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REVIEW ARTICLE

Promising drug repurposing approach targeted for cytokine storm implicated in SARS-CoV-2 complications

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ABSTRACT

A global threat has emerged in 2019 due to the rapid spread of Coronavirus disease (COVID-19). As of January 2021, the number of cases worldwide reached 103 million cases and 2.22 million deaths which were confirmed as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This global pandemic galvanized the scientific community to study the causative virus (SARS-CoV2) pathogenesis, transmission, and clinical symptoms. Remarkably, the most common complication associated with this disease is the cytokine storm which is responsible for COVID-19 mortality. Thus, targeting the cytokine storm with new medications is needed to hamper COVID-19 complications where the most prominent strategy for the treatment is drug repurposing. Through this strategy, several steps are skipped especially those required for testing drug safety and thus may help in reducing the dissemination of this pandemic. Accordingly, the aim of this review is to outline the pathogenesis, clinical features, and immune complications of SARS-CoV2 in addition to suggesting several repurposed drugs with their plausible mechanism of action for possible management of severe COVID-19 cases.

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Introduction

Coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome (SARS)-coronavirus 2 (SARS-CoV-2), and 2019-nCoV are all names of the new β-coronavirus which appeared in China on December 2019 [1]. World Health Organization (WHO) primary identified this virus as the 2019-novel coronavirus (2019-nCoV) on 12 January 2020 and then officially named the causative disease as COVID-19. However, on 11th February 2020 the Coronavirus Study Group of the international committee suggested the name to be SARS-CoV-2. A lot of questions have been raised since that date about the properties of this virus along with its transmission, pathogenesis, and ultimately its treatment.

This pandemic started when numerous pneumonia cases were detected and epidemiologically connected to the seafood wholesale market in Wuhan, China [2]. Afterwards, COVID-19 was reported in hospitalized patients after examining the bronchoalveolar-lavage fluid of three patients using virus culture, genome sequencing, and polymerase chain reaction. Then, the phylogenetic analysis of the complete genome of SARS-CoV-2 revealed that it belongs to the β-coronavirus genus [3]. The best-known members of this genus were (SARS-CoV) that appeared in China in 2002 and led to 774 deaths and Middle East respiratory syndrome coronavirus (MERS-CoV) that was identified in Saudi Arabia in 2012 with 858 reported deaths [2,4].

After identification of the SARS-CoV-2 in the China outbreak, Lu and his coworkers [2] examined nine patients in Wuhan hospital and discovered that this virus is a member of the subgenus Sarbecovirus and shared a similarity to two bat-derived coronavirus strains, bat-SL-CoVZC45 and bat-SL-CoVZXC21, but less related to the known human-infecting coronaviruses. Moreover, Benvenuto et al. [5] performed a phylogenetic analysis and concluded that the SARS-CoV-2 genetic sequence clustered with the 2015 bat SARS-like coronavirus sequence. Also, Wu and his coworkers [6] found 89.1% similarity between the SARS-CoV-2 and the bat corona virus which suggests the virus may spill over from animals to humans. Critically, COVID-19 severity has been associated with a cytokine storm which is considered one of the major causes of acute respiratory distress syndrome (ARDS) and widespread tissue damage resulting in multiple-organ failure [7]. Accordingly, this article has discussed the transmission, pathogenesis, and clinical features of SARS-CoV-2. Moreover, we have reviewed the mechanism underlying SARS-CoV-2-induced cytokine storm to suggest some therapeutic agents that might have potential roles in hindering COVID-19 severity.

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Transmission

As depicted in Figure 1(A), SARS-CoV-2 has been reported to be transmitted between humans mostly through respiratory secretions [1,8]. However, Zhang and his coworkers [9] found that SARS-CoV-2 was spread from infected to non-infected individuals through multiple routes such as aerosol droplets, fecal-oral or body fluid route which is not a surprising finding because SARS-CoV and MERS-CoV were previously detected in the human intestine in late infections [10]. Thus, numerous agents, including clothing and beddings, could be considered as route of transmission of COVID-19 but the infection aggressiveness of this disease is related to both droplets and aerosols especially indoors [11]. Moreover, Kampf et al. [12] reported that the human coronaviruses can remain infectious for 9 days at room temperature which suggests that hospital setting can be a major source of infection. With respect to vertical transmission, previous studies showed no evidence of intrauterine or transplacental transmission from infected pregnant mothers to their fetuses [13] although the angiotensin-converting enzyme 2 (ACE2); receptor responsible for binding of SARS-CoV2, as well as the transmembrane serine protease 2 (TMPRSS2) are found in the placenta. Conversely, a recent study reported that 3.2% of pregnant mothers transmit COVID-19 to the fetus in the third trimester [14].

Pathogenesis

Studying the pathogenesis of SARS-CoV-2 virus and its receptors in the body (Figure 2) is of great help in finding the proper therapy. SARS-CoV-2 has an envelope-anchored spike protein which is responsible for its entry into the host cell where the receptor-binding domain precisely attaches to its ACE2 receptor [15]. For a complete entry of the virus, the spike protein should be primed by transmembrane protease enzyme TMPRSS2 [16]. At this stage, the patient is asymptomatic and highly infectious and the viral load is low but can be detected by nasal swabs [17]. Afterwards, the virus migrates down the respiratory tract where a fusion of the virus with epithelial cell membrane takes place with the aid of the spike (S2) protein and the RNA genome is released into the cytoplasm of the host cell. Subsequently, the genome will code for nonstructural proteins, and form replication-transcription complex in the double-membrane vesicle leading to production of a set of sub-genomic RNAs that will further code for accessory and structural proteins. At this point, clinical manifestations of the disease are identified, and the innate immune response starts. Then, the virus binds to the cell membrane to release new virions [1]. Mostly, the later propagation of viral infection occurs in 20% of the population where the virus spreads to the gas exchange units of the lung and infects alveolar type II cells. When the

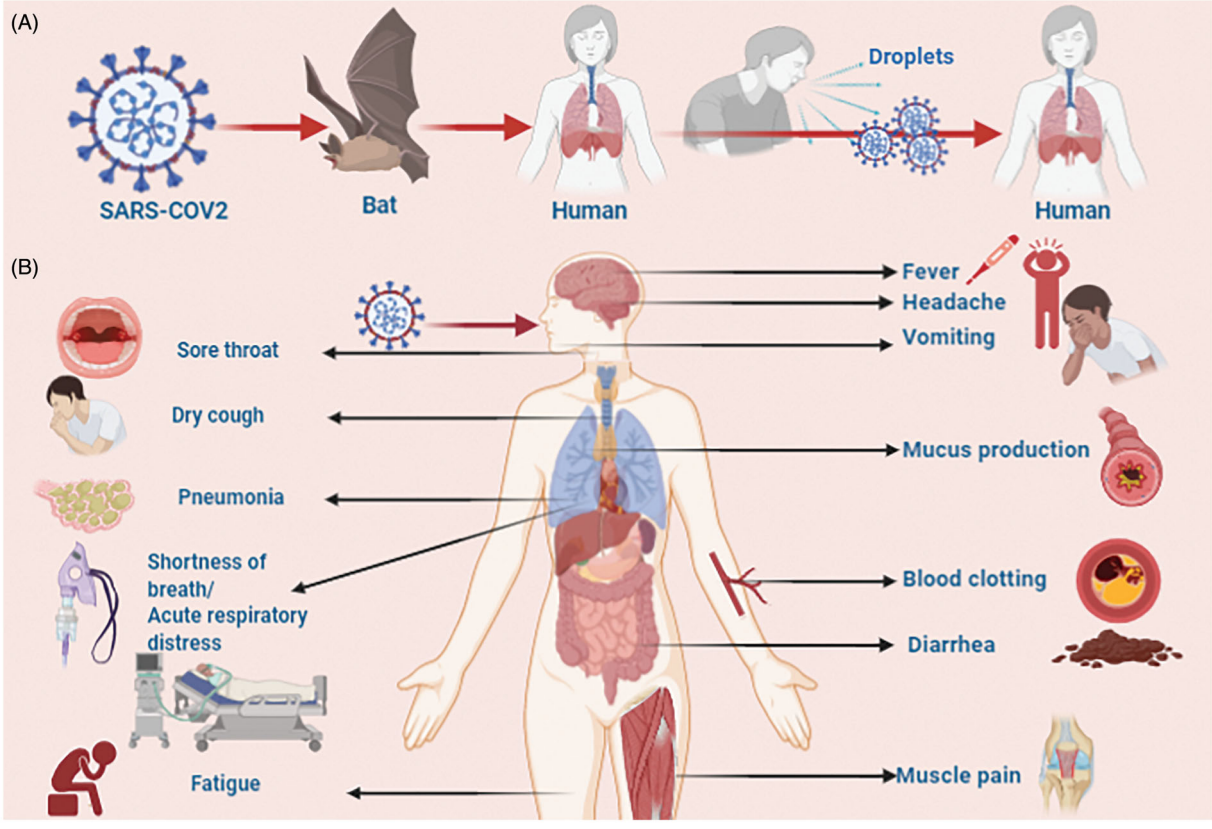

Figure 1. SARS-CoV-2 transmission, clinical symptoms, and complications. (A) Bats are the likely reservoir of SARS-CoV-2 which crosses the species barrier into humans. Then, Human-to-human transmission of SARS-CoV-2 occurs via a nosocomial transmission (droplets). (B) The common clinical manifestation of SARS-CoV-2 include fever, headache, vomiting, diarrhea, sore throat, dry/wet cough, fatigue, and muscle pain. Severe pneumonia, acute respiratory distress, and blood clotting are the most serious complications. Figure generated in Biorender (https://biorender.com/).

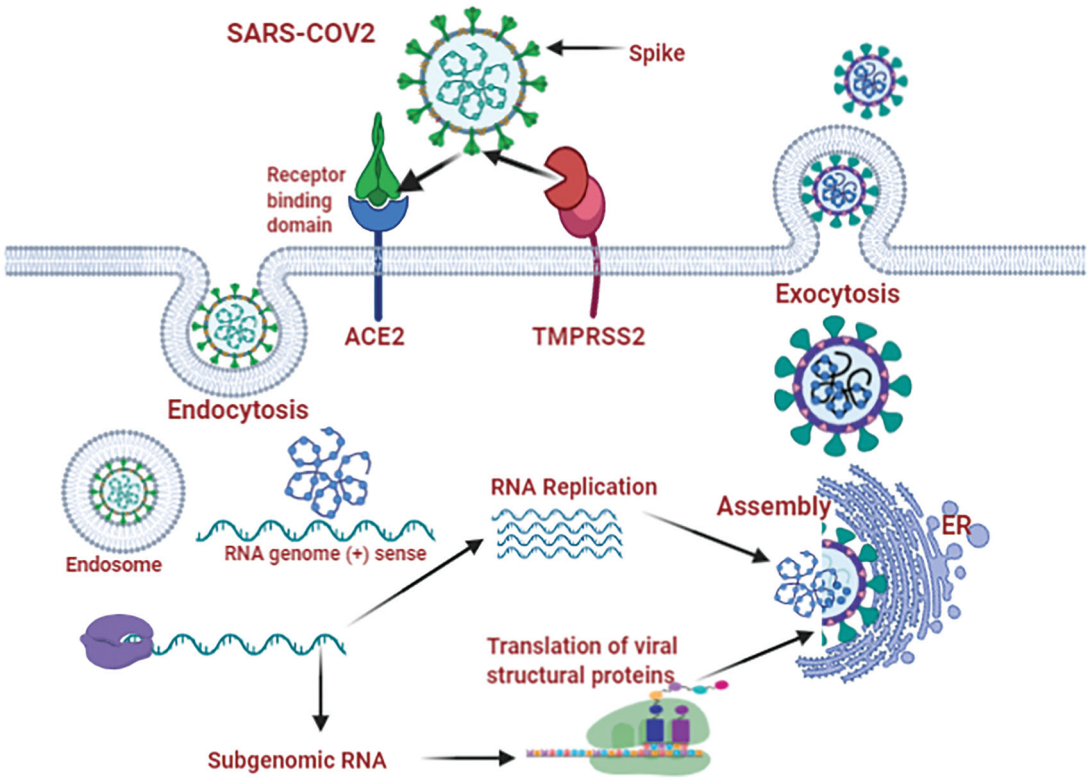

Figure 2. Schematic diagram of the life cycle of SARS-COV-2. The viral spike protein binds to angiotensin-converting enzyme 2 (ACE2) and enters the human cell by endocytosis. Afterward, the viral genome represented in positive-strand RNA is released into the cytoplasm. Then transcription of subgenomic RNA and RNA replication takes place and the formed structural proteins and nucleocapsids are assembled in the endoplasmic-Golgi apparatus intermediate compartment to form a mature virus which is further released by exocytosis from a human cell. Figure generated in Biorender (https://biorender.com/).

virus is released from Type II cells, a pulmonary toxin is concurrently released. Pathologically, diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells will develop [17].

Symptoms and complications

The incubation period of COVID-19 is approximately 5 days with a median duration of symptoms of 14 days (range 6-41days) [18,19]. The length of this period mainly depends on the age and immune status of the patient. The SARS-CoV-2 virus causes variable clinical features among the patients that can range from asymptomatic or mild symptoms, including fever, cough, breathlessness, weakness, headache, myalgia, nausea/vomiting, diarrhea, and nasal congestion to severe pneumonia and ARDS requiring intensive care unit (ICU) admission and oxygen therapy [20,21]. Nevertheless, sputum production and hemoptysis (coughing up blood) have been reported in some cases [1,20]. On the other side, atypical symptoms such as cardiovascular or nervous system symptoms can develop which complicates the diagnosis [21]. Besides, a few patients show some dermatological symptoms such as erythematous rash and generalized urticaria in addition to acral ischemia in the form of toe cyanosis and skin blisters [22]. However, the most unusual symptoms for COVID-19 were anosmia and dysgeusia as reported by Gelardi et al. [23]. The clinical presentation of COVID-19 infection is presented in Figure 1(B).

According to the clinical laboratory results, most SARS-CoV-2 patients show normal or decreased white blood cells and sometimes develop lymphocytopenia and thrombocytopenia. Also, most of the patients had high values of C reactive protein and some of them showed high levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and d-dimer [20,21]. For radiological imaging, although some cases were reported to have normal CT imaging, others were reported to have radiographic changes including multiple small patch-like shadows and interstitial changes which could develop to multiple ground-glass opacities in both lungs [21,24].

One of the major complications of COVID-19 is both venous and arterial thromboembolism. The reasons attributed to these fatal complications are excessive inflammatory response with a lack of oxygen in addition to diffuse intravascular coagulation [25]. Additionally, there are neurological and psychiatric complications with COVID-19 which include altered mental status, encephalopathy, and psychosis [26]. However, the most fatal complication is hypercytokinemia, also termed as a cytokine storm. Due to severe pneumonia caused by COVID-19 disease, high production of inflammatory cytokines resulted in acute lung injury and ARDS [27] due to inflammation of the alveolar membrane leading to high lung permeability and release of pulmonary fluid into air spaces [28].

Cytokine storm

Cytokine storm is a potentially life-threatening immune phenomena emerging from massive stimulation of inflammatory

signaling cascades with subsequent overproduction of inflammatory cytokines. It is considered as the foremost cause for ARDS and hence mortality in COVID-19 infection [29]. This is mainly caused by hyperactivation and dysregulation of immune cells such as T cells and macrophages which lead to massive tissue damage [27]. Normally the immune system responds to various pathogens by activation of inflammatory pathways. However, an exaggerated response leads to dysregulated and uncontrolled disease [30].

The inflammatory pathways involve the secretion of cytokines by both innate and adaptive immune cells. At the entry of the virus inside the body, the innate immune system response starts by detecting pathogen- associated molecular patterns (PAMP). In the case of the positive-strand RNA virus, the dsRNA and 5-triphosphate-bearing RNA molecules, replication intermediates of the virus, are all PAMPs. They are sensed by the cytoplasmic RNA sensors like the retinoic acid-inducible gene I (RIG-I)-like receptors composing of RIG-I, MDA5, and LGP2 [26]. Moreover, toll like receptors (TLR3 and TLR4) play a key role in the recognition of PAMPs [27]. All of these cytoplasmic sensors activate the transcription factors interferon (IFN)-regulatory factor 3 and 7 (IRF3, IRF7) and nuclear factor Kappa B (NF-kB) which lead to excretion of Type-I IFN and pro-inflammatory cytokines (Figure 3(A,B)). Subsequently, the Janus kinase/signal transducers and activators of transcription (JAK-STAT) signaling pathway will be activated followed by stimulation of the expression of antiviral interferon-stimulated genes (ISGs), (Figure 3(C)). These ISGs target the viral cycle steps to block viral replication [30]. Following these events, the leukocytes and plasma proteins are recruited to the site of infection.

The most important proinflammatory cytokines produced by macrophages and mast cells are interleukin (IL)-1, tumor necrosis factor alpha (TNF- α), and IL-6 [31]. Particularly, IL-6 is a prominent inflammatory agent of ARDS which has two pathways of signal transduction as illustrated in Figure 3. The first pathway is the classical signal transduction pathway in which IL-6 binds to its receptor IL-6R, then together they bind to the membrane protein gp130 to trigger downstream signal transduction and gene expression. The second pathway is the trans signal transduction pathway where IL-6 binds to soluble interleukin 6 receptor (sIL-6R) which is similar to IL-6R, and subsequently the complex binds to gp130. It is interesting that the trans signaling pathways are responsible for this inflammatory response associated with COVID-19, but the classic signal transduction is the protective pathways against the viral infection. The trans signaling pathway recruits macrophages, inhibit T cells apoptosis, and inhibits differentiation of regulatory T cells (Treg). As shown in Figure 3(D), both the trans-signaling and the classic-signaling pathways of IL-6 activate the JAK/STAT pathway and the mitogen activated protein kinase (MAPK) cascade [32]. These pathways play a major role in the differentiation of T helper (Th) cells [33]. In COVID-19 disease Th1 cells are hyperactivated as evidenced by high numbers of HLADR4 and CD38 positive cells [34]. However, lymphopenia is a hallmark in early diagnosis of COVID-19 where reduced numbers of $CD8^+$ T cells, B cells and Natural killer (NK) cells were demonstrated [35]. The defective responses of cytotoxic T cells, B cells and NK cells toward viral eradication provokes exaggerated and protracted generation of proinflammatory mediators most notably IL-6 by Th1 cells and macrophages, thereby aggravating the hyperinflammatory syndrome [36].

Crucially, the produced cytokines (IFN-γ and TNF-α) are responsible for the clinical features of COVID-19 such as fever, headaches, dizziness, and fatigue. Moreover, IL-6 causes vascular leakage, activation of complement and the coagulation cascade which can lead ultimately to disseminated intravascular coagulation (DIC) [37]. Soy et al. (2020) reported that increasing blood viscosity by the inflammatory mediators and immunoglobulins may be the reason for DIC [38]. Indeed, clinical laboratory studies of COVID-19 patients have reported significant elevation of serum levels of pro-inflammatory cytokines (IL-6, IFN-γ and TNF-α) especially in critically ill patients admitted to the ICU [39]. Consequently, inflammatory mediators, primarily IL-6, can serve as useful prognostic biomarkers for the severity of COVID-19 disease [40,41].

Given the crucial role of the cytokine storm to the tremendous morbidity and mortality rates of COVID-19 disease worldwide, investigators are examining effective medications for combating this phenomenon in order to improve the survival rates. In this regard, various anti-inflammatory drugs and immunomodulators have been proposed for their efficacy in diminishing the COVID-19 associated cytokine storm including cytokine inhibitors: IL1-β antagonist (Anakinra), IL-6 inhibitor (Tocilizumab), TNF-α inhibitor (adalimumab), Janus kinase (JAK) inhibitors (Baricitinib), chloroquine, hydroxychloroquine, and corticosteroids [42]. Nonetheless, the quest continues toward delineating optimum therapeutic agents that target various inflammatory signaling cascades implicated in the pathogenesis of COVID-19. Accordingly, in this review, we have proposed a drug repurposing approach for combating COVID-19 associated cytokine storm.

Drugs that might affect the cytokines storm in COVID-19

Statins

Statins are widely used anti-hyperlipidemic agents that act as 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA-reductase) inhibitors [43]. Not only do statins lower cholesterol levels but they also have many pleiotropic effects including reduction of vascular inflammation, improvement of endothelial function, and inhibition of platelet aggregation [44]. Statins exert an anti-inflammatory effect that might decrease the release of cytokines during the cytokine storm. The inhibitory effect of statins on inflammatory cascade was confirmed in an animal model of neuronal damage where statins decreased the release of proinflammatory cytokines such as TNF-α, IL-1β, and cyclo-oxygenase enzyme (COX)-2 in a cholesterol independent mechanism through NF-κB signaling pathway inhibition [45]. Besides, a statin was reported to decrease IL-6 in a cardiac fibrosis model and hence, inhibiting the IL-6/STAT3 pathway [46]. Moreover, this anti-inflammatory effect could also enhance the effect of the statin on

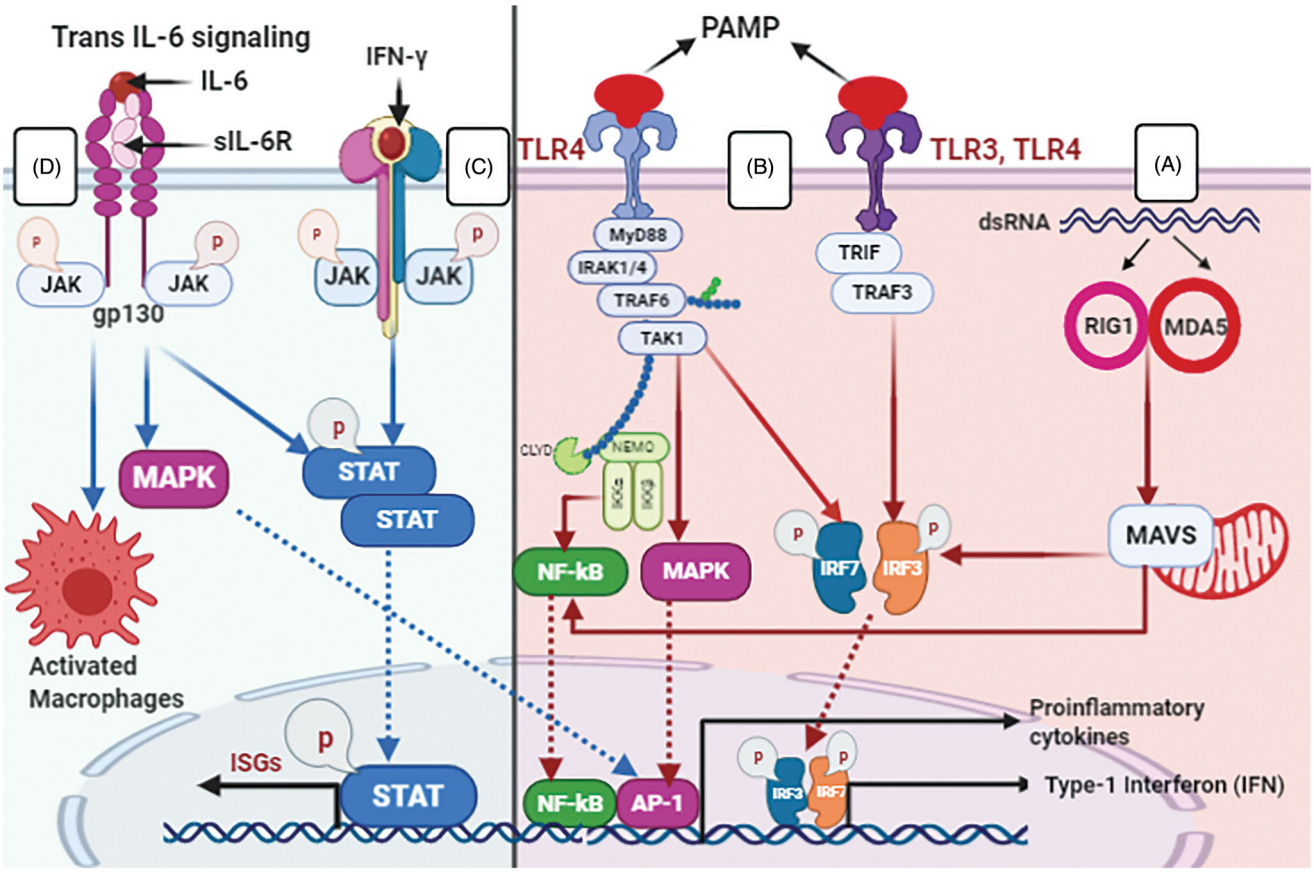

Figure 3. Schematic diagram illustrating inflammatory signaling cascades implicated in the pathophysiology of COVID-19-induced cytokine storm. (A) The viral RNA (dsRNA) is sensed by the cytoplasmic RNA sensors retinoic-acid inducible gene I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) which recruit adaptors, including mitochondrial antiviral-signaling protein (MAVS) leading to the activation of the transcription factor nuclear factor-κB (NF-κB) and interferon regulatory factor 3 (IRF3) and the production of type I Interferons and a series of pro-inflammatory cytokines. (B) Toll-like receptors (TLRs) pathway: Upon binding of pathogen-associated molecular patterns (PAMPs), TLRs are dimerized, which leads to recruiting myeloid differentiation primary response protein 88 (MyD88) and the TIR domain-containing adaptor-inducing IFN-β (TRIF). Then, MyD88 binds with IL-1 receptor-associated kinase 4 (IRAK4) resulting in the activation of IRAK1. Subsequently, the protein tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) and TAK1 are activated which further stimulate two signaling cascades; nuclear factor κB (NF-κB) pathway and mitogen-activated protein kinase (MAPK) pathway. The IκB kinase (IKK) complex consists of the catalytic subunits; IKKα and IKKβ and the regulatory subunit NEMO. TAK1 binds to the IKK complex inducing phosphorylation of IKKβ allowing NF-κB translocation into the nucleus to switch on the transcription machinery of a cluster of pro-inflammatory cytokines. TAK1 also induces stimulation of MAPK family members which mediates activation of AP-1 family transcription factors that further induces expression of diverse inflammatory mediators. Furthermore, the MyD88-dependent pathway can trigger phosphorylation of IRF7 that in turn induces expression of type 1 interferon (IFN). The TRIF-dependent pathway is utilized by only a few TLRs, such as TLR3 and TLR4. Upon recruitment and binding of TRIF to TLRs, it initiates the TRAF3-dependent signaling cascade which leads to phosphorylation of IRF3 that translocates to the nucleus commencing generation of type 1 IFN-β. (C) Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. Interferons (IFN-γ) trigger activation of the JAK/STAT pathway. The activated JAKs consequently phosphorylate the major substrates, STATs prompting their dimerization and then translocation into the nucleus to stimulate the expression of antiviral interferon-stimulated genes (ISGs). (D) IL-6 trans signal transduction pathway. IL-6 binds to soluble interleukin 6 receptor (sIL-6R) and subsequently bind to gp130. The trans signaling pathway stimulates JAK/STAT pathway and MAPK cascade, and recruits the macrophages. Figure generated in Biorender (https://biorender.com/).

promoting autophagy. It has been reported that a statin plays a role in the upregulation of autophagy by modulating AKT. and blocking the mammalian target of rapamycin (mTOR)/ribosomal protein S6 kinase (P70S6K) signaling pathway and decreasing the production of IL-1β, TNFα [47]. Moreover, statins have been reported to reduce TLR4 expression in immune cells with subsequent suppression of NF-κB and its downstream proinflammatory cytokines including IL-6 and IL-1β [48]. Also, statins were observed to have a pulmonary protective effect in an in-vivo model through mitigating alveolar damage and lung inflammation caused by paraquat intoxication [49]. Therefore, statins are suggested to have a beneficial effect as an adjunctive treatment of COVID-19. Moreover, statins displayed an immunomodulatory effect attributed to the inhibition of expression of major histocompatibility complex (MHC) class II, besides modulation of antigen presentation and T-cell co-stimulation which result in reducing the inflammatory effect of Th-1 cells and increasing the production of protective Th-2 cytokines [50]

In addition, statins have been reported to have an antithrombotic effect through inhibition of platelet endothelial cell adhesion molecule-1 signaling [51]. This might help in the management of microvascular pulmonary thrombosis that occurs in severe pulmonary coronavirus disease 2019 [52]. Clinically, statins demonstrated positive results in previous influenza pandemics *via* decreasing inflammation and negative outcomes in patients with influenza infection [53]. Furthermore, statins have been reported to reduce the mortality due to influenza virus H3N2 pandemics in 2007-2008 [54]. Also, statin users with seasonal influenza demonstrated

a reduction in vasopressor use and mechanical ventilation compared to non-statin users but with no significant effect on 30-day mortality [55].

Fibrates

Fibrates are another class of lipid lowering drugs *via* their impact on hepatic peroxisome proliferator activated receptors (PPARs) that are responsible for the regulation of lipid synthesis and secretion [56]. The activation of PPARα also leads to inhibition of NF-κB thus, reducing inflammation [57]. Moreover, PPAR agonists have been reported to exert an antiplatelet effect through inhibition of COX-1, thromboxane A2, and calcium mobilization [58].

Fenofibrates were stated to suppress inflammation and apoptosis cascades through inactivation of NF-kB and stimulation of adenosine monophosphate-activated protein kinase (AMPK) signaling [59]. Gemfibrozil has been reported to have anti-inflammatory immunomodulatory effects through the reduction of matrix metalloproteinase (MMP)-9 and the rise in adiponectin and the anti-inflammatory cytokine IL-10 [60]. Alternatively, fibrates can have an effect on reduction of viral replication as it has been reported that the combination of oseltamivir and fenofibrate in H7N9 infected mice resulted in a reduction of the viral titer in the lung tissue together with decreased pulmonary inflammation, and prolonged survival time [61]. Thus, fibrates could be a promising candidate to counteract cytokine storm and hinder viral replication in COVID-19 patients.

Thiazolidinediones

Thiazolidinediones or glitazones are oral insulin sensitizing medications that are used for management of type -II diabetes mellitus with minimal risk to develop hypoglycemia [62]. The mechanism of action of glizatones is through modulation of PPARs [63]. Pioglitazone reduced the level of IL-6 in a rat model of autism [64], and decreased the levels of proinflammatory cytokines TNF-α, IL-1β, and IL-6 in an acute pancreatitis model [65]. *via* PPARs activation, pioglitazone induced adiponectin leading to suppression of chemokine monocyte chemoattractant protein-1 (MCP-1) and reduced the level of transforming growth factor beta (TGF-β) in an animal model [66]. Moreover, rosiglitazone was reported to exert an anti-inflammatory effect through TLR-4 inhibition [67]. In addition, PPARs activation not only hinders the inflammatory response but is also responsible for the immunomodulatory effect of glitazones. In a multiple sclerosis model, pioglitazone has been observed to inhibit T-cell proliferation and reduce the secretion of IFN-γ and TNF-α proinflammatory cytokines suggesting its potential role in ameliorating the cytokine storm in COVID-19 patients [68] Moreover, the agents exert antiplatelet effect attributed to the activation of AMPK signaling pathway making platelet less responsive to stimuli such as collagen and thrombin [69]. Consequently, the activation of AMPK and PPARs by glitazones could target multiple complications associated with the COVID-19 cytokine storm such as marked inflammatory/immune response and coagulation, and thus they may help in decreasing the severity of cases.

Apremilast

Apremilast is an orally administered, inhibitor of phosphodiesterase enzyme (PDE) 4 thereby blocking degradation of intracellular cyclic adenosine monophosphate (cAMP) and modulating downstream influences on numerous intracellular signaling cascades in distinct cell types including inflammatory and immune cells [70]. It is approved in many countries for the treatment of psoriasis and psoriatic arthritis [71]. Several studies have confirmed the anti-inflammatory and immunomodulatory capabilities of apremilast; it diminishes the expression of a substantial number of pro-inflammatory cytokines and chemokines [72]. Elevation of intracellular cAMP leads to stimulating protein kinase (A) enzyme which in turn catalyzes phosphorylation of various transcription factors, such as cAMP response element binding protein (CREB) resulting in induced expression of particular genes encoding anti-inflammatory mediators such as IL-10 [73]. Activated CREB interferes with NFκB transcriptional activity leading to downregulated expression of a distinct set of NFκB-dependent proinflammatory genes such as TNF-α and IL-6 [74]. Indeed, in lipopolysaccharide (LPS)- challenged peripheral blood mononuclear cells, apremilast upregulated *in vitro* expression of IL-10 while downregulating the expression of several proinflammatory cytokines: TNF-α, IFN-γ, IL-12 and IL-23 [75]. Furthermore, it markedly blunted the production of TNF-α, IL-7, and MMP1, MMP3, MMP13, and MMP14 *in vitro* in human synovial cells and also substantially ameliorated experimental arthritis [76]. Clinically, in patients with psoriatic arthritis, treatment with apremilast dramatically reduced the plasma levels of proinflammatory mediators, comprising TNF-α, IL-6, IL-8, macrophage inflammatory protein (MIP)-1 β, (MCP)-1, ferritin, IL-17 and IL-23, and increased plasma levels of the anti-inflammatory cytokines; IL-10 [77]. Apremilast has been reported to have substantial effects on innate immunity in patients with recalcitrant plaque psoriasis through impeding epidermal and dermal infiltration of myeloid dendritic cell, T cells, and NK cells. Besides, it considerably abrogated inflammatory cytokines production in Th1, Th17, and Th22 pathways in psoriatic skin lesions, including IL-12/IL-23p40, IL-23p19, IL-17A, and IL-22 [78]. Strikingly, in an experimental model of ulcerative colitis in mice, apremilast showed suppressive effects on IL-6 inflammatory cytokine by impeding JAK–STAT signaling through inhibiting the phosphorylation of STATs. Moreover, phosphodiesterase (PDE)-4 inhibition by apremilast extensively hindered activation of numerous pathways such as MAPK, NF-κB, and phosphatidylinositol-3-kinase-mTOR pathways, which are implicated in the regulation of both innate and adaptive immunity [79]. Indeed, the promising anti-inflammatory properties of apremilast conferred protection against carfilzomib-induced pulmonary and vascular injuries [80]. Taken together, the anti-inflammatory and immunomodulatory effects of apremilast could have therapeutic potential in the management of Covid-19.

Cilostazol

Cilostazol is a selective inhibitor of PDE 3 enzyme which inhibits cAMP degradation in both platelets and vascular smooth muscle cells leading ultimately to the suppression of platelet aggregation and induction of peripheral vasodilation [81]. In addition to its anti–platelet, activity, cilostazol has recently been reported to have a diversity of pharmacological properties, including anti-inflammatory, antioxidant, and anti-apoptotic effects through the cAMP-dependent and -independent pathways [82]. The antiinflammatory effect of cliostazole has been demonstrated in numerous experimental models of inflammation, through upregulation of cAMP and consequently inhibition of NF-kB. Cilostazol significantly downregulated the inflammatory biomarkers, including IL-6, TNF-α, and TGF-β in a liver fibrosis model and hence, protected against thioacetamide-induced liver fibrosis [83]. The inhibitory effects on NFκB also account for its ability to blunt generation of adhesion molecules such as MCP-1 and vascular cell adhesion molecule-1 (VCAM-1) in a culture of endothelial cells taken from a human umbilical cord [84,85].

Multiple molecular mechanisms are implicated in the inhibitory effects of cilostazol on NFκB signaling. It directly disrupts TLR-4 and TLR-3 ligand- stimulated NF-κB transcriptional activity as evidenced by attenuating the recruitment and DNA binding activity of NF-κB p65 to the pro-inflammatory gene promoters in RAW264.7 macrophage cells stimulated with different TLR ligands [86]. Moreover, cilostazol blocked upstream activation of NF-kB by repressing phosphorylation of MAPKs, extracellular signal-regulated kinases 1 and 2 (ERK1/2) and c-Jun N-terminal kinase (JNK) in LPS-stimulated microglial cells which further led to significant attenuation of the release of proinflammatory markers such as NO, prostaglandin E2, IL-1, TNF-α, and MCP-1 in LPS stimulated microglial cells [87]. Furthermore, cilostazol effectively mitigated the inflammatory responses in an animal model of ischemia-reperfusion injury in the kidney mainly *via* increasing PPAR-ϒ transcriptional activity and expression in renal tissues, hence downregulating expression of inflammatory markers which include: IL-18, caspase-1, inducible nitric oxide synthase (iNOS), myeloperoxidase, intracellular adhesion molecule-1 (ICAM- 1) and VCAM-1[88]. These results from animal model were further confirmed by the clinical studies where cilostazol markedly diminished the expression of various inflammatory markers such as ICAM-1, VCAM-1 IL-1β, IL-6 and TNF-α in plasma of patients with thromboangiitis obliterans [89]. Alongside these anti-inflammatory effects, cilostazol has been shown to substantially modulate the immune responses by blocking differentiation of pro-inflammatory Th1 and Th17 cells and up-regulating anti-inflammatory Treg cells. This successfully ameliorated the severity of experimental autoimmune encephalomyelitis [90]. Other studies have reported that cilostazol can also decrease C-C chemokine receptor type 2 gene expression hence reduce MCP-1-induced chemotaxis and adhesion of monocytes [91]. Remarkably, cilostazol has displayed promising bronchodilator and bronchoprotective effects in humans implying its clinical usefulness in management of asthma [92]. In addition, due to its anti-platelet activity, cilostazol could aid in diminishing the thrombotic complications that increase the morbidity and mortality of Covid-19. The aforementioned date points out that cilostazol can offer therapeutic benefits for patients with Covid-19.

Acitretin: retinoic acid analogue

Retinoid compounds could regulate the immune system because of their similar action to vitamin A [93]. Currently, three generations of synthetic retinoids exist. Acitretin is an FDA-approved second generation retinoid used to treat psoriasis [94]. Retinoids bind cytosolic retinoic acid-binding protein transporting it to the nucleus where retinoids interact with retinoic acid receptor and retinoid receptor X along with binding to retinoic acid responsive elements on the DNA to regulate the transcription of several genes [95].

Retinoids have multiple pharmacological activities including anti-inflammatory and apoptotic effects, besides inhibition of tumor promotion [96,97]. Remarkably, retinoic acid (RA) hinders IL-6, IL-21, and IL-23 signaling that results in blocking the differentiation of naïve T cells to Th17 cells [98]. Furthermore, RA inhibits $CD4^{+}CD44^{high}$ cells in production of IL-4, IL-21, and IFN-ϒ cytokines, therefore promoting the differentiation of Tregs [99]. Additionally, RA together with IL-2 and TGF-β enhance and sustain Forkhead family transcription factor (FOXP3) expression thereby further activates Tregs differentiation [100,101]. Curiously, combination of TGF-β with IL-6 can stimulate Th17 cells. However, RA maintains the Treg–Th17 balance through blocking IL-6 signaling [99]. In addition to inhibiting inflammatory cytokines, RA stimulates the production of IL-10, an anti-inflammatory cytokine, in Tregs [102]. IL-22 is a crucial factor in tissue repair. Nevertheless, it is associated with an autoimmune response [103]. Notably, RA could regulate IL-22 function initially *via* enhancing IL-22 production in ϒδ T cells and innate lymphoid cells followed by its neutralization and inactivation through attaching free IL-22 to binding a protein derived from immature dendritic cells [104].

Recognition of viral pathogens through the innate immune response including RIG-I can stimulate innate antiviral signaling [105]. Acitretin, at clinically achievable concentrations boosts RIG-I expression and augments its signaling thus arming innate immune defense [106]. Based on antiviral, anti-inflammatory, and immunomodulatory roles of retinoids, acitretin is suggested as a promising agent to counteract CIVID-19-mediated cytokine storm.

Olaparib: PARP inhibitor

Poly (ADP-ribose) polymerase (PARP) is a family of nuclear enzymes that have a crucial role in DNA repair. Currently, PARP is broadly involved in regulation of a wide variety of nuclear events, including the regulation of protein-nucleic acid interactions [107]. The epigenetic role of PARP occurs *via* 1- regulation of chromatin re-modelling, 2- functioning as a transcriptional co-regulator, 3- modulating DNA methylation, 4-poly (ADP) ribosylation of target proteins involved in

gene transcription and/or 5- regulation of RNA metabolism and function [108,109].

PARP activation is involved in various pathophysiological conditions leading to cell necrosis and activation of signal transduction by acting as a co-activator in NF-κB-mediated transcription and stimulating the AKT pathway that contributes to the activation of a variety of inflammation-related transcription factors including activator protein-1(AP1), activator protein-2 (AP2), and STAT1 [110]. In this context, PARP inhibitors were reported to inhibit the overproduction of proinflammatory cytokines such as IL-6, pro-IL-1, ICAM-1, TNF-α, COX-2, iNOS, MIP-1α and MIP-2 [111].

Olaparib is the first PARP inhibitor approved by the US Food and Drug Administration for the treatment of ovarian cancer [112]. Most of the effects of olaparib are due to the inhibition of PARP1, PARP2, and other PARP isoforms [108]. Olaparib has demonstrated cytoprotective efficacy in preclinical studies of acute lung injury and chronic asthma [113,114]. In addition, the immunomodulatory role of Olaparib is mediated by reducing the production of Th2 cytokines in human CD4+ T-cells besides increasing Treg cells. Accordingly, the repurposing of olaparib with a short administration duration could offer beneficial outcomes for COVID-19 patients who have a high risk of mortality.

Vorinostat: Histone deacetylase inhibitor

Histone deacetylases (HDACs) are a class of enzymes that remove the acetyl moiety from specific lysine residues on histone proteins leading to the tight wrapping of DNA. Therefore, HDACs act as key epigenetic modulators of essentially biological processes including transcription factors, chaperones and signaling molecules, resulting in changes in protein stability, protein-protein interactions, and protein-DNA interactions to control diverse cell functions [115,116].

Vorinostat is the most widely used of the HDAC inhibitors (HDACs) that target HDACs I and II and is approved for the treatment of cutaneous T cell lymphomas with good oral bioavailability and tolerability [117]. In addition to their anticancer role, HDACis are novel therapeutic tools in the management of viral infections through reactivating the latent virus present in infected cells, and then its clearance from cellular reservoirs through cytolysis or immune-mediated clearance, as demonstrated in human immune-deficiency virus (HIV), hepatitis C virus (HCV), and human cytomegalovirus infections [118,119].

Although high concentrations of vorinostat are required for anti-tumor effects, low concentrations of vorinostat can reduce the secretion of inflammatory cytokines, and thus ameliorate the cytokine storm syndrome [120]. Interestingly, HDACs such as Vorinostat modulates STAT1, STAT3, MAPKs, and NF-κB signaling pathways [120–122]. Therefore, HDACs were approved as anti-inflammatory and cell-protective agents in various pathological conditions [123–125]. In this regard, Vorinostat significantly alleviated respiratory syncytial virus-induced airway inflammation through reducing pro-inflammatory cytokine production, besides decreasing neutrophil and T cell infiltration [126]. Interestingly, HDACs reduced the production of the macrophage migration inhibitory factor (MIF) which is a pro-inflammatory cytokine expressed by immune cells. MIF binds the Human Leukocyte Antigen (HLA) class II histocompatibility antigen gamma chain, CD74, causing its phosphorylation and the recruitment of CD44, which allows the activation of ERK/MAPK pathway [127].

Strikingly, Vorinostat exhibits an immunomodulatory role [128]. Tregs express FOXP3, which activates many suppressive genes in Tregs and inhibits many effector T cell genes. HADCs could regulate Treg function through enhancing FOXP3 acetylation and hence relieve autoimmune diseases [129]. Vorinostat could enhance suppressive function of Treg to constrain Th17 cell differentiation, repress Th1 cell activities, and inhibit antigen presenting cells functions *via* targeting NF-κB signaling pathways [124]. Interestingly, the function of exhausted CD8 T cells in chronic viral infection was shown to be restored upon HDACis treatment [130]. Consequently, Vorinostat is a promising agent to manage COVID-19 comorbidities *via* its antiviral and anti-inflammatory effects, besides its immunomodulatory role.

Pirfenidone

Pirfenidone is a novel anti-inflammatory, antifibrotic, antiproliferative medication approved for management of idiopathic pulmonary fibrosis [131]. Pirfenidone has been shown to have PPAR agonistic activity in a mouse model of nonalcoholic steatohepatitis and it also mediates potent anti-inflammatory activity [132]. It reduces the expression of several inflammatory cytokines such as IL-3 and IL-4 and downregulates IL-1β which is otherwise responsible for stimulation of fibroblast to produce platelet derived growth factor (PDGF) and TGF-β [133]. In an acute pancreatitis model, it suppressed the expression of NF-κB and hence decreased the level of TNF-α and IL-6 [134]. It also has been observed to block the activation of the nucleotide-binding oligomerization domain-like receptor with pyrin domain 3 (NLRP3) inflammasome, a mechanism involved in acute lung injury and alveolar damage in ARDS, which potentially leads to secretion of caspase protein, active IL-1β and reactive oxygen species [135]. These promising anti-inflammatory effects of pirfenidone suggest it as a possible candidate to be investigated for its capabilities for abrogating COVID-19 associated cytokine storm.

Nintedanib

Nintedanib is a novel triple angiokinase inhibitor that acts on PDGF receptor, vascular endothelial growth factor receptor, and fibroblast growth factor receptor. Clinically, nintedanib is used for management of idiopathic pulmonary fibrosis [136]. Nintedanib decreased the inflammatory cytokines IL-6, TNF-α and TGF-β induced by bleomycin in an experimental rat model which otherwise mediated responsible for alveolar damage, thus supporting its anti-inflammatory and lung protective effect [137]. It also normalized the lung microvasculature and improved lung function [138]. These activities

suggest the lung protective effect of nintedanib could be used during ARDS associated with sever COVID-19 cases.

Rivaroxaban: protease-activated receptor (PAR) modulator

In severe COVID-19 cases, coagulation dysfunction may occur within a few days as a result of severe inflammatory storms which can be fatal [139]. Tissue factor (TF) is primary initiator of the blood coagulation and is strongly activated by inflammatory cytokines [140]. Upregulation of TF induces fibrin deposition and thrombin generation that are crucial for inflammation [141]. Strikingly, TF-coagulation factor VIIa complex and coagulation FXa can activate protease-activated receptors (PAR)-2 signaling that has crucial roles in inflammation and is involved in autoimmune diseases like inflammatory bowel disease, autoimmune encephalitis, and multiple sclerosis [142,143]. In the process, coagulation factor VIIa/FXa-PAR-2 signaling activates NF-κB and MAPK, which play key roles role in cytokine production [144]. PAR-2 signaling has been reported to promote cytokine production by mouse CD4+ T cells [145], leukocyte activation, and their recruitment toward the site of inflammation or infection. Therefore, PARs have important actions in innate and adaptive immune response and represent an attractive target for the therapy of inflammatory, infectious, or autoimmune diseases [146].

Rivaroxaban is a novel anticoagulant approved for the prevention of stroke in patients with atrial fibrillation, and is also used for prophylaxis of deep venous thromboembolic and pulmonary embolism [147]. Rivaroxaban is a direct factor Xa inhibitor, and consequently reduces thrombin activation responsible for the induction of inflammatory processes, such as activation of microglia [148] or induction of pro-inflammatory cytokines (e.g. IL-1β, TNF-α) and cell adhesion molecules under different pathological conditions [149]. Besides its anticoagulant role, rivaroxaban mediated anti-inflammatory effects in several experimental studies by modulating the levels of inflammatory cytokines including IL-1β, IL-6, TNF-α and MCP-1[150], besides decreasing MMP-9 [151]. Noteworthy, rivaroxaban was reported as a new therapeutic approach to prevent the progression of acute lung injury and atrial inflammatory fibrosis *via* suppression of PAR-2-NFκB signaling and inflammation [152,153]. Thus, rivaroxaban represents a promising antithrombotic/anti-inflammatory strategy to hinder the coagulation disorders and cytokine storm implicated in the fatal complications of COVID 19.

Forskolin

Forskolin is a diterpene derivative extracted from the roots of the plant *Coleus forskohlii*. It directly stimulates adenylate cyclase enzyme thereby rising levels of cAMP in a variety of cells [154]. Forskolin exhibited anti-inflammatory activities as it could effectively mitigate inflammation in mononuclear leukocytes induced by LPS by diminishing the expression of a wide array of inflammatory cytokines including IL-6, IL-21, IL-23, and TNF-α. This anti-inflammatory effect was mainly attributed to down-regulating the TLR4/myeloid differentiation protein 88 (MyD88)/NF-κB inflammatory signaling cascades [155]. In an ischemia-reperfusion liver injury model, forskolin mediated a hepatoprotective effect by diminishing neutrophil and macrophage infiltration. These effects were associated with augmenting actions of anti-inflammatory cytokine IL-10 while repressing the generation of pro-inflammatory cytokines; TNF-α/IL-6/IL-12 [156].

Similarly, forskolin exhibited nephroprotective properties by relieving uro-pathogenic Escherichia coli-induced pyelonephritis in mice as shown by reducing renal generation of proinflammatory mediators (TNF-; keratinocyte chemoattractant; IFN; MCP; macrophage inflammatory protein; Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES)) and renal myeloperoxidase activity [157]. Besides, it was documented that forskolin hampers the secretion of IL-1β from human macrophages by enhancing production of cAMP, which further binds to the NLRP3 protein and targets it for degradation [158]. Additionally, forskolin has been proven to have immunomodulatory effects in an experimental model of auto-immune encephalomyelitis through interruption of macrophage/microglia activation, and infiltration and production of IFN-γ by CD4 T cells [159]. Furthermore, there was evidence for the bronchodilator effects of forskolin attributed to suppressing generation of various inflammatory cytokines and chemokines; NFkB-p65, IL-4, interleukin-5 (IL-5), IL-17 and ICAM-1 together with downregulation expression of MMP-9, and tissue inhibitor of metalloproteinase-1 (TIMP-1) in lung tissue by stabilizing the extracellular matrix [160]. In addition, forskolin has been shown to possess anti-platelet activity mediated by elevating levels of platelet cAMP [161]. Collectively, these data indicate that forskolin could be a potential candidate for management of COVID-19.

Conclusion

The recently emerging outbreak of COVID-19 was declared as a pandemic by the WHO in March 2020 poses enormous threat to the public health. Numerous critically ill patients died from devastating viral pneumonia and overwhelming inflammatory reactions where the virus triggers overproduction of substantial quantities of inflammatory cytokines in a phenomenon termed as 'cytokine storm.' These inflammatory responses are considered as prime causative factors of ARDS and multiple-organ failure associated with COVID-19 and thus contributes to disease progression. Hence, elucidating the underlying molecular mechanisms responsible for this potentially life-threatening event is challenging medical health systems worldwide. In addition, exploring effective therapeutic modalities for combating the cytokine storm represents an urgent necessity as it can provide a path forward to diminish the morbidity and mortality in COVID-19 infection. In this review, we have highlighted the pathophysiology of COVID-19 -induced cytokine storm focusing on the precise molecular mechanisms an underlying this phenomenon. Moreover, we have postulated a drug repurposing approach to be effective weapon in the battle against cytokine storm

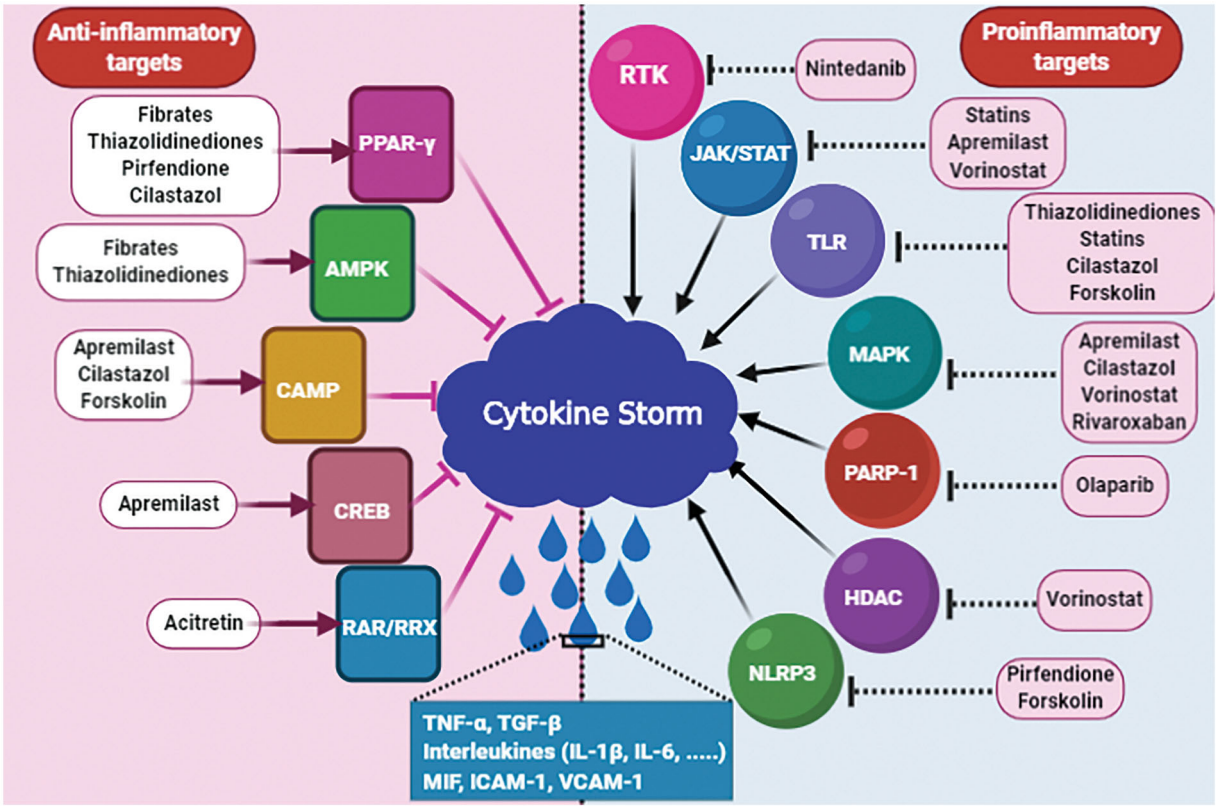

Figure 4. Schematic diagram summarizing mechanistic (pro/anti-inflammatory) targets that influence generation of inflammatory cytokines and chemokines (cytokine storm) associated with COVID-19 together with the corresponding drugs influencing each target. Pro-inflammatory targets: Receptor tyrosine kinase (RTK), Janus kinase/signal transducers and activators of transcription (JAK/STAT), Toll like receptors (TLR), mitogen-activated protein kinase (MAPK), Poly(ADP-ribose) polymerase (PARP-1), Histone deacetylases (HDAC) and nucleotide-binding oligomerization domain-like receptor with pyrin domain 3 (NLRP3). Anti-inflammatory targets: peroxisome proliferator activated receptors- γ (PPAR- γ), adenosine monophosphate-activated protein kinase (AMPK), cyclic adenosine monophosphate (cAMP), cAMP response element binding protein (CREB) and retinoic acid receptors (RAR)/retinoid receptor X (RRX). Cytokines & chemokines: Tumor necrosis factor alpha (TNF-α), Transforming growth factor beta (TGF-β), interleukins (IL-1β & IL-6), macrophage migration inhibitory factor (MIF), intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion protein-1 (VCAM-1). Figure generated in Biorender (https://biorender.com/).

Table 1. Summary of candidate repurposed drugs and its potential mechanisms of action for the management of COVID-19.

Drug	Status/ FDA approval	Mechanism of action	References
Statins	Anti-hyperlipidemic	• Anti-inflammatory effect via inhibiting NF-κB, IL-6/STAT3, and TLR4 signaling pathways. • Upregulation of autophagy by modulating AKT/mTOR signaling cascade. • Modulation of immune system. • Antithrombotic activity through inhibition of platelet endothelial cell adhesion molecule-1 signaling.	[45,47,48,51]
Fibrates	Anti-hyperlipidemic	• Anti-inflammatory through activation of PPAR and AMPK signaling as well as inhibition of NF- κB. • Antiplatelet activity via inhibition of COX-1, thromboxane A2, and calcium mobilization.	[57,59]
Thiazolidinediones	Oral anti-diabetic	• Inhibit inflammatory response by activating PPARs and reducing TLR4 expression. • Anti-platelet effect by activating AMPK signaling pathway. • Modulation of immune system.	[66,67,69]
Apremilast	Treatment of psoriasis and psoriatic arthritis	• Elevation of intracellular cAMP by inhibiting PDE-4 leads to phosphorylation of CREB and down regulation of NF-κB. • Inhibition of MAPK, PI3K/mTOR, and JAK–STAT signaling. • Modulation of immune system.	[74,79]
Cilostazole	Anti-platelet	• Selective inhibition of PDE 3 enzyme. • Anti-inflammatoy activity through upregulation of cAMP and enhancing PPAR-ϒ transcriptional activity with down regulation of NF-κB, MAPK, and TLR signaling pathways. • Modulation of immune system.	[81,83,86–88]
Acitretin	Treatment of psoriasis	• Blocking the differentiation of naïve T cells to Th17 cells, while promote the differentiation of Tregs through enhancement of FOXP3 expression. • Increase RIG-I expression that stimulate innate antiviral signaling.	[98,100,106]
Olaparib	Treatment of ovarian cancer	• PARP inhibitor.	[111]

(*continued*)

Table 1. Continued.

Drug	Status/ FDA approval	Mechanism of action	References
		• Inhibiting overproduction of pro-inflammatory cytokines. • Modulation of immune system.	
Vorinostat	Treatment of cutaneous T cell lymphomas	• HDAC inhibitor. • Anti-inflammatory effect through hindering STAT1, STAT3, MAPKs, and NF-κB signaling pathways, besides decreasing MIF production. • Immunomodulator through augmenting FOXP3 acetylation.	[117,120–122,127,129]
Pirfenidone	Management of idiopathic pulmonary fibrosis	• PPAR agonist. • Potent anti-inflammatory and anti-fibrotic properties through inhibiting NF-κB and IL-1β signaling. • Blocking the activation of NLRP3 involved in acute lung injury.	[133–135]
Nintedanib	Management of idiopathic pulmonary fibrosis	• Triple angiokinase inhibitor. • Reduction the production of inflammatory cytokines.	[136,137]
Rivaroxaban	Anticoagulant for prevention of stroke in atrial fibrillation patients, and prophylaxis of deep venous thromboembolic and pulmonary embolism	• Anti-coagulant through direct inhibition of factor Xa. • Anti-inflammatory and anti-fibrotic activities through suppressing PAR-2-NF-κB signaling.	[148,152]
Forskolin	No clinical data available as of yet.	• Direct stimulation of adenylate cyclase enzyme thus enhance the production of cAMP and degradation of NLRP3. • Down-regulating the TLR4/ (MyD88)/NF-κB inflammatory signaling pathways. • Modulating immune system. • Anti-platelet effect through increasing cAMP levels.	[154,155,158,159,161]

AMPK: AMP-activated Protein Kinase; cAMP: cyclic adenosine monophosphate; COX-1: cyclo-oxygenase-1 enzyme; CREB: cAMP response element binding protein; FOXP3: Forkhead family transcription factor; HDAC: Histone deacetylase; IL-6: interleukin 6; JAK: Janus kinase; MAPK: mitogen activated protein kinase; MIF: migration inhibitory factor; MyD88: myeloid differentiation protein 88; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear Factor Kappa B; NLRP3: nucleotide-binding oligomerization domain-like receptor with pyrin domain 3; PAR2: protease-activated receptors 2; PARP: Poly (ADP-ribose) polymerase; PDE: Phosphodiesterase enzyme; PPAR: Peroxisome Proliferator Activated Receptors; RIG-I: Retinoic acid-inducible gene I; STAT: signal transducer and activator of transcription; TGF-β: tissue growth factor beta; Th: T-helper; TLR: Toll-like Receptor; TNF-α: Tumor necrosis factor alpha.

via searching the literature for drugs that can target distinct inflammatory signaling cascades implicated in the pathogenesis of cytokine storm as shown in Figure 4. Accordingly, the discussed drugs could be promising candidates for further experimental and clinical studies investigating their therapeutic potential against COVID-19-induced cytokine storm. Summary of the discussed drugs with their potential mechanism of action in COVID-19 is presented in Table 1.

Disclosure statement

The authors declare that there are no conflicts of interest.

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