs poison only mammals. The SARS-CoV-2 and MERS-CoV-2 are grouped under β coronaviruses.

The virus has a five step protocol on adhering to the host species before they make newer viral proteins as attachment, penetration, biosynthesis, maturation and release (Yuki et al., 2020). The genomic analyses predict that the SARS-CoV-2 virus might have been evolved from a strain originated from bats. In addition, the virus transmission from the bats to humans still needs to be explored. This type of viruses cause infections in birds and mammals and have revealed to be harmful for humans even leading to mortality (Schoeman and Fielding, 2019). These viruses are identified to have four structural proteins, as shown in Fig. 1. This includes E, M, N protein and S- Spike glycoprotein (Li, 2016). Among these the S protein is the most crucial. The spike protein acts as a recognition factor as it attaches to the membrane receptor on the host cells, facilitating the fusion with cellular membrane (Elfiky et al., 2017). It exists on the virion's outer surface. In order to gain a clear insight about the invasion of COVID-19, a number of investigators have modelled and validated the spike protein of SARS-CoV 2 using the available structures from the protein data bank (Berman et al., 2003). They have then performed the molecular docking studies to test its affinity against different receptors for understanding the binding of spike protein on the host cell membrane (Zhu et al., 2018). The S protein on the surface of the virus is a key factor involved in infection. It is a trimeric class I TM glycoprotein responsible for viral entry. It mediates receptor recognition, cell attachment, and fusion during viral infection. once the virus interacts with the host cell, extensive structural rearrangement of the S protein occurs, allowing the virus to fuse with the host cell membrane. The spikes are coated with polysaccharide molecules to camouflage them, evading surveillance of the host immune system during entry (Watanabe et al., 2020) The trimer of the S protein located on the surface of the viral envelope is the basic unit by which the S protein binds to the receptor (Walls et al., 2020; Yan et al., 2020). In the native state, the S protein exists as an inactive precursor. During viral infection, target cell proteases activate the S protein by cleaving it into S1 and S2 subunits (Bertram et al., 2013) which is necessary for activating the membrane fusion domain after viral entry into target cells (Hoffmann et al., 2020) Similar to other coronaviruses, the S protein of SARS-CoV-2 is cleaved into S1 and S2 subunits by cellular proteases The S1 domain contains the Receptor binding domain (RBD), which is mainly responsible for binding of the virus to the receptor, while the S2 domain mainly contains the heptad repeat (HR) domain, including HR1 and HR2, which is closely related to virus fusion (Cui et al., 2019).

3. Invasions of SARS-CoV-2

From the results of genome sequencing it has been understood that SARS-CoV-2 is more related to SARS-CoV (~79 % similarity) than MERS-CoV (~50 % similarity) and it is a part of the β-coronavirus family. After an exhaustive literature survey, we have identified and categorized four major entry molecules which can be host cell receptors or host proteases adopted by the virus to enter the respiratory mucosa in humans. They are (i) ACE2 (ii) the host proteases TMPRSS2 and Furin (iii) GRP78 and (iv) CD147 for SARS-CoV-2 to the best of our knowledge.

3.1. ACE2

In the initial couple of day's infection, i.e., the asymptomatic stage,

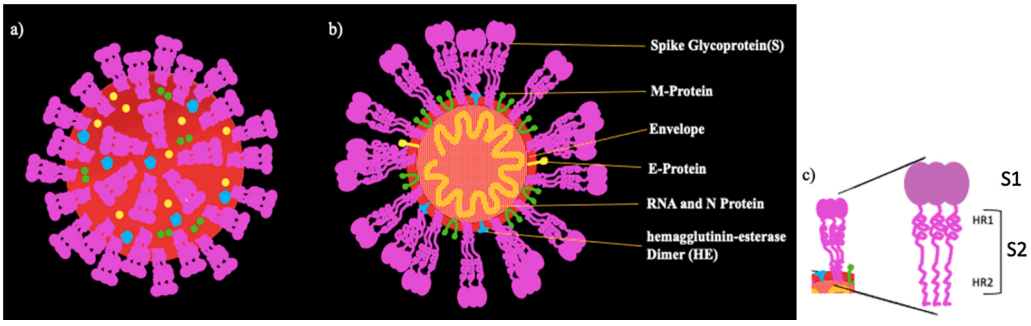

Fig. 1. a), b) Structure of SARS-CoV-2 virus depicting the envelope small membrane protein (E), membrane protein (M), Nucleoprotein protein (N) and S- Spike glycoprotein, c) Spike protein (Trimer).

SARS-CoV-2 probably attaches to the nasal cavity epithelial cells and immediately replicates during the inhalation of the deadly virus. According to the preliminary examinations, Angiotensin-converting enzyme 2 (ACE2) has been accepted as one of the foremost receptors for both SARS-CoV2 and SARS-CoV (Ge et al., 2013). The binding of spike protein and ACE2 supports the penetration of SAR-CoV 2 into the host cells as shown in Fig. 2. At first the S protein of the coronavirus binds to the ACE2 receptor. The affinity of the receptor binding site of S-protein and ACE2 determines the susceptibility of the host. S-protein binds to the claw structure of ACE2 due to which a fusion is created between the viral and host cell membrane. It has been reported that SARS-CoV 2 virus manipulates the angiotensin-converting enzyme 2 (ACE2) receptor to acquire the host cell (Liu et al., 2020). The symptomatic characteristics of majority of the COVID-19 patients include respiratory distress followed by severe breathing difficulty. Few patients also suffer from headache, nausea and vomiting which are classified under neurological symptoms. Several evidences support the fact that apart from respiratory issues coronavirus may also lead to neurological diseases by invading the central nervous system (CNS) (Manuela et al., 2020; Li et al., 2020d; Baig and Sanders, 2020) SARS-CoV has been identified creating infections in the brains of both patients and experimental animals (Li et al., 2020c). This finding has aroused the interest of researchers towards understanding the reciprocation of ACE2 in neurological tissue in defining the possible damage to this tissue leading to the illness and death caused by SARS-CoV-2. Although still under investigation, there are several mechanisms proposed by which the virus can enter the central nervous system (CNS). SARS CoV-2 can affect the CNS through direct routes—hematogenous through a direct invasion of capillary endothelium binding to ACE2 receptors and disrupting the blood-brain-barrier (Cuervo and Grandvaux, 2020). An underestimated damage to nervous system and trans-neuronal pathways via retrograde axonal transport, using several cranial nerves has been reported by (Von Weyhern et al., 2020). Razia Rehmani et al. have reported indirect mechanisms which include cytokine dysregulation, peripheral immune cell transmigration, neuroinflammation, postinfectious autoimmunity and, hypercoagulability (Rehmani et al., 2021).

Baig et al. have investigated the impact of ACE2 in the Central Nervous System, the interaction of ACE2 and SARS-CoV-2 (Baig et al., 2020). They have elaborated the pathogenesis and related risks due to the outbreak of COVID-19. According to them, SARS-CoV-2 virus is disseminated in the bloodstream and it reaches the entire body. The virus can reach the brain via circulation or nasal route, where they are hosted by the ACE2 receptors. Docking of spike protein on the host cell supports this happening. Several organs such as lungs, brain, heart, intestines, kidneys and testicles that are well-known for the expression of ACE2 receptors are the most probable targets of SARS-CoV-2. In addition to the complications due to cerebral damage, it has been concluded that the major impact comes from the dysregulation of homeostasis caused by respiratory, cardiac, renal and circulatory failure resulting in fatality of COVID-19 patients (Tsatsakis et al., 2020; Periklis et al., 2020) Mysteriously, the SARS-CoV-2 SP structure is in close proximity to that of SARS-CoV SP. At the same time SARS-CoV-2 SP shows higher affinity towards binding to ACE2 than SARS-CoV SP, which ensures a fervent competence of SAR-CoV-2 in invading the host cells (Wrapp et al., 2020). On the other side, the animal model (mice) studies by Jason et al. have showed that SARS-CoV virus makes an entry to the brain through the olfactory bulb which in turn results in rapid spread of the infection to interconnected areas of the brain (Netland et al., 2008). This massive neuronal infection has been reported to be the major cause of fatality. Whereas, a uniformly lethal disease has been resulted after intracranial vaccination in case of low doses of virus in spite of mild infection in the lungs. It is the dysfunction and/or death of infected neurons, primarily located in cardiorespiratory centres in the medulla that are likely to have resulted in the death of the animal. According to their results neurons were observed to be easily influenced by SARS-CoV that the dearth of host cell receptor becomes a mandate to prevent the severe murine brain disease. One of the most commonly used class of antihypertensive drug namely angiotensin receptor-blocker (ARB) drugs aids in an extreme increase of ACE2 expression (perhaps two-fold to five-fold) (Ferrario et al., 2005; Gallagher et al., 2008). Esler et al. have reported that there would be an adverse effect due to an boosted expression of ACE2 with SARS-CoV-2 infection (Esler and Esler, 2020). In the presence of angiotensin receptor blockers an augmented ACE2 expression has been demonstrated in the heart and kidneys (Ishiyama et al., 2004; Jessup et al., 2006). The key point to be noted is the remarkable increase in ACE2 expression due to the usage of angiotensin receptor blocker drugs which becomes a major demerit. Therefore the prescription of such angiotensin receptor-blocking drugs during the COVID-19 pandemic might be unsafe and it has been recommended to prefer other antihypertensive drug classes.

Finally, the above concepts might need some revision, since low level of ACE2 expression is indicated in single-cell RNA in conducting airway cells without noticing any obvious cell type preference (Reyfman et al., 2019). There is a natural immune response to the propagation of this virus but it is limited. During this stage nasal swabs can be tested to detect the virus.

3.2. *TMPRSS2 & TMPRSS4 and Furin*

TMPRSS2 is a cell surface protease known to cleave both ACE2 and the spike protein of coronaviruses. SARS-CoV-2 S proteins are primed/activated by the transmembrane protease serine 2 (TMPRSS2), which also play a key role in this viral infection (Hoffmann et al., 2020; Iwata-Yoshikawa et al., 2019). More recently, it has been demonstrated that transmembrane protease serine 4 (TMPRSS4) along with TMPRSS2 activate the SARS-CoV2 S proteins, and enhance the viral infection of human small intestinal enterocytes (Hoffmann et al., 2020; Periklis et al., 2020) have documented a high TMPRSS4 expression in the

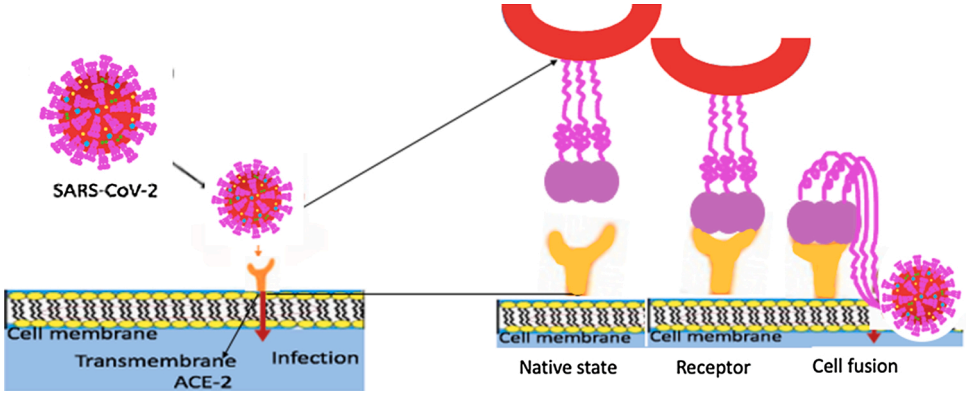

Fig. 2. Interaction between ACE-2 receptor and SARS- CoV-2.

olfactory tubercle, paraolfactory gyrus and frontal operculum, all brain regions which are associated with the sense of smell and taste. TMPRSS4 - along with TMPRSS2 - appear to activate the SARS-CoV-2 S proteins, and enhance subsequent viral infection of human small intestinal enterocytes (Zang et al., 2020). A recent report demonstrated that both ACE2 and TMPRSS2 genes were abundantly expressed in enterocytes of the lower gastrointestinal (GI) tract, whilst also exhibiting co-expression with TMPRSS4, particularly in the small intestine.

A paired basic amino acid cleaving enzyme, furin is important in prorenin receptor processing, and furin variants participate in multiple aspects of blood pressure (BP) regulation (Ren et al., 2017). Furin splits and stimulates a variety of substrates including mammalian, viral and bacterial. The flow chart in Fig. 3 depicts the furin creating proteolytic activation on mammalian, viral and bacterial substrates which results in various diseases. It can be observed that several viruses utilize furin for the activation of their glycoproteins, including the spike protein of COVID-19 (Fig. 3). Also it has to be noticed that unlike SARS-CoV, a significantly high efficiency of trypsin digestion is evidenced at the CS1 digestion site with SARS-CoV-2 which contains polybasic amino acids (RRAR) (Belouzard et al., 2009). More importantly, the furin enzyme can recognize and cleave the CS1 digestion site with SARS-CoV-2. This in turn results in the cleavage of Spike protein that promotes a rearrangement in the structure of RBD for the required modification to receptor, thus enhancing the affinity. The strong infectious capacity of SARS-CoV-2 is more likely to occur during endocytosis process during which the membrane fusion of SARS-CoV-2 would take place. In order to block the transmissibility of the virus the development of furin inhibitors may be an encouraging route. Wu et al. have performed protein-protein docking for furin and Spike protein. The putative furin cut site (Arg685) of SARS-CoV-2 Spike was chosen to dock furin (Wu et al., 2020). The results showed a perfect stable (-18.43 Kcal/mol) fitting of SARS-CoV-2 Spike basic/positive S1/S2 protease cleavage loop and the furin acidic/negative active pocket implying that the extra “PRRAR” loop of SARS-CoV-2 Spike renders it more fragile to the protease. This may efficiently enhance the infection efficiency by allowing the site to be cut during the maturation. However, the more infectious problem still can’t be fully explained by stronger receptor binding. They have put forward, the following hypotheses: (1) There can be other receptors to which SARS-CoV-2 gets bind to (2) the earliest infection site may not be the lung (3) The easier to cut SARS-CoV-2 can more easily fuse with cell membranes. The expression of furin has been analysed it is found that furin is distributed with little difference in expression level in various organs. The widespread distribution of furin, combined with the possible infection mechanism of SARS-CoV-2, increases infection of other organs. The probability of other organ attack is reliable based on the multiple symptoms observed in clinic of COVID-19. Studies reported the possibility of intensifying the activity of SARS-CoV spike owing to the overexpression of furin, but it did not result in the cleavage of spike. Proteolytic activation by cathepsins B and L in host cells are the two ways that can be used to activate SARS-CoV Spikes by means of cleavage (Simmons et al., 2011, 2005). The cleavage of Spike protein of SARS-CoV-2 at multiple stages, can greatly increase the efficiency of union. It is possible that there will be a release of genome when the virus fuses with the cell during endocytosis. An augmented binding ability of the cleaved Spike to the ACE2 receptor has been observed (Park et al., 2016). From the database of 78 antiviral drugs, a series of HIV-1, hepatitis C, and hand-foot-and-mouth disease therapeutic drugs, such as Indinavir, Tenofoviralafenamide, Tenofovir, Disoproxil, Dolutdegravir, Boceprevir, Telaprevir and Suramin also showed high attraction towards furin. These potential furin inhibitors and traditional medicinal plants containing these compounds as major constituents might be beneficial for the treatment COVID-19. However, all these stands at modelling level and further *in vitro* and *in vivo* studies should be carried out to confirm the suitable drug. The deficiency of impact of furin cleavage on virion infectivity illustrates that noticed in the normally cleaved S glycoprotein of the murine coronavirus and emphasizes an additional level of intricacy in coronavirus entry (Follis et al., 2006).

3.3. GRP78

The third way of invasion is through the glucose regulating protein 78 (GRP78). The master protein of the unfolded/misfolded proteins, Binding immunoglobulin protein (BiP) is nothing but the Glucose Regulating Protein 78 (GRP78) (Lee, 2005; Li and Lee, 2006; Quinones et al., 2008; Rao et al., 2001). Under practical conditions, GRP78 is observed in the lumen of the endoplasmic reticulum (ER) inactivating three enzymes viz activating transcription factor 6 (ATF6), Inositol-requiring Enzyme 1 (IRE1) and protein kinase RNA-like endoplasmic reticulum kinase (PERK) which are responsible for cell death or differentiation (Ibrahim et al., 2019). Above a threshold of collected unfolded proteins, GRP78 discharges ATF6, PERK, and IRE1, leading to their stimulation as depicted in Fig. 4. Augmentation of the refolding by

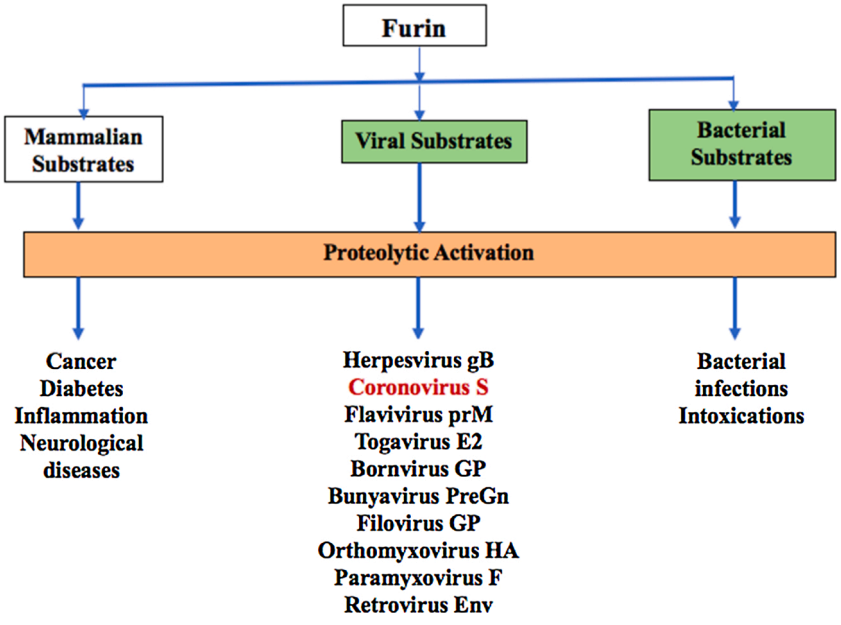

Fig. 3. Flow chart depicting the Furin creating proteolytic activation.

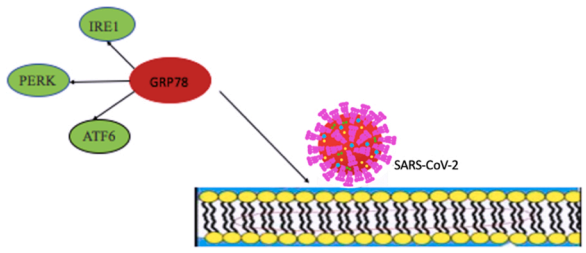

Fig. 4. Interaction between GRP78 receptor and COVID-19.

inhibition of protein synthesis is the end result of the enzymes' activation (Shen et al., 2002). Overexpression of GRP78 increases the chance for GRP78 to dodge ER retention and translocate to the cell membrane which is often initiated upon cell stress. GRP78 can arbitrate the entry of the virus in the cell upon translocating to the cell membrane as it is liable in recognition of the virus by its substrate-binding domain (SBD). The spike protein of COVID-19 has been modelled by Ibrahim et al. using the solved structures in the protein data bank (Ibrahim et al., 2020). This was followed by the model validation and then molecular docking to understand its binding affinity against GRP78. They have hypothesized the binding of GRP78 to COVID-19, similar to that of MERS-CoV coronavirus (Chu et al., 2018). Based on sequence and structural similarity four regions of the spike were identified to be the binding site to GRP78. 13 different cyclic regions originating from the 13 disulphide bonds in the COVID-19 spike protein model has been identified to resemble the cyclic Pep42. It is interesting to note that this structure has been reported to precisely target the cell-surface GRP78 in cancer cells (Lee, 2005; Rao et al., 2001). Four of these disulphides are noticed in the outer surface of the spike receptor-binding domain that is turned towards the outside part of the virion. This zone has been besieged with neutralizing antibodies in opposition to the SARS and MERS spikes. Hampering the contact between the COVID-19 spike protein and the host cell receptor GRP78 would probably subside viral infection rate. Further work relating the dynamics of GRP78 and the experimental proof is mandatory to propose potent peptidomimetic inhibitors.

3.4. CD147

Basigin (BSG), an extracellular matrix metalloproteinase inducer (EMMPRIN) or cluster of differentiation 147 (CD147) is a highly glycosylated transmembrane protein of the immunoglobulin super family which is encoded by the *BSG*gene in humans (Frances et al., 1997; Miyauchi et al., 1991; Yurchenko et al., 2006). In the cancer progression, inflammatory processes and in tumours the active existence of CD147 and MMPs are often found to be in increased levels (Kong et al., 2014). Furthermore, literature reports reveals that cancer stem cells and patients with severe asthma are characterized by high cell surface CD147 expression and have high levels of MMP-9 in sputum respectively (Mattos et al., 2002; Toole, 2020). Also, CD147 expression in cells were found to be increased in influenza A virus infection and also induced by high glucose (25 mM) concentration in monocytes etc. (Bao et al., 2010; Moheimani et al., 2018). This elevated glucose *in vitro* also increases the expression of MMP-1 and MMP-9, and could be returned by suppression of CD147 expression by the interfering RNA and activity inhibition by an anti-CD147 antibody as the MMPs function in monocyte migration. Nonetheless, this protein is a determinant for the Ok blood group system. OK1, OK2 and OK3 are the 3 known antigens in this system. Whereas a key receptor on red blood cells for the human malaria parasite, *Plasmodium falciparum* has been identified as basigin (Crosnier et al., 2011). Spike protein of SARS-CoV-2 may bind to the host-cell-expressed basigin (CD147) and invade the host cell (Wang et al., 2020b). Consequently, the patients affected by SARS-CoV-2 pneumonia were tested by a humanized anti-CD147 antibody- meplazumab (Bian et al., 2020). Chen et al. have reported that CD147 aids the SARS-CoV to invade the host cells, at the same time CD147-antagonistic peptide-9 exhibits an inhibitory effect on this virus due to its high binding rate to HEK293 cells (Chen et al., 2005). Owing to the similarity between SARS-CoV and SARS-CoV-2, they have investigated the possible function of CD147 in invasion of host cells by SARS-CoV-2. They have reported that a novel route of CD147-SP has been utilized by SARS-CoV-2 in invading the host cells. A humanized anti-CD147 antibody Meplazumab, could remarkably inhibit their binding and prevent the viruses from entering the host cells, which offers a promising target for forming suitable antiviral drugs.

4. Diagnosis of COVID-19 infection

The diagnosis of COVID-19 infection, though it was slow in detecting, many rapid tests have been developed at present based up the symptomatic and asymptomatic individuals. Scientists and researchers were tirelessly working on the exceedingly consistent diagnostic methods in order to efficiently and precisely diagnose the infection which in turn can control its diffusion. The government, and private research laboratories along with various pharma and biomedical companies joined hands in developing multivarious diagnostic strategies to identify the COIVD-19. Currently, RT-PCR-based molecular tests, rapid antigen and rapid antibody tests, rapid antigen or antibody tests, immunoenzymatic serological tests are the authenticated and valid techniques used (Luca et al., 2021). Nevertheless, besides these conservative methods, several other techniques, such as clusters of regularly interspaced short palindromic repeats/Cas (CRISPR/Cas)-based approaches, isothermal nucleic acid amplification techniques, or digital PCR methods are currently underway either implemented or waiting for approval (Matteo et al., 2021).

5. Pathogenesis of COVID-19

Ground-glass opacities and acute cardiac injury are noticed in the patients affected by COVID-19 infection, a respiratory system targeting virus resulting in severe pneumonia (Zhu et al., 2020). Also considerably high blood levels of cytokines and chemokines were noted in these patients. The binding of coronavirus spike proteins downregulate ACE2 expression in cells. Hence, less ACE2 is capable of converting angiotensin II to the vasodilator heptapeptide angiotensin 1–7 (Cheng et al., 2020; Zhang et al., 2020). This could contribute to more hypertension and severe lung injury. SARS-CoV-2 S protein can recognize and bind to the GRP78 SBDβ, facilitating viral entry when the cell is under stressful conditions (Ibrahim et al., 2019). Thus CD147 is highly expressed in tumor tissues, inflamed tissues and pathogen infected cells (Kosugi et al., 2015). SARS-CoV-2 exhibited increased infectivity in cells in the presence of TMPRSS2 (Hoffmann et al., 2020). The spike glycoprotein has a potential cleavage site for furin proteases (Li et al., 2020a, b, c, d). Furin is well expressed in the cells of the respiratory tract, hence increasing the infectivity of SARS-CoV-2.

Based on a thorough analysis on the pathogenesis of coronavirus, a flowchart as shown in Fig. 5 on the pathogenesis of coronavirus has been broadly framed considering the four possible entry points *viz* i) ACE2 receptors, ii) Furin mediated, iii) GRP78 mediated and iv) CD147 (Basigin) mediated.

6. Symptoms

SARS-CoV-2 virus in particular is responsible massive number of infections and deaths globally. Until now, the United States is the most affected nation. The medical management along with the World Health Organization, which includes, doctors, scientists and other staff are learning first-hand things about this deadly virus day by day. The investigations and the data collected as of now on COVID-19 reveals that the virus may not primarily cause any symptoms for several humans. The host may carry the virus for two days or up to two weeks as an

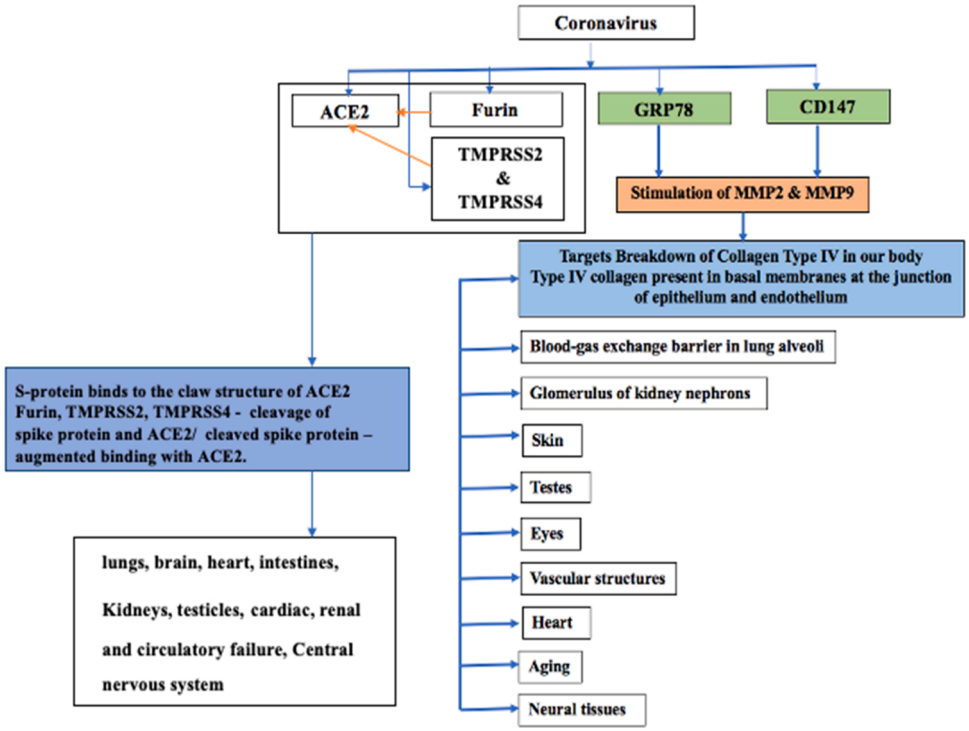

Fig. 5. Flow chart depicting the pathogenesis of SARS-CoV-2 virus explaining the possible entry points and their targets.

incubation period before noticing any symptoms (Li et al., 2020b). During this period the rigorousness of the infection depends on the individual human immune system and age, particularly above seventy years (Wang et al., 2020d). The entry or the beginning of the COVID-19 disease can be categorized *via* three major symptoms. Firstly, the less common symptoms which include, sore throat, headache, muscle aches and pains, chills, repeated shaking with chills etc. Secondly, the most common symptoms such as fatigue, having a cough that gets more severe over time, shortness of breath, loss of taste, haemoptysis, a low-grade fever that gradually increases in temperature, diarrhoea. Lastly, the critical symptoms like excessive drowsiness, persistent pain or pressure in the chest, blue lips or face, trouble breathing, confusion etc. (Graham Carlos et al., 2020; Wang et al., 2020d). Anosmia (loss of smell), and ageusia (loss of taste) become more frequently cited as independent symptoms or in association with the most common manifestations of the disease, such as fever, cough and dyspnea (Ingrid et al., 2020). It is noteworthy to mention that some of the symptoms are similar on comparing the COVID-19 and the earlier beta corona virus such as dry cough, headache, fever etc. Nevertheless, COVID-19 has some exclusive features including targeting the lower airways as apparent by upper respiratory tract symptoms like sneezing and sore throat (Assiri et al., 2013; Lee et al., 2003). Some of the clinical features shown by a chest computed tomography scan there were abnormal features such as, acute respiratory distress syndrome, severe cardiac injury and pneumonia leading to death (Huang et al., 2020). Furthermore, some cases show an infiltrate in the upper lobe of the lung and patients infected develop gastrointestinal symptoms (Phan et al., 2020). Although, we have discussed the above symptoms, it is very important to test the urine and faecal samples which could give some potential information as an alternative route of transmission. Similarly, the waste water released in the hospitals and the water used by the people who are infected are to be tested to identify various other modes of transmission in order to develop specific management and medical strategies to completely eradicate or inhibit or even minimize the spread of COVID-19 thereby developing theragnostic agents to control the disease and the pandemic. However, the complete diagnostic symptoms are constantly being investigated.

Patients with severe and critical COVID-19, even prior to the appearance of acute respiratory distress syndrome, exhibit lymphocytopenia and suffer from T-cell exhaustion, which may lead to viral sepsis and an increased mortality rate. It has been observed that cancer patients, who usually are immunocompromised, may restore their antitumoral immune response when treated with ICIs. Moreover, viral-infected mice and humans, exhibit a T-cell exhaustion, which is also observed following SARS-CoV-2 infection. Importantly, when treated with anti-PD-1 and anti-PD-L1 antibodies, they restore their T-cell competence and efficiently counteract the viral infection. Silvia Vivarelli et al. have examined the efficacy of anti-PD-1 antibody administration to both cancer and non-cancer individuals affected by COVID-19 (Vivarelli et al., 2021). The results may prove the hypothesis that restoring exhausted T-cells may be a winning strategy to beat SARS-CoV-2 infection. The presence of diabetes mellitus and the individual degree of hyperglycaemia seem to be independently associated with COVID-19 severity and increased mortality (Holman, 2020). Furthermore, the presence of typical complications of diabetes mellitus (CVD, heart failure and chronic kidney disease) increases COVID-19 mortality (Barron et al., 2020). Cardiovascular manifestations of COVID-19 infection range from mild elevation of serum troponin and BNP levels to fulminant myocarditis, life-threatening arrhythmias and refractory shock. All patients need close haemodynamic and electrocardiographic monitoring especially if they are on COVID-19 treatment (Bishnu et al., 2020).

6.1. *Alternative medical therapy*

Presently, to be best of our knowledge for COVID-19 disease, there are no unambiguous and detailed antiviral drugs in spite of some vaccines and already existing medicines for prospective treatment of humans. Scientists and researchers are on a war footing investigations day in and day out to develop innovative coronavirus vaccines and drugs which includes the biotech industries and pharmaceutical companies around the world. On the other hand, experts from Siddha, Ayurveda, homeopathy, Unani etc are thriving hard for a possible cure for COVID-19. In particular at the southern part of India certain sectors of people use the siddha way of consuming the drink called “kabasura kudineer”

which is used to treat the respiratory problems (Bathala and Lakshminarayanan, 2019; Natarajan et al., 2020). In addition to this several other people include turmeric, lemon, ginger, pepper etc as immunity boosters in their daily food. Several biotech industries / universities / pharma companies which are involved in the development of vaccines and drugs for the novel COVID-19 since its outburst (Dance, 2020; Beigel et al., 2020).

6.2. Towards vaccine development for COVID-19

US company Aegis Life has initiated dosing of the first participants in a Phase I/II clinical trial with parent company Entos Pharmaceuticals' novel DNA COVID-19 vaccine, Covigenix VAX-001, to induce immunity against SARS-CoV-2. The trails are conducted in Canada (https://www.clinicaltrialsarena.com/news/aegis-entos-commence-dosing/). Covigenix VAX-001 encodes the SARS-CoV-2 Spike (S) protein using new Fusogenix technology for delivery, where the Fusogenix drug delivery platform is a proteo-lipid vehicle that introduces genetic payload directly into the cells (https://www.entospharma.com/fusogenix). DNA vaccines are stable at room temperature for a month and 4–8 °C for a year, which would aid in streamlining shipping, storage as well as vaccine distribution. Aegis and Entos have also developed another DNA vaccine candidate called Covigenix VAX-002. Covigenix VAX-002 is designed as a pan-coronavirus and emerging variant vaccine, which is currently in preclinical studies. (https://www.scienceboard.net/index.aspx?sec=ser&sub=def&pag=dis&ItemID=2532)

The University of Oxford's ChAdOx1 nCoV-19 vaccine has been developed by inserting the genetic material that encodes the spike protein from SARS-CoV-2 into a very weak, non-replicating adenovirus. Vaccine administration results in a very mild viral infection, which ultimately stimulates the body to produce an immune response against the spike protein (and therefore SARS-CoV-2) produced by the virus (Maria and Wonodi, 2021). The ChAdOx1 nCoV-19 vaccine can also use routine refrigerated cold chain, which is important since the ultra-low temperature freezers required to store mRNA vaccines. Gimsilumab is a monoclonal antibody against granulocyte macrophage-colony stimulating factor (GM-CSF), which is a myeloid cell growth factor and pro-inflammatory cytokine. Late stages of COVID-19 can be marked by a "cytokine storm" and the overactivation of inflammatory myeloid cells that infiltrate and damage tissue, such as the lungs. Inhibition of GM-CSF may be able to reverse this pathology. The anti-GM-CSF mechanism is distinct from antiviral therapeutic mechanisms and may provide synergistic effects when used in combination. Phase II clinical trial for this vccine was conducted on April 1, 2021 and no study results are posted yet (https://clinicaltrials.gov/ct2/show/record/NCT04351243)

University of Alabama at Birmingham (UAB) has developed a single dose intranasal vaccine for COVID-19 named AdCOVID (https://www.al.com/news/2020/03/uab-to-study-potential-covid-19-vaccine-in-mice.html). AdCOVID has been designed to stimulate a broad immune response including both systemic immunity (neutralizing IgG) and local immunity (mucosal IgA, T cells) in the nasal cavity and respiratory tract (https://altimmune.com/adcovid/) and I-Mab Biopharma is in the process of establishing TJM2 vaccine (https://www.contractpharma.com/contents/view_breaking-news/2020-03-13/i-mab-explores-tjm2-in-treating-severe-covid-19-disease/). This vaccine is aimed at treating cytokine releases syndrome associated with severe and critically ill patients with COVID-19 (https://www.i-mabbiopharma.com/en/news.aspx). Medicago has collaborated with Laval University to develop antibodies against and Airway Therapeutics is investigating its newer human recombinant protein named AT-100 (https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/). Tiziana Life Sciences is in the process of creating its monoclonal antibody named TZLS-501 which works by binding to IL-6R and depleting the amount of IL-6, thereby reducing chronic lung inflammation (http://www.tizianalifesciences.com/drug-pipeline/anti-il-6r/).

OYA1 by OyaGen, BPI-002 by BeyondSpring and INO-4800 by Inovio Pharmaceuticals have started pre-clinical testing for clinical product manufacturing (https://medicospace.com/corona-treatment-vaccines-drugs-in-the-pipeline-for-covid-19-updated/). An intranasal Covid-19 vaccine by biopharmaceutical company, Altimmune, NP-120 (Ifenprodil) by Algernon Pharmaceuticals (https://microcapdaily.com/np-120-ifenprodil-the-rise-of-algernon-pharmaceuticals-inc-otcmkts-agnpf-cnsx-agn/129095/) and APN01 by University of British Columbia (http://pharmabiz.com/NewsDetails.aspx?aid=121445&sid=2) and APEIRON Biologics are being tested in China in a phase one pilot trial as a treatment for COVID-19 (https://www.clinicaltrialsarena.com/news/apeiron-biologics-phaseii-covid-19/). mRNA-1273 vaccine by Moderna and Vaccine Research Center which targets the Spike (S) protein of COVID-19 and Avian Coronavirus Infectious Bronchitis Virus (IBV) vaccine by MIGAL Research Institute have been demonstrated efficacy in pre-clinical trials and used for vaccination (https://www.migal.org.il/en/coronavirus-vaccine-project). TNX-1800 by Tonix Pharmaceuticals (https://www.tonixpharma.com/therapeutic-areas/coronavirus-disease-2019-covid-19) and recombinant subunit vaccine by Clover Biopharmaceuticals have recognized an antigen-specific antibody in the serum of completely recovered COVID-19 patients (http://www.cloverbiopharma.com/index.php?m=content&c=index&a=show&catid=11&id=41&mod=article_inline).

Vaxart is developing an oral recombinant vaccine VAAST (https://investors.vaxart.com/news-releases/news-release-details/vaxart-announces-initiation-coronavirus-vaccine-program) and Linear DNA Vaccine by Applied DNA Sciences and Takis Biotech utilizes a Polymerase Chain Reaction (PCR)-based DNA manufacturing technology to develop the vaccine. BXT-25 by BIOXYTRAN and Novavax's MERS coronavirus vaccine candidate has produced several nanoparticle vaccine candidates for testing in animal models and aims to carry out human trials in 2020 (https://www.novavax.com/our-pipeline#nvx-cov2373). INO-4700 (GLS-5300) by the Inovio, the investigational DNA immunotherapy, is being developed which is delivered as vaccine intramuscularly (https://www.precisionvaccinations.com/vaccines/ino-4700-mers-cov-vaccine). Presently, people are being vaccinated with various types of vaccines which are approved by the respective administrators and the regulatory bodies across many countries. A wide variety of potential vaccines for COVID-19 are in developed, which includes, Inactivated or weakened virus vaccines, which use a form of the virus that has been inactivated or weakened so it doesn't cause disease, but still generates an immune response. Protein-based vaccines, which use harmless fragments of proteins or protein shells that mimic the COVID-19 virus to safely generate an immune response. Viral vector vaccines, which use a safe virus that cannot cause disease but serves as a platform to produce coronavirus proteins to generate an immune response and the RNA and DNA vaccines, a cutting-edge approach that uses genetically engineered RNA or DNA to generate a protein that itself safely prompts an immune response.

Vaccines like Covishield by Oxford-AstraZeneca, Covaxin by Bharat Biotech International limited, Sputnik V vaccine by Gamaleya Research Institute of Epidemiology and Microbiology in Moscow, CoronaVac from Sinovac China and Sinopharm by China, Novavax from the United states etc., have been approved so far (https://www.bbc.com/news/world-asia-china-56967973). Besides the above-mentioned biotech industries, pharma sectors, there are several other industries, medical sectors and academic institutions are working hard to find a suitable solution to COVID-19 with a suitable vaccine development. Table 1. (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines). Further details on the current development and status of the Covid-19 Vaccines within WHO EUL/PQ evaluation process can be found here. (https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_15July2021.pdf)

6.3. Towards drug development for COVID-19

The COVID-19 drugs, which are in a number of phases of

Table 1
A comparison of different important COVID-19 vaccines.

Pfizer-BioNTech vaccine	Moderna vaccine	Janssen/Johnson & Johnson
mRNA vaccine	mRNA vaccine	Vector vaccine
95 % effective at preventing the COVID-19 virus with symptoms	94 % effective at preventing the COVID-19 virus with symptoms	66 % effective at preventing the COVID-19 virus with symptoms
FDA emergency use authorization	FDA emergency use authorization	FDA emergency use authorization
Greater than 89 % effective in preventing people with health conditions, such as diabetes or obesity, from developing the COVID-19 virus with symptoms	Greater than 90 % effective in preventing people with health conditions, such as diabetes or obesity, from developing the COVID-19 virus with symptoms	85 % effective at preventing the COVID-19 virus with severe illness and continues to be recommended by the FDA and CDC after a pause because the benefits outweigh the risks
Doesn't contain eggs, latex or preservative	Doesn't contain eggs, latex or preservatives	Doesn't contain eggs, latex or preservatives
Two doses are needed, 21 days apart (or up to six weeks apart, if needed)	Two doses are needed, 28 days apart (or up to six weeks apart, if needed)	One dose is needed
Some protection provided after the first dose	Some protection provided after the first dose	Some protection provided two weeks after vaccination

improvement and development internationally by some of the biotech industries / pharmaceutical companies, are as follows. Considering the emergency due to pandemic for the treatment of COVID-19, the US Food and Drug Administration (FDA) approved limited use of Chloroquine and Hydroxychloroquine which are being tested in several clinical trials conducted by government agencies [https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-continues-facilitate-development-treatments]. Subsequently, it was withdrawn due to its ineffectiveness against COVID-19. The orally-administered antiviral drug favipiravir is an inhibitor of viral RNA polymerase that was initially developed against influenza (Joshi et al., 2021). Similarly, Favilavir, the first approved coronavirus drug in China has reportedly shown efficacy in treating the disease with minimal side effects [https://www.sciencetimes.com/articles/25053/20200317/favilavir-first-approve-drug-treat-coronavirus.htm]. Remdesivir (GS-5734) by Gilead Sciences, an ebola drug which was found to be ineffective is now being tested in two phase III randomised clinical trials. WHO have made a conditional recommendation against the use of Remdesivir for hospitalised Covid patients, regardless of the disease's severity, because of lack of evidence showing that it improves survival rate (https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients)

Recently China has approved the use of Roche's Actemra for severe complications related to coronavirus. Brilacidin by Innovation Pharmaceuticals and leronlimab (PRO 140) by CytoDyn a CCR5 antagonist, is being tested as a potential coronavirus drug. The antiviral drug Galidesivir (BCX4430) by Biocryst Pharma is a wide spectrum antibiotic inhibits several pathogens including coronavirus. REGN3048 and REGN3051 is being studied against coronavirus infection in a first-in-human clinical trial discovered by Regeneron (https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/). SNG001 by Synairgen Research, an inhaled drug is being tested for the lower respiratory tract illnesses due to COVID -19. The safety and efficacy of SNG001 has been reported recently by Philip D Monk et al. (Monk et al., 2020) based on a randomised, double-blind, placebo-controlled, phase 2 pilot trail at 9 UK sites. They have interpreted that patients who received SNG001 had greater recovery rate from SARS-CoV-2 infection than patients who received placebo, providing a strong rational for further trials. Lattice Biologics is investigating the efficiency of its amniotic fluid concentrate, AmnioBoost, in healing acute respiratory distress syndrome (ARDS) in COVID-19 patients (https://www.businesswire.com/news/home/20200313005049/en/Lattice-Biologics-Evaluate-Anti-Inflammatory-Stem-Cell-Therapy). At the same time, several other companies such as Enanta Pharmaceuticals, Predictive Oncology, Emergent BioSolutions, Integral Molecular, CEL-SCI, AJ Vaccines, Takeda Pharmaceutical Company, Heat Biologics, Pfizer, Mateon Therapeutics, Zydus Cadila, NanoViricides, Cipla etc., are using different methodologies which include Mutagenesis Epitope Mapping and the Membrane Proteome Array, Virtual Screening and artificial intelligence (AI) platforms.

A quite a few numbers of academic institutions are also involved in developing vaccines/ drug for COVID – 19 such as Hong Kong University of Science and Technology, Tulane University, Columbia University, Serum Institute of India, Southwest Research Institute etc. The Drugs Controller General of India (DCGI) approved the 2-deoxy-D-glucose (2-DG) drug developed by the Defence Research and Development Organisation (DRDO) and released on 17th May 2021 for emergency use as an adjunct therapy in moderate to severe coronavirus patients. But it has been mentioned that 2DG should not be given to pregnant and lactating women and patients below18 years of age.

(https://timesofindia.indiatimes.com/india/drdo-issues-directions-on-usage-of-anti-covid-drug-2-dg/articleshow/83145870.cms)

Currently, the only option is to use wide-spectrum antiviral drugs to treat COVID-19 (Lu et al., 2020). Based on the reported literature, 99 infected humans have been given with existing anti-viral drugs. Two times a day oral intake of 500 mg ritonavir, 500 mg lopinavir, 75 mg oseltamivir and the IV intake of 0·25 g ganciclovir for 2–15 days was the treatment procedure and also antiviral remdesivir and chloroquine are found to be operating contrast to COVID-19 (Chen et al., 2020; Wang et al., 2020c). Several other industries are tirelessly working to develop newer compounds and also testing number of other scaffolds like that of EIDD-2801 and very many antiviral drugs (Toots et al., 2019). Therefore, there is a crucial requirement to establish an animal model to replicate the deadly disease which is observed in humans. Moreover, extensive research should be performed immediately to detect some novel chemotherapeutic drugs for remedying COVID-19 infections and to have a better knowledge of the virus-host connections. Till then as the WHO requests, it is safe to maintain social distancing, washing hands frequently and drinking plenty of fluids, eating nutritious food and to keep a healthy lifestyle as measures of self-care system.

7. Conclusions

In conclusion we have discussed about the different possible entry of the SARS-CoV- 2 virus in the host cell. Based on the literature we have identified different receptors viz ACE-2, Furin mediated, GRP78, CD147 and other receptor sites. Although these receptors have been identified for the invasions, until now there is no particular inhibitors to arrest the receptors. Even though several drugs have been tested against COVID-19, none of them were able to prevent the virus invasion. Hence, no curative medicines have been developed as of now besides the potential vaccines developed which reduces the maximum infection rate on the humans. Our review will be a pathway for further research on the invasions of COVID-19 into the human body. Until a proper cure has been identified, we shall follow the guidelines of the government which include social distancing, wearing masks and boosting the immune system. Apart from these the mental health due to the prevailing stress among people has to be taken care through proper counselling by health care professionals as per requirements.

Data availability

No data was used for the research described in the article.
Data will be made available on request.
All data is within the manuscript and figure.
The authors do not have permission to share data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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