Novel Coronavirus disease (COVID-19): physiology to pathophysiology and therapeutics including herbal medicines

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Abstract

COVID-19 emerged as a public health emergency of international concern in 2019 and spread globally. The spectrum of the diseases varied from asymptomatic to severe, even resulting in mortality. Gender and pre-existing co-morbidities were identifiable risk factors. Diabetes, hypertension, and chronic respiratory and cardiovascular diseases pose a risk of severe infections and manifestations. The vulnerability was due to ACE 2 receptors, thereby enhancing the entry and subsequent multiplication of the virus. Immune responses acted as the two-way sword, with cytokine storms posing a risk of severe complications. COVID-19 is also associated with long-term effects varying from neuropsychiatric to other complications. Mutations are expected to pose a challenge in the future. The second wave was also related to fungal infections due to varied causes like side effects of treatment and opportunistic infection due to immune suppression from using steroids. Naturopathy is also expected to work wonders. However, scientific and evidence-based results are required. COVID combat requires a multi-level approach. Nutrition and strict adherence to health and hygiene are essential preventive strategies.

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Introduction

WHO declared that COVID-19 was a public health threat with the potential to affect populations across the globe and thus called for a coordinated effort at various levels meaning that COVID-19 was not just restricted to Wuhan, China, but was declared as Public Health Emergency of International Concern (PHEIC). Coronavirus is an encapsulated virus with spikes like membrane glycoproteins and a single positive sense RNA (ss RNA) genome. Lower respiratory tract infection is caused by Severe Acute Respiratory Syndrome (SARS) beta Coronavirus-2, commonly called COVID-19.[1] The secondary attack rate in India was comparable to that of the USA during the second wave, and the B.1.617 variant was responsible for the emergence and surge of the second wave of COVID-19 worldwide, including India. The later wave was primarily attributed to the Omicron variant (B.1.1.529). Other possible contributory factors were non-strict compliance to COVID-appropriate behavior, the decline in fear levels compared to the first wave, ignorance about the spread of infection during the incubation period, and initial hesitancy for vaccination.[2-4] Mutations affecting the spike proteins, thereby influencing the virus entry, have been reported. These are mainly H69/V70 deletion and, thereby, D614G. The concerns raised are the effectiveness of the vaccines and available treatment regimes. However, the currently available vaccines are said to be effective against the mutant strain as well.[5]

Immunological mechanisms associated with the virus

The S protein of the virus binds to its cellular receptors after entering the host cells. The entry could be clathrin-mediated or even without it. Once inside the cells, the virus begins to replicate after releasing the RNA into the host cell cytoplasm, finally culminating in the release of the virus from the cell due to the formation of new envelope glycoproteins, which help the virus to propagate in the endoplasmic Golgi intermediate compartment referred to as Endoplasmic Reticulum Golgi Intermediate Compartment (ERGIC). Once the virus is released, it stimulates the host's immune response in response to antigen presentation by Major Histo Compatibility (MHC). Evidence suggests a role of mainly MHC I in presenting the virus to cytotoxic T cells, but the role of

MHC II cannot be ruled out completely. Thus COVID-19 is expected to stimulate both cellular and humoral immunity. Reports from previous infections have shown that CD4 and CD8 T cells are reduced in patients with COVID. Evidence from recovered patients of coronavirus attacks earlier has highlighted the role of memory T cells, thus giving an insight into developing a vaccine. Coronavirus is also shown to upregulate the production of cytokines and chemokines, which are responsible for systemic inflammatory response and subsequent development of respiratory distress, multi-organ dysfunction, and even death. Another exciting feature of the infection is the ability of the virus to form double-membrane vesicles lacking pattern recognition receptors which play a vital role in immunity against the invading pathogen. The absence of a pattern recognition receptor helps the virus to evade the recognition by the host immune system and thus helps in virus survival. The Pathogen Associated Molecular Patterns (PAMPs) are recognized by endosomal RNA receptors, namely TLR3 and TLR7, and also by RIG –I (MDA 5) cytosolic RNA sensor, activating JAK-STAT by Type I interferons, thus resulting in the activation of innate immune response providing immunity against the virus. COVID-19 has been shown to affect the above immune mechanisms, thus resulting in either suppression or delayed Type I interferons immune response, which ultimately leads to excess viral replication or increased inflammation mediated (via mononuclear macrophages and neutrophil activity) lung injury.[6,7]

Role of the ACE 2

Researchers have also highlighted the role of Angiotensin Converting Enzyme (ACE) 2, which is utilized by the virus to gain access into the host cell, thus indicating human-to-human and cross-species transmission and spread. ACE 2 is highly expressed in various tissues of the human body like heart myocardium, renal epithelial cells of proximal convoluted tubules, esophagus, type II alveolar pneumocytes, epithelial cells of the small and large intestine, epithelial cells of the urinary bladder, gall bladder cells and oral mucosa cells and thus act as potential sites of viral infection.[8,9] The glycoprotein S of COVID-19 binds to the ACE 2 receptors and gains access to the host cell, and after subsequent replication, the virions are released.[10] Earlier research has shown that the down-regulation or shedding of ACE 2 by SARS-CoV results in the pathophysiological changes in the lung associated with SARS virus infection by diminishing the protective role of ACE 2.[11,12] Interestingly, studies have shown low levels of antibodies against SARS-COV-2 virus in smokers and those taking anti-inflammatory medications. Higher levels were reported in hospitalized and elderly patients. Smoking is considered to be a risk factor by its ability to enhance the ACE 2, which aids virus entry by acting as a receptor.[13]

Antibody-Dependent Enhancement

SARS-COV-2 is being postulated to be associated with Antibody-Dependent Enhancement (ADE).[14] Molecular mechanisms for ADE of coronavirus entry are shown in Figures 1 and 2 (adapted).[15]

ADE helps enter the viruses into the host cells by antibody dependant mechanism. In a nutshell, if an individual is infected by one serotype of the virus, then the antibodies developing against it may not be able to completely neutralize the infection caused by another serotype of the same virus but instead may aid in virus entry inside the immune cells by binding to the receptors present on the cells.[15]

However, if the monoclonal antibody targets any other parts of the spikes, then it is expected to contribute less to ADE by the inability to induce conformational changes. The effect of monoclonal antibodies appears dose-dependent, and the receptors targeted. DDP4 or Fc Receptor expressing cells appear to be affected differently by the monoclonal antibody regarding the virus entry. The knowledge of such mechanisms is postulated to be important in antibody-dependant treatment and vaccine development.[15] The severity of ADE is expected to depend upon the vaccine-induced enhancement of the non-neutralizing antibodies, which in turn bind to the FC receptors (Fcr dependant ADE) and activate the complement system (C-mediated ADE) by interacting with the cells of the immune system.[16] The role of ADE is well documented in the dengue virus infection. Researchers have shown that there appears to be an imbalance in the cytokine levels in more severe cases of dengue associated with ADE. IL4 and 10 are increased, but those of IFN ϒ are decreased. Similarly, in such cases, TH1-mediated immune responses show a decline.

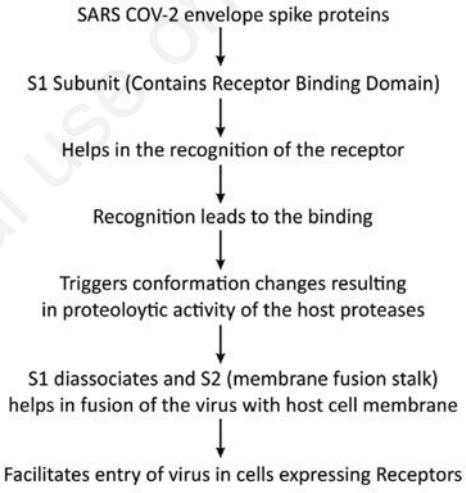

Figure 1. Mechanism of virus entry into host cell.

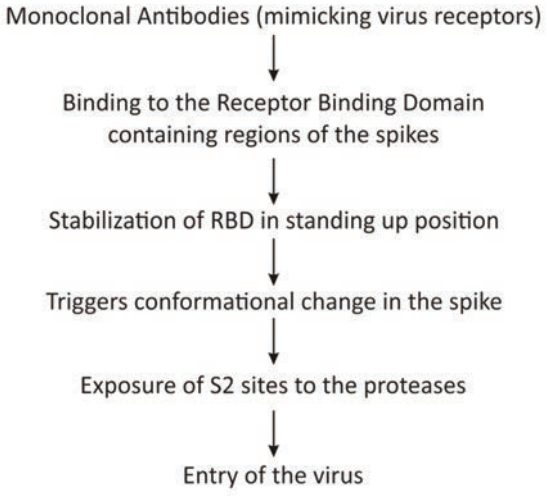

Figure 2. Antibody enhancement of the virus.

Similar studies in Respiratory Syncytial Virus (RSV) have shown up-regulation of IL 4, 5, and 13. ADE is also reported in research on Human Immunodeficiency Virus (HIV), leishmaniasis, yellow fever, and certain bacterial infections.

These effects, in turn, help the survival and entry of the infective agent into the host cell and produce infection and are also implicated in the failure of vaccines or even loss of immunological memory or vaccine-induced increase in the manifestations and severity.[17] Interestingly, complement mediated ADE in HIV is mainly through binding gp 41 of the virus to the C3 and type 2 complement receptor. Monoclonal antibodies have been shown to enhance the gp 41 binding to C1q, which in turn is shown to facilitate the virus entry and further the viremia.[18]

Why is COVID-19 contagious?

The incubation period is long. The infectivity of the virus having spike protein D614G is higher.[19,20] The infection spreads through contact with the infected person. Reportedly, even an asymptomatic person could be a potential source of spread of infection.[21] Another important aspect is the shedding of the virus even after six weeks in symptomatic and asymptomatic healthy patients.[22] The virus is also subjected to mutations making it more contagious. The research has shown that mutations in the NSP 2 protein endosome-associated protein-like domain make the virus more contagious. [23] Similarly, the NSP1 helps the virus evade a host's defenses by influencing the innate immune responses and declining the anti-viral interferon production. [24]

Route of spread

Researchers have raised questions and worked to establish various infection spread modes. Apart from droplet and contact spread, researchers have highlighted the need to study the other possible routes like aerosols, waste systems like sewage, contaminated water, and even air conditioning.[25]

Gender differences

There may be multiple reasons ranging from the protective roles of estrogen and progesterone in females by inhibiting the expression of TMPRSS2 microRNA (mRNA) expression and stimulatory influence on anti-inflammatory cytokines like IL 4 and IL 10. ACE 2 expression is also found in seminal vesicles and Sertoli and Leydig cells of the testes, thereby increasing the vulnerability. Male hormones enhance the expression of TMPRSS2. At the same time, the females express higher levels of TLR 7, thereby helping in virus recognition and resulting in higher production of Type I IFNs, inhibiting viral replication and limiting infection. Studies have reported higher levels of IL 21 and 27, B cell maturation due to enhanced Follicular T cells in females. Antibody responses are also reportedly maintained for more extended periods in females. Regulatory helper T cells and B cells enhanced activity via CD4 + T cells is found to be more in females, thereby preventing excessive inflammation and protecting against severe infections.

IL 22 and 17 are found to be expressed more in females, thus providing preventing inflammation and also helping in tissue repair.[26] Socioeconomic factors also appear to be contributing factors. ACE 2 is present on the X chromosome, and females are expected to have better anti-inflammatory responses than males. Female reproductive hormone estrogen down-regulates the ACE 2, and ACE 2 expression is less in female respiratory tissue.[19,27] Diseases like cardiovascular, diabetes, hepatic, and certain tumors appear to have a higher pre-inclination towards the male gender. Since the diseases mentioned above appear as co-morbidity in COVID-19, thus giving a possible explanation for higher risk and mortality in males. The other possible reasons could be higher endurance in females to cope with stress, higher life expectancy, and decreased immune response with advancing age. In females, age-related decline of B, T, and natural killer cells was slower than in females.[28] Gender-based differences exist in terms of susceptibility and severity of infection. Higher severity in males may be attributed to increased levels of cytokines of innate immunity like IL8 and 18. On the other hand, severity is low in females due to enhanced activation of T Cells. Sex-based differences may also occur due to extra X chromosomes in females, thereby conferring cushion even when the membrane ACE2 is lost due to the actions of SARS-COV-2.[29] Gender-based differences in socioeconomic conditions, employment, access to health care, and basic needs like food and education also play a role in susceptibility and vulnerability to disease[30] and thus require evaluation once WHO declares the pandemic over.

The symptoms (Table 1) may range from mild, moderate to severe. Importantly, immune status, co-morbid conditions and age play an important role in determining the outcome (Table 2).

Why people with co-morbid conditions like hyperglycemia, hypertension and cardio vascular diseases are more susceptible to infection by COVID-19?

Diabetes, Congestive Heart Failure (CHF), obesity, obstructive airway disease, and chronic renal diseases are expected to be associated with a greater risk of infection, severity, and mortality in COVID-19.[43]

The risk of mortality with COVID-19 infection is associated with the elderly age group, high values of d dimer (>1 µgm/mL), and higher values of the SOFA score. There appears a decrease in

Table 1. Clinical manifestations of the infection.[4,21,25,31-33]

Pyrexia; however, absence of fever doesn't rule out infection, as reported in study
Fatigue, malaise, myalgia
Sore throat and hoarseness of voice
Anorexia
Difficulty in breathing
Nausea and diarrhoea (though less common)
Headache, rhinnorhea
Progression to respiratory distress, acid base abnormalities like metabolic acidosis and multi-organ dysfunction or failure occur in severe cases
Coagulation abnormalities
Systemic inflammation and septic shock
Fulminant myocarditis; mortality has been reported from this condition and physicians were alerted to pay attention to the condition

both humoral and cellular immunity and an increase in the pro-inflammatory response mediated by Type II interferons in old age, which in turn reduces the ability of the body to fight against the viral infection and replication, thus increasing the susceptibility of elderly. On the other hand, pneumonia affects cardiac functions resulting in increased chances of heart attacks, abnormal rhythm, infractions, and even arrest. Thus individuals with prior history of cardiovascular diseases appear to be at higher risk of mortality from COVID-19. An increase in D-dimers increases the chances of coagulation and thrombosis by increasing the systemic inflammation and activating the coagulation cascade.[44]

WHO recommends that Tuberculosis (TB) patients continue the prescribed treatment and follow every step required to prevent contracting the COVID-19 virus infection. Moreover, TB-positive patients having COVID-19 have been shown to have a poor prognosis, especially if they are to be taken off the anti-tubercular medicines.[45] Researchers have shown that higher D dimer Lactate Dehydrogenase (LDH), thus reflecting organ and coagulation disorder, increase in the neutrophil counts, and older age is associated with a higher risk of Acute Respiratory Distress Syndrome (ARDS), even culminating in mortality in COVID-19 infection. The study has shown that factors like glucose, creatinine, albumin, ferritin, Low-Density Lipoprotein (LDL), lymphocyte counts, CD4 T cell counts, and co-morbidities result in the development of ARDS but may not necessarily result in mortality.[46]

Similarly, obesity also acts as the risk for COVID-19 because of higher numbers of ACE 2 receptors available in adipose tissue and increased levels of cytokines like MCP-1, IL6, and TNF α. Patients with primary adrenal insufficiency are also at higher risk. COVID-19 amino acids mimic the host Adrenocorticotropic Hormone (ACTH), thus making them the target for host immune response-induced response-induced destruction, reducing the ACTH levels and decreasing the cortisol-induced stress response.[47] Obesity is linked with more excellent virus shedding, and excess adipose tissue interferes with diagnostic procedures like pulmonary imaging.[48]

Abnormality in glucose homeostasis and hyperglycemia affect the immune responses negatively. Excess blood glucose levels impair the activation of the complement system and inhibit lymphocytic proliferation, neutrophil degranulation, and phagocytosis. Moreover, in diabetics, there is an imbalance between M2 and M2 macrophages, thus shifting the balance toward inflammation and infection. Hyperglycemia also results in protein kinase C activation, negatively affecting neutrophil functions.[49] Researchers have shown that poor glucose control is associated with increased permeability of the alveolo-capillary membrane and alveolar epithelia membrane collapse.[48] SARS COV 2 is believed to precipitate the onset of Type 1 Diabetes. In order to further explore the link and get better insight into mechanisms and therapeutic potentials, a worldwide registry by the name Covi DIAB was launched in June 2020.[50]

Why the knowledge about the cytokines is important as far as COVID-19 is concerned?

The COVID-19-causing virus stimulates the Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), resulting in the enhanced production of IL-6. The inflammatory cytokines produce widespread effects, including lung injury and multi-organ dysfunction. Monitoring these cytokines would help assess the disease progression and act as therapeutic targets in disease management.[51] Increase in IL-6 has been reported earlier in patients suffering from Middle East Respiratory Syndrome (MERS) and SARS-COV infection. The NLRP3 increases inflammatory cytokines in response to stimulation by Damage-Associated Molecular Patterns (DAMPs).[52,53] NLRP3 aid in virus elimination by recognizing the pathogen-associated and damage-associated molecular patterns, *i.e.*, PAMPs and DAMPs. Transcription of the NLRP3 involves NF-κB. The subsequent increase in inflammatory cytokines has an anti-viral effect by increasing the recruitment of neutrophils and enhancing the adaptive immune response. Viruses have been shown to evade the NLRP3 by employing various mechanisms, as shown in measles and paramyxovirus. Limiting the NLRP3 response by the virus helps it evade the host's innate immune mechanism and helps in further survival.[54] Researchers have raised the question of the ability or efficiency/strength of SARS-COV-2 in suppressing the activation of NLRP3 and antiviral responses and have emphasized the role and need for extensive research.[25] Cellular damage due to RNA viruses results in the cytosolic DNA, which causes activation of the IFN genes like STING by phosphorylation mechanism. There appears to be increased response and activation of Type I IFN and inflammasome.[55]

Table 2. Few systematic effects of COVID-19.[4, 34-42]

Cardiovascular	Hypoxia resulting in vasodilatation poses the risk of vessel rupture and plaque formation, dysregulation of blood pressure control, hypotension, myocarditis, vasculitis, arrhythmia, and drugs enhancing ACE 2 increases the risk of COVID-19
Renal	Kidney injury, fluid, electrolyte imbalance, renal perfusion decline, hematuria, and proteinuria
Hepatobiliary	Hepatocyte injury due to hypoxia and ischemia, drug induced hepatic injury
Gastro-intestinal tract	inflammatory response and negative effect on the gut microbiota
Neurological	Sleep disturbances, fatigue, stress, anxiety, depression, the risk for encephalopathy, stroke, seizures, neuro-cognitive and autonomic dysfunctions, the decline in metabolic functions due to long-term effects, post-traumatic stress, and neuropathy
Hematological	Endothelial dysfunction resulting in pro-coagulant cascade
Skin	They are skin lesions like erythematous, vesicular, and macula widespread rashes
Special senses	Decreased or loss of taste and smell sensation, risk of retinal hemorrhages, cotton wool spots, central retinal vein occlusion, optic neuritis, third and sixth nerve paralysis, chemosis, and hemorrhagic conjunctivitis
Endocrine	Risk of obesity, issues with sugar control, ketoacidosis, hypoglycemia, dyslipidemia
Reproductive	Testicular inflammation, deterioration of sperm quality, adverse effects of steroids and interferons on the reproductive system, the role of coronavirus on the reproductive system and hypothalamic-pituitary-gonadal axis requires research and evaluation, oxidative stress-induced ovarian dysfunction, pre-eclampsia, intrauterine growth of the fetus is effected, preterm labor and miscarriages
Musculo skeletal	Myalgia, musculoskeletal pain, arthralgia, reactive arthritis , osteo and rheumatoid arthritis, sarcopenia in geriatric group

The respiratory system, especially the alveolar epithelium, and macrophages, prevents the over-activation of the innate immune system. There is a role of balance between pro and anti-inflammatory cytokines to maintain homeostasis. Reportedly, an increase in the levels of pro-inflammatory cytokines is associated with acute lung injury in patients with SARS-COV. In a cytokine storm, the inflammation spills into the systemic circulation resulting in systemic sepsis. TNF αand IL 1 has been shown to enhance the production of IL 6. Anti-inflammatory cytokines (TGF β and IL 10) suppress the hyper inflammation. Similarly, cytokines produced by TH1 and TH2 cells act in cohesion to suppress the activation of others. This homeostasis appears to prevent the cytokine storm.[56] However, pro and anti-inflammatory effects appear to be a two-edged sword. Reports are suggestive that the phase of the initial storm is followed by a phase commonly referred to as immune paralysis, which occurs in response to immune systems counter inflammatory mechanisms like an increase in IL 10. The immune paralysis stage, if not resolved, could also lead to death, as is true with the storm phase. Earlier reports suggest the role of excessive inflammatory responses in causing lung damage in influenza infections and immune protection provided by interferons.[57] Suppression of the host innate immune response appears to be a major mechanism by RNA viruses implicated in lung pathology.[58] NSP of Corona Virus has been documented to alter and downregulate the innate immunity of the infected. The excessive production of cytokines may occur in response to the alteration in the antigen presentation.[58,59] Patients with COVID-19 are screened for hyperinflammation. The battery of tests includes ESR, thrombocyte counts, serum ferritin, and H score. The purpose is to identify the patients in whom immune suppression could result in a favorable outcome.[60] The severity and extent of the cytokine storm are expected to correlate with the extent of the tissue damage.[61] COVID-19 has been shown to increase the production of TH2, which in turn decreases the production of IL10 and IL4. Similarly, lymphocyte release is increased due to an increase in the platelet-induced platelet 4 inhibitory influence on agglutinin A. Recent studies suggest that Platelet to Lymphocyte Ratio (PLR) is an important indicator of the severity of the diseases and also the duration of stay and prognosis. The higher the PLR greater its severity. There appears to be a relation between the severity of cytokine storms and the PLR.[62]

Sequel, post recovery and long term effects of the COVID -19

Symptoms may persist in COVID-19 patients even after recovery. The study results from Wuhan, China, showed that approximately 50% of patients had deterioration in their physical health and complained of fatigue and myalgia even after three months of discharge from the hospital. However, respiratory-related problems showed early improvement, but the cough persisted. Patients also had tachycardia, and seven out of the 538 surveyed telephonically in the study complained of chest pain. Socio-economic and psychological impacts after discharge and recovery included isolation, economic constraints, stress, and insomnia. Gender-based variations were also reported, with females complaining of fall of hair.[63]

Coronavirus can enter the Central Nervous System (CNS) through a variety of routes. It can be through the fifth cranial nerve innervating the nasal cavities or through sensory fibers of the tenth nerve innervating the respiratory tract. NF Kв and hypoxia-inducible factor expression in response to hypoxia triggers inflammation and is the key to the neuropsychiatric manifestations of COVID-19. Another important consideration seems to be the age. Major depressive disorders and inflammation appear to increase with advancing age.

On the other hand, there seems to be a correlation between cytokines and psychiatric illnesses. Research has shown a correlation between motor inhibition and apathy with IL2 and TNF α and between suicidal tendencies and anhedonia and IL6. The obsessive-compulsive disorder also correlates with IL1, 6, and TNF α. Moreover, seizures risk increases with the increase in IL1 and IL6. These cytokines are elevated in COVID-19. The stress caused to the imbalance between the inflammatory (IL1, 6, IFN ϒ, TNF α) and anti-inflammatory (IL 10, TGF β) cytokines also play an essential role in the pathophysiology of bipolar illness. Post-traumatic stress disorder is another area of concern in COVID-19. Studies have shown a correlation between enhanced levels of IL 1, 6, TNF α, and IL 10 with PTSD.[64]

ACE 2 receptors are widely expressed in the cerebellum, cortex, hippocampus, and spinal cord, and weak expression of TMPRSS2. ACE 2 and TMPRSS2 are expressed in the olfactory epithelium as well. Both play a role in virus binding and entry, and resultant hypoxia, inflammation, and thrombosis are thought to play essential roles in the neuropsychiatric effects. Increased Activated Partial Thromboplastin Time (APTT), D dimer, and fibrinogen result in coagulation defects and subsequent ischemia in small vessels of the brain and lung.[65] Resultant inflammation enables the virus to pass the blood-brain barrier. At the same time, the antegrade and retrograde axonal transport helps the viral movement. The binding of the virus to ACE 2 receptors on the surface of the macrophages also helps the virus to invade the CNS for further multiplication. The mitochondrial dysfunction and replication of the viral RNA resulting in oxidative stress and calcium influx, ultimately leading to neuronal apoptosis and necrosis, also play a role in the long-term neurological features of COVID-19. ACE 2 is expressed in both GABAergic and glutamatergic neurons, producing excite-toxicity following the infection. Inflammation and potential demyelinating effects of SARS-COV2 result in symptoms mimicking neurodegenerative diseases.[66] Both short and long terms effects in the form of delirium and post-traumatic stress and depression are expected to occur in patients with COVID-19.[67]

Another area of importance is the vulnerability of developing fetuses in COVID-19 mothers. Placenta has an ACE 2 receptor, but varying reports regarding transmission to the fetus have been suggested. Both positive and negative results of RT-PCR have been reported. In utero, the production of IgM is reported in response to infection. Inflammatory cytokines produced in the mother get transferred through the placenta to the developing fetus and pose risks. Placental hypoxia also poses a severe challenge to developing fetus in utero. The presence of risk factors like low Red Blood Cell (RBC) count, low hemoglobin, low iron, and diabetes in the mother may also have deleterious effects on the developing fetus due to the mother's vulnerability to COVID-19 infection. [65]

Decrease in the diffusion capacity of the lung, lower FEV1, FVC, and TLC, and increase in FEV1/FVC, thereby reflecting restrictive patterns, ventilation-perfusion mismatch owing to airway involvement due to primary vascular disease, vasoconstriction, and distal airway abnormalities have been argued and found in studies.[68] Lung fibrosis is another complication associated with COVID-19, and the mechanism leading to it is depicted in Figure 3 (adapted).[69]

SARS 2 specific antibodies and neutralizing antibodies have been reported in patients following recovery from COVID-19. Another area of attention is the role of NK cells. NK is richly present in the lungs, providing immunity against viral infections and affecting adaptive T-cell responses. Studies have shown varying

levels of NK cells in patients with moderate and severe infections. Low and high levels have been reported in peripheral blood and lung fluid on lavage, respectively, primarily due to increased expression of attractants like CCL4, 9, 10, 11, 3, and 3 L1 in the lungs of COVID-19 patients. A detailed analysis has shown that the functional phenotype of NK cells was present despite the overall decline in count in peripheral blood. Phenotype studies revealed that NK cells expressed high levels of HLA-DR, CD25, granzyme B, Tim 3, and Ksp 37. Adaptive immune response phenotype NKG2C+CD57+ NK of NK cells persisted in severely ill patients. The cells can identify the target via KG2C directly recognizing HLA-E, which is reportedly increased in alveolar lavage fluid in lungs and stromal cells.[70]

COVID-19 post-recovery peri myocarditis has been reported; thus, patients were advised to restrain themselves from strenuous exercise. Neuro–psychiatric effects in the form of mania, depression, catatonia, and cerebrovascular events have been reported. Of the effects of the Coronavirus on ACE 2 receptors in the brain and lungs, cardio-pulmonary events like emboli and coagulation abnormalities like clots in vessels, lungs, and brain were also reported. Adverse drug effects of steroid use, like necrosis of the head of the long bone femur, have been reported in studies. One of the consequences of the pandemic, which requires much attention, is the decline in patients reporting to hospitals during the pandemic and, subsequently sudden surge in patients presenting with arrhythmias, CHF and Acute Kidney Injury (AKI), thereby indicating the complicated co-morbidities. Similarly, screening of health status and detection of illnesses like cancers got affected due to the sudden pandemic. Stress-induced upregulation of systemic inflammation and related catecholamine-induced vasoconstriction and ischemia of the heart were also reported in COVID-19 patients. Pre-existing conditions like diabetes, obesity, and myalgias resulted in poor prognosis and death.[71, 72] Destruction of beta cells is one possible effect of the SRS-CoV virus due to increased TNF α, IFNϒ, Monocyte chemoattractant protein 1, and IL 1β. Glycoprotein fetuin-A plays a role in reducing insulin sensitivity and is enhanced by COVID-19. Hypokalemia resulting due to effects of COVID-19 on ACE Receptors, a decrease in the degradation of ATII, and a subsequent increase in aldosterone, negatively influences glucose regulation in COVID-19 patients with pre-existing diabetes. Reports suggest increased levels of ferritin, CRP, d dimers, and IL 6 in pre-existing diabetics and thus may worsen the prognosis.[47]

COVID-19 also posed a severe challenge in terms of psychosocial impact. Studies have shown that the younger age group, from 18 years to mid-thirties, had more psychological impacts manifested in anxiety, depression, and personality changes than the

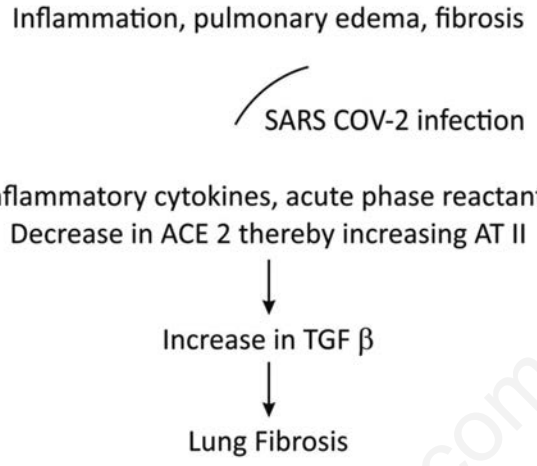

Figure 3. Mechanism of lung fibrosis in COVID-19.

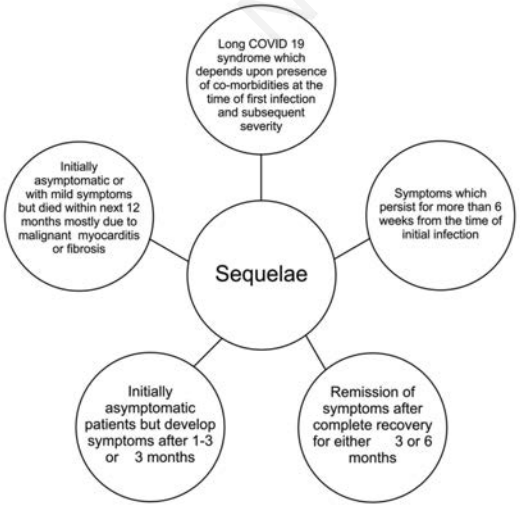

Figure 4. Sequel of COVID-19.

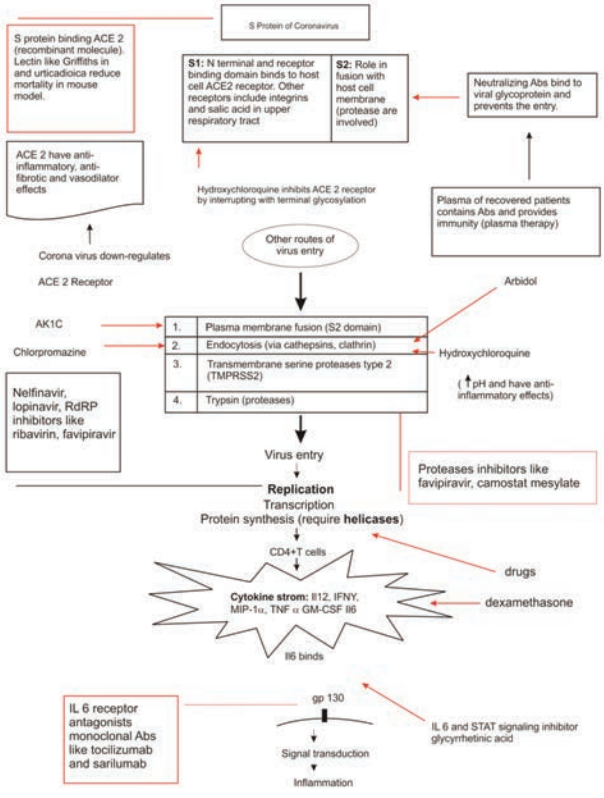

Figure 5. Treatment strategies of COVID-19.

older age group. Other strata affected were those having poor wages, low socioeconomic status, and smokers.[73] Various sequels of COVID-19 are depicted in Figure 4 (adapted).[74]

Possible insights into fungal infections associated with COVID-19

It has been proposed that hypoxia causes a metabolism shift from carbohydrates to fats in fungal species like mucor, thereby causing the fungus to utilize the host serum lipid as an extracellular nutrient. This explains specific lesions in the face wherein the sebaceous glands are abundant. Moreover, opportunistic fungal infections are expected in patients on steroids and those with associated co-morbid immune debilitating conditions.[75] A study has reported that approximately 80-97% of COVID-19 patients with mucormycosis had diabetes, and around 88% were on steroids. Glucocorticoids cause immune suppression by down-regulating the pro-inflammatory cytokines like IL-6, IL-8, IL-12, and TNF-α. Another possible contributory factor was the excess use of zinc, enhancing fungus growth.[76] Virus-induced mucociliary clearance defect, epithelial damage, and immune cell dysfunction, particularly T and B cells and natural killer cells, also aid infection by other pathogens. Drugs like tocilizumab used to prevent IL-6 storm in COVID-19 patients can reduce the clearance of microbes and could be one of the possible reasons for fungal infection.[77]

Conclusions

The etiological and clinical profile of COVID-19, macro and micro effects, and molecular mechanisms of the pathogenesis will help add to the literature, better understand COVID, and add to the

Table 3. Therapeutics of COVID-19.

Treatment	Reason/effect
Thalidomide[78]	Decreases the TNF α and enhances cell-mediated immunity
Natural Killer cells[79]	Enhances immunity
Anakinra and emapalumab and LMWH[80]	IL 1 receptor antagonist and IFN γ inhibitor cause reduction in hyper inflammation and respiratory distress; LMWH effective in sepsis induced coagulopathy and elevated D dimers
Bevacizumab[81]	Helps reduce the pulmonary edema by inhibiting the VEGF
Valporic acid[82]	Early use may counter inflammation and lung injury; it has anti-thrombotic and anti-platelet effects also
JANUS kinases and numb-associated kinase inhibitors[83,84]	Prevent the endocytosis-mediated entry of the virus into the host cell and also has anti-cytokine effects
Mesechymal stem cells transplant[85]	These lack the TMPRSS2 and ACE2 gene expression, which is vital for viral activity; increases the expression of IFN -1 and indoleamine-2,3-dioxygenase
Melatonin[86]	It improves immunity, prevents the oxidant-antioxidant imbalance, *i.e.*, oxidative stress, and has anti-inflammatory roles
Tissue plasminogen inhibitors[87]	Fibrinolytic and thus have potential role in the treatment of the coagulopathy associated with COVID-19 infection
Artificial Intelligence and machine learning approach88 other lung diseases	Play a role in monitoring and critically evaluating the trials and are also valuable for optimizing the treatment protocols; helpful in differentiating the X-raay patterns of COVID-19 from community-acquired pneumonia and
Nanotechnology[89]	Use of nanotechnology as therapeutics and diagnostics, or as immunomodulator
Basic health and hygiene[90]	Hand hygiene, nutrition, regular disinfection, flushing of toilet seats
Probiotics like bifidobacteria or lactobacillus[91,92]	Increase the antigen presenting cells, NK cells, T and B cells, and Type 1 interferons in the lungs, which reduces/clears the viremia and prevents complications and damage to the lungs; adaptive immunity by increasing the cytokines like IL 10; immunostimulatory role: activation of TH1, TH2 and NK cells via IL 12; immunoregulatory role: enhances adaptive immunity by TH2, B cell monocytes, and dendritic cell activation of IL10 and Tregs; pho phoinositide 1 kinase is activated due to toll-like receptor 1 and 3 signaling, which in turn leads to the inactivation of the glycogen synthase 3 β kinase resulting in anti-inflammatory gene expression via CAMP response element binding protein
Fibre rich diet[93]	Acted upon by the gut flora and subsequently short chain fatty acids are formed; there is upregulation of the anti inflammatory pathways, enhanced pathogen killing by reactive oxygen species, and increased phagocytosis actions
Zinc94	Inhibitory to RNA dependant RNA polymerase activity. Inhibitory to viral proteases and disrupts viral infection, attachment and coating; excessive use should be avoided to prevent toxicity
Balance healthy nutritious diet rich in vitamins and minerals along with proper sleep[95,96]	Avoid saturated fats, red meat, carbonated beverages (as they enhance ACTH via catecholamines). Include fresh fruits and vegetables and nuts; stay hydrated and avoid too much salt; enhance immune system and provide protection
Vitamin D[91,95]	Inhibitory to production of pro inflammatory cytokines like IL 2 and IFN γ; vitamin D increases the TH2 mediated cytokine production, indirectly reducing the TH1 mediated responses; enhances Treg and thereby inhibiting the inflammation.
Selinexor[97]	Inhibitor of XPO1 plays an essential role in virus replication by mediating the export of viral proteins into the nucleus and cytoplasm of host cell once the virus enters the host; clinical trials are underway
Repiratory involvement[98]	Non-invasive ventilation like continuous positive airway pressure/bilevel positive airway pressure; extracorporeal membrane oxygenation; septic shock: intravenous crystalloids and vasoactive agents; fluid overload is to be avoided; inotropic agents like dobutamine for cardiac improper perfusion and dysfunction

LMWH, Low-Molecular-Weight Heparin; NK, Natural Killer cells; ACTH, Adrenocorticotropic Hormone.

Table 4. Naturopathy in COVID -19 (brief).

Candidate	Effect/ possible role
Glycyrrhizin the active component of the liquorice roots99	Inhibitory to replication of virus
Flavanoid baicalin from *Radix Scutellaria*[84]	Exhibits in vitro anti viral activity
Diarylheptanoids from *Alnus Japonica* bark[84]	Proteases inhibitor in Coronavirus
Echinacea purpurea[100,101]	It prevents oxidative stress, has an immunomodulator effect, and is cardio and neuroprotective; it increases the production of microbiota and also activates PPAR ; the extract of the root is shown to have anti–inflammatory effects due to its ability to inhibit the expression of cell adhesion molecules, platelet-activating receptor factor, and fibronectin and is postulated to increase the release of the cytokine by macrophages that have none or deficient ACE2 receptors and thus help them to phagocytize the virus; however, cautious use is warranted as t hey tend to increase the pro-inflammatory cytokines
Decoction of sunthi (*Zingiber officinale* Roscoe), lavanga (*Syzygium aromaticum*) and maricha (*Piper nigrum*)[102]	It improves adaptive immune responses and acts as a decongestant, and reduces hyper-inflammatory responses
Arsenicum album 30, *Tinospora cordifolia, Andrograhis paniculata, Ydonia oblonga, Zizyphus jujube and Cordia myxa*[102]	Varying effects like antipyretic lowers oxidative stress, decongestant, effective in cough and cold, anti-viral and anti-allergic, and immunomodulatory actions
Stephania tetrandra or Menispermaceae[103]	Compunds bis-benzylisoquinoline alkaloids namely fangchinoline, tetrandrine and cepharanthine are reportedly inhibitory to protein expression and replication of corona virus in human host
Curcuma longa[101]	Inhibited ATII receptor and thus helps reduce blood pressure; potentially valuable for COVID-19 patients with hypertension as co-morbidity; it also has an anti-inflammatory role; however, cautious use and more data are required for its safety as it increases ACE2 and thus predisposes to more severe COVID-19 infection; inhibitory to pro-inflammatory cytokines like IL1, 6, TNFα . ACE 2 enzyme activation property warrants cautious use
Thymoquinone from *Nigella Sativa*[104]	Interferes with the binding of SARS-COV 2 to HSPA5 substrate binding domain B
Betulinic acid a pentacyclic triterpenoid which was extracted from the bark of white *Betula alba* var. pubescens tree[105]	Protease inhibitor
Glycyrrhiza glabra root rich in flavonoids; similarly there are other herbal formulations with potent and potential role as therapeutics in COVID-19102	Interferes with the ability of the virus to attach to host cells in early stages
Java turmeric or Curcuma xanthorrhiza[101,106]	Anti-inflammatory and reduces the production of CRP, IL 1 β, and TNF α; the active compound is xanthorrhizol
Jararacussu pit viper venom amino acids or peptide[107]	Animal experiments (on monkeys) have shown that the molecule attaches to the enzyme PLPro of the virus and inhibits its reproduction
Ashwagandha (*Withania somnifera*)[108]	*In silico* studies have shown inhibitory effects on RNA polymerase

available literature. Gender-wise differences also assume importance and require extensive research. The presence and absence of co-morbidities assume significance in light of the literature suggesting a higher risk of contracting the infection and a higher chance of poor prognosis and mortality. The emphasis is also needed on screening for noncommunicable diseases to identify at-risk populations. The treatment and management protocol kept changing as the pandemic evolved, and thus there is a need to do retrospective and prospective research related to the therapeutics of COVID-19 (Tables 3 and 4, Figure 5). Many drugs used earlier may result in serious side effects. Thus, it is essential to follow up with the patients treated for COVID, which will help in early identification and, thus, treatment of drug-induced side effects. Promotion of primary prevention by emphasizing health, hygiene, and nutrition is required.

Similarly, research to provide evidence-based support for using naturopathy as a treatment for COVID-19 is also essential. The impact of COVID-19 on noncommunicable diseases is also a matter of concern and requires urgent attention. Research on the psychosocial and mental health impacts of COVID is required to be addressed. Appropriate measures to prevent the burden on healthcare facilities due to the long-term effects of COVID are required. Importantly, appropriate behavior and measures to break the transmission need to be implemented and followed strictly, irrespective of whether vaccination has occurred or not.

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