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.

CHAPTER ONE

COVID-19: Origin, epidemiology, virology, pathogenesis, and treatment

Anuj Sharma[a], Ashok Kumar Ahirwar[b], Smita R. Sorte[c], and Sachin B. Rathod[d]

[a]All India Institute of Medical Sciences, Nagpur, Maharashtra, India
[b]Department of Biochemistry, UCMS, Delhi, India
[c]Department of Physiology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India
[d]Department of Physiology, Indira Gandhi Government Medical College, Nagpur, Maharashtra, India

1 Introduction

COVID-19 (or Coronavirus Disease) originated in China (Hubei provenance, Wuhan city). The first recorded illness occurred in December 2019. It has affected all parts of the world, and the WHO designated the COVID-19 illness, caused by the new Coronavirus SARS-CoV-2, a pandemic on March 11, 2020 (Cucinotta and Vanelli, 2020). It now accounted for the worse-hit and most dreaded pandemic after the Spanish flu in 1920. From December 18, 2019, to December 29, 2019, 5 patients were hospitalized with acute respiratory distress syndrome (ARDS), and one died in China. This progressed to 41 confirmed cases of COVID-19 by January 2, 2020 (most of the patients were suffering from other comorbidities like hypertension, diabetes, or cardiovascular diseases). By January 22, 2020, 571 cases were positive in 25 provinces of China. By January 25, 2020, 1975 positive cases with 56 deaths were reported. By January 30, 2020, this progressed to 7731 cases in China, and along with this, 90 more cases were reported from other countries including India. This progressed to 31,161 cases in China on February 7, 2020 (Zhu et al., 2020; Singhal, 2020; Wu et al., 2020a; Sohrabi, 2020).

The initial source of origin of COVID-19 is unclear, but many possible theories are being proposed. Notable cases have been natural selection in an animal source followed by zoonotic transmission, natural selection in a human source followed by zoonotic transfer, selection during the passage, and genetically modified organisms artificially manufactured in the laboratory. The primitive theory suggested the spread from the Hunan seafood

Lessons from COVID-19
https://doi.org/10.1016/B978-0-323-99878-9.00012-1

market of China probably from an animal source. The COVID-19 caused by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus-2), and the Coronavirus isolated from bats have 96% similarity, while the Coronavirus isolated from pangolins has 85.5 to 92.4% similarity to SARS-CoV-2, according to research. An examination of the phylogenetic relationship of SARS-CoV-2 suggested that it may have evolved from bats or pangolins. Some debatable speculations suggest that it is a man-made virus, intentionally synthesized in the laboratory but was unintentionally emancipated from a laboratory of Wuhan, China though this theory is not fully supported (Sun et al., 2020).

Coronavirus has been responsible for numerous outbreaks, including the SARS-CoV-1 (severe acute respiratory syndrome) epidemic in China in 2003, which resulted in 8098 cases and 774 fatalities (Pal et al., 2020); moreover, other outbreaks in Saudi Arabia (2012) included the Middle East respiratory syndrome MERS, which resulted in 2143 laboratory-confirmed cases with 750 fatalities in 24 countries (Park, 2020).

The pandemic is straining healthcare systems all over the world. Even the developed nations are finding it difficult to cope up with the situation. USA, UK, Spain, and Italy have engaged the assistance of retired health professionals in the battle against the Pandemic. In developing countries like India, the situation is even worse. The Pandemic is posing a significant challenge to the already fragile healthcare system of the country. India is a developing country struggling to provide quality and affordable healthcare facilities with inadequate health personnel, limited financial resources, and unavailable medications (Agampodi et al., 2015; McGregor et al., 2014). The ongoing Pandemic further worsens the situation. The health care system was under tremendous pressure due to the increased infectivity of the SARS-Cov-2 virus. The testing capacity was inadequate for the large Indian population. In order to control the pandemic situation, the government implemented certain tough decisions like the closure of public places, mass lockdown, restricted people's movement, enlisted containment zones, mobilization of health personnel to treat patients of the COVID-19 infection. Government converted hospitals, hotels, and many complexes to COVID care centers, COVID Isolation centers, and COVID wards for COVID-suspected and -infected patients. This has presented a significant issue for chronic illnesses, which requires regular visits, check-ups, and prescriptions since it became difficult for them to visit healthcare facilities and meet their physicians in lockdown (Kretchy et al., 2021). Health care workers (HCW) were undergoing tremendous physical and mental stress due to long working hours and were at the risk of acquiring COVID-19 due to increased virus load exposure.

For prevention of infection, to deliver state of the art patient care and treatment, and reduce the load on the health care system, it is necessary to understand in depth the viral morphology, pathogenesis, clinical features, diagnosis, targeted drugs, and vaccine.

2 Viral morphology

SARS-CoV-2 is an affiliate of the genus *Beta-coronaviruses*, sub-*sarbeco virus*, *coronaviridae* family. It has two subfamilies, *orthrocoroanviridae* and *Toroviridae*. SARS-CoV-2 belongs to the subfamily *orthrocoronaviridae*; order *Nidovirales* belongs to the genus of *Betacoronaviridae* (Pal et al., 2020).

SARS-CoV-2 is an enclosed virus with positive-sense RNA that is single-stranded (ssRNA), and under electron microscopy, Coronavirus appears as coroneted round or elliptical, often polymorphic form with a 70 to 90 nm diameter. Its carrier's dub, petal, or crown-shaped peplomer spikes give the solar Corona's appearance; it has helical symmetry, as shown in Fig. 1.

Coronaviruses have a genomic size ranging from 26 to 32 kilobases. The hemagglutinin-esterase gene is absent in the SARS-CoV-2 genome: genome expresses structural proteins, nonstructural proteins, and accessory proteins such as ORFs. The virus has four main structural proteins: spike surface glycoprotein (S), transmembrane protein (M), nucleocapsid protein (N), and envelope polypeptide (E). It has 16 nonstructural proteins (nsps); the critical nonstructural proteins are 3-chymotrypsin-like protease (3CL), Papain-like Protease (P.L.), helicase (H), and RNA-dependent

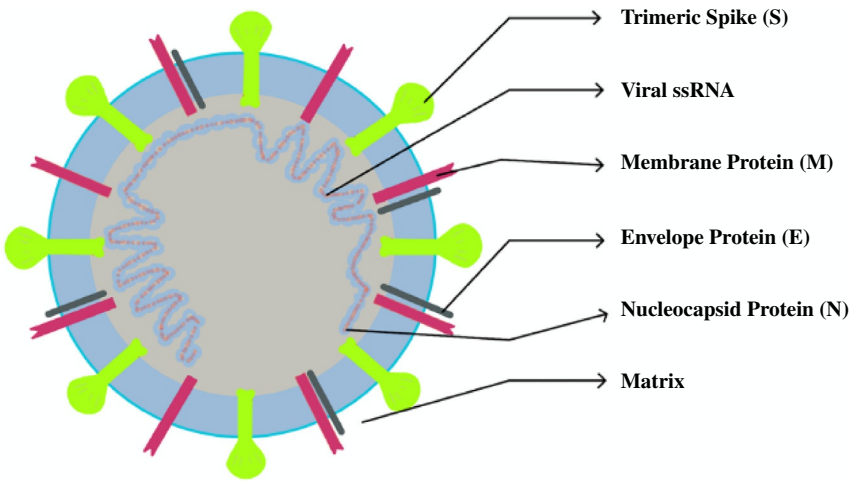


Fig. 1 SARS-CoV-2 structure. *(Credit: Drawn by Author Dr. Ashok Ahirwar.)*

RNA Polymerase (RDRP) are the most significant. A lipid bilayer is formed from the host membrane, the Coronavirus surface protein- spike, membrane, and envelope are encased, with the helical nucleocapsid holding viral RNA enclosed within it (Kumar et al., 2020).

The M and E proteins are needed for the assembly and budding of the virus to be replicated. The fusion viral glycoprotein S comprises two subassemblies, S1 and S2, that interact with the ACE2 receptor to internalize the virus into the host cell and form virions and its assembly. S protein also governs host tropism and transmission capability. (N) protein serves as a structural component of the helical nucleocapsid. It is necessary for the pathogenesis, replication, and packaging of viral RNA. Coronavirus is UV- and heat-sensitive. This virus is inactivated by lipid solvents, including ethanol, chlorine disinfectants, chlorhexidine, peroxyacetic acid, and chloroform (Pal et al., 2020).

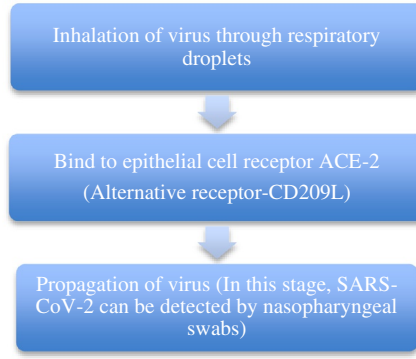
3 Viral pathogenesis

The key element determining the COVID infection is the triumphant entry of the virus in the host cell followed by its replication and multiplication in the host cell utilizing the host cellular apparatus followed by spreading the virus by shedding out of the host cells. The viral envelope of SARS-CoV has spike (S) protein. The S protein has a receptor-binding region that demonstrates an intense binding affinity for the extracellular region of angiotensin-converting enzyme 2 (ACE2) of host cells of various organs, mainly the lungs and the heart. As the S protein connects with the ACE2 receptor, the host serine two transmembrane protease TMPRSS2 induces splitting of S protein to produce S1 and S2 subunits. This is essential for fusing the virus membrane with the host cell membrane and endocytosis-mediated internalization of the complex (Hoffman et al., 2020; Iwata-Yoshikawa et al., 2019). The virus-encoded proteinases are released into the host cytoplasm, where they translate the viral RNA and transform it into the polyprotein replicator polyproteins pp1a and pp1b, which are then broken down into smaller proteins by virus-encoded proteinases. Following the triumphant entry of the virus in the host cell, the virus replicates and multiplication using host cellular equipment and apparatus. The replicated virus then breaks the host cell and gets shed off to infect the other tissues. The spike protein also activates ADAM-17/TACE, which increases the release of TNF-α (Heurich et al., 2014). The disease's incubation period is 5 to 7 days, i.e., the time between viral entry in the body and the appearance of symptoms. Depending upon the multiple factors, including individual

genetic makeup and the immune response, the person can be asymptomatic or develop symptomatic diseases, which may progress to various stages of COVID-19.

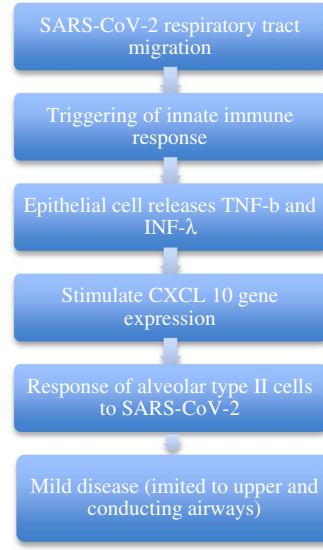
4 Stages of COVID-19

Stage 1-Asymptomatic stage



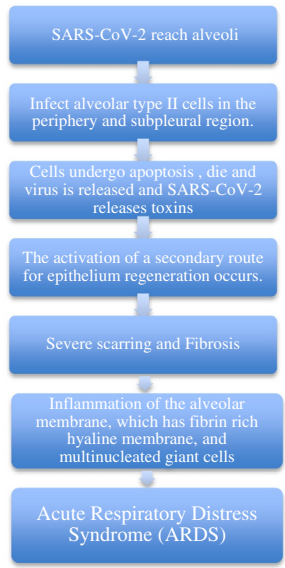
During this stage, the virus multiplies in the body. The person does not develop any symptoms.

Stage 2 – Response of upper airway and conducting airway



After five days of contact with the symptomatic patient or entry of the virus into the body, the person can be tested positive on RT-PCR tests. COVID-19 illness primarily affects the respiratory system, although it may manifest in other extrapulmonary organs like the nervous system, gastrointestinal system, liver, heart, and kidney. Clinical manifestations are seen in this stage. COVID-19 symptoms range from mild to severe dry cough, fatigue, fever, headache, sore throat, myalgia or arthralgia, chills, loss of taste, loss of smell (anosmia), nausea, vomiting, diarrhea, hemoptysis, nasal congestion, conjunctival congestion, rhinitis, metabolic acidosis, septic shock, coagulation dysfunction, lymphopenia, and hypoxemia (Baj et al., 2020).

Stage 3 – Hypoxia and ground glass infiltration in lungs and progression to ARDS (20% patients progress to this stage.)



Although most people's symptoms vary from mild to moderate, the disease's severity and medical complications may vary. The case fatality rate is approximately 2.2%. As the disease progress to this stage, pneumonia develops on the 9th day of infection. Other complications include pneumonia, acute respiratory distress syndrome (ARDS), superimposed viral and bacterial infections, thrombosis and embolism, acute renal damage, gastrointestinal illness, hepatocellular damage, ketosis, hyperglycemia, neurological complications, ocular complications,

dermatologic manifestations, cardiac abnormalities, myocardial dysfunction, myocarditis, acute coronary syndrome, multiple organ dysfunction syndromes (Sarkesh et al., 2020).

The development of poor outcomes and mortality among patients with comorbidities such as obesity, diabetes mellitus, hypertension, cardiovascular disease, renal disease, and cancer is more likely. SARS-CoV-2 induces the innate immune system and the adaptive immune system. The activated immune system releases many cytokines into the body, including interleukin 6 (IL-6), often known as a "cytokine storm" or cytokine released syndrome (CRS). The term "cytokine storm" refers to raised inflammatory markers, particularly cytokines 5 and 6 (Chau et al., 2020). Many patients with severe COVID-19 have been diagnosed with cytokine released syndrome, which had resulted in the deaths of COVID-19 patients (Zhang et al., 2020). The essential factor in preventing the progression of diseases and reducing mortality is the early detection of disease, which helps clinicians provide necessary and timely patient care and treatment.

5 Laboratory diagnosis for screening and diagnosis of patients with COVID-19

Membrane protein (M), Spike protein (S), nucleocapsid protein (N), and envelope protein (E) are the structural proteins of the COVID virus. The test detects antibodies against S protein. Lateral flow immunoassays are being developed to find COVID-19 virus antigens or antibodies in a short period. Immunoassays are designed to detect COVID-19 monoclonal antibodies IgM or IgG against COVID-19 infection. Nevertheless, these methods have poor sensitivity. Serology is helpful but nonspecific, and several weeks are required for specific IgG responses. Time is crucial in diagnosis hence serology detection may not be beneficial in active case diagnosis but can be used to find the previous exposure via infection or vaccine. The use of cell culture for diagnostic purposes is not advised (la Marca et al., 2020). Randomization of the amplification deep sequencing techniques is useful for the identification of COVID-19 in its early stages. These technologies will discover future mutations of the virus, but they are currently impractical for diagnosis. RT-PCR is a molecular diagnostic test (Tang et al., 2020). Amplification occurs in closed systems, which reduces the number of false-positive outcomes. ssRNA, structural proteins such as helicase protein (HEL), an envelope protein (E), transmembrane protein (M), and nucleocapsid protein (N) can be employed in PCR experiments.

Additionally, accessory genes such as RNA-dependent RNA polymerase (RdRp), hemagglutinin-esterase (HE), open reading frames ORF 1a, and ORF 1b can be targeted. High viral loads in specimens obtained from the upper and lower respiratory tracts may be identified within 5 to 6 days after the onset of symptoms. For diagnosis of COVID-19, the preferred site for specimen collection in the upper respiratory tract is nasopharynx swab or oropharynx swab and lower respiratory tract is sputum or bronchoalveolar lavage after intubation. Due to the inherent quality control, oropharyngeal (O.P.) swabs are more used than nasopharyngeal (N.P.) swabs. The greatest concentration of COVID-19 viral is obtained in bronchoalveolar lavage. Following collection, these samples are placed into a universal viral transport medium kept refrigerated (Tang et al., 2020).

Enteric involvement in individuals with severe Coronavirus infection was associated with high viral RNA levels in fecal material and late sledding from the respiratory system. As a result, a stool sample or a rectal swab may be employed. The SARS Coronavirus was also discovered inside erythrocytes (Cheng et al., 2007).

In contrast to the Centers for Disease Control and Prevention, which recommends screening with two nucleocapsid proteins (N1 and N2), the World Health Organization recommends screening with the E gene first, followed by the RdRp gene. It is preferable to have at least one conserved area and one unique region to guard against the effects of genetic drift, which is especially essential when the virus grows inside a new population (Tang et al., 2020).

Blood tests: Leukocytosis, raised serum ferritin, D-dimer, C-reactive protein, raised concentrations of plasma proinflammatory cytokines like IL-1B**,** IL-1RA**,** IL-2, IL-7,8,9,10**,** basic PGF 2**,** GCSF**,** GMCSF**,** IPN-ϒ**,** TNF-α**,** and VEGF-A are seen in COVID-19-infected person (Costela-Ruiz et al., 2020).

X-ray findings of COVID-19: Chest X-ray (CXR) is an essential noninvasive supporting diagnostic for detecting SARS-COV-2 infection in patients. X-ray of the patient's chest reveals patchy reticulonodular or reticulonodular opacities, multifocal, bilateral ground-glass opacities, and extensive pulmonary consolidations in the lungs, consistent with the diagnosis of COVID-19 (Chandra et al., 2021).

CT scan findings of COVID-19: Bilateral diffusely distributed rounded nodules, ground-glass appearance, and small patchy shadows are seen in pulmonary parenchymal. Sometimes, irregular interlobular pleural thickening and pleural effusion are also evident in COVID-19-infected patients.

Histopathology of COVID-19: On biopsy of lung tissue, specific characteristic findings are seen such as infiltration of mononuclear inflammatory cells into the interstitial space, development of hyaline membranes, and desquamation of pneumocytes, multinucleated giant cells along with atypically enlarged pneumocytes featured with large and prominent nuclei, and amphiphilic granular cytoplasm in interalveolar spaces, which all suggests viral cytopathology (Cheung et al., 2004; Tian et al., 2020).

6 Drugs used in COVID-19 till now with newer drug possibilities tried for infection

To date, there are no single drugs against COVID-19, but they can be combated pharmacologically with combinations of drugs, interferon therapies, oligonucleotides, peptides, monoclonal antibodies, and supportive treatments with steroids, antibiotics, antiparasitic, anticoagulants, multivitamin, and oxygen therapy. The combination of drugs treatment varies according to the severity of diseases and blood oxygen levels (Spo2) of the patient.

RT-PCR-positive and asymptomatic patients need home or institution quarantine with supportive treatments with multivitamins, viz., vitamin D, vitamin C, vitamin E, and minerals like Zinc.

Vitamins A, C, D, and E play potentially beneficial function like immunomodulation, antioxidant effects, augmenting local paracrine signaling and enhancing natural barriers in the fight against COVID-19 (Jovic et al., 2020). Vitamin D (1,25(O.H.)2D3) demonstrates potent antimicrobial and antiinflammatory effects. It may exhibit immunomodulatory effects by regulating both adaptive and innate immunity in COVID-19 patients. Vitamin D can inhibit interleukin IL-2 and IL-17, the inflammatory T cell cytokines. Vitamin D can inhibit toll-like receptors found on the surface of monocytes. Vitamin D supplementation at high doses lowers the levels of the pro-inflammatory cytokine IL-6, which is produced by peripheral mononuclear cells (PMNs) (Cutolo et al., 2020; Leaf and Ginde, 2021). Zinc has been claimed to augment the ability of polymorphonuclear cells to combat infection. Zinc plays an essential role in pathogen removal signal transduction pathways and stimulating cell-mediated immunity by controlling differentiating factors (Gammoh and Rink, 2017).

Depending on the severity of the patient, a symptomatic patient needs to be transferred to a COVID care center or admitted to COVID hospital and needs a combination of drugs, interferon therapies, oligonucleotides,

peptides, monoclonal antibodies, and supportive treatments with steroids, antibiotics, antiparasitic, anticoagulants, multivitamin, and oxygen therapy. Based on the mechanisms of action, the anti-COVID drugs can be divided into following categories: Viral entry inhibitors, those that inhibit RNA polymerase or RNA synthesis by acting on work on viral proteins and enzymes or human enzymes or receptors; Inhibitors of viral protein synthesis; those that work on membrane, nucleocapsid, or envelope proteins; drugs that target structural proteins, such as those that impede self-assembly or those that prevent the virus from attaching itself to ACE2 (Wu et al., 2020b).

Viral entry inhibitors—It is believed that aminoquinolines, such as hydroxychloroquine and chloroquine, prevent viral particles from adhering to cell surface receptors by interfering with the glycosylation of these receptors. This results in the cell not being able to accept COVID-19 into the cell. The medication operates on quinone reductase-2, similar to UDP-*N*-acetylglucosamine 2-epimerases (UNEs), and inhibits quinone reductase-2 by binding to the enzyme. The synthesis of sialic acid involves the use of UNEs in the process. In cell transmembrane proteins, sialic acids are structural components of sugar molecules that are accessible for binding, and they are essential factors in recognizing ligands by the protein. It is also possible that chloroquine hinders the pH-dependent access of COVID viruses into endosomes, preventing virus cell fusion (Devaux et al., 2020). For the fusion of endosomal and viral membranes, the pH of the cell must be acidic. This results in the transport of the SARS-CoV genome to the cytoplasm of the cell. Absent an antiviral medication, the virus enters the cell and travels to the lysosome, where the combination of enzymatic activity and low pH causes the virus to be cleaved, releasing replication enzymes and viral RNA. In addition to the rapid increase in endosomal pH, the inhibition of endocytosis and the disruption of endosome-virus fusion have all been hypothesized to be the mechanisms of chloroquine's antiviral effect (Colson et al., 2020). These medications have been associated with the side effects of nausea, vomiting, anorexia, uncontrolled itching, epigastric discomfort, unease, trouble adjusting to new surroundings, and headaches. Using this product for an extended period can result in vision loss owing to retinal damage; corneal deposits can also form; hearing loss; rashes; photo allergies; mental abnormalities; myopathy; and graying of the hair. It should be avoided in the presence of liver damage, severe gastrointestinal symptoms (including diarrhea), neurological, retinal, and hematological illnesses. Attacks of seizure, porphyria, and psoriasis are all possible side effects of this medication. The drug should never be administered in conjunction with

mefloquine, amiodarone, or other antiarrhythmic medications (Geleris et al., 2020).

6.1 Viral RNA polymerase inhibitors/RNA synthetase inhibitors

Favipiravir (T-705) is a synthetic prodrug, Guanosine nucleotide analog, enzyme RNA-dependent-RNA-polymerase (RdRp) inhibitor. RdRp is a protease enzyme involved in RNA replication from an intermediate template (Lung et al., 2020). The RNA virus converts favipiravir into an active phosphoribosylated form; it is mistaken by the enzyme RNA-dependent RNA-polymerase (RdRp) and replaces purine nucleotide. It gets amalgamated in the viral RNA strand, preventing further extension. Thus inhibits the activity and terminates the viral protein synthesis (Jean et al., 2020; McKee et al., 2020). As a chain terminator, the medication prevents the creation of viral genomic RNA (Shiraki and Daikoku, 2020). It is approved in Japan for treating the emergency influenza infections pandemic in the year 2014.

Remdesivir (RDV) is a 10-cyano-substituted adenosine analog, a phosphoramidite prodrug, and an enzyme that blocks RdRp and hampering viral nucleic acid amalgamation by establishing a link with the active region of RdRp (Jean et al., 2020). In addition, the exoribonuclease of SRS-CoV-2, which is involved in the prevention of proofreading, is involved in the action of RDV. The viral RNA transcription is prevented from progressing further than necessary (Cao et al., 2020). Ribavirin, Sofosbuvir, Galidesivir, and Tenofovir are other effective medicines against SARS-CoV-2 with a strong affinity for its RdRp (Elfiky, 2020).

6.2 Inhibitors of viral protein synthesis

Lopinavir is a protease inhibitor that may prevent the activity of 3CLpro, hence interrupt viral replication and liberation from host cells. It is an antiretroviral drug used for the treating of HIV.

Ritonavir increases the half-life of lopinavir by inhibiting its metabolizing enzyme cytochrome P450 3A (Dorward et al., 2020). The protease inhibitors target enzymes involved in virus replication like 3C-like protease and papain-like protease (Jean et al., 2020).

6.3 Immunomodulators

Ivermectin is an FDA-approved antiparasitic medication with a broad spectrum of activity. After 48 h of SARS-CoV-2 infection, this medication reduced viral RNA by up to 5000-fold by preventing nuclear of host and

viral proteins via inhibition of importin (Caly et al., 2020). Combining Ivermectin with doxycycline (antibiotic) improved the recovery and prevented the progression of diseases to severe outcomes in adults with COVID-19 infection (Mahmud et al., 2021).

Tocilizumab (TZM) is a monoclonal antibody against membrane-bound and soluble interleukin-6 receptors. The drug blocks signal transduction through the mIL-6R and sIL-6R, which are found on the membrane of the immune system (Mihara et al., 2005).

Itolizumab is a monoclonal antibody anti-CD6 *humanized IgG1*. CD-6 plays a vital role in grooming, stimulation, and T-cell differentiation. Itolizumab binds to domain-1 of CD-6, thus drastically decreases the T-cell proliferation and downregulation of cytokines/chemokines production. Steroids are known for their antiinflammatory property hence beneficial in the treatment of COVID-19 (Dogra et al., 2017). Additionally, leronlimab (PRO140), a C—C chemokine receptor type 5 (CCR5) antagonist, and a humanized monoclonal antibody are being investigated as an experimental new medication to treat COVID-19 (Agresti et al., 2021). A serine protease is a type of enzyme that breaks down amino acids. TMPRSS2 is a host cell factor that is required for the priming of S proteins. The serine protease inhibitor "camostat mesylate," which inhibits the activity of the TMPRSS2 enzyme, has been licensed for human use in Japan (Zhou et al., 2015; Kawase et al., 2012).

7 Potential sites for the target for vaccine and drug development

A vaccine strategy may be used to reduce illness severity, limit viral transmission, and prevent future infections. It is also effective in preventing future infections. The critical target for vaccine development is structural proteins, positive-sense RNA of the virus, DNA, and biopolymers. The targets for protein vaccine are two subunits S1 and S2 of S protein (Spike) protein of Coronavirus that facilitate virus entry using ACE-2, E protein embedded in an envelope of the virus, Matrix (M) protein responsible for budding of the virus, Nucleocapsid protein which encapsulates the genetic material ssRNA of virus and also facilitates RNA synthesis (Naz et al., 2020).

Vaccines are often designed to elicit humoral immunity and cell-mediated immunity via T killer cells that detect and destroy contaminated cells. A straightforward technique is to introduce a virus into the body after

being inactivated using chemicals, gamma irradiation, or heat. The expressed proteins or the degraded viral surface act as an antigen and triggered neutralizing antibiotics (Gilbert, 2012).

Another approach is to introduce weakened or attenuated copies of the virus that replicate exclusively inside the host cell but still include enough antigens to trigger an immune response from the host cell itself. While employing a nonvirulent organism for demonstration purposes is less safe than using an inactivated virus and has been linked to disease outbreaks, it is preferable to generate the mild infection necessary for developing an efficient adaptive immune response (Lee et al., 2012).

The type of immune response produced and its intensity depend on the strain of the virus used. A more targeted approach induces an adaptive immune response immunogenic viral protein, or their fragments are introduced into the body to stimulate humoral immunity as well as cell-mediated immunity. Another method can be targeting RNA of virus for the vaccine, i.e., RNA-specific vaccines of Coronavirus can be developed. However, the limitations and difficulties are the high mutation rates of the virus, antigenic drift seen in viruses, and genetic variability. The selection of the most appropriate viral genome sequence is of tremendous significance. Because a virus is an obligatory intracellular parasite that needs the presence of a matched host cell in order to reproduce, all vaccine development methods should aim to prevent the virus from attaching itself to the host cell or from being recognized by the host cell's receptors (Pandey et al., 2020). Also, safer attenuated vaccines can be tried for vaccine development via recombinant DNA technology; replicating vectors can be adenoviruses, measles virus, poxviruses, and vesicular stomatitis viruses, which are earlier used as vectors for vaccine delivery to target sites earlier. Previously, these viruses were not dangerous to humans and did not have a genetically changed genome. The genome is changed to contain the coding sequence for the protein/subunit antigen required for optimal expression, assembly, and packaging into the recombinant virus throughout the recombinant viral production process. The creation of mRNA vaccines is similar to the creation of DNA viruses; however, they run the risk of being integrated into the host genome. They might be conventional mRNA vaccinations or ones that utilize mRNA amplifying vaccines. Nonetheless, developing a vaccine resistant to a pandemic like SARS-CoV-2 is critical for humanity's protection, particularly for infectious diseases. As a result, work must be done on these issues (Tse et al., 2020).

8 Conclusion

According to phylogenetic analysis, the SARS-CoV-2 virus may have originated from bats or pangolins, which had affected millions with the severity of symptoms like pulmonary edema, ARDS, sepsis, metabolic syndrome, acidosis, coagulation, lymphopenia, hypoxemia, multiorgan failure, and eventually mortality. Medications, interferon treatments, oligonucleotides, peptides, and monoclonal antibodies may be used to treat COVID-19 pharmacologically. There have been a variety of antivirals used in the treatment of COVID-19, including Favipiravir, Remdesivir (an RNA dependent RNA polymerase inhibitor), Lopinavir and Ritonavir (Retroviral protease inhibitors), Tocilizumab (TZM), Itolizumab, and the combination of doxycycline (an antibiotic) and Ivermectin (antiparasitic). Ribavirin, Sofosbuvir, Galidesivir, and Tenofovir are some of the other effective medicines against SARS-CoV-2. In order to prevent the spread of the pandemic, world health agencies have advised preventive measures such as hand washing, the use of face masks and hand sanitizer, and keeping a safe distance. However, vaccination is a possible strategy to prevent the pandemic from spreading.

References

Agampodi, T.C., et al., 2015. Measurement of social capital in relation to health in low- and middle-income countries (LMIC): a systematic review. Soc. Sci. Med. 1982 (128), 95–104. https://doi.org/10.1016/J.SOCSCIMED.2015.01.005.

Agresti, N., et al., 2021. Disruption of CCR5 signaling to treat COVID-19-associated cytokine storm: case series of four critically ill patients treated with leronlimab. J. Translat. Autoimmun. 4. https://doi.org/10.1016/J.JTAUTO.2021.100083, 100083.

Baj, J., et al., 2020. COVID-19: specific and non-specific clinical manifestations and symptoms: the current state of knowledge. J. Clin. Med. 9, 1753. https://doi.org/10.3390/JCM9061753.

Caly, L., et al., 2020. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 178. https://doi.org/10.1016/J.ANTIVIRAL.2020.104787.

Cao, Y., Deng, Q., Dai, S., 2020. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: an evaluation of the evidence. Travel Med. Infect. Dis. 35. https://doi.org/10.1016/J.TMAID.2020.101647, 101647.

Chandra, T.B., et al., 2021. Coronavirus disease (COVID-19) detection in chest X-ray images using majority voting-based classifier ensemble. Expert Syst. Appl. 165. https://doi.org/10.1016/J.ESWA.2020.113909, 113909.

Chau, V.Q., et al., 2020. The imperfect cytokine storm: severe COVID-19 with ARDS in a patient on durable LVAD support. JACC. Case Rep. 2, 1315–1320. https://doi.org/10.1016/J.JACCAS.2020.04.001.

Cheng, V.C., et al., 2007. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin. Microbiol. Rev. 20, 660–694. https://doi.org/10.1128/CMR.00023-07.

Cheung, O.Y., et al., 2004. The spectrum of pathological changes in severe acute respiratory syndrome (SARS). Histopathology 45, 119–124. https://doi.org/10.1111/J.1365-2559.2004.01926.X.

Colson, P., et al., 2020. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. Int. J. Antimicrob. Agents 55. https://doi.org/10.1016/J.IJANTIMICAG.2020.105932, 105932.

Costela-Ruiz, V.J., et al., 2020. SARS-CoV-2 infection: the role of cytokines in COVID-19 disease. Cytokine Growth Factor Rev. 54, 62. https://doi.org/10.1016/J.CYTOGFR.2020.06.001.

Cucinotta, D., Vanelli, M., 2020. WHO declares COVID-19 a pandemic. Acta Biomedica 91, 157–160. https://doi.org/10.23750/abm.v91i1.9397.

Cutolo, M., Paolino, S., Smith, V., 2020. Evidences for a protective role of vitamin D in COVID-19. RMD Open 6, e001454. https://doi.org/10.1136/RMDOPEN-2020-001454.

Devaux, C.A., et al., 2020. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int. J. Antimicrob. Agents 55. https://doi.org/10.1016/J.IJANTIMICAG.2020.105938, 105938.

Dogra, S., Uprety, S., Suresh, S.H., 2017. Itolizumab, a novel anti-CD6 monoclonal antibody: a safe and efficacious biologic agent for management of psoriasis. Expert Opin. Biol. Ther. 17, 395–402. https://doi.org/10.1080/14712598.2017.1279601.

Dorward, J., et al., 2020. The protease inhibitor lopinavir, boosted with ritonavir, as treatment for COVID-19: a rapid review. Antivir. Ther. 25, 365–376. https://doi.org/10.3851/IMP3385.

Elfiky, A., 2020. Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2 RNA dependent RNA polymerase (RdRp): a molecular docking study. Life Sci. 253, 117592. https://doi.org/10.1016/J.LFS.2020.117592.

Gammoh, N.Z., Rink, L., 2017. Zinc in infection and inflammation. Nutrients 9, 624. https://doi.org/10.3390/NU9060624.

Geleris, J., et al., 2020. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. N. Engl. J. Med. 382, 2411–2418. https://doi.org/10.1056/NEJMOA2012410.

Gilbert, S.C., 2012. T-cell-inducing vaccines—what's the future. Immunology 135, 19. https://doi.org/10.1111/J.1365-2567.2011.03517.X.

Heurich, A., et al., 2014. TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. J. Virol. 88, 1293–1307. https://doi.org/10.1128/JVI.02202-13.

Hoffman, M., et al., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181, 271–280.e8. https://doi.org/10.1016/J.CELL.2020.02.052.

Iwata-Yoshikawa, N., et al., 2019. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. J. Virol. 93. https://doi.org/10.1128/JVI.01815-18, e01815-18.

Jean, S.S., Lee, P.I., Hsueh, P.R., 2020. Treatment options for COVID-19: the reality and challenges. J. Microbiol. Immunol. Infect. Wei mian yu gan ran za zhi 53, 436–443. https://doi.org/10.1016/J.JMII.2020.03.034.

Jovic, T.H., et al., 2020. Could vitamins help in the fight against COVID-19? Nutrients 12, 1–30. https://doi.org/10.3390/NU12092550.

Kawase, M., et al., 2012. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. J. Virol. 86, 6537–6545. https://doi.org/10.1128/JVI.00094-12.

Kretchy, I.A., Asiedu-Danso, M., Kretchy, J.-P., 2021. Medication management and adherence during the COVID-19 pandemic: perspectives and experiences from low-and middle-income countries. Res. Social Adm. Pharm. 17, 2023. https://doi.org/10.1016/J.SAPHARM.2020.04.007.

Kumar, S., et al., 2020. Morphology, genome organization, replication, and pathogenesis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus Dis. 2019 (COVID-19), 23. https://doi.org/10.1007/978-981-15-4814-7_3.

la Marca, A., et al., 2020. Testing for SARS-CoV-2 (COVID-19): a systematic review and clinical guide to molecular and serological in-vitro diagnostic assays. Reprod. Biomed. Online 41, 483. https://doi.org/10.1016/J.RBMO.2020.06.001.

Leaf, D., Ginde, A.A., 2021. Vitamin D3 to treat COVID-19: different disease, same answer. JAMA 325, 1047–1048. https://doi.org/10.1001/JAMA.2020.26850.

Lee, N.H., et al., 2012. A review of vaccine development and research for industry animals in Korea. Clin. Exp. Vaccine Res. 1, 18. https://doi.org/10.7774/CEVR.2012.1.1.18.

Lung, J., et al., 2020. The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase. J. Med. Virol. 92, 693–697. https://doi.org/10.1002/JMV.25761.

Mahmud, R., et al., 2021. Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial. 49 (5). https://doi.org/10.1177/03000605211013550, 3000605211013550.

McGregor, S., Henderson, K.J., Kaldor, J.M., 2014. How are health research priorities set in low and middle income countries? A systematic review of published reports. PLoS One 9, e108787. https://doi.org/10.1371/JOURNAL.PONE.0108787.

McKee, D.L., et al., 2020. Candidate drugs against SARS-CoV-2 and COVID-19. Pharmacol. Res. 157. https://doi.org/10.1016/J.PHRS.2020.104859, 104859.

Mihara, M., et al., 2005. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. Int. Immunopharmacol. 5, 1731–1740. https://doi.org/10.1016/J.INTIMP.2005.05.010.

Naz, A., et al., 2020. Designing multi-epitope vaccines to combat emerging coronavirus disease 2019 (COVID-19) by employing immuno-informatics approach. Front. Immunol. 11. https://doi.org/10.3389/FIMMU.2020.01663.

Pal, M., et al., 2020. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2): an update. Cureus 12, e7423. https://doi.org/10.7759/CUREUS.7423.

Pandey, S.C., et al., 2020. Vaccination strategies to combat novel corona virus SARS-CoV-2. Life Sci. 256, 117956. https://doi.org/10.1016/J.LFS.2020.117956.

Park, S.E., 2020. Epidemiology, virology, and clinical features of severe acute respiratory syndrome -coronavirus-2 (SARS-CoV-2; coronavirus disease-19). Clin. Exp. Pediatr. 63, 119–124. https://doi.org/10.3345/CEP.2020.00493.

Sarkesh, A., et al., 2020. Extrapulmonary clinical manifestations in COVID-19 patients. Am. J. Trop. Med. Hyg. 103, 1783. https://doi.org/10.4269/AJTMH.20-0986.

Shiraki, K., Daikoku, T., 2020. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol. Ther. 209. https://doi.org/10.1016/J.PHARMTHERA.2020.107512, 107512.

Singhal, T., 2020. A review of coronavirus Disease-2019 (COVID-19). Indian J. Pediatr. 87, 281–286. https://doi.org/10.1007/S12098-020-03263-6.

Sohrabi, C., 2020. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). Int. J. Surg. 76, 71–76. https://doi.org/10.1016/J.IJSU.2020.02.034.

Sun, Z., et al., 2020. Potential factors influencing repeated SARS outbreaks in China. Int. J. Environ. Res. Public Health 17, 1633. https://doi.org/10.3390/IJERPH17051633.
Tang, Y.W., et al., 2020. Laboratory diagnosis of COVID-19: current issues and challenges. J. Clin. Microbiol. 58. https://doi.org/10.1128/JCM.00512-20, e00512-20.
Tian, S., et al., 2020. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. J. Thorac. Oncol. 15, 700–704. https://doi.org/10.1016/J.JTHO.2020.02.010.
Tse, L.V., et al., 2020. The current and future state of vaccines, antivirals and gene therapies against emerging coronaviruses. Front. Microbiol. 11. https://doi.org/10.3389/FMICB.2020.00658.
Wu, C., et al., 2020b. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm. Sin. B 10, 766–788. https://doi.org/10.1016/J.APSB.2020.02.008.
Wu, Y.-C., Chen, C.-S., Chan, Y.-J., 2020a. The outbreak of COVID-19: an overview. J. Chin. Med. Assoc. 83, 217. https://doi.org/10.1097/JCMA.0000000000000270.
Zhang, C., et al., 2020. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int. J. Antimicrob. Agents 55. https://doi.org/10.1016/J.IJANTIMICAG.2020.105954, 105954.
Zhou, Y., et al., 2015. Protease inhibitors targeting coronavirus and filovirus entry. Antiviral Res. 116, 76. https://doi.org/10.1016/J.ANTIVIRAL.2015.01.011.
Zhu, N., et al., 2020. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733. https://doi.org/10.1056/NEJMOA2001017.