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# The interplay between inflammatory pathways and COVID-19: A critical review on pathogenesis and therapeutic options

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## ABSTRACT

COVID-19, caused by SARS-CoV-2, emerged as the deadliest outbreak that has now become a serious health issue to mankind. Activation of inflammatory signaling pathways and cytokine storm are crucial factors that lead to acute respiratory distress syndrome (ARDS) in COVID-19 patients. Excessive secretion of pro-inflammatory cytokines and chemokines leads to the dysregulation of the innate immune system. The cytokine storm attracts many inflammatory cells that infiltrate into the lung tissues and ultimately cause immune damage. In addition to the dysregulation of the immune system, dysfunction of the renin-angiotensin system (RAS) due to the down-regulation of ACE2 is also associated with the mortality of COVID-19 patients. Both the mechanisms are directly or indirectly associated with cytokine storm that promotes vascular hyperpermeability, vascular edema leading to hypercoagulation and hence multiorgan damage. As of now, there is no specific treatment available for COVID-19, but scientists have purposed several treatment options including cytokine inhibitors, JAK inhibitors, immunomodulators, plasma therapy, etc. In this article, we have provided the detailed mechanism of occurrence of SARS-CoV-2 induced inflammatory storm and its connection with the pre-existing inflammatory conditions. Possible treatment options to cope up with the severe clinical manifestations of COVID-19 are also discussed.

## 1. Introduction

A sudden outbreak of coronavirus disease 2019 (COVID-19) has become a global health threat since it first emerged from Wuhan city, China in December 2019 [1]. The causative pathogen of this disease was formerly called 2019 novel coronavirus (2019-nCoV), but later it has been officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO). On January 30, 2020, the WHO Director-General declared this pandemic a Public Health Emergency of International Concern (PHEIC), indicating that it may cause serious risks to multiple countries and urges a coordinated global response to curtail its effect on global health and economy [2]. Currently, more than 185 countries are infected with COVID-19 and cases are still increasing at an alarming rate. At the time of writing, about 1,49,26,111 people have been infected with SARS-CoV-2, of which 6,15,070 were dead, and 89,59,152 were cured. Many patients with COVID-19 become seriously ill, developing life-threatening complications with a mortality rate of about 6% [3]. The elderly and individuals with pre-existing medical health conditions like diabetes,

cardiovascular disease, cancer, auto-immune disorders, etc are more prone to SARS-CoV-2 infection [4]. The diagnosis is made through nasopharyngeal or oropharyngeal swab, allowing the virus isolation and confirms the infection. The clinical manifestations of COVID-19 range from asymptomatic to severe. The symptoms appear after an incubation period of 2–14 days. The clinical signs appearing at the early stage of infection are fever, fatigue, dry cough, myalgia, anorexia, dyspnea, rhinorrhea, arthralgia, ageusia, and anosmia [5]. The rapid spread of COVID-19 makes its prevention and control extremely unmanageable. Several meticulous measures are being implemented to limit SARS-CoV-2 propagation [6]. SARS-CoV-2 belongs to the beta family of coronaviruses previously reported in the literature [7]. This virus can propagate at a faster rate and has a high index of person to person transmission than the other coronaviruses of the same clad, therefore, isolation of the patient is necessary. SARS-CoV-2 has a high reproduction number ( $R_0 = 2.2$ ) i.e., a high extent of transmission as compared to the previously reported coronavirus SARS-CoV. Moreover, SARS-CoV-2 binds to the functional receptor angiotensin-converting enzyme 2 (ACE2) with 10–20 folds more affinity than SARS-CoV [8,9]. The

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pathogenesis of SARS-CoV-2 infection involves virus entry into the host, binding with the host cell receptor, and viral replication. The virus enters the targeted cells through the ACE2 receptor, which is a membrane protein expressed in the lungs, kidney, heart, liver, testes, and intestine. The spike protein (S-protein) present on the surface of the pathogen binds with the ACE2 receptor with the help of the cellular protease TMPRSS2 (transmembrane protease serine 2) and another protein clathrin by endocytosis [2,10]. On viral attack, the immune system upregulates to eliminate the virus from the body but the body then fails to downregulate it; this dysregulation of the immune system ultimately leads to the hyperinflammatory stage of COVID-19 called cytokine storm [11]. Excessive secretion of pro-inflammatory cytokines (Interleukins; IL-1 $\beta$ , IL-2R, IL-6, interferon; IFN- $\gamma$ , tumor necrosis factor; TNF- $\alpha$ ), chemokines (C-motif chemokine ligands; CCL-2, CCL-3, CCL-10) and other inflammatory factors progress uncontrolled systemic inflammation. High levels of IL-1 $\beta$ , IL-6 and TNF- $\alpha$  are mainly associated with the severity of the disease. Inflammatory cells cause the recruitment of immune cells which accelerates the inflammatory response. Cytokine storm worsens the infection and can lead to ARDS or multiorgan damage that leads to death. In severe cases, the patient may develop lymphopenia, ground-glass infiltrates, hyperferritinemia, elevated lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and IL-6. These laboratory findings are a close determinant of cytokine storm in the body [5,12]. Studies suggest various complications associated with COVID-19: cardiovascular complications, neurological, thrombotic, hematological, rhabdomyolysis, etc. and results probably due to dysfunctioned immune system [13–16]. Moreover, the dysregulated RAS system also plays a critical role in the pathogenesis of SARS-CoV-2. Systemic hypotension, hypokalemia and lung injury progressed through downregulation of ACE2 and increased stimulation of angiotensin II receptor1 (AT1R) results in disease deterioration [17]. Scientists are struggling to find a specific vaccine or treatment for COVID-19. Various medications have been purposed to provide valuable treatment. These include cytokine inhibitors: IL-1 $\beta$  antagonist (Anakinra), IL-6 inhibitor (Tocilizumab), IL-12/23 inhibitor (Ustekinumab), IL-17A inhibitor (brodalumab), TNF- $\alpha$  inhibitor (adalimumab), IFN- $\alpha$  inhibitors (Sifalimumab), antivirals (arbidol, lopinavir, ritonavir, remdesivir), Janus kinase (JAK) inhibitors (Baricitinib), immunomodulators (chloroquine, hydroxychloroquine, corticosteroids, vitamin therapy) have been listed in the guidelines for the prevention, diagnosis, and treatment of COVID-19 [1]. The current review provides detailed knowledge about the inflammatory pathways that are interconnected with the pathology of COVID-19 and how the over-expression of these pathways led to the mortality in COVID-19 patients. The therapeutic options that may act as a potential treatment for the inflammatory conditions associated with COVID-19 are also discussed.

## 2. Activation of inflammatory pathways and cytokine storm in COVID-19

Coronavirus enters the human body through various transferrable modes like respiratory droplets, direct/indirect contact, fecal-oral transmission, and others. The virus first enters the upper respiratory tract (nasal, pharynx) in the initial days of infection where ACE2 acts as a keyhole for the entry of pathogens. After entering the host cell, the virus releases its RNA genome inside the nucleus and the replication starts in the lower respiratory tract that leads to viremia. This condition can be easily cured because the patients are asymptomatic during this stage [12]. At this stage, the dendritic cells, macrophages, and respiratory epithelial cells secrete cytokines and chemokines to produce immune responses, to clear out the pathogen from the body. However, in further stages, the severity of infection increases as soon as the inflammatory pathways get activated and lead to cytokine storm or cytokine storm syndrome (CSS) [18]. All the three stages of severity of SARS-CoV-2 infection owing to the activation of inflammatory pathways are displayed in Fig. 1.

### 2.1. Inflammatory signaling in COVID-19

Mostly, inflammatory pathways including interleukin-6/Janus kinase/STAT (IL-6/JAK/STAT) signaling pathway [19,20], interferon (IFN) cell signaling pathway [21,22], tumor necrosis factor- $\alpha$ -nuclear factor-kappa (TNF $\alpha$ -NF- $\kappa$ B) pathway [23], toll-like receptor (TLR) pathway [24,25], T-cell receptor (TCR) pathway [20,26], JAK-STAT pathway [27,28], etc are activated after SARS-CoV-2 infection. Briefly, low levels of the antiviral IFNs and high levels of proinflammatory cytokines (IL-1 $\beta$ , IL-2R, IL-6, IL-7, IL-8, IL-17 and TNF- $\alpha$ ) and chemokines (CCL-2, CCL-3, CCL-5, CCL-7, CXCL-10) are produced by various immunological cells. These secretions from pro-inflammatory cells lead to an uncontrolled inflammatory response that plays a key role in the pathogenesis of COVID-19 and worsens the infection [11]. Here, in the below sections, we provide a brief note on different inflammatory pathways that are mainly involved in the pathogenesis of COVID-19. The schematic representation of the same is displayed in Fig. 2.

#### 2.1.1. Interleukin-6/Janus kinase/STAT (IL-6/JAK/STAT)

IL-6 is mainly produced by immune cells such as B lymphocytes, T lymphocytes, macrophages, dendritic cells, monocytes, mast cells and many non-lymphocytes, such as fibroblast and endothelial cells. Factors like TNF- $\alpha$  and TLRs mainly contribute to the secretion and activation of IL-6 [29]. It is a type of pro-inflammatory cytokine that release at a high level in critical patients of COVID-19 [30]. A recent study published by Prof. Magro in the journal Cytokine evidenced the role of the IL-6 pathway in the pathology of COVID-19 [19]. Literature reports

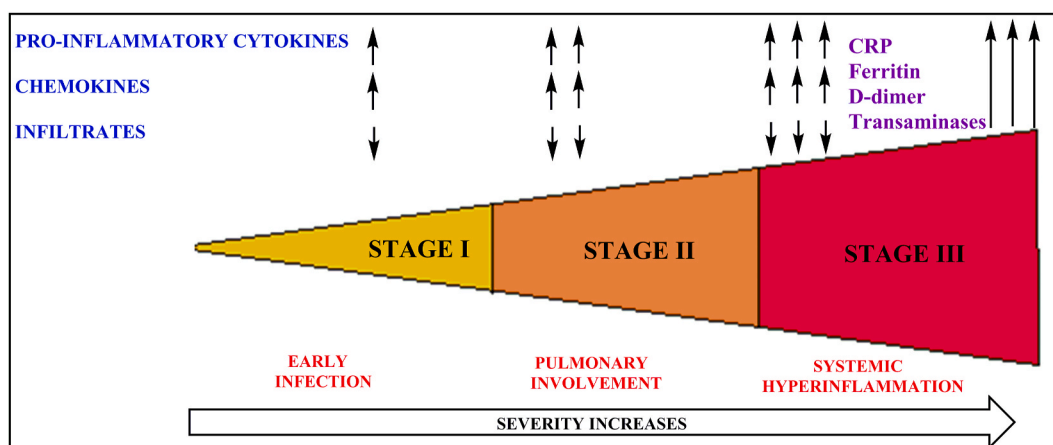


Fig. 1. Three stages of increased COVID-19 severity due to the activation of inflammatory pathways.

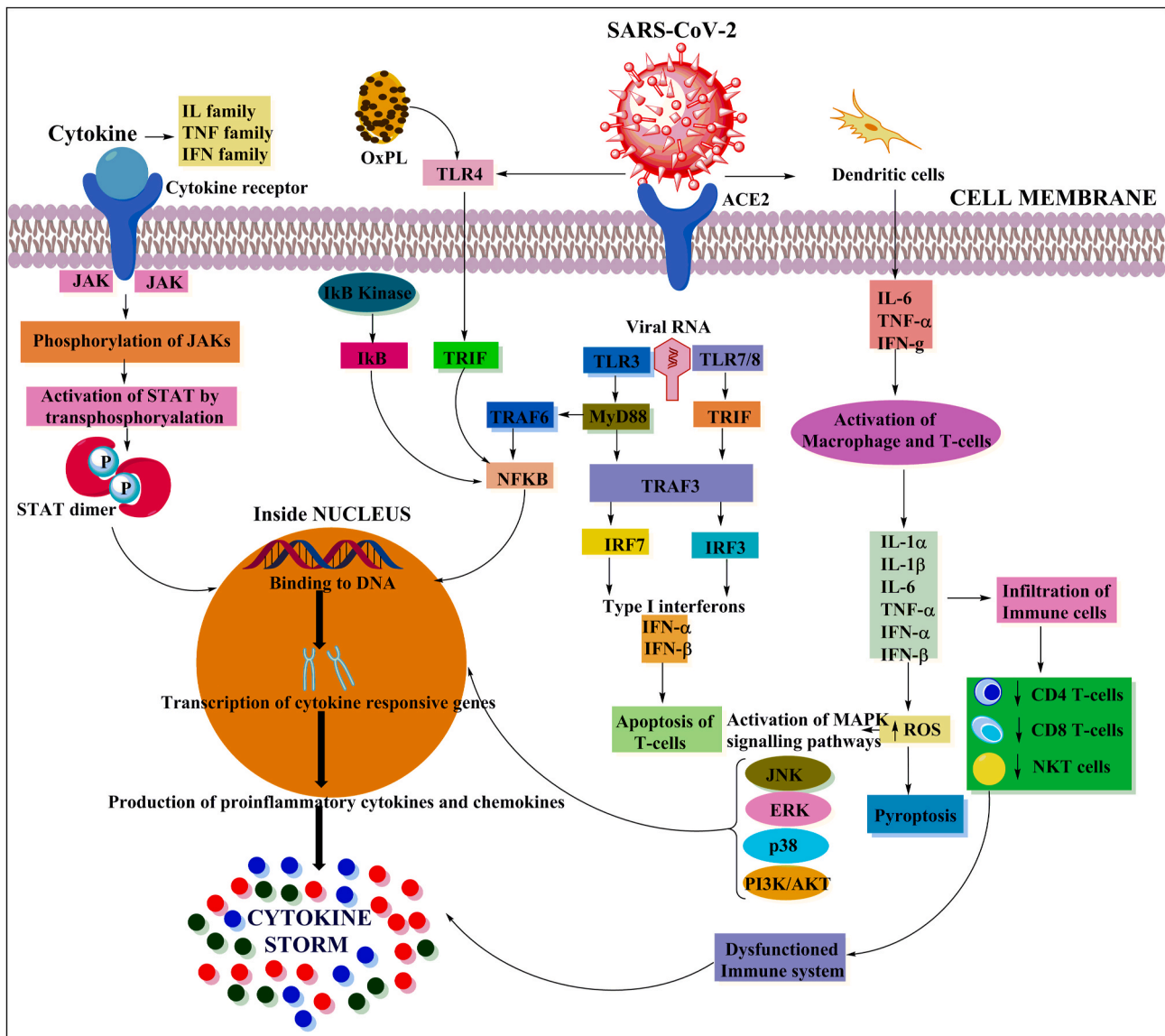


Fig. 2. Inflammatory signaling cascade activated in COVID-19.

suggest that IL-6 signal transduction is induced by binding to  $\alpha$ -interleukin-6 receptor ( $\alpha$ -IL-6R) and this complex, in turn, activates the dimerization of  $\beta$ -receptor gp130 [31]. The dimerized  $\beta$ -receptor gp130 then initiates the signal transduction by activating JAK/STAT kinase pathway. This way, IL-6 and JAK/STAT pathways are interconnected in COVID-19 that produce cytokine storm. Owing to the important role of IL-6 in the JAK/STAT signaling pathway and cytokine storm, researchers suggest IL-6 inhibitor tocilizumab and JAK inhibitors ruxolitinib and baricitinib as possible therapies for COVID-19 patients suffering from ARDS [32].

### 2.1.2. Interferon (IFN) cell signaling pathway

IFN is one of the most powerful innate immune responses to prevent viral replication during the early phases of infection [33]. IFNs are involved in signaling transduction through the JAK-STAT signaling pathway (mainly JAK1 and JAK2) that cause the upregulation of various genes that are controlled by IFN to kill the viruses in host cells [28]. Since most of the viruses have developed the counter strategies to neutralize the effect of IFNs mediated signaling, this defense mechanism seems to be a very crucial determinants of viral infection. Recent reports suggest the role of IFNs mediated cell signaling in COVID-19 [34]. In a

recent report by Favalli et al. the use of baricitinib (a selective JAK1 and JAK2 inhibitor) for the impairment of IFN mediated JAK-STAT signaling is recommended to combat the SARS-CoV-2 infection [35].

### 2.1.3. TNF $\alpha$ -NF- $\kappa$ B inflammatory signaling pathway

Cytokine TNF- $\alpha$  is one of the most significant pro-inflammatory cytokines that affect the different aspects of the immune system and regulates various pathological and physiological processes [36]. A most recent study published by Feldmann and group in the journal "The Lancet" suggests the urgent need to start trials of anti-TNF therapy against COVID-19 to reduce cytokine storm [23]. NF- $\kappa$ B light chain enhancer of B cells (NF- $\kappa$ B) is another mechanism associated with cytokine storm. NF- $\kappa$ B dimers are encoded by NF- $\kappa$ B genes and regulate transcription of several crucial proteins of inflammation including TNF $\alpha$  [37]. Since TNF- $\alpha$  induces signaling transduction through NF- $\kappa$ B, TNF $\alpha$ -NF- $\kappa$ B inflammatory signaling pathway can also be considered as a potential target of COVID-19 [38]. NF- $\kappa$ B is a family of transcription factors constitutes five homo and heterodimer proteins: NF- $\kappa$ B1 (p50), NF- $\kappa$ B2 (p52), Rel A (p65), c-Rel and Rel B. NF- $\kappa$ B is involved in various cellular and immune responses such as cell proliferation, apoptosis, and inflammation. Activation of NF- $\kappa$ B signaling pathway leads to the

transcription of cytokines responsive genes [39,40]. Inhibitory proteins including I $\kappa$ B $\alpha$ , I $\kappa$ B $\beta$ , I $\kappa$ B $\gamma$ , I $\kappa$ B $\epsilon$ , Bcl-3, p100, and p105 also mediate the activation of NF $\kappa$ B. Initially NF $\kappa$ B present inside the cytoplasm, after the activation of I $\kappa$ B through phosphorylation via I $\kappa$ B kinase, NF $\kappa$ B activates and translocates to the nucleus where it regulates the transcription of various targeted genes [39,41]. Catanzaro et al. have recently published a report discussing the role of TNF $\alpha$ -NF- $\kappa$ B inflammatory pathway in COVID-19. They suggested that inhibiting these pathways may avoid pulmonary complications in COVID-19 patients [38].

#### 2.1.4. JAK/STAT pathway

Various kinase pathways are involved in the release of cytokines however, the Janus kinase signal transducer and activator transcription (JAK/STAT) pathway is the main pathway involved in COVID-19 [27, 42]. JAK/STAT is a major cytokine signaling pathway, plays a key role in the progression of the cytokine storm. This pathway converts the extracellular signals to transcriptional responses. JAKs are ATP-dependent enzymes bound to cytokine receptors in the cytoplasm constitute four members: JAK1, JAK2, JAK3, and TYK2. The STAT family comprises seven members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. JAKs are drastically involved in cell proliferation and inflammation. Dysregulation in JAK/STAT signaling leads to abnormal immune functions. Attachment of various cytokines to the cytokine receptor activates JAK and causes its phosphorylation. The phosphorylated JAK in turn activates STAT through transphosphorylation. The activated STAT translocates into the cell nucleus where it binds to specific DNA sequences to influence (activate or repress) transcription of target genes (cytokines encoding genes), which regulate different immune responses implicated in cytokine storm. In addition to cytokine signaling, the JAK/STAT pathway is also involved in angiotensin II and AT1R signaling. Angiotensin II amplifies the production of pro-inflammatory cytokines and recruitment of immune cells at the site of infection. AT1R mediates JAK2 activation and phosphorylation which in turn phosphorylates one of the STAT and thus carries out the transcription of targeted genes. The inhibition of JAK plays a vital role in reducing the cytokine release [42]. As per a recent report by Bagca et al. ruxolitinib can be recommended for the inhibition of JAK/STAT pathway to combat COVID-19 [27].

#### 2.1.5. Toll-like receptor (TLR) pathway

The TLR, especially TLR-3, TLR-7 and TLR-8, present on plasmacytoid dendritic cells (pDCs) also recognize SARS-CoV-2 pathogen [43]. Elevated inflammatory cytokines during SARS-CoV-2 infection induce apoptosis of T-cells and reduce the numbers of virus-specific CD4 and CD8 T-cells. SARS-CoV-2 hit the innate immune system through TLR-3, TLR-7 and TLR-8 to infect the host cells [44]. Therefore, the immunomodulators that activate these TLRs are recommended as potential therapeutic options to enhance innate immunity. Imiquimod is an immune-stimulator that activates TLR 7 and can be used to enhance innate and adaptive immunity [24,45]. Moreover, TLR4 plays an important role in the progression of SARS-CoV-2 infection. Here, the high accumulation of oxidized phospholipids (OxPL) in COVID-19 patients promotes the risk of acute lung injury (ALI). OxPL augments the level of cytokines and chemokines production in the lung macrophages via TLR4. Therefore, inhibition of TLR4 can be act as a potential way to prevent ALI. Eritoran is a TLR4 receptor blocker, it has an immunomodulatory action [46].

#### 2.1.6. Antibody-mediated pathway

Antibody-dependent enhancement (ADE) is a phenomenon that is hypothesized to be a reason for disease severity and mortality in SARS-CoV-2 infected patients [47]. It occurs in case the individual has prior exposure to an antigenic epitope like SARS-CoV-2. There are several coronavirus strains have been identified existing antigenic epitope heterogeneity with SARS-CoV-2. ADE exerts a modifying action on the immune system that involves elevated IgG response. ADE is associated

with disease severity as it causes systemic hyper-inflammation ultimately causing cytokine storm. The outlined mechanism behind the modulation of the immune response was found to be anti-spike antibodies. Reports suggest that the dilution of these antibodies may help to counteract ADE in COVID-19 [48]. The main complications associated with ADE are ARDS, myocardial injury, lung and kidney injury and secondary bacterial infections [48]. The SARS-CoV-2 can also enter macrophages via an antibody-mediated pathway and can replicate in these cells. Therefore, macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH) another severe complication of COVID-19 that is associated with ADE. It occurs particularly in systemic Juvenile Idiopathic Arthritis (sJIA). MAS represents a condition of uncontrolled activation and proliferation of T lymphocytes and macrophages. Whenever a pathogen invades inside the host body macrophages rapidly (within 20–30 min) respond to it by phagocytosis. However, uncontrolled activation of macrophages provoked by viruses can lead to cytokine storm and eventually multi-organ failure and death. MAS is associated with increased mortality and delayed viral clearance. Increased serum ferritin level is the hallmark of MAS. IL-6 levels also elevate significantly in hospitalized patients. Hyperferritinemia, elevated H score and IL-6 are some laboratory findings of MAS [49].

#### 2.1.7. Bruton tyrosine kinase (BTK) pathway

Bruton tyrosine kinase (BTK) is a non-receptor tyrosine kinase, encoded by the *BTK* gene in humans. The role of BTK was first illustrated in X-linked agammaglobulinemia XLA (B cell immunodeficiency). BTK plays a significant role in B cell development as it is responsible for the transmission of pre-B cell receptor signals after immunoglobulin heavy chain rearrangement. Besides, it has a role in the activation of mast cells via the high-affinity IgE receptor. BTK controls the signaling and activation of macrophage also. It accounts for TLR-mediated activation of NF- $\kappa$ B during virus infection, as a result of which the production of various inflammatory cytokines and chemokines are triggered. BTK induces the production of IL-6, which plays a vital role in an exacerbated inflammatory response. Furthermore, BTK results in maturation and secretion of IL-1 $\beta$  through the activation of the NLRP3 inflammasome. Dysregulation of BTK-dependent macrophage signaling is integral to the cytokine storm in SARS-CoV-2 infection [50].

#### 2.1.8. Renin-angiotensin system (RAS) pathway

Besides the above-mentioned signaling cascades, many other pathways are also involved in the progression of the cytokine storm in COVID-19 patients, for instance, dysfunction of the rennin angiotensin system (RAS) due to the downregulation of the ACE2 receptor [51]. RAS system has a pivotal role in severe acute lung injury because ACE2 has a crucial role in lung protection. Binding of the S-protein of SAR-CoV-2 with ACE2 downregulates the expression of ACE2 [5]. Since ACE2 catalyzes the degradation of angiotensin II into angiotensin (1–7), the low level of ACE2 increases angiotensin II level which in turn causes AT1R stimulation and angiotensin II receptor 2 (AT2R) inactivation. The main functions of AT1R are aldosterone, vasopressin and ACTH secretion, hypokalemia, sodium reabsorption, inflammation, cell proliferation, and lung injury while on the flip side, AT2R has a lung-protective function. Due to the imbalance between these two, the AT1R dominates the action and results in lung injury. The main biomarker of this imbalance appears to be hypokalemia. Both the cytokine storm and ACE2 downregulation leads to pulmonary vascular hyperpermeability and pulmonary edema, which eventually induce ARDS. Due to increased vascular permeability, blood clot formation occurs (coagulation) which leads to multiorgan damage and ultimately leads to death [17].

## 2.2. Cytokine storm in COVID-19

Cytokines are cell signaling molecules, the term “cytokine” is derived from two words “cyto” means cell and “kinos” means movement. The

massive activation of the immune system leads to a severe complication called cytokine storm or cytokine release syndrome (CRS) involving immense and uncontrolled release of pro-inflammatory cytokines and other inflammatory cells which causes excessive inflammation. Cytokine storm, generated due to the activation of various inflammatory signaling pathways, is reported to be the foremost reason for mortality in COVID-19 patients. After the attack of a pathogen, the activation of immune cells (T-cells, endothelial cells, dendritic cells (DC), macrophages, monocytes, natural killer (NK) cells and cytotoxic lymphocytes) occur. This causes the release of cytokines and chemokines for producing an inflammatory response for the virus clearance [52]. The main cytokines

involved in the development of cytokine storm are IL-1 $\beta$ , IL-6, and TNF- $\alpha$  and are associated with the disease severity. IL-1 $\beta$ , IL-2R, IL-6, and TNF- $\alpha$  are the key contributors to the cytokine storm. Cytokines may perform actions on different cells it may be on the cells that secrete them (autocrine), on the nearby cells (paracrine), and on the distant cells (endocrine) [53]. At the initial stages, the moderate release of cytokines shows a good inflammatory action and acts on the viral cells only but after the over-activation of the immune system, the over-produced cytokines rush to kill the host cells also. The immune response is necessary to fight the infection and get back to normal after combating the pathogen but in some cases, it doesn't get back to normal and cause

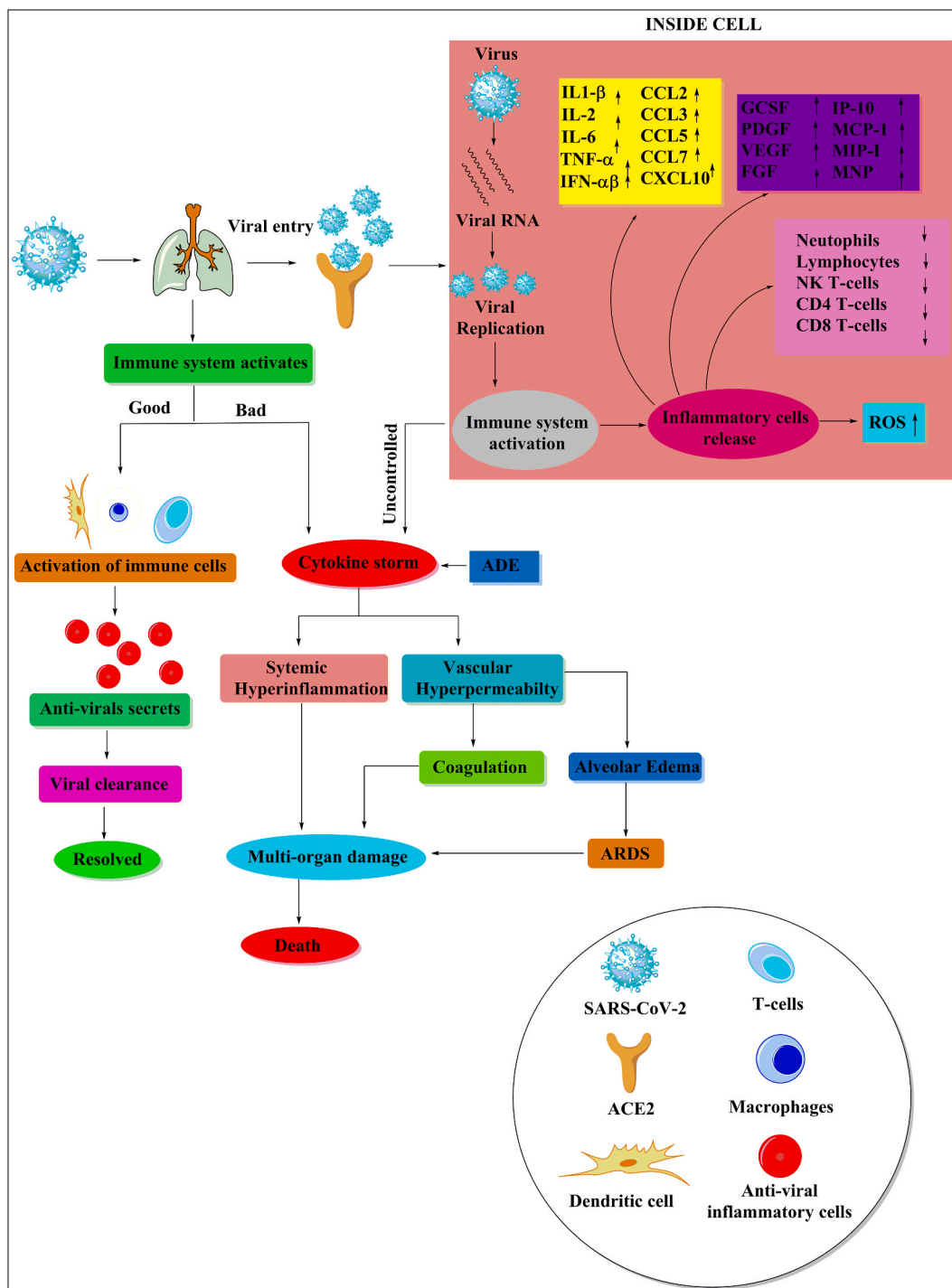


Fig. 3. Role of cytokine storm in COVID-19.

overactivation of the immune system and kindle the inflammatory responses. This is a delicate balance between the good and bad immune system and any imbalance between these lead to the pathological complications [12]. Cytokine storm is often associated with ARDS, hypercoagulation, vascular hyperpermeability and gangrene of extremities [54]. The role of cytokine storm in COVID-19 is shown in Fig. 3.

### 3. Cytokine storm and COVID-19 co-morbidities

As discussed in the previous section, cytokine storm plays an important role in the aggravation of SARS-CoV-2 infection that further leads to co-morbidity in COVID-19 patients. Coagulopathy, thrombosis and pulmonary complications are the most common co-morbidities associated with the COVID-19. IL-1 $\beta$ , IL-2R, IL-6, and TNF- $\alpha$  are the key contributors to cytokine storm. Due to cytokine storm in the body, blood serum level of various inflammatory cells increases. These cells recruit immune cells at the target site and along with this, cytokines moved out of the blood vessel to enter the infected cell. Owing to these cellular events, blood vessel becomes thin and more permeable. The uncontrolled cycle of this process increases the vascular permeability and eventually leads to systemic capillary leakage. Massive leakage of blood plasma into the neighboring cells form a blood clot inside the blood vessel that ultimately give rise to coagulation and cause thrombosis. This results in hypoxia as organs deprive of oxygen leading to failure of one or many organs. Briefly, thrombin stimulates clot formation by converting fibrinogen into fibrin and by activating platelets. It also regulates cellular functions and can aggravate inflammation through PAR-1. The anticoagulant mechanisms that control thrombin generation get impaired and develop micro-thrombosis, disseminated intravascular coagulation (DIC) and multi-organ damage [55].

Similarly, cytokine storm harms alveolar cells and give rise to pulmonary complications. Moreover, as ACE2 is mostly expressed in alveolar cells, bronchial epithelium and vascular endothelium, SARS-CoV-2 infection would result in ARDS and pulmonary/alveolar edema [11]. ARDS occurs due to excess fluid retention in the elastic air sacs (alveoli) of the lungs: alveolar edema. It prevents the lungs from filling with sufficient air. Less oxygen reaches the bloodstream leading to hypoxemia. Organs failed to get enough oxygen which disturbs their normal functioning. ARDS is associated with increased severity of disease and is the leading cause of mortality in COVID-19 patients. Patients with ARDS suffer from severe shortness of breath and/or unable to breathe on their own. Proper mechanical ventilation is required at this stage [5]. Fluid management therapies, antibiotics to prevent secondary infections and other medications are implementing in ARDS [56]. On the other hand, in coagulopathy, antithrombin, anti-coagulator factor Xa, proteinase-activated receptors-1 (PAR-1) antagonists can be potentially valuable to prevent coagulation and venous thromboembolism. A diagram showing the connection between cytokine storm and COVID-19 associated morbidities such as coagulopathy and pulmonary complications is shown in Fig. 4.

### 4. Other strategic players involved in the pathophysiology of COVID-19

#### 4.1. Iron metabolism

Iron metabolism plays a significant role in supporting the innate immune system to fight against attacking microorganisms (bacteria, viruses, or fungi). As a response to viral infections, the innate immune system control iron metabolism. Adequate iron levels within the host cells are required for viral replication. Subsequently, the innate immune

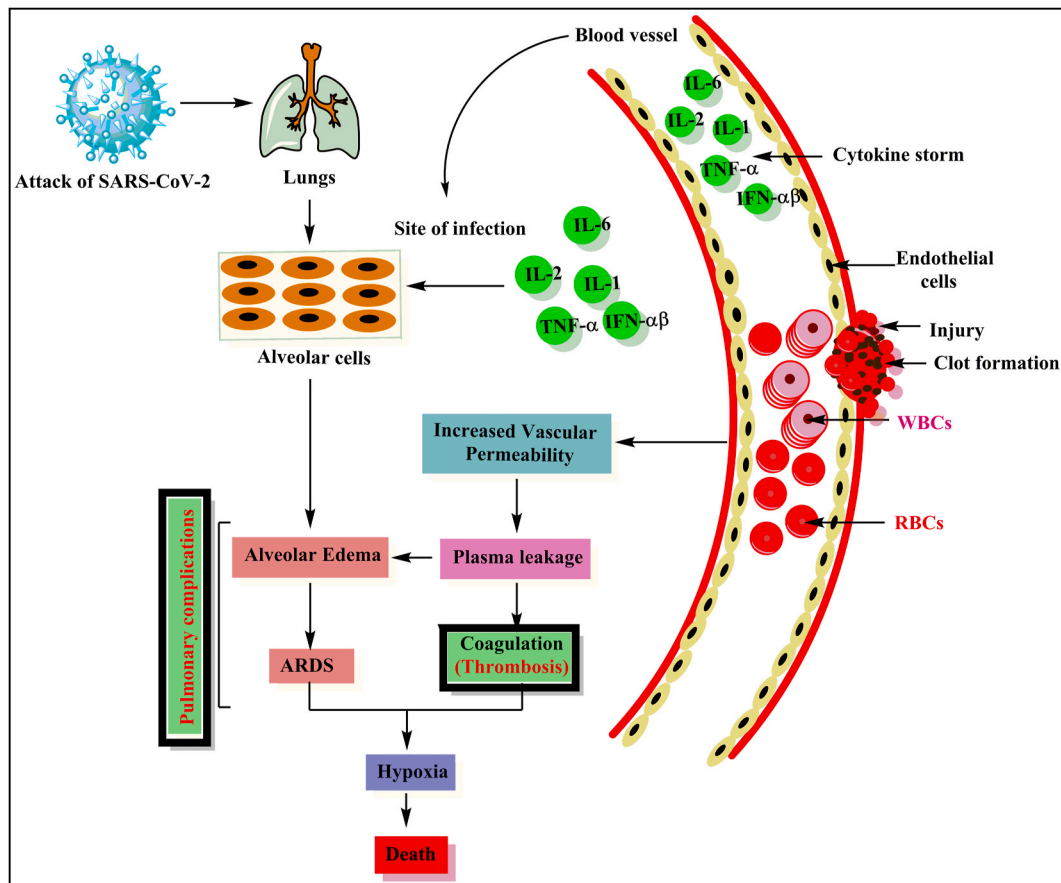


Fig. 4. An interplay of cytokine storm, coagulopathy and pulmonary complications in COVID-19.

system will respond by diminishing the bioavailability of iron to restrict viral replication. Helicases of SARS-CoV-2 require ATP hydrolysis for replication which needs the presence of iron, making it deprive of iron will help in combating the virus. This mechanism would also result in anemia, which, in turn decrease the oxygen delivery to the tissue and may lead to the development of multi-organ failure. There are various biomarkers associated with iron metabolism including haemoglobin, ferritin, hepcidin, transferrin, soluble transferrin receptor, haptoglobin, unsaturated iron-binding capacity, erythropoietin, and prevalence of anemia. Ferritin is the most important component of iron metabolism. It is a shell-like molecule deposit in macrophages. The primary role of ferritin is to store the iron during infections to provide a protective response. Ferritin stores iron in the ferric state ( $\text{Fe}^{3+}$ ) and can store up to 450 iron molecules. Due to decreased cellular efflux of iron, serum concentration of iron decreases, and ferritin increases. This leads to hyperferritinemia, which is a biomarker of cytokine storm. Increased ferritin levels result in the activation of macrophages and secretion of various pro-inflammatory cytokines. H-chain of ferritin plays a vital role in inducing Macrophage activation syndrome. Reports suggest extremely high levels of ferritin (>3000 ng/ml) seem to be associated with increased mortality in a dose-response manner. Additionally, hepcidin, an 84-amino-acid long prepropeptide hormone is also a major regulator of iron metabolism, modifying intracellular and extracellular iron concentration. It performs two important functions: the first one is to store iron into the cell to allow cellular multiplication and DNA and RNA synthesis; the second one is its antimicrobial action by depriving the pathogen of iron for replication [57]. Hepcidin acts by inhibiting the activity of the cellular iron exporter ferroportin (via its internalization and eventual degradation), which is involved in iron transport, thus reduces extracellular iron bioavailability. HAMP (hepcidin antimicrobial protein) is the gene responsible for hepcidin production that may be found predominantly in the liver, but also the brain, lungs, body fat, and other organs. The production of hepcidin seems to be influenced by many factors with a complex up and down-regulation mechanism. The factors that appeared to upregulate the production of hepcidin are Hereditary Hemochromatosis Gene (HFE), Transferrin Receptors (TfR1 and TfR2), TLR4, IL6, STAT, and Bone Morphogenic Protein (BMP). Among the exogenous molecules that induce hepcidin is Metformin and virus (Cov/SARS). Among the exogenous molecules that reduce hepcidin are Vitamin D, Vitamin C, Adenosyl-L-Methionine, chloroquine, tocilizumab, ritonavir, atazanavir and carvedilol, and the endogenous one are Insulin, heparin and erythropoietin. Several symptoms of COVID-19 disease can be attributed to hepcidin action and iron imbalance suggesting that hepcidin is among the several key biomarkers highly involved in the inflammatory cascade in COVID-19 disease [58].

#### 4.2. Ferroptosis

Ferroptosis is a recently identified form of programmed cell death that depends on iron accumulation. Generally, it is iron-dependent non-apoptotic cell death. A high concentration of iron particles accumulated in ferritin contributes to ferroptosis. Ferroptosis results in an irreversible alteration of mitochondrial morphology. Certain studies have revealed that ferroptosis can be triggered by inflammation which in turn may activate innate immune cells that play a key role in controlling inflammation damage, signal transduction, and cell growth [59].

#### 4.3. Mitochondria alteration

Mitochondria is the origin of cellular oxidative homeostasis. Dysregulation in iron metabolism triggers the generation of reactive oxygen species (ROS) and elevates oxidative stress [60]. The increased inflammatory/oxidative stress may lead to mitochondrial dysfunction leading to ferroptosis, platelet damage, and eventually multiple organ damage [61]. Reports suggest intracellular as well as extracellular mitochondria dysfunction is a consequence of COVID-19 infection [62]. The

extracellular mitochondria represent critical mediators specifically platelets mitochondria that may affect blood coagulation, clot, and thrombosis formation. Moreover, a dysfunctional mitochondrion would result in iron accumulation due to its inability to metabolize iron, causing deficient iron sequestration leading to ROS production. Moreover, excess intracellular iron interacts with molecular oxygen, generating ROS through Haber-Weiss and Fenton reactions and reactive nitrogen species (RNS) and reactive sulfur species (RSS). The mitochondria are the core organelle of ROS generation. Increased generation of ROS contributes to intra-mitochondrial and extra-mitochondrial damage resulting in microbiota dysbiosis and platelet dysfunction. Mitochondrial damage results in the release of contents including proteins, lipids and DNA "spinoffs" that further exacerbate the inflammatory response in COVID-19 disease. The upregulation of mitochondrial genes and genes that respond to oxidative stress has been reported to facilitate the interplay between inflammation and oxidative stress. Inflammatory mediators and immunocytes activate intracellular pathways that result in mitochondrial alteration. Pro-inflammatory cytokines such as  $\text{TNF-}\alpha$  induces a calcium-dependent increase in mitochondrial ROS. Furthermore,  $\text{IFN-}\gamma$  was found to upregulate genes inducing mitochondrial ROS generation. IL-6 and IL-10 were found to modulate mitochondrial ROS generation by directly modulating the activity of the electron transport chain. It was reported that mitochondrial ROS itself was found to directly activate the production of proinflammatory cytokines as well. IL-6 and  $\text{TNF-}\alpha$  inhibit mitochondrial oxidative phosphorylation and subsequent ATP production and induces mitochondrial ROS production in the cell. This can lead to permeabilization of mitochondrial membrane, altered mitochondrial dynamics, and eventually, result in cell death (apoptosis). Furthermore, hyperferritinemia disrupts mitochondrial homeostasis driving mitochondrial respiration from aerobic into an anaerobic state. Decreased mitochondrial respiration results in abnormal metal distribution including manganese, copper and zinc. Consequently, reduced mitochondrial manganese can result in mitochondrial dysfunction, possibly due to diminished activity of mitochondrial manganese-dependent superoxide dismutase, an enzyme that prevents free radical generation in mitochondria. All these pieces of evidence explain the potential role of the inflammatory signals in propagating a series of events that aggravate mitochondrial oxidative damage and contribute to other serious systemic alterations including coagulopathy, ferroptosis, and microbial dysbiosis [63].

#### 4.4. Microbiota dysbiosis

From the findings that SARS-CoV-2 nucleic acid has been detected in the stool of patients with COVID-19 pneumonia, it is well indicated that SARS-CoV-2 can colonize in the gastrointestinal tract, which would disturb gut microbiota. The interaction between microbiota and mitochondria tends to appear primarily through endocrine, immune, and humoral links. The commensal gut microbiota affects mitochondrial functions related to energy production, mitochondrial biogenesis, redox balance, and inflammatory cascades. Gut commensal microbiota produces metabolites including the secondary bile acids and beneficial short-chain fatty acids (SCFA) such as N-butyrate that reduce oxidative stress and subsequent ROS production, suggesting it as a possible therapeutic target [63]. In contrast, mitochondrial functions could cause alterations in the composition and activity of gut microbiota. As mitochondria can modulate immune responses under stressful conditions (bacterial or viral infection), it leads to amplification of inflammation. This unbalanced immune response can result in microbiota dysbiosis. Moreover, mitochondria have been shown to modify the microbial community by altering the functions of intestinal effector cells, such as immune cells, epithelial cells, and enterochromaffin cells. These mechanisms explain intra-mitochondrial and extra-mitochondrial dysfunction is the key in resulting microbiota dysbiosis (Fig. 5) [63].



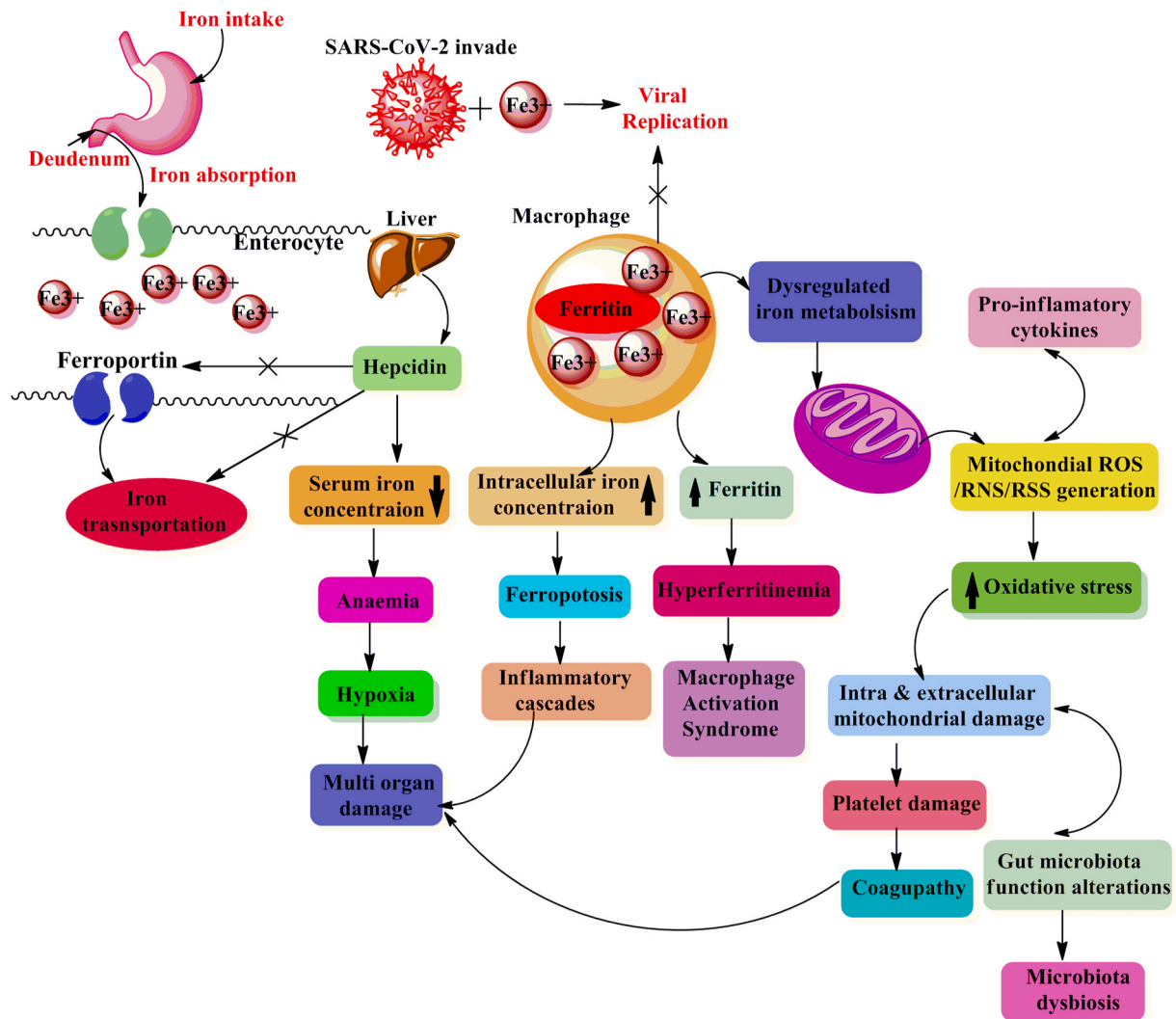


Fig. 5. SARS-CoV-2 infection and microbiota dysbiosis.

4.5. Auto-antibodies against type-1 IFNs

Type I IFN (IFN $\alpha$  and IFN $\beta$ ) plays a pivotal role in restricting viral replication through type I IFN receptor (IFNAR) signaling. Type I IFNs are critical in providing protective immunity against SARS-CoV-2. Clinical reports reveal that some individuals have neutralizing auto-antibodies against type I IFN. It has been reported that these auto-antibodies neutralizes the ability of the corresponding type I IFNs to restrict SARS-CoV-2 infection but are clinically silent until the patients are infected with SARS-CoV-2 [64]. Bastard et al. conducted a clinical study on 987 patients with severe COVID-19 pneumonia and reported that at least 10% of patients have auto-antibodies against type I IFNs. Early treatment with IFN- $\alpha$  is unlikely to be beneficial in such patients but treatment with IFN- $\beta$  may have promising effects, as auto-antibodies against IFN- $\beta$  appears to be rare in patients that developed auto-antibodies against type I IFNs. It is well reported that SARS-CoV-2-infected patients should be tested to identify individuals with auto-antibodies at risk of developing severe infection. These patients recovering from severe COVID-19 should be either excluded from donating convalescent plasma for an ongoing clinical trial or at least tested before plasma donations [65].

4.6. Impaired type I IFNs activity

Certain clinical studies report some individuals to have inborn errors

of type I IFN immunity. The type I IFN immunity in such individuals is impaired by defects of TLR3, Interferon Regulatory factor: IRF7 and IRF9. The neutralizing auto-antibodies and inborn errors of type I IFN production results in devastating disease through deleterious, innate and adaptive immune responses [66]. Many studies reported that IFN-I responses are highly impaired in patients with severe or critical COVID-19, as indicated by activation of NF- $\kappa$ B by over-production of pro-inflammatory cytokines and chemokines. Lee et al. performed a clinical study on patients with mild to severe COVID-19, and patients with severe influenza to identify factors driving COVID-19 disease severity. In patients with severe COVID-19, type I IFN response co-existed with the TNF/IL-1 $\beta$  driven inflammation, and this was not seen in patients with milder COVID-19. Based on these clinical observations, it was proposed that the type I IFN response plays a pivotal role in exacerbating inflammation in severe COVID-19. Timing of the IFN-I response is a critical factor determining outcomes of infection as delayed IFN-I response contributes to pathological inflammation whereas early IFN-I response controls viral replication. A delayed, but considerable IFN-I response is critical for the development of ARDS and increased mortality during SARS-CoV-2 infection [67]. Hadjad et al. performed an integrated immune analysis on 50 COVID-19 patients with varying degrees of severity. The clinical findings report highly impaired type I IFN activity in severely ill patients. These findings proposed that type I IFN deficiency could be a hallmark in the severe progression of COVID-19. It will be worth determining exactly how SARS-CoV-2

antagonizes IFN induction and IFNAR signaling [68].

#### 4.7. MAIT cells implication

Mucosa-associated invariant T (MAIT) cells are antimicrobial T cells that recognize bacterial metabolites and may also serve as innate-like sensors and mediate antiviral responses via activation by pro-inflammatory cytokines. MAIT cells constitute 1–10% of T cells in the circulation and have potent tissue homing characteristics and are particularly abundant in the lung and liver. MAIT cells are activated by TCR recognition of microbial vitamin B2 (riboflavin) metabolites from several microbes presented by MHC-Ib associated protein 1 (MR1) molecules. MAIT cells rapidly produce IL-17, IFN- $\gamma$  and TNF- $\alpha$ , and mediate effective cytolytic functions. Parrot et al. investigated the MAIT cell compartment in moderate and severe COVID-19 patients as well as those in the convalescent phase. Reports show a significant decline in MAIT cells in the circulation of patients with COVID-19. These findings indicate that MAIT cells are engaged in the immune response against SARS-CoV-2 and suggest their possible involvement in COVID-19 immunopathogenesis. Chronic depletion of MAIT cells can have adverse long term consequences for immune defense against infection. The rapid recovery of the MAIT cell compartment to monitor microbial infections will require dedicated longitudinal studies [69]. On the contrary, Akasov et al. suggest that dysregulated MAIT cell activation result in over-production of pro-inflammation cytokines (IFN $\gamma$ , TNF $\alpha$  and IL-17) in response to a SARS-CoV-2 and contribute to an inflammatory response associated with COVID-19. It was hypothesized that MAIT-targeted therapy may be useful to reduce the severity of COVID-19 disease. These include inhibition of riboflavin biosynthesis in the microbiota (e.g. with roseoflavin or analogues) or by ligand-dependent downregulation of the MR1 cell surface expression in antigen-presenting cells (e.g. with DB28 or analogues). The first alternative seems easier to incorporate as the inhibition of riboflavin biosynthesis pathway can lead to toxicity for microbiota, including viruses, bacteria, and yeasts, but not to the host. MAIT cells possess powerful effector and regulatory functions and should be considered in prophylactic and therapeutic approaches. Comprehensive clinical investigations using large cohorts and mechanistic studies in relevant animal models will be worthwhile to address a presumptive link between MAIT cell functions and COVID-19 manifestations [70].

#### 4.8. Haploinsufficiency of suppressor of cytokine signaling (SOCS) 1

SOCS1 is a negative regulator of type I and type II IFN signaling that binds with high affinity to the substrate-binding pocket of JAK1 and JAK2 and consequently inhibits the phosphorylation of STAT1 and STAT2 [71]. The Haploinsufficiency of SOCS1 and its reduced activity are reported to develop autoimmune complications of SARS-CoV-2, including multisystem inflammatory syndrome in children (MIS-C). SARS-CoV-2 infected patients are more prone to MIS-C. As per a recent study performed on patients with immune thrombocytopenia and autoimmune hemolytic anemia, it was observed that the peripheral blood mononuclear cells (PBMCs) of these patients have increased levels of STAT1 phosphorylation and increased expression of type I and type II IFN-stimulated genes. The enhanced IFN signature exhibited by the patients' unstimulated PBMCs parallels the hyperinflammatory state associated with multisystem inflammatory syndrome in children, suggest the contributions of SOCS1 in regulating the inflammatory response associated with MIS-C [72]. These type I and type II driven inflammatory complications of SARS-CoV-2 can be reduced by neutralizing antibodies of either type I or type II IFNs. Also, the patients of these complications respond well to treatment with intravenous immunoglobulins and corticosteroids.

## 5. Patients with inflammatory conditions are more prone to SARS-CoV-2 infection

Various recent reports unfold the fact that SARS-CoV-2 infection is preceded by various inflammatory diseases [73]. Also, it is reported that the patients with pre-existing inflammatory conditions such as inflammatory bowel disease (IBD) [74], rheumatoid arthritis (RA) [75], psoriasis [4], tuberculosis (TB) [76], asthma [77,78] diabetes [79–81], etc are more prone to SARS-CoV-2 infection.

### 5.1. Rheumatoid arthritis (RA)

RA is a chronic autoimmune inflammatory disorder. Corticosteroids and immunosuppressive drugs are mainly used for the management of RA. Due to the iatrogenic effect of these drugs, the impairment of the immune system occurs leading to an increased risk of several infections and other comorbidities. A study carried out in the United States shows that patients with RA are at higher risk of a viral infection than the general population. Corticosteroids and immunosuppressive drugs inhibit immune responses and thus delay the virus clearance. COVID-19 certainly interferes with the management of this complex disorder. However, several reports suggest that patients with RA are not at much risk of COVID-19 [82]. In a case study performed on COVID-19 patients, having a previous history of RA, it was observed that all the patients responded well to antiviral therapy and cured [83]. One more study was performed on 530 patients of COVID-19 with RA history at Research Center for Adult and Pediatric Rheumatic Diseases in Milan, Italy. Most of the patients were treated with anti-TNF, IL-6 blockers and JAK inhibitors which were already at anti-RA therapy (bDMARDs and abatacept). Out of 530 patients, only 3 were detected positive suggesting the low risk of COVID-19 in RA patients who continue their anti-RA therapy [84]. Therefore, patients of RA are recommended to continue with the ongoing treatment during the SARS-CoV-2 outbreak. This aims to prevent the worsening of disease and control disease flares [75].

### 5.2. Psoriasis

Psoriasis is a chronic auto-immune disorder characterized by hyperinflammation. The treatment of psoriasis constitutes biological agents and immunosuppressants such as cyclosporin, methotrexate, adalimumab, ustekinumab, etc. The utilization of these medications increases the risk of opportunistic infections. No recommendations have been made to discontinue the therapy as it will lead to the worsening of psoriasis condition [85]. The treatment options are made on an individual basis by considering age and other comorbidities. No specific data on psoriasis about COVID-19 is reported. A phase III clinical trial on the effects of psoriasis biologicals on upper respiratory infections, influenza, and other serious infections is going on [86].

### 5.3. Inflammatory bowel disease (IBD)

Crohn's disease and Ulcerative colitis are the two main IBD, characterized by chronic inflammation. The virus utilizes the ACE2 receptor for entry into the host cell. ACE2 is highly present in the terminal ileum and colon. The level of ACE2 gets elevated in the inflamed gut of IBD patients, suggesting higher in case of CD than UC. Test results positive for SARS-CoV-2 in fecal matter. Despite being negative in the nasopharyngeal PCR test, over 20% of patients stayed positive in stools. This evidences the fact of gastrointestinal upsets and oral-fecal transmission of COVID-19. Binding of SARS-CoV-2 with ACE2 requires protease enzymes, whose activity is reported to be increased in IBD. These findings propose that the inflamed gut of IBD patients is the ideal gateway through which the person exists the virus [87]. The treatment to manage IBD (immunosuppressants) increases the risk of infection. But the discontinuation of IBD therapy is not recommended. Various statements have been declared by the International Organization for the Study of

Inflammatory Bowel Diseases (IOIBD) for the management and association of IBD in the COVID-19 era. The patients with IBD are considered to be at higher risk of infection as compared to the population without IBD. Good hygiene practices are highly advised to IBD patients to have control over being infected with the virus. Elective surgeries and endoscopies are recommended to be a delay at this time. IOIBD states that IBD therapy should be stopped if the person gets infected with SARS-CoV-2. After recovery, the treatment can again be restarted [88].

#### 5.4. Diabetes mellitus (DM)

DM is a chronic auto-immune condition in which the body's system of blood glucose regulation is impaired. It is characterized by less production of insulin or insulin resistance leading to increased blood glucose levels. Certain studies reported a higher risk of infection and mortality in DM patients as compared to the non-diabetic population. Immune response impairment due to decreased T-cell activity and increased predisposition to hyperinflammation and cytokine storm in DM patients represents potential ways to increase the susceptibility of COVID-19. Reduced viral clearance is reported to be associated with COVID-19 pathogenicity. Increased ACE2 expression and the level of cellular protease enzyme (involved in the binding of a virus with an ACE receptor) were reported to be linked with DM. Therefore higher viral uptake, increased cellular binding affinity rises in DM patients, and in this way these patients are more prone to SARS-CoV-2 infection [80]. Increased expression of ACE2 can be cured by the use of ACE inhibitors and Angiotensin receptor blocker (ARBs) therapies used for treating DM. Thiazolidinediones are also ACE2-stimulating drugs used in DM treatment. Presence of other comorbidities like cardiovascular disorders CVD can also make DM patients more susceptible to COVID-19 infection [89]. From all these mechanisms due to the high risk of COVID-infection, patients with DM must take special precautions. There are no reports suggesting discontinuation of any DM therapy during the COVID-19 pandemic [80,89].

#### 5.5. Asthma

Asthma is a chronic respiratory disorder that has been listed as a risk factor by the center of disease control (CDC) in the mortality of COVID-19 patients. Weak immune responses, owing to the delayed release of IFN- $\lambda$  (which act as anti-viral) in asthmatic patients increase the risk of asthma exacerbation [77,90]. In a study conducted on asthmatic patients of different age groups, it was observed that the patients of age group 18–49 years are at high risk of SARS-CoV-2 infection (27.3%) than the children (1.7%). The virus infection triggers asthma exacerbations and the symptoms are somewhat similar to COVID-19 i.e. dry cough, shortness of breath making it quite difficult to differentiate between COVID-19 and asthma. Asthma exacerbations are associated with bronchial hyperactivity and eosinophilic inflammation. It is highly recommended to continue with the current asthma regimen as it helps in reducing the severity of the infection. It is advised to avoid the use of nebulizer as it increases the risk of transmission due to aerosolization. The generation of a high volume of respiratory droplets during nebulization may be propelled over a longer distance can persist there for hours and increases the risk of transmission. Therefore, the metered-dose inhaler (MDI) or dry powder inhaler (Turbuhaler or Diskus) is recommended instead of a nebulizer. The CDC and WHO asked not to use oral corticosteroids (OCS) for the treatment of COVID-19 as it reduces the viral clearance from the body and increases the risk of secondary complications. However, many organizations have recommended the use of OCS for the treatment of asthma [90]. Moreover, since asthma patients are associated with high expression of ACE2 and TMPRSS2, the use of inhaled corticosteroids (ICS) may help in reducing their expression and ultimately lowers the susceptibility to SARS-CoV-2 infection [91].

#### 5.6. Tuberculosis (TB)

Tuberculosis is a serious bacterial infection generally affecting the lungs. It is characterized by similar signs and symptoms as those that occurred in SARS-CoV-2 infection. The presence of chronic respiratory diseases like TB is related to poor outcomes in COVID-19 [92]. A report by Guiqing He et al. suggests that there is a high risk of SARS-CoV-2 infection in TB patients. Generally, increased severity and delayed virus clearance is observed in these patients [93]. The TB infected persons are advised to strictly follow preventive measures to combat COVID-19 infection.

### 6. Therapeutic options

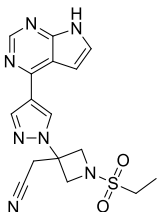
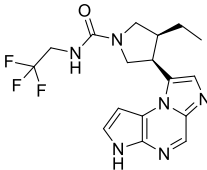
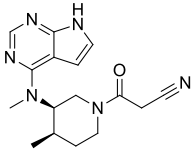
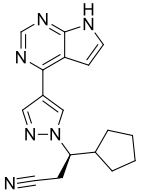
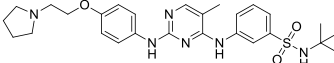
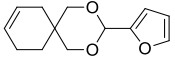
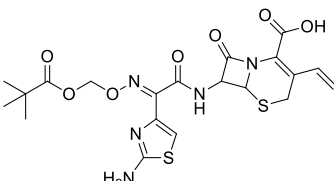
There is no secret that the research community throughout the globe is making efforts toward finding an effective therapy to fight COVID-19 [1,94,95]. Given the fragility of time, the rapid development of remedial treatment has become an urgent need of the hour. Therefore, drug repurposing or the use of already approved drugs has emerged as an effective approach that paves the way towards clinical trials [96,97]. The safety profile of these medicines is one of the advantages of these drugs over newly designed therapy. Most of the drugs which are being repurposed and are in clinical trials also target inflammatory signaling pathways and reduce the cytokine storm. A list of some approved drugs that are being repurposed against COVID-19 is given in Table 1. Further, based on pathophysiological and clinical manifestations as well as literature reports, we discussed different categories of drugs in this section that might show surprising results against SARS-CoV-2 infection to combat COVID-19.

#### 6.1. Kinase inhibitors

##### 6.1.1. JAK and NAK inhibitors

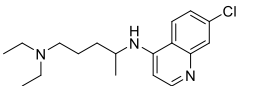
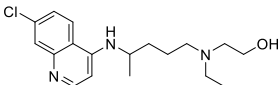
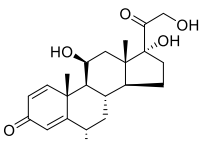
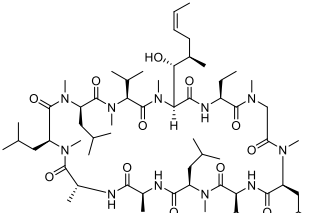
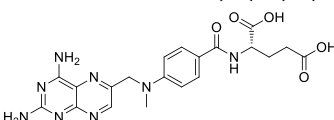
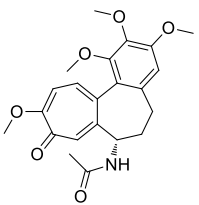
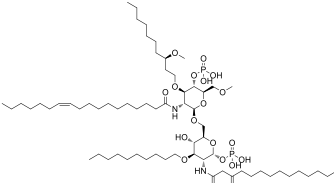
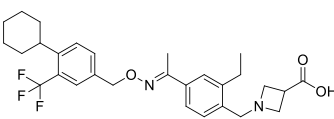
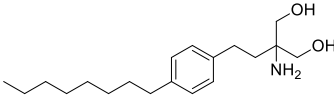
Various kinase enzymes are involved in the progression of cytokine storm therefore, inhibition of these kinases suggests a promising method of the treatment of COVID-19. Both type I and type II cytokine receptors using the JAK/STAT pathway for action. Inhibition of the JAK/STAT pathway could be a valuable treatment for preventing cytokine storm [98]. JAK inhibitors (JAKinibs) are the biological agents that bind to catalytic ATP binding sites of JAKs and inhibit them. Baricitinib is a JAK1/2 inhibitor approved for the treatment of rheumatoid arthritis [123]. Recent studies show the potential in this drug to treat ARDS associated with COVID-19. Besides, baricitinib inhibits numb associated kinases (NAK) family: AP2 associated protein kinase (AAK1) and cyclin G-protein associated kinase (GAK). Both AAK1 and GAK regulate the mechanism for clathrin-dependent viral endocytosis. Disruption of NAKs might interrupt the virus entry into the host cells. Baricitinib has particularly more affinity to inhibit AAK1 as compared to GAK [35,124]. Tofacitinib is another JAK1/2/3 inhibitor approved for rheumatoid arthritis [125]. It is reported to decrease CRP and ESR levels in RA patients but does not inhibit AAK1. Treatment for COVID-19 with tofacitinib has not been reported yet. Upadacitinib is one more JAK inhibitor selectively targets JAK, approved for the treatment of RA. Currently, it is being investigated for the treatment of IBD, psoriatic arthritis, and atopic dermatitis AD [126]. Various literature reports revealed that upadacitinib administration disrupts JAK1 signaling and reduces the expression of Th-2 and Th22 cytokines. As inhibition of JAK1 will inhibit phosphorylation of STAT3, upadacitinib decreases the level of IL-6. Stebbing et al. reported that JAKinibs, including baricitinib, ruxolitinib, and fedratinib possess almost equal affinity towards JAK, but baricitinib is the only drug among these JAKinibs that also has a good affinity towards AAK1. Contrary to the other JAK inhibitors, baricitinib can inhibit clathrin-dependent endocytosis and this merit made it the best of other JAKinibs. It is recommended to use baricitinib or other JAKinibs as a potential therapeutic option for COVID-19. A combination of baricitinib with other drugs such as methotrexate (Mtx) and

**Table 1**  
Approved drugs repurposed for COVID-19 and their mechanism of action.

Sr. No	Name	Structure	Mechanism/Target	References
1	Baricitinib		Inhibits JAK1/2 Inhibits AAK1 Inhibits GAK	[35]
2	Upadacitinib		Inhibits JAK1	[98]
3	Tofacitinib		Inhibits JAK1/2/3	[42]
4	Ruxolitinib		Inhibits JAK1/2	[99]
5	Fedratinib		Inhibits JAK1/2	[100]
6	Tocilizumab	Monoclonal antibody	Binds IL-6 receptor Prevent IL-6 activation Inhibit IL-6 signaling	[101]
7	Ulinastatin		Inhibit serine protease Binds IL-6 receptor Prevent IL-6 activation Inhibit IL-6 signaling	[102]
8	Sarilumab	Monoclonal antibody	Binds IL-6 receptor Prevent IL-6 activation Inhibit IL-6 signaling	[103]
9	Siltuximab	Monoclonal antibody	Binds IL-6 receptor Prevent IL-6 activation Inhibit IL-6 signaling	[104]
10	Anakinra		Binds IL-1 receptor Prevent IL-1 activation Inhibit IL-1 signaling	[105]
11	Canakinumab	Monoclonal antibody	Binds IL-1 receptor Prevent IL-1 activation Inhibit IL-1 signaling	[106]
12	Rilonacept	Monoclonal antibody	Binds IL-1 receptor Prevent IL-1 activation Inhibit IL-1 signaling	[107]
13	Secukinumab	Monoclonal antibody	Binds IL-17 receptor Prevent IL-17 activation Inhibit IL-17 signaling	[28] [108]
14	Ixekizumab	Monoclonal antibody	Binds IL-17 receptor Prevent IL-17 activation Inhibit IL-17 signaling	[109]
15	Brodalumab	Monoclonal antibody	Binds IL-17 receptor Prevent IL-17 activation Inhibit IL-17 signaling	[108]

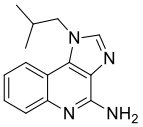
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Table 1 (continued)

Sr. No	Name	Structure	Mechanism/Target	References
16	Ustekinumab	Monoclonal antibody	Binds IL-12/23 receptor Prevent IL-12/23 activation Inhibit IL-12/23 signaling	[110]
17	Adalimumab	Monoclonal antibody	Binds TNF- $\alpha$ receptor Prevent TNF- $\alpha$ activation Inhibit TNF- $\alpha$ signaling	[111]
18	Infliximab	Monoclonal antibody	Binds TNF- $\alpha$ receptor Prevent TNF- $\alpha$ activation Inhibit TNF- $\alpha$ signaling	[112]
19	Etanercept	Monoclonal antibody	Binds TNF- $\alpha$ receptor Prevent TNF- $\alpha$ activation Inhibit TNF- $\alpha$ signaling	[113]
20	Sifalimumab	Monoclonal antibody	Binds INF- $\alpha$ receptor Prevent INF- $\alpha$ activation Inhibit INF- $\alpha$ signaling	[46]
21	Bevacizumab	Monoclonal antibody	Inhibit VEGF	[114]
22	Chloroquine		Inhibit viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects	[115]
23	Hydroxychloroquine		Inhibit viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects	[116]
24	Methylprednisolone		Immunomodulator (inhibition of proinflammatory cytokine production)	[117]
25	Cyclosporin A		Immunomodulator (inhibit calcineurin-NFAT pathway)	[118]
26	Methotrexate		Immunomodulator Inhibit DHFRase Inhibits JAK2 Inhibits TYK2	[119]
27	Colchicine		Immunomodulator Binds to tubulin Prevent mitosis	[120]
28	Eritoran		Inhibit TLR4	[52]
28	Siponimod		S1P1 agonist	[11]
30	Fingolimod		S1P1 agonist	[121]

(continued on next page)

Table 1 (continued)

Sr. No	Name	Structure	Mechanism/Target	References
31	Imiquimod		TLR7 agonist	[122]

direct-acting antivirals (lopinavir, ritonavir, and remdesivir) may provide synergistic effects. However, there are some serious side effects such as herpes zoster infection, herpes simplex, and cellulitis infection that are associated with the long-term use of JAK inhibitors. Short-term use of baricitinib (7–14 days) do not cause any latent infections. Prospective studies (i.e., NCT04320277 and NCT04321993) are ongoing with baricitinib which with the evaluation of cytokine levels during the early and late phases of the disease, may provide new insights into the treatment of COVID-19 [10,42].

### 6.1.2. BTK inhibitors

Ex vivo analysis studies indicate significantly elevated BTK activity in blood monocytes from patients with severe COVID-19 compared with blood monocytes from healthy volunteers. These observations showed that targeting excessive host inflammation with a BTK inhibitor is a therapeutic approach in severe COVID-19 and has resulted in a confirmatory international prospective randomized controlled clinical trial. BTK inhibitors are currently approved for the treatment of B-cell malignancies but are still under investigation for the treatment of autoimmune disease. Based on the role of BTK in the inflammatory cascades, clinical trials for the selective BTK inhibitors acalabrutinib and zanubrutinib on COVID-19 have been conducted by AstraZeneca (Acalabrutinib: NCT04346199) and BeiGene (Zanubrutinib: NCT04382586), respectively [127]. Furthermore, Roschewski et al. conducted a clinical study on severely ill COVID-19 patients. These patients underwent off-label administration of Acalabrutinib. The drug was shown to improve oxygenation in a majority of patients over 10–14 days of treatment course and had no perceptible toxicity. Biomarkers of inflammation (C-reactive protein and IL-6) and lymphopenia are standardised rapidly in most patients [128]. These shreds of evidence have been shown that drugs have potent anti-inflammatory action resulting in decreased levels of proinflammatory cytokines that are usually increased in severe COVID-19. The results of two clinical trials assessing the effect of zanubrutinib and acalabrutinib in hospitalized COVID-19 patients will help to clarify the role of BTK inhibitors in this context [127].

## 6.2. Cytokine inhibitors

Cytokine inhibitors are a heterogeneous group of drugs that can decrease the synthesis of cytokines, reduce their concentration in free active form, block their interaction with specific receptors, and interfere with signaling pathways [129]. Various cytokine inhibitors have been reported to reduce the cytokine storm associated with COVID-19 [11].

### 6.2.1. Interleukin inhibitors

**6.2.1.1. IL-1 inhibitors.** IL-1 is a proinflammatory cytokine and a major local and systemic inflammatory mediator that cause pyroptosis through IL-1 $\beta$ . Suppression of IL-1 may be helpful in minimizing cytokine storm and MAS or sHLH. By blocking the IL-1 signaling, NF- $\kappa$ B-mediated upregulation of numerous cytokines including IL-6 can be managed. In a randomized controlled trial in COVID-19 patients with sepsis, who also had highlights of transaminitis and coagulopathy, it was observed that IL-1 inhibition displays beneficial effects [32]. Anakinra was the first recombinant IL-1R antagonist (rHIL-1Ra) that blocks the binding of both

IL-1 $\alpha$  and IL-1 $\beta$  to IL-1R, thus minimize the proinflammatory effects of IL-1 [107]. Cavalli et al. in their retrospective analysis of COVID-19 and ARDS patients revealed that treatment with high-dose anakinra was safe and effective with clinical improvement in 72% of patients [105]. Canakinumab is another fully-humanized monoclonal anti-IL-1 $\beta$  antibody with IgG1/ $\kappa$  isotype. Another molecule developed for IL-1 blockade is riloncept, which is a recombinant soluble IL-1 receptor blocker. However, the utilization of canakinumab and riloncept for severe COVID-19 has not been accounted for yet [107].

**6.2.1.2. IL-6 inhibitors.** IL-6 was first discovered by Weissenbach in 1980. It is a multifunctional cytokine, regulates metabolism, cell differentiation, proliferation, production of antibodies and other immune responses. IL-6 is produced by B-lymphocytes, T-lymphocytes, dendritic cells, macrophages, monocytes, mast cells and non-lymphocytes such as endothelial cells, keratinocytes, fibroblasts, and tumor cells. IL-6 plays a key role in the cytokine storm. It acts by binding to the IL-6 receptor (IL-6R). There are two types of IL-6R: membrane-bound IL-6R (mIL-6R) and soluble IL-6R (sIL-6R). IL-6 forms a complex with both mIL-6R and sIL-6R, binding of which with signal-transducing component gp130 activates inflammatory pathways (JAK/STAT, MAPK, AKT-PI3K) and promotes inflammatory responses. Tocilizumab (TCZ) is a recombinant humanized monoclonal antibody against human IL-6. It binds with IL-6R (mIL-6R and sIL-6R) and inhibits IL-6 signal transduction pathway. TCZ is an approved drug for the treatment of RA [20]. In 2017, it was approved for the treatment of CRS caused by CAR-T (Chimeric Antigen Receptor T-Cell Immunotherapy) in cancer. Reports claim improvement in certain disease conditions, that are caused by CAR-T, by utilization of TCZ. In severe or critically ill patients with COVID-19 level of IL-6 raises and therefore TCZ can be a valuable approach to save patient's life [107]. A retrospective study shows the beneficial effects of TCZ in various symptoms such as fever, hypoxemia and decreased level of CRP, in patients with juvenile idiopathic arthritis (JIA) infected with Influenza A. There are well-documented alerts about an increased risk of opportunistic infections (general infections, hepatotoxicity, hypertriglyceridemia, and diverticulitis) caused by IL-6 monoclonal antibodies during RA treatment. High costs and safety risks can pose a barrier to the wide utilization of TCZ in the treatment of COVID-19. The recommended dose of TCZ for the treatment of cytokine storm is 8 mg/kg IV as single or divided into two doses at 12–24 h intervals [107]. At the beginning of March 2020, Chinese clinicians explored the utilization of other immunomodulatory agents, for example, ulinastatin, for treatment of the cytokine storm in COVID-19 [130]. Ulinastatin is a natural anti-inflammatory substance present in the body is a serine protease inhibitor. It is commonly used to treat pancreatitis and acute circulatory failure. Ulinastatin reduces the level of pro-inflammatory mediators (IL-1, IL-6, TNF- $\alpha$  and IFN- $\gamma$ ) and raises the level of anti-inflammatory mediator (IL-10) [52]. Hai Huang et al. performed a retrospective investigation revealing that a high dose of ulinastatin therapy was safe and had a possible beneficial effect for patients with Covid-19, with significant amelioration in clinical signs, blood parameters and absorption of the pulmonary lesions [102]. Therefore ulinastatin has great potential for use in COVID-19 treatment. Sarilumab, another IL-6 receptor inhibitor approved for RA, is being tested in a multicenter, double-blind, phase 2/3 studies for critical patients of COVID-19 admitted in ICU [131]. Siltuximab is also another IL-6

blocker, used for controlling cytokine storm induced by CAR-T therapy. Gritti et al. conducted a cohort study on critically ill patients and suggested that the use of siltuximab at the beginning of ventilator support decreases mortality in COVID-19 patients due to respiratory failure [132]. Further randomized controlled investigations are recommended to affirm the safety and effectiveness of this drug.

**6.2.1.3. IL-17 inhibitors.** IL-17 plays an important role in the progression of cytokine storm and augmenting inflammation. It acts as an upstream for both IL-1 and IL-6 and enhances neutrophils recruitment. Therefore, targeting IL-17 should be considered as a conceivable objective as it may hinder various parameters involved in the severity of COVID-19. Blockade of IL-17 and IL-17R is also reported to significantly inhibit Th-17 immune response [100,108]. Secukinumab, ixekizumab, and brodalumab monoclonal antibodies are selective inhibitors of IL-17A. Secukinumab and ixekizumab are human monoclonal antibodies effective against IL-17 and approved for the treatment of psoriasis and psoriatic arthritis while brodalumab is a human monoclonal antibody effective against IL-17 receptor (IL-17R) and approved for the treatment of psoriasis only. Brodalumab is more efficacious than secukinumab and ixekizumab because it targets more cytokines and has a rapid onset of action [108]. Ongoing studies are being conducted to evaluate the safety and effectiveness of these biological agents [133].

**6.2.1.4. IL-12/23 inhibitors.** IL-12 plays a key role in T-cell mediated responses. IL-23 shares a common p40 subunit of IL-12. Monoclonal antibody ustekinumab inhibits both IL-12 and IL-23. It was approved by FDA for plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, and inflammatory bowel disease. Ustekinumab directly inhibits the p40 subunit of IL-12 and IL-23. IL-12 and IL-23 are involved in the activation of Th-1 and Th-17 pathways respectively. Thus targeting IL-12/23 would result in the downregulation of Th-1 and Th-17. Severe side effects have been related to ustekinumab such as nasopharyngitis and upper respiratory tract infection [134,135]. Moreover, the risk of opportunistic infections increases due to suppression of the immune system. No information related to the use of ustekinumab for COVID-19 is reported to date.

### 6.2.2. IFN therapy

IFN- $\lambda$  has a protective action against the viruses by stimulation of anti-viral genes. Early administration of IFN provides clinical benefits in reducing virus load and disease severity while delayed application of IFN is of no benefit. Therefore the timing of administration of IFN is critically important to have the required benefits. The use of pegylated and non-pegylated IFN has been under investigation for the treatment of SARS-CoV-2 infection. IFN- $\lambda$  primarily reduces the proinflammatory activity of IFN- $\alpha\beta$ . Also, IFN- $\lambda$  inhibits the recruitment of neutrophils to the site of infection. IFN- $\lambda$  activates antiviral gene expression without over-stimulating the immune system therefore IFN- $\lambda$  might be an ideal therapeutic option in the treatment of COVID-19 infection [46,52].

**6.2.2.1. IFN- $\alpha\beta$  inhibitors.** IFN- $\alpha\beta$  exerts an inflammatory action by enhancing the recruitment and function of mononuclear macrophages and other innate immune cells. Suppression of IFN- $\alpha\beta$  might provide potential benefits in alleviating hyper-inflammation in severe COVID-19 infection. Sifalimumab is a fully human monoclonal antibody act as IFN- $\alpha\beta$  receptor inhibitor or antagonist. Clinical trials for the use of Sifalimumab in combating auto-immune disorders are currently underway. Application of IFN- $\alpha\beta$  receptor blockers in the later stages of infection might provide plausible outcomes in controlling excessive inflammatory responses [46,52].

### 6.2.3. TNF- $\alpha$ inhibitors

TNF- $\alpha$  is a main proinflammatory cytokine that leads to numerous acute and chronic inflammatory diseases. Anti-TNF agents are widely

used to combat RA, ankylosing spondylitis, IBD, psoriasis, and psoriatic arthritis. The serum level of TNF- $\alpha$  was drastically raised in patients infected with SARS-CoV-2 that decide the severity of COVID-19 illness. TNF- $\alpha$  employs its activity via signaling through two receptors; TNFR-1 and TNFR-2 and further stimulate intracellular signaling through NF $\kappa$ B. Infliximab, adalimumab, and etanercept are the monoclonal antibodies that specifically target TNF- $\alpha$ . Among these, adalimumab is an immunosuppressant commonly used in inflammatory conditions. A clinical study reports the use of one more TNF inhibitor; certolizumab pegol along with other antiviral drugs that can show a positive effect in COVID-19. Besides, a recent meta-analysis of randomized controlled trials recommended the use of melatonin in a substantial reduction of TNF- $\alpha$  and IL-6 levels. This clinical study suggests the use of melatonin as a supplement that can viably decrease the degrees of circulating cytokines and may decrease the pro-inflammatory cytokine levels in patients with COVID-19 [136].

### 6.3. Immunomodulators

Immunomodulatory treatment to downregulate the cytokine storm may give insights into the treatment of COVID-19. Consolidated utilization of an immunomodulatory agent in combination with antiviral agents (lopinavir, ritonavir) may allow doctors to provide an effective treatment to the patients of COVID-19 [137].

#### 6.3.1. Chloroquine and hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) reduce IL-1, IL-6, IFN- $\alpha$  and TNF $\alpha$  by inhibiting major histocompatibility complex (MHC II), antigen presentation and immune activation. Depending on their immunomodulatory effects, these two anti-malarial drugs are commonly used to treat RA, systemic lupus erythematosus (SLE), and Sjögren's syndrome. Previously, in addition to the anti-malarial activity, CQ and HCQ have also documented antiviral action against different viruses such as Ebola, dengue, SARS and H5N1. These have been now reportedly useful for the treatment of COVID-19. Moreover, CQ and HCQ may reduce the ACE-2 receptors glycosylation, thereby preventing successful attachment of SARS-CoV-2 from to host cells [107].

#### 6.3.2. Corticosteroids

Corticosteroids are a class of non-inflammatory steroidal hormones, used to alleviate inflammation. These are among the most widely used immunomodulatory therapy used in infectious diseases. Corticosteroids were used as primary options for immunomodulation during the SARS-CoV outbreak in the year 2003 [138]. Timely administration of corticosteroids provides relief from fever, lung infiltration and improve oxygenation. The timing and dosage of corticosteroids administration are very critical as too early administration prevents the activation of the body's immune system, increases viral load and eventually promotes adverse effects. Therefore, these are mainly used in critically ill patients with cytokine storm. Short-term application (3–5 days) of glucocorticoid with a low dose (not  $\geq$  methylprednisolone 1–2 mg/kg/day) is recommended [52]. Certain reports revealed clinical improvements associated with methylprednisolone therapy during the SARS epidemic but in patients with MARS, glucocorticoid therapy delays virus clearance [139]. A retrospective cohort study conducted by Wang et al. showed that the short-term and low-dose use of methylprednisolone can show better results in critically ill patients of COVID-19 [140].

#### 6.3.3. Methotrexate

MTX is an affordable and widely available immunosuppressant drug acts by inhibiting dihydrofolate reductase (DHFR) and prevent DNA synthesis [141]. Additionally, MTX also exerts anti-proliferative and anti-inflammatory actions that may be beneficial against SARS-CoV-2 infection [142]. Administration of MTX induces the release of adenosine, a potent anti-inflammatory agent that employs neutrophils, macrophages, and T cells regulation. MTX significantly reduces IL-6 and

TNF- $\alpha$  levels. Reports suggest that low-dose administration of MTX during mild to moderate COVID-19 infection could be beneficial. Further clinical trials are required to justify the safety and efficacy of MTX in COVID-19 infection [141,143].

#### 6.3.4. Cyclosporin

Cyclosporine is a potent immunomodulator drug used for immunosuppression to prevent organ transplantation failure and to treat autoimmune disorders [144]. Cyclosporin acts by binding to the cyclophilin-1 receptor and inhibiting calcineurin that eventually suppresses the production of pro-inflammatory cytokines. It is approved for the treatment of psoriasis, psoriatic arthritis, atopic dermatitis, ulcerative colitis, and lupus nephritis. Cyclosporin can potentially prevent excessive inflammatory response and acute lung injury. Recent reports revealed that cyclosporine administration inhibits SARS-CoV-2 viral replication at very low and non-toxic doses [145]. It is reported to inhibit activation of T-cell response however, the use of cyclosporine to alleviate SARS-CoV-2 infection is not clear. Serious side effects and many drug interactions are associated with the use of cyclosporin. Considerable studies are required to investigate whether the use of cyclosporine is clinically advantageous in the patients infected with SARS-CoV-2 or not [118,146].

#### 6.3.5. Colchicine

Colchicine is an alkaloid derivative, anti-inflammatory, and immunomodulatory drug widely used to treat gout, FMF, and Behçet's syndrome. It acts by binding to tubulin and inhibiting tubulin polymerization and thus inhibits mitosis. It can inhibit IL-1 production, thereby suggested to be useful for the treatment of COVID-19 infection. A multi-centered, randomized, double-blind, placebo-controlled phase 3 trial is currently going on to evaluate the safety and efficacy of colchicine in COVID-19 patients (COLCORONA (Colchicine Coronavirus SARS-CoV2)). At present, the results of this study have not been reported yet (NCT04322682) [107].

#### 6.3.6. Oxidized phospholipids (OxPLs) inhibitor

OxPLs are reported to increase the production of cytokines and chemokines from lung macrophages through TLR4-TRIF signaling. In cytokine storm during SARS-CoV-2 infection, the production of OxPL elevates in the lungs and can cause acute lung injury. A recent animal study reports that the administration of Eritoran (TLR4 antagonist) decreases the levels of OxPL and inflammatory cytokines/chemokines. The suppression of OxPL by using Eritoran or other TLR-4 blockers may provide benefits in controlling the severity of COVID19 [46].

#### 6.3.7. Sphingosine-1-phosphate receptor 1 (S1P1) agonist therapy

S1P1 is a signaling lysophospholipid involved in the synthesis of pro-inflammatory cytokines. A study reports that the use of S1P1 agonists may inhibit the recruitment of inflammatory cells, decreased pro-inflammatory cytokine/chemokine production, and reduced mortality and morbidity due to the influenza A virus (IAV). Few studies suggest that SIPI significantly prevents pathological damages induced by innate and adaptive immune responses, thereby reducing the cytokine storm associated with IAV [46]. Therefore, S1P1 agonists may be potential therapeutic drugs for reducing cytokine storm in COVID-19 patients. A S1P1 receptor modulating drug, siponimod, was approved in the year 2019 to treat multiple sclerosis. However, clinical trials are needed to further verify whether siponimod is an ideal alternative for the treatment of cytokine storm or not [52]. Fingolimod is another S1P1 receptor agonist with an effective immunomodulation action. It is currently approved for the treatment of multiple sclerosis. Clinical trials are underway to investigate the safety and efficacy of fingolimod in COVID-19 (NCT04280588) [121].

#### 6.3.8. TLR-7 agonists

TLR-7 is a protein encoded by TLR-7 genes in humans. It performs

the important function of pathogen recognition and activation of the innate immune response. Imiquimod (IMQ) is a TLR-7 receptor agonist and can be used to stimulate the immune system by upgrading innate and adaptive immunity. IMQ exerts its action by binding to cell surface receptors, especially TLR-7 and TLR-8. This leads to the activation of a signaling cascade, which results in the translocation of NF- $\kappa$ B. The binding of NF- $\kappa$ B to DNA induces the expression of many pro-inflammatory cytokines and chemokines. Certain preclinical and clinical trials proposed that IMQ is an innate and adaptive immunity stimulator and in this way demonstrates to have the ability to treat viral infections [24].

#### 6.4. Intravenous immunoglobulin (IVIG)

Intravenous immunoglobulin (IVIG) is a pooled formulation of normal immunoglobulin IgG collected from several thousand healthy donors. It is broadly utilized in the immunotherapy of a significant number of autoimmune and inflammatory diseases at high doses (1–2 g/kg). The therapeutic advantage of IVIG therapy is because of several mutually nonexclusive pathways involving soluble mediators and cellular elements of the immune system. Of the five classes of immunoglobulins in the human body, IgG is the predominant class, represents almost 80% of the overall amount of immunoglobulin, and one of the key players in defending against invading pathogens [147]. IgG consists of two fragments F(ab')<sub>2</sub> and Fc fragment. F(ab')<sub>2</sub> fragment recognizes specific antigens and Fc fragment performs effector functions upon binding to Fc $\gamma$  receptors (Fc $\gamma$ Rs). IVIG acts by blocking the activation of Fc $\gamma$ Rs and innate immune cells like monocytes, macrophages, and dendritic cells (DCs). Besides, IVIG induces anti-inflammatory cytokines like IL-1 receptor antagonist (IL-1RA), TGF- $\beta$ , and IL-10. These actions are correlated with the inhibition of NF- $\kappa$ B, ERK1/ERK2 and p38 MAPK signaling pathways and hence the production of various cytokines. Reports demonstrate that IVIG exerts anti-inflammatory actions by stimulating and restoring the functions of regulatory T (Treg) cells. Moreover, IVIG inhibits the activation and proliferation of B cells [148]. Several studies suggest the use of IVIG in the treatment of other coronaviruses, including SARS and MARS. A high dose of IVIG may help in combating severe COVID-19 infection also [149].

#### 6.5. Convalescent plasma therapy

Convalescent plasma is the only antibody-based therapy that is presently available for COVID-19 patients. Convalescent plasma contains antibodies obtained from recently recovered COVID-19 patients with high neutralizing antibody titer to treat currently infected COVID-19 patients. In the previous two viral outbreaks of SARS-CoV due to high mortality and absence of appropriate treatment convalescent plasma therapy was utilized. Reports suggest the successful use of convalescent plasma therapy in the treatment of SARS, MERS, and 2009H1N1 pandemic with satisfactory safety and efficacy [150]. Despite its strong historical evidence and biological plausibility, convalescent plasma has not yet been reported as a safe therapeutic option against COVID-19. Joyner et al. performed a clinical study for indicating key safety metrics following transfusion of convalescent plasma in 5000 patients with severe COVID-19. The observations have shown less rates of mortality and serious adverse events following the transfusion of convalescent plasma [151]. Shen et al. conducted a preliminary uncontrolled case study of 5 patients with severe COVID-19 and ARDS. Administration of convalescent plasma containing neutralizing antibody was shown to have an improvement in their clinical status. These preliminary observations raise the possibility that convalescent plasma therapy may potentially benefit in the treatment of COVID-19 and ARDS, but it requires evaluation in randomized clinical trials [152].



## 6.6. Regulatory T cell therapy

Regulatory T-cells (Tregs) ensure the monitoring of inflammation during any pathogen attack. Tregs typically migrate into inflamed tissues, reducing inflammatory responses and triggering tissue repair. Tregs are either thymus-derived or induced in the periphery and are historically considered to induce immune tolerance, and prevent autoimmune and inflammatory diseases. Tregs inhibit the activation of both innate and adaptive immune cells via inhibitory surface molecules (such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and lymphocyte activation gene3) and production of immunosuppressive cytokines (IL-10, TGF- $\beta$  and IL-35). The latest research suggests that the level of peripheral Tregs is prominently decreased in severe COVID-19 patients. Considering the role of Tregs in immune homeostasis, a drop in the levels of Tregs could be one of the reasons for the hyperactivated immune system and damaged lungs in severe COVID-19 patients. Because of the dysregulated immune response in severely ill COVID-19 patients, CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup> regulatory T cell-based therapeutic strategies could be considered for patient management. Adoptive transfer of ex vivo expanded polyclonal Tregs has been used recently to treat autoimmune and inflammatory disorders. However, polyclonal Treg therapy is time-consuming, taking nearly two weeks to expand adequate quantities of viable clinical-grade Tregs for immunotherapy, which makes it a non-viable option to treat SARS-CoV-2 infection. Alternatively, allogeneic HLA-matched umbilical cord-derived Tregs are under investigation for inflammatory conditions (Ongoing clinical trials: NCT02932826, NCT03011021) and could be considered for severe COVID-19 patients. Another strategy to boost Tregs is by using low dose IL-2. The high affinity of CD25 towards IL-2 would result in selective Treg expansion. But increased levels of soluble IL-2 receptor (IL-2R) displayed in severe COVID-19 patients could potentially scavenge IL-2 and renders it unavailable for Treg expansion. Despite these challenges, a clinical trial is organized with low-dose IL-2 for ARDS associated with COVID-19 (NCT04357444). Furthermore, the recombinant Fc-fused CTLA-4 protein abatacept has been used for several years for the immunotherapy of systematic autoimmune diseases. Abatacept enhances T cell signaling and activation by different mechanisms. However, no clinical trials for abatacept therapy in COVID-19 patients are yet registered [153]. Gladstone et al. conducted a case study on two COVID-19 patients using Tregs. Both patients were treated with Tregs using allogeneic, off the shelf and cord blood-derived Tregs. The observations suggest a decline in IL-6, TNF- $\alpha$  and IFN- $\gamma$  levels in both patients and no infusion reaction or any other adverse effects were shown by the patients. These findings suggest considering Tregs as a potential therapeutic approach for COVID-19 [154].

## 6.7. Neutralizing monoclonal antibody therapy

Monoclonal neutralizing antibodies represent the major class of biotherapeutics for passive immunotherapy to treat viral infections. These neutralizing antibodies target receptor-binding domain in surface spike glycoprotein of SARS-CoV-1 and SARS-CoV-2 that mediates viral entry into host cells, explaining their ability to cross-neutralize the virus [155]. Neutralizing monoclonal antibodies to SARS-CoV-2 has the ability for both therapeutic and prophylactic uses. Numerous monoclonal antibodies against SARS-CoV-2 have been isolated by various research groups, often from B cells of the patients who have recovered recently from COVID-19, and in some cases, from severely infected individuals from ARDS or SARS-CoV. Over the next few months, many monoclonal antibody products will enter clinical trials to be assessed for their ability to restrict or modify SARS-CoV-2 infection. Considering the long half-life of most monoclonal antibodies (approximately 3 weeks for IgG1), these protect from the infection that could last weeks or months so a single infusion should be sufficient. The possible disadvantage of monoclonal antibodies to COVID-19 therapy is the uncertain bioavailability of passively infused IgG in disease-affected tissues, especially in

the lungs, which are the main target of SARS-CoV-2 infection [156]. Even though there is major progress towards the development of monoclonal antibody therapy for coronavirus infection, no monoclonal antibodies have yet been successfully marketed [155]. Wang et al. reports a human monoclonal antibody 47D11 that neutralizes SARS-CoV-2 in cell culture. The identification of monoclonal antibody was done by cloning of the human variable heavy and light chain regions into a human IgG1 isotype backbone. This antibody would be useful for the development of antigen detection tests and serological assays in order to target SARS-CoV-2. Therefore, this antibody provides the potential to prevent and/or treat COVID-19, either alone or in combination. Monoclonal antibodies provide a possible alternative avenue for the prevention of COVID-19. Identification of the therapeutic or prophylactic potency of monoclonal antibodies would be a significant development in the management of the COVID-19 pandemic [157].

## 6.8. Growth factor inhibitors

Various growth factors are reported to be associated with the pathology of COVID-19, most importantly, VEGF, an angiogenesis factor responsible for vascular permeability [158]. The level of VEGF increases in critical patients with COVID-19 infection. A high level of VEGF is associated with increased susceptibility to ALI and ARDS. Therefore, VEGF emerged as a vital target of various inflammatory conditions associated with COVID-19 [159]. Bevacizumab is a humanized monoclonal antibody that inhibits VEGF and in this way might suppress the edema in COVID-19 patients [159]. Bevacizumab has anti-angiogenic properties and is approved for the treatment of metastatic colorectal cancer, non-small cell lung cancer; metastatic renal cell carcinoma and other specific cancers. Bevacizumab is currently under investigation for the treatment of COVID-19 [121,133].

## 6.9. Vitamin therapy

### 6.9.1. Vitamin C

Vitamin C is a key antioxidant of the body. It protects the body's cells and tissues from damage caused due to increased oxidative stress by scavenging the ROS. Vitamin C improves vasopressor synthesis, endothelial function, enhances immune cell functions and produces epigenetic immunologic modifications. The level of vitamin C depletes critically during infection and its requirement increases with the severity of the infection. In severe cases, gram doses of intravenous administration may require in order to achieve an adequate amount in the body to counteract decreased vitamin turnover. Recently in China, clinical trials to investigate vitamin C infusion (NCT04264533) for the treatment of COVID-19 in critically ill patients [160]. Certain studies on vitamin C demonstrated positive outcomes on mortality improvement in sepsis, but a broad investigation is required to confirm these findings. Vitamin C is a safe and inexpensive essential supplement and therefore extensive studies of its promising effects on COVID-19 should be encouraged [121].

### 6.9.2. Vitamin D

Vitamin D shows the immunomodulatory effect by regulating cytokine signaling pathways in COVID-19 [161]. Vitamin D supplementation reduces oxidative stress by enhancing the expression of genes related to antioxidation (glutathione reductase and glutamate-cysteine ligase modifier subunit). Reports from a meta-analysis suggest that the regular oral intake of vitamin D2/D3 (in doses up to 2000 IU/d without additional bolus) is safe and protective against COVID-19 and its associated complication ARDS, especially in individuals with vitamin D deficiency. However, the monitoring of COVID-19 spread in vitamin D deficient patients is more difficult due to lack of sunlight exposure as an outcome of "lockdown". Extensive studies are critically required to investigate the possible outcomes of vitamin D deficiency on COVID-19 [162]. Reports indicate that the supplementation with multiple micronutrients

having immunomodulatory roles may reduce the risk of infection. Vitamins C, vitamin D and zinc are the best micronutrients providing the strongest evidence for the immune-supportive role. Human clinical trials are needed to evaluate the dosage and combinations of micronutrients in different populations for their promising benefits in SARS-CoV-2 infection [163].

## 6.10. Iron metabolism regulators

### 6.10.1. Iron chelators

As SARS-CoV-2 requires iron for viral replication and its functions, it suggests a potential therapeutic option to decrease plasma iron concentration to make the virus deprive of it. Iron chelation represents a promising therapeutic option in reducing extracellular iron and thus virus replication. This therapy was proven to have an anti-viral and anti-fibrotic activity as well. Deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX) are some common iron chelators. DFO can induce the upregulation of IFN- $\gamma$ R2 expression on the cell surface only in activated T cells. This can restore T cell response to SARS-CoV-2 infection by restoring the sensitivity of T lymphocytes to IFN- $\gamma$  and inhibiting clathrin-mediated SARS-CoV-2 cell entry. DFO causes ferritin degradation in lysosomes by inducing autophagy, while both deferiprone and deferasirox are likely to chelate extracellular iron and iron derived from ferritin before ferritin degradation by proteasomes. Several studies have been conducted on the potential anti-viral role of iron-chelating therapy. However, it is reasonable to speculate that iron chelation may affect free radicals and pro-inflammatory cytokines production that is strongly involved in the severity of COVID-19. Given promising outcomes in other viral diseases, iron chelation using deferiprone or deferoxamine has been suggested in COVID-19 also [164].

### 6.10.2. Hepcidin agonists

Due to a short half-life of natural hepcidin, hepcidin mimics, or other drugs that could stimulate hepcidin level undergone clinical use. Numerous hepcidin agonists have been developed to mimic hepcidin activity or stimulate endogenous hepcidin production and majorly used to treat iron disorders such as  $\beta$ -thalassemia major (TM) and hereditary Hemochromatosis (HH) [165]. The 7-9 N-terminal amino acid segment of hepcidin is sufficient to induce ferroportin internalization and degradation *in vitro*. Thus, a series of mini-hepcidin (MH) were designed through computer modeling which are short peptides based on this N-terminal segment of hepcidin. These MH have been shown to function using a similar mechanism to full-length hepcidin, reducing ferroportin and iron levels. It has been demonstrated that the administration of MH to mice mimics the iron-restrictive effect of endogenous hepcidin. PR73, PR65, mHS17, mHS26, M004, M009 are the various reported MH. Multiple other strategies have been developed to mimic hepcidin activity or increase the production of endogenous hepcidin. These include synthetic full-length human hepcidin, other peptide-based hepcidin mimetics, small molecules, ferroportin inhibitors, or *Tmprss6* inhibitors [166]. Through high-throughput screening, several small molecules including genistein, Epitiostaol, progesterone and Mifepristo were identified as they were shown to have excellent efficacy in hepcidin induction. TMPRSS6 takes part in hepcidin regulation through HJV cleavage, suggesting it a possible therapeutic target to induce Hamp expression [165]. Lipid nanoparticles (LNP) targeting TMPRSS6 have been shown to decrease TMPRSS6 mRNA while simultaneously increasing hepcidin expression. Studies suggest administration of TMPRSS6-ASO either alone or with DFP increased hepcidin levels, while DFP alone did not. TMPRSS6-ASO and DFP treatment displayed a synergistic effect on liver iron content. Recently, Pandur et al. created a hepcidin analogue that exhibits similar ferroportin binding and ubiquitination characteristics as wild type (WT) hepcidin. Several phytoestrogens (naringenin, quercetin and resveratrol) present in fruits and vegetables have been found to increase hepcidin expression through interactions with Nrf2 and an antioxidant response element located

within the hepcidin promoter within a rat model [167]. Furthermore, an *in-vitro* analysis revealed that Sorafenib, Wortmannin, Rapamycin, and metformin have been shown to increase hepcidin level by targeting RAS/RAF/MAPK and mTOR signaling pathway in hepatoma cells and primary hepatocytes [168]. Metformin administration for long period was reported to cause a marked increase in serum hepcidin indicating iron overload in liver of these patients [169].

### 6.10.3. N -acetylcysteine (NAC) therapy

N-Acetylcysteine (NAC) is a well-known mucolytic agent used to treat various respiratory infections and disorders involving glutathione (GSH) depletion and oxidative stress. NAC is a thiol-containing free-radical scavenger and an effective precursor of glutathione [170]. NAC is being clinically used since the 1960s as a mucolytic agent, due to its ability to break the disulfide bonds of mucus and depolymerize mucin. Breaking disulfide bonds into thiol groups may also lower the affinity for the virus to attach to ACE2 sites. At very high doses, NAC is also used as an antidote against paracetamol intoxication [171]. Based on a wide range of antioxidant and anti-inflammatory mechanisms, the oral administration of NAC is likely to attenuate the risk of developing COVID-19 disease severity. NAC has better oral and topical bioavailability than GSH and has a wide safety margin. Increased ROS and oxidative stress activate important redox-sensitive transcription factors like NF $\kappa$ B and AP-1, which lead to the secretion of various pro-inflammatory cytokines, explaining the anti-inflammatory role of NAC by scavenging ROS species (especially of HOCl and  $\bullet$ OH). Moreover, NAC exhibits anti-inflammatory action by inhibiting epidermal growth factor receptor (EGFR), a tyrosine kinase involved in inflammation. NAC was reported to reduce IL-8 and CRP levels, and improved clinical outcomes in patients with COPD exacerbations [170]. As drug repurposing is the fastest approach toward an effective and accessible treatment against COVID-19 before a vaccine is developed so molecules working through multiple mechanisms of action, such as NAC, could be potentially effective as compared with drugs having a single target. Certain studies suggest a reasonable basis for the addition of 1200 mg/d oral NAC on therapeutic schemes of patients with COVID19, as a measure to prevent the development of the cytokine storm and ARDS [171]. It has been hypothesized that NAC along with conventional therapy may be treated as a potential therapeutic strategy against COVID-19. However, this hypothesis requires appropriately designed clinical studies for further clarification [172].

## 6. Conclusions

COVID-19 is an ongoing pandemic that imposed a global health emergency, inevitably affecting the large population, especially the patients with pre-existing medical health conditions. Predominantly, individuals with chronic inflammatory disorders such as IBD, asthma, TB, psoriasis, lung disorders, CVD, etc carry a higher risk of SARS-CoV-2 infection than the normal population. Most of the inflammatory disorders are autoimmune disorders in which the body's immune system get overactivated and attack healthy cells instead of attacking pathogens. Normally, the activation of the immune system provides a defense mechanism against the invaded pathogen but the uncontrolled immune responses lead to excessive production of inflammatory cells and the recruitment of immune cells. These cellular events lead to the activation of inflammatory pathways such as IL-6/JAK/STAT signaling pathway, IFN cell signaling pathway, TNF $\alpha$ -NF- $\kappa$ B pathway, TLR pathway, and many more. Consequently, the increased flux of cytokine and chemokines through these signaling cascades induce cytokine storm in the later stages of SARS-CoV-2. Cytokine storm is associated with disease severity and mortality, therefore, early recognition and timely control of cytokine storms are very important. In this context, various treatment options have been proposed by researchers such as Kinase inhibitors, IL Inhibitors, IFN therapy, plasma therapy, immunomodulators, TLR-7 agonists, immunoglobulins, vitamin therapy, growth factor inhibitors,

etc that can control cytokine storm and reduce the mortality rate in the critically ill patients of COVID-19 admitted in ICU. Moreover, patients with pre-existing inflammatory conditions are encouraged to continue their treatment during this pandemic.

### Declaration of competing interest

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

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