Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Full length article

Coronavirus diseases 2019: Current biological situation and potential therapeutic perspective

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) caused by a Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was first reported in Wuhan, China at the end of December 2019. SARS-CoV-2 is a highly pathogenic zoonotic virus and closely related to the Severe Acute Respiratory Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The COVID-19 was declared as a global pandemic due to its high infectiousness, and worldwide morbidities and mortalities. The Chinese scientists at the start of the outbreak reported genome sequences, which made the characterization of glycoproteins and other structural proteins possible. Moreover, researchers across the world have widely focused on understanding basic biology, developing vaccines, and therapeutic drugs against the COVID-19. However, until now, no promising treatment options, as well as vaccines, are available. In this review, we have described SARS-CoV-2's genome, transmission, and pathogenicity. We also discussed novel potential therapeutic agents that can help to treat the COVID-19 patients.

1. Introduction

COVID-19 is a highly pathogenic and transmissible disease, caused by a beta coronavirus called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (Khan et al., 2020b). COVID-19 originated in Wuhan, China is considered the continuation of previous outbreaks of coronaviruses (CoV), namely Severe Acute Respiratory Syndrome (SARS-) and Middle East Respiratory Syndrome (MERS) that emerged in 2003 and 2012, respectively (Khan et al., 2020b). Based on the similarity of SARS-CoV-2 with SARS-CoV and other bat coronaviruses, bats have been suggested as the possible source of its origin (Zhou and Liu, 2020). Moreover, an earlier claim that pangolin could be an intermediate source of transmission from bat to humans was later discredited (Khan et al., 2020a, 2020c). The generated data indicated that SARS-CoV-2 is highly transmissible and can infect both lungs with atypical clinical symptoms, resulting in either misdiagnosis or missed diagnosis (Zhou and Liu, 2020). These might be among the possible reasons for unstoppable spread, and high rates of mortalities and morbidities.

COVID-19 is transmitted from human to human through inhalation

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or contact with respiratory droplets of infected individuals. The time from infection to the manifestation of symptoms ranges from 2 to 14 days (Khan et al., 2020a). Clinical manifestations represent a wide spectrum of diseases ranging from mild to severe respiratory syndrome influenza-like illness with lower respiratory tract symptoms, loss of taste and smell, and severe gastrointestinal symptoms. Although, COVID-19 is mild in most cases, however, it can be a life-threatening disease by developing severe pneumonia, acute respiratory distress syndrome (ARDS), high fever, headache, and multi-organ dysfunction (Singhal, 2020). In this review, we have described the route of transmission and virus entry mediating cellular receptors. We further discussed therapeutic options, susceptibility to the disease, and immunological responses that could play a role in the prevention and eradication of COVID-19 infection.

2. SARS-CoV-2; classification and transmission

SARS-CoV-2 belongs to the genus *Betacoronavirus* and subgenus *Sarbecovirus*. The polyprotein 1 ab (pp1ab) that consists of nonstructural proteins 1–16 is similar to other members in the subgenus *Sarbecovirus*. Analysis of the pp1ab protein from SARS-CoV-2 indicated that the protein sequence remained conserved in samples isolated from different regions during the outbreak. However, a remarkable deletion of eight amino acids in the virulence factor of the SARS-CoV-2 was identified in an isolate from an asymptomatic Japanese patient (Cardenas-Conejo et al., 2020). Moreover, a 42 amino acid signature in the pp1ab was detected only in SARS-CoV-2. These data suggest that the SARS-CoV-2 might have emerged by genetic drift from a bat origin coronavirus (bat-SL-CoV-RaTG13), however, this conclusion requires further investigations for confirmation (Cardenas-Conejo et al., 2020).

Similar to SARS-CoV, the SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a cell entry receptor to enter the cells by endocytosis (Fig. 1), while other CoVs such as MERS-CoV uses the dipeptidyl peptidase-IV (DPP-IV) host cell receptor for entry (Cui et al., 2013). A recent molecular dynamics simulation revealed that spike protein–ACE2 receptor interaction contains a higher number of contacts, a larger interface area, and decreased interface residue fluctuations in SARS-CoV-2 as compared to other coronaviruses (SARS-CoV and HCoV-NL63) (Brielle et al., 2020). ACE2 plays a critical role in the renin-angiotensin system (RAS) and the discrepancy of ACE/Ang II/AT1R and ACE2/Ang (1–7)/Mas receptor can develop an inflammatory response. In addition, elevated ACE and Ang II are bad prognosis for severe pneumonia (Sun et al., 2020). Whether SARS-CoV-2 can attack neurological tissues expressing ACE2, still needs intensive research (Baig et al., 2020). However, the manifestations including headache and nausea in response to COVID-19 infection suggest the effect of SARS-CoV-2 on the neurological system.

3. Origin of SARS-CoV-2

Since the outbreak of SARS-CoV, several strains of humans coronaviruses have been originated, causing deadly outbreaks and epidemics or pandemics in the Middle East and China., threatening global security, economy, and public health (Khan et al., 2020b). Full genome sequencing of SARS-CoV-2 indicates a similarity score of 79.6% with SARS-CoV, relating its origin to bats, however, the transmission to humans through an unknown intermediate animal in Wuhan, China is still controversial (Khan et al., 2020a; Zaman et al., 2020).

Bats are the natural reservoirs of highly pathogenic viruses especially, coronaviruses which constitute 31% of their virome. They are immune to viral infection and the characteristics such as higher species diversity (over 1400), roosting, longer life span (over 30 years), and migration transmit the viral pathogens across the political and geographical boundaries (Allocati et al.). Globally, only 77 countries reported 5717 bat-associated animal viruses in 207 different bat species (Chan et al.). However, in bats, the traits including roosting, grouping, and unique immune system can interfere with the genetic system of the viruses to generate novel mutant and recombinant viruses (Han et al.). Han et al. (2019), investigated 831 bats belonging to 15 species and reported 11 coronavirus strains in four bat species. Further investigation revealed that the four α-CoVs from bats species were similar to that previously isolated from porcine epidemic diarrhea virus (PEDV), indicating a common ancestor of the CoVs in both bats and pigs. Moreover, a synthesized CoV revealed that the PEDV possibly evolved from the CoV of bats, while another α-CoV (α-YN2018) might be originated from other bat species. These observations suggest that SARS-CoV-2 may have multiple host origins. An intensive study on immortalized bat cell lines indicated that human CoVs can spread *via* zoonotic-reverse zoonotic transmission cycles, and this might give some CoVs the chance to circulate and exchange segments of genetic material between strains detected in bats and other mammals, including humans. Furthermore, CoV can infect other vertebrates including ducks, geese, chickens,

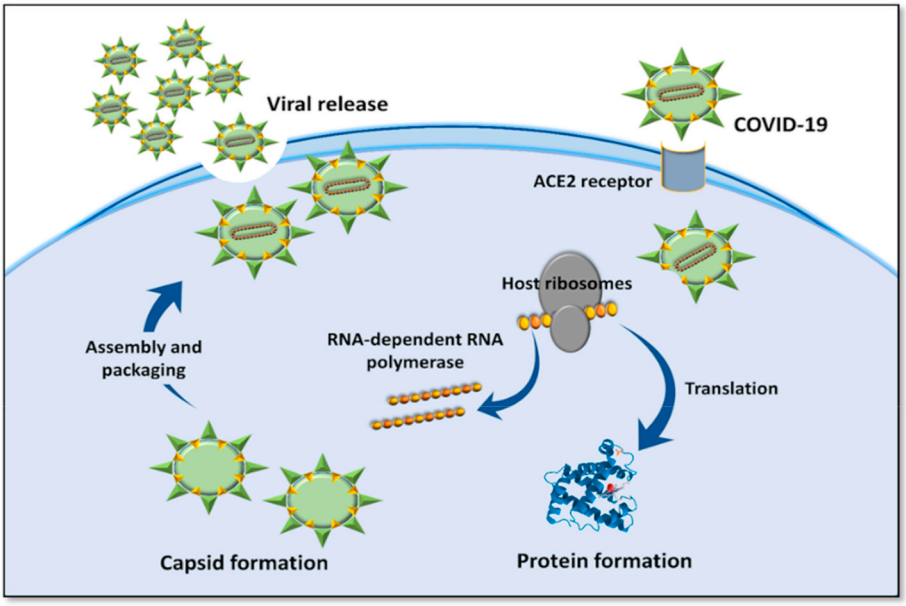

Fig. 1. Viral entry. COVID-19 particles attach to ACE2 receptor on the host cell membrane and then enters *via* endocytosis. The virus ejects its ssRNA molecules into the cytoplasm, where it attaches to the translational machinery to be translated into polyprotein molecules. Simultaneously, ssRNA is replicated *via* RNA-dependent RNA polymerase to produce viral RNA. Next step is to produce empty capsids and them to pack these capsids with RNA. The viral particles are ready depart *via* exocytosis.

quails, pigeons, and sparrows, and use these hosts as a natural reservoir (Zhuang et al., 2020).

To identify the type of CoV in the recent outbreak in Wuhan, China, Zhang et al. (2020c), analyzed 169 genomes of SARS-CoV-2 and classified them into two major genotypes; type I and Type II. Type I is further sub-divided into type IA and IB. Furthermore, phylogenetic analysis indicated that type IA is similar to the ancestral SARS-CoV-2, whereas type II was probably evolved from the type I and prevalent in the infections.

We generated a bioinformatic analysis for the coronavirus family to predict the potential origin of SARS-CoV-2. Gorbalenya et al., (Gorbalenya et al., 2020), reported that the emergence of SARS-CoV-2 as a human pathogen may be perceived completely independent from the other SARS-CoV outbreak. Although, SARS-CoV-2 is indeed not a descendent of SARS-CoV, and the introduction of each of these viruses into humans was likely facilitated by independent unknown external factors. Our findings indicated that SARS-CoV-2 is most probably derived from bat coronavirus (BM48-31/BGR/2008 (Refseq ID: NC_014470.1, Taxonomy ID: 864596), which also comes from bat coronavirus BtCoV/279/2005 (GenBank ID: DQ648857.1, Taxonomy ID: 389167) (Fig. 2).

3.1. Immunological responses

In COVID-19, the immune response is less rigorous, as a result, the elder people and individuals with underlying conditions are prone to develop Acute Respiratory Distress Syndrome (ARDS) and death (Khan et al., 2020a). However, fever associated with ARDS may lead to better outcomes among patients. COVID-19-infected individuals demonstrate increased levels of infection-related biomarkers and inflammatory cytokines. For example, attenuation or even reduction in the number of T cells was observed in severe cases. Moreover, suppressor T cells, regulatory T cells, memory helper T cells, and helper T cells were negatively affected while naive helper T cells showed an increased level in severe cases, suggesting that the primary target of COVID-19 infection is T lymphocytes (Qin et al., 2020). Similarly, Shi et al. (2020) (Shi et al., 2020) reported a comprehensive decline of lymphocytes including $CD4^{+}$ and $CD8^{+}$ T cells, B cells, and NK cells, and the elevation of interleukins (IL-2 and IL-6), which can be considered as reliable biomarkers in severe COVID-19 disease (Fig. 3). Furthermore, analysis of ILs in the serum samples of critical, severe, and mild COVID-19 cases showed that the expression of Interleukins (IL-2 receptor and IL-6) was comparatively higher in the critical cases than severe and mild ones. However, no statistical differences in the expression of tumor necrosis factor-alpha (TNF-α), Interleukins (IL-1, IL-8, IL-10), High-sensitivity C-reactive Protein (hs-CRP), lymphocyte count, and lactate dehydrogenase (LDH) between the three patient groups were reported (Chen et al., 2020b). Zhang et al. (2020a) suggested that the severity of COVID-19 is correlated with increased IgG response, where the blood group is linked with the susceptibility of SARS-CoV-2 infection. A recent study in COVID-19 patients (n = 1775) reported that individuals with blood group A have a substantially higher risk, whereas those with blood group O are comparatively at lower risk for contracting COVID-19 infection (Zhao et al., 2020). Although it is very early to conclude, however, the results obtained in this study were similar to a previous study on SARS, where SARS-CoV was reported with a lower rate of infectiousness in

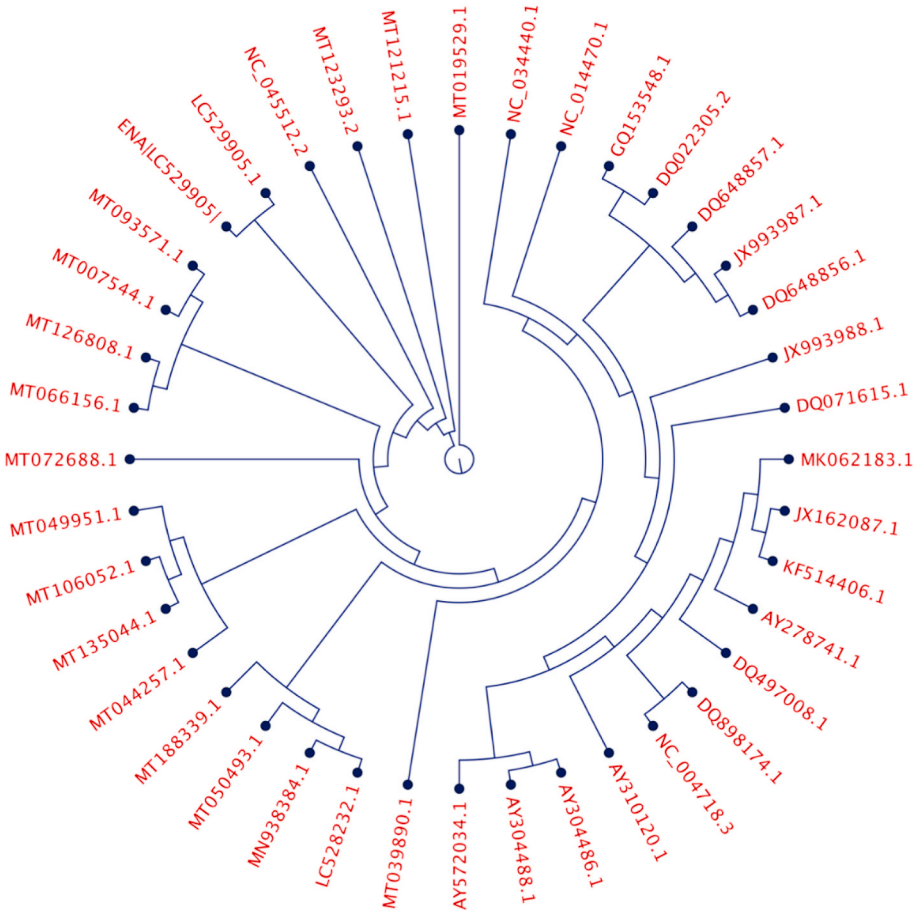

Fig. 2. Circular Cladogram phylogenetic tree based on maximum-likelihood method was constructed by Phylogeny software based on the maximum-likelihood (PhyML 3.1_1, https://ngphylogeny.fr/tools/tool/271/form) using 40 sequences with the best fitting evolutionary model. Subsequently, the tree was purged from the most similar sequences and midpoint rooted.

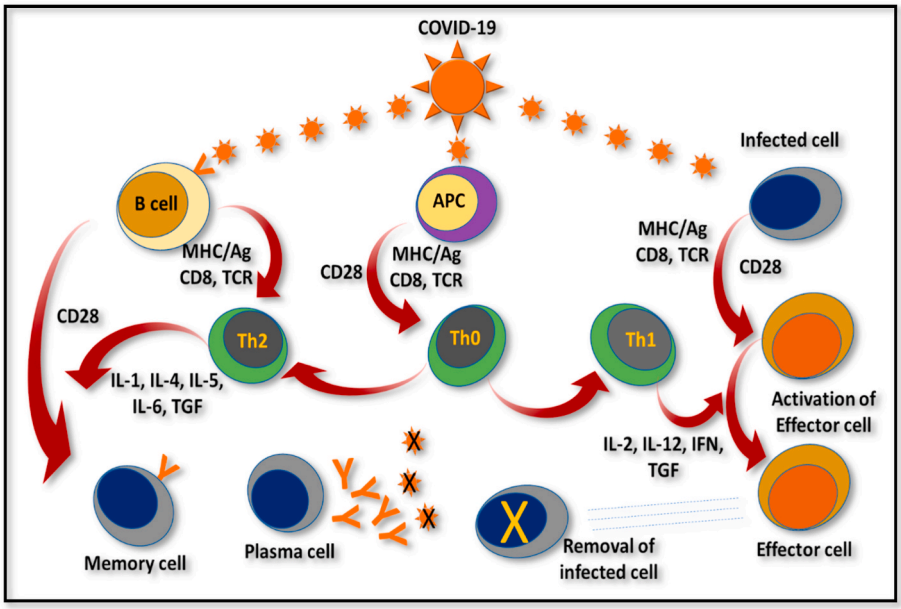

Fig. 3. The immune response to COVID-19 infection. Upon its entry, COVID-19 presents its antigenic peptide to the antigen presenting cells (APC) which play a crucial role in the antiviral activity in human. APCs, with the aid of major histocompatibility complex/antigen (MHC/Ag), induce Th_0 cells, which activate both Th_1 and Th_2. When a cell is infected, the effector cells are stimulated by the function of major histocompatibility complex I/Ag complex, T-cell receptors (TCR) and its coreceptor CD8. With the aid of Th_1 cells, IL2, IL-12, interferon gamma (IFN-γ), and transforming growth factor alpha (TGF-α), effector cells produce antibodies to destroy the infected cell. On the other side, Th_2 cells produce IL-1, IL-4, IL-5, IL-6, TGF-α that trigger B cells to transform into memory cells carrying the viral antigen. Then plasma cells produce the viral antibody to defend the cells against the next viral attack. APC: antigen presenting cells, TCR: T-cell receptors, IL: Interleukin, CD: cluster differentiation, IFN-γ: interferon gamma, MHC: major histocompatibility complex, Ag: antigen, TGF-α: transforming growth factor alpha.

individuals with blood group O (Zhao et al., 2020).

3.2. Clinical manifestations

Pneumonia appears to be the most frequent manifestation of SARS-CoV-2 infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging (Khan et al., 2020a). Li et al. (2020c), observed fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%) as the main clinical manifestations in COVID-19 patients (n = 1994). They also reported less common symptoms including headache or dizziness (12.1%), diarrhea (4.8%), and nausea or vomiting (3.9%). Furthermore, laboratory tests indicated the presence of lymphocytopenia (64.5%) and an elevation in CRP (44.3%), LDH (28.3%), and leukocytopenia (29.4%). In the same study, Li et al. (2020d), found that lymphocytopenia, eosinophil cytopenia, and leukopenia were observed in 10 COVID-19 patients. In another study on 29 COVID-19 patients, Meng et al. (2020) observed decreased white blood cell count (79.3%), decreased lymphocyte count (68.9%), increased levels of hs-CRP (93.1%), and normal level of procalcitonin. Similarly, serum LDH was found increased (68.9%) while albumin was decreased (51.7%) in this study. Overall, these indications suggest that LDH and High-sensitivity C-reactive Protein (α-HBDH) could be reliable biomarkers for investigating COVID-19. Moreover, by investigating 140 COVID-19 patients, Zhang et al. (2020b), reported eosinopenia and lymphopenia as potential diagnostic factors for the disease while asthma and chronic obstructive pulmonary disease (COPD) are unlikely to be the risk factors. Older age and underlying health conditions including cardiovascular problems, hypertension, diabetes, and pulmonary aberrations were found to be associated with the development of severe symptoms in COVID-19 infected patients.

4. Therapeutic options

The overall risks associated with COVID-19 infection can be mitigated with effective eradication of the infection. Currently, no promising treatment options are available against COVID19 that can be recommended globally. However, Remdesivir, baricitinib, chloroquine, hydroxychloroquine, and favipiravir have been found with significant efficacy against COVID-19. Among the trialed antiviral drugs, remdesivir alone or in combination with chloroquine or interferon beta showed effectiveness against COVID-19 infection (Sheahan et al., 2020). In addition, W.H.O and C.D.C recommend glucocorticoids should not be used in patients with COVID-19 pneumonia unless required such in case of exacerbation of the chronic obstructive pulmonary disease. Nevertheless, the development of clinical drugs for coronaviruses is challenging because the repeatedly emerging novel coronaviruses with diverse features require the specific drug for each newly emerged virus (Khan et al., 2020b).

Researchers all over the globe are striving to develop effective vaccines or therapeutic molecules to combat the deadly COVID-19 infection. For the sake of developing novel drugs, the COVID-19 main protease was made publicly available to expedite the process. Ton et al. (2020), have developed a tool, namely Deep Docking for the computer-based screening of a large number of molecules in a very short time. They identified 1000 potential ligands for the main protease of COVID-19 from nearly 1.3 billion compounds available in the ZINC15 library. These generated compounds are available for further characterization and improvements. Since no specific antiviral agents are available, therefore, the provided treatment options to COVID-19 patients are all supportive in nature. Besides effective treatment options and preventive strategies must be developed and practiced as the COVID-19 has the highest potential to spread compared to its family members; SARS-CoV and MERS-CoV (Singhal, 2020).

Matsuyama et al. (2020), reported that VeroE6 cell line expressing transmembrane serine protease 2 (TMPRSS2) is highly susceptible to COVID-19 infection, thus, it can be used for isolating and propagating SARS-CoV-2, and developing novel anti-SARS-CoV-2 agents. Despite their effectiveness against COVID-19 infection, ganciclovir, acyclovir, ribavirin, oseltamivir, peramivir, and zanamivir are not promising options to treat COVID-19. However, remdesivir, lopinavir/ritonavir, and monoclonal antibodies can be used to treat COVID-19 after evaluating their safety and efficacy on a large scale until, a promising drug is developed (Li et al., 2020b). Other possible options to manage COVID-19 is the combination of antiviral drugs with traditional Chinese medicines, which have been found effective against the COVID-19 infection (Chan et al., 2020). Previous studies have shown that chloroquine (broadly used antimalarial drug) exhibits antiviral properties against several viruses, including SARS-CoV-2 (Colson et al., 2020). However, the toxic effects of chloroquine such as increasing the risk for cardiovascular disorders have limited its use against the COVID-19 (Frisk-Holmberg et al., 1983). Overall, 17 clinical trials have been registered in the Chinese Clinical Trial Registry (www.chictr.org.cn),

proposing the use of chloroquine in controlling COVID-19 (under registration numbers: ChiCTR-20000-29542, 29559, 29609, 29741, 29761, 29803, 29826, 29837, 29868, 29935, 29939, 29975, 29988, 29992, 30031, 30054, and 30417).

An inhaled corticosteroid compound, ciclesonide has been suggested as a potential drug against the COVID-19 (Matsuyama et al., 2020). The compound suppressed SARS-CoV-2 replication in cultured cells, where the suppression was mainly related to the targeting viral nonstructural protein 15 (nsp 15) (Matsuyama et al., 2020). It is expected that inhaled ciclesonide can reduce viral replication and host inflammation in the lungs.

ACE2 negatively regulates the renin-angiotensin system (RAS) by converting Ang II to Ang 1–7, where it functions as a carboxypeptidase. SARS-CoV-2 was found to attack cells using this type I integral membrane protein (Matsuyama et al., 2020). Depletion of ACE2 by SARS-CoV-2 inhibits the ACE2/Ang (1–7)/Mas receptor pathway, leading to disruption of the RAS, which then leads to the progression of acute severe pneumonia. Thus, inhibiting ACE2 may alleviate pneumonia in COVID-19 patients, provided that blood pressure is controlled (Sun et al., 2020) (Fig. 4).

5. Susceptibility to COVID-19

In terms of clinical manifestations, lung cancer and COVID-19 are similar, making it difficult for clinicians to differentiate (Yang et al., 2020a). Lung cancer patients receiving systemic immunosuppressive agents are more prone to be infected with COVID-19 as compared to healthy individuals (Xu et al., 2020b). Liang et al. (2020), surveyed 1590 COVID-19 cases, where 18 cases had a history of cancer, while five of these 18 cases had a history of lung cancer (Xia et al., 2020). However, any conclusion to associate COVID-19 infection with cancer should be drawn carefully, as no convincing evidence is available to confirm that patients with cancer have an increased risk of being infected with COVID-19. To draw a clear conclusion, a reasonable sample size with less heterogeneity must be studied.

It is well known that MERS-CoVs penetrate human cells *via* DPP-IV) receptor protein. An animal model expressing DPP-IV receptor on the pulmonary alveolar cells has been designed to elucidate how diabetes worsens disease severity, and the obtained data indicated an association of diabetes with macrophage infiltrates (Bloomgarden, 2020). Therefore, diabetic patients seem to be more susceptible to COVID-19 infection than others. Yang et al., (!!! INVALID CITATION (Yang et al., 2020c)!!!) reported that out of 52 COVID-19 patients, 32 were suffering from chronic diseases such as cerebrovascular diseases (22%) and diabetes (22%). Meanwhile, Guan et al. (2020), analyzed data from 1099 COVID-19 patients and found that 173 patients had chronic diseases: diabetes mellitus (16.2%), coronary heart diseases (5.8%), cerebrovascular disease (2.3%), and hypertension (23.7%). The expression of ACE2 is elevated in diabetic and hypertensive patients, which are treated with inhibitors for ACE and angiotensin II type-I receptor. ACE inhibitors and ARBs increase the expression of ACE2. Consequently, this would facilitate the infection with SARS-CoV-2, which uses this protein as an entry point to the cells (Fang et al., 2020; Li et al., 2017). In addition, ACE2 is not only expressed in the alveolar epithelial cells, but also in the heart, gastrointestinal tract, kidney, testis, and pancreas, and thus makes these tissues and organs susceptible to COVID-19 infection and damage to multiple organs (Liu et al., 2020; Xu et al., 2020a).

A meta-analysis study conducted by Li et al. (2020a), summarized the proportion of cardiovascular disease (16.4%), diabetes (9.7%), and hypertension (17.1%) in COVID-19 patients. They concluded that patients with previous cardiovascular diseases may have an increased risk of developing severe conditions, while, COVID-19 infection can exacerbate the damage of the heart. In COVID-19 patients with underlying cardiovascular disease, hypersensitive C-reactive protein, and serum creatinine levels were elevated compared with COVID-19 patients with no underlying cardiovascular disease. Overall these indications suggest that COVID-19 can affect cardiovascular function and lead to myocardial injury (Chen et al., 2020a).

6. Genome of SARS-CoV-2

Genome of the SARS-CoV-2 consists of 29,900 nucleotides (nt), predicted with 14 open reading frames (ORFs) (5′–3′) such as *nucleocapsid* (*N,*1,260 nt), *spike* (*S*, 3822 nt), *ORF1ab* (P, 21,291 nt), *membrane* (*M,* 669 nt), *envelope* (*E,* 228 nt), *ORF3a* (828 nt), and *ORF8* (366 nt) (Wu et al., 2020). The viral spike (S) glycoprotein encoded by *spike* gene facilitates viral binding to ACE2 receptor of the host cell membrane. After the viral fusion and entry through the ACE2 receptor, its RNA is translated to non-structural proteins (nsps) from ORF1a and ORF1b. The first ORF (1a) produces a 440–500 kDa polypeptide 1a (pp1a), undergoes cleavage to produce 11 nsps. Ribosome frameshift exits immediately upstream of the ORF1a stop codon, allowing translation of the

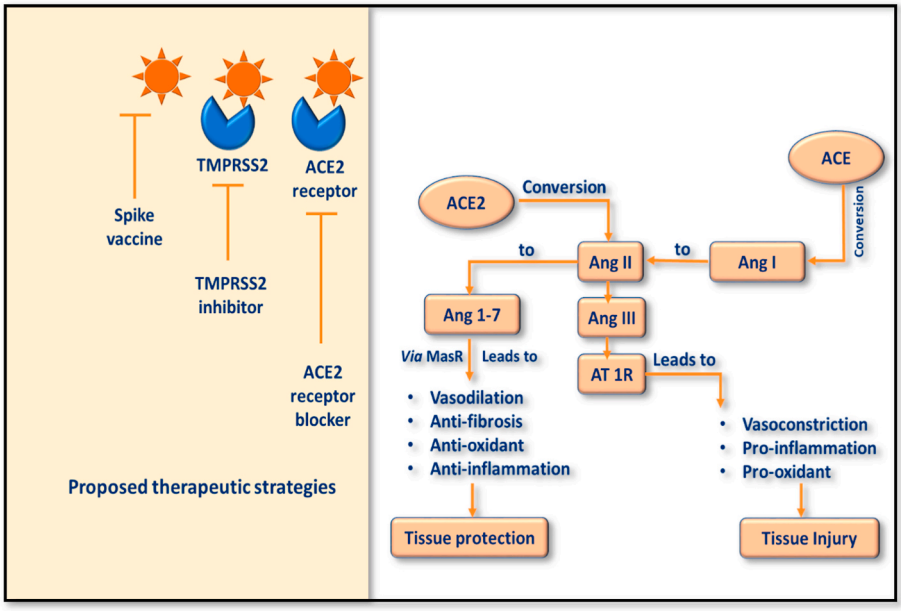

Fig. 4. The potential therapeutic strategies for COVID-19. The spikes of the virus attach ACE2 receptor on the host cell membrane and this ACE2 could be a target to prevent viral entry. Moreover, Transmembrane Serine Protease 2 (TMPRSS2) is helper membrane protein for the viral entry, on which any modification could control cellular infection. The same also could be applied to ACE2 receptor, which when blocked, the viral particle would not be able to enter the host cell. Although the blocking ACE2 will affect patients as they will suffer from the negative effect of angiotensin II. Vaccines against spike protein is also a proposed intervention strategy.

second ORF (1 b) to produce a 740–810 kDa large polypeptide (pp1ab), which is then cleaved and as result, 16 nsps are produced. This cleavage property is mediated by viral proteases nsp 3 and nsp 5 that contain a papain-like protease domain and a 3C-like protease domain, respectively (Kim et al., 2020). The sequence of the *spike* gene is extremely divergent when compared with that of bat-SARSr-CoV RaTG13 (93.1% nucleotide identity) (Lu et al., 2020; Wu et al., 2020).

SARS-CoV-2 is a positive-sense single-stranded RNA (+)ssRNA) virus that can infect mammalian and avian hosts, where its nucleotide substitution rate is higher than their hosts (Lin et al., 2019). At the whole genome level, the sequence identity of the SARS-CoV-2 was 50% to MERS-CoV, 79% to SARS-CoV, 88% to Bat-SL-CoVZC45 and Bat-SL-CoVZXC21, and 96% to Bat-SARSr-CoV RaTG13 (Zhou et al., 2020). Genomic analyses of SARS-CoV-2 and 20 closely related coronavirus strains highlighted identical mutations in both the SARS-CoV-2 and RaTG13, which could indicate that SARS-CoV-2 is probably originated from the Bat-SARSr-CoV RaTG13 (Lv et al., 2020).

7. Detection methods

For patients who meet specified criteria, in addition to testing for other respiratory pathogens, the CDC recommends collection of specimens to test for COVID-19 virus from the upper respiratory tract (nasopharyngeal and oropharyngeal swab) and, if possible, the lower respiratory tract (sputum, tracheal aspirate, or bronchoalveolar lavage). Additional specimens (eg, stool, urine) can also be collected (Patel and Jernigan, 2020). The world health organization (WHO) has also provided detailed descriptions of approved methods being used for coronavirus detection (WHO, 2020), which is based on the detection of unique sequences of viral RNA. In routine-based testing for COVID-19 patients, the presence of SARS-COV-2 is determined through the detection of viral genes namely *N*, *E*, *S,* and *RdRP* using real-time polymerase chain reaction (RT-PCR). Moreover, the RNA-sequencing technique is also employed for further confirmation of SARS-CoV-2, if needed. However, these methods require expert personnel and expensive laboratory equipment whereas, low viral load in the throat or nasal swab of patients may give false-negative results during RT- PCR-based detection (Lucia et al., 2020).

Besides PCR-based methods, researchers and clinical laboratory workers are making efforts to develop and use faster, reliable, and more efficient techniques for COVID-19 detection. For instance, a CRISPR-Cas12-based method has been developed with an estimated detection limit of 10 copies/μL (Lucia et al., 2020). Another method known as droplet digital PCR (ddPCR) has recently been developed to detect SARS-CoV-2 with a detection efficiency of at least 500 times higher than RT-PCR (Yang et al., 2020b). More interestingly, Yang et al. (2020b) developed a reverse transcription loop-mediated isothermal amplification (RT-LAMP) method, using RNA reverse transcription and nucleic acid amplification in a single step within 30 min. According to Wang et al. (2020), nanopore target sequencing (NTS) method can be used to detect SARS-CoV-2 and other respiratory viruses simultaneously within 6–10 h. Nonetheless, an efficient, rapid, and cost-effective technique is still required to be developed so that testing procedures could become easy in low income and hardest hit countries.

8. Future directions

Recent pandemic of COVID-19 has encouraged several research groups all over the world to develop promising vaccines, diagnostic, and therapeutic strategies. The traditional antiviral agents are not promisingly effective against the COVID-19, therefore, searching for novel therapeutic options is global demand. Recently, several research groups have investigated various options to treat COVID-19 disease, however, until now, they have not found any drug that could be approved and recommended worldwide. Therefore, further investigations and experiments are necessary to reach an effective treatment strategy. Active hexose correlated compound (AHCC) is an α-glucan-based mushroom extract that has been widely used as an immune-stimulant in patients with avian influenza virus, West Nile virus, influenza virus, hepatitis C virus, papillomavirus, herpes virus, and many other viruses. Although the efficacy of AHCC has not been investigated in COVID-19 patients, it could be used at least to boost the immune response against the COVID-19 (Di Pierro et al., 2020). Other approaches to cope with the current pandemic include the utilization of bioinformatics tools such as the Immune Epitope Database (IEDB) software to predict a computational vaccine for pathogenic viruses, including SARS-CoV-2 (Ibrahim and Kafi, 2020).

In addition, bio-nanotechnology approaches should be used to develop various nano architectural electrochemical immunosensors that can be utilized for the detection of pathogenic viral organisms. Electrochemistry guided immunosensors have become feasible because of their practical use, high sensitivity, and cost-effectiveness, and miniaturization opportunities. The immunosensors with various microchip electrodes were used to detect avian influenza A (H7N9) virus (Han et al., 2016) and H1N1 type influenza virus (Singh et al., 2017), human immunodeficiency virus (HIV), human papillomavirus (HPV) (Huang et al., 2015), and coronavirus (MERS-CoV) (Layqah and Eissa, 2019), thus can be used against COVID-19 infection.

The need for a faster sensing process at a lower detection limit is an important but challenging strategy. Designing novel antibody conjugated composite electrodes is critical for more sensitive and rapid practical applications. It is clear that the electrical charge transport improves the sensing characteristics of the biosensor, thus, conducting polymers such as polyaniline (PAN) can be proposed as a host matrix. It is well known that the chain length and positive charge in its backbone are reversible with the applied electrical pulse (Chowdhury et al., 2019). Doping gold nanoparticles with antibody onto PAN can accumulate more SARS-CoV-2 particles for rapid detection. These cost-effective and eco-friendly composite assays can be developed from disposable electrodes for multi detection purposes.

9. Conclusion

The deadly and highly infectious COVID-19 pandemic is spreading unstoppably in almost all countries of the world. Until now, no promising vaccines or drugs are available that could be recommended on a large scale. The actual numbers of the infected people may be larger than reported figures due to the lack of high testing capacity in some countries, accurate data recording systems in different countries, or the presence of weak systems for data collection. This pandemic may get worsened in the near future if not effective treatment or vaccine is developed to combat or prevent the virus. The genome of SARS-CoV-2 and other CoVs have been sequenced and are available online, as well as all research reports on COVID-19 are freely available, therefore, the scientific community should take advantage of them in order to develop strategies to control the rapid spread of COVID-19 and eradicate the SARS-CoV-2. There is a possibility that more coronaviruses could emerge in the future and cause deadly outbreaks. Therefore, strategies should be developed that could prevent the emergence of new viruses and/or minimizing the health consequences if any new pathogenic virus emerges.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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