



# Immunomodulatory agents for COVID-19 treatment: possible mechanism of action and immunopathology features

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## Abstract

The novel coronavirus pandemic has emerged as one of the significant medical-health challenges of the current century. The World Health Organization has named this new virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since the first detection of SARS-CoV-2 in November 2019 in Wuhan, China, physicians, researchers, and others have made it their top priority to find drugs and cures that can effectively treat patients and reduce mortality rates. The symptoms of Coronavirus Disease 2019 (COVID-19) include fever, dry cough, body aches, and anosmia. Various therapeutic compounds have been investigated and applied to mitigate the symptoms in COVID-19 patients and cure the disease. Degenerative virus analyses of the infection incidence and COVID-19 have demonstrated that SARS-CoV-2 penetrates the pulmonary alveoli's endothelial cells through Angiotensin-Converting Enzyme 2 (ACE2) receptors on the membrane, stimulates various signaling pathways and causes excessive secretion of cytokines. The continuous triggering of the innate and acquired immune system, as well as the overproduction of pro-inflammatory factors, cause a severe condition in the COVID-19 patients, which is called "cytokine storm". It can lead to acute respiratory distress syndrome (ARDS) in critical patients. Severe and critical COVID-19 cases demand oxygen therapy and mechanical ventilator support. Various drugs, including immunomodulatory and immunosuppressive agents (e.g., monoclonal antibodies (mAbs) and interleukin antagonists) have been utilized in clinical trials. However, the studies and clinical trials have documented diverging findings, which seem to be due to the differences in these drugs' possible mechanisms of action. These drugs' mechanism of action generally includes suppressing or modulating the immune system, preventing the development of cytokine storm via various signaling pathways, and enhancing the blood vessels' diameter in the lungs. In this review article, multiple medications from different drug families are discussed, and their possible mechanisms of action are also described.

**Keywords** SARS-CoV-2 · Pathophysiology · COVID-19 treatment · Inflammatory responses · Immunosuppressive agents · Cytokine storm

## Introduction

The newest member of the coronavirus family, named SARS-CoV-2 or formerly 2019 novel coronavirus (2019-nCoV)—a beta-coronavirus from RNA viruses—is a causative agent of a crucial respiratory infection known as COVID-19 in

patients [1]. The genetic material of SARS-CoV-2, which is attached to the virus's Nucleocapsid protein, consists of 26 to 32 Kbps [1, 2]. This virus was first identified in December 2019 in Wuhan, Hubei Province, Mainland China [3]. In March 2020, SARS-CoV-2 spread to more than 114 countries, prompting the World Health Organization to announce a pandemic for SARS-CoV-2 [4]. The virus is hypothesized to have been originally a zoonotic virus transmitted from animals to humans, although human-to-human transmission of the 2019-nCoV has led to its spread [5].

Coronaviruses are generally classified into four primary groups: alpha, beta, delta, and gamma [6]. SARS-CoV-2, as a beta-coronavirus, has various structural proteins. Spike protein, nucleocapsid protein, and membrane proteins are among the most crucial structural proteins of SARS-CoV-2

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that can stimulate the immune system [1, 2]. The virus enters host cells through endocytosis by binding to Angiotensin-Converting Enzyme 2 (ACE2) receptors present on the cell membrane and begins to replicate by exploiting the host cell replication machine [7]. In addition to the lungs, ACE2 is present on the cell membrane of other tissues such as the heart, kidneys, testes, and intestines, enabling SARS-CoV-2 to infect these organs [8, 9].

COVID-19 is generally considered a respiratory disease that involves the lungs. It can cause disparate symptoms such as fever, dry cough, fatigue and headache. [10]. Although in most patients SARS-CoV-2 results in mild symptoms, however in some patients, this infection may cause acute and widespread damages such as septic shock, acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS) [11, 12]. In COVID-19, like other infectious diseases, fever occurs due to the release of various cytokines and their effects on the hypothalamus. All symptoms of SARS-CoV-2 infection occur due to the stimulation of the immune system and activation of innate and acquired immunity against this virus [13]. When SARS-CoV-2 enters the body, it is firstly detected by innate immunity cells and their receptors (such as Toll-like receptor 3 (TLR-3)) [14] which results in the formation of NLRP3 inflammasomes and inflammatory responses [15]. CD4+ and CD8+ cells have a remarkable role in the synthesis of cytokines and chemokine and acquired immunity activation [16]. CD8+ cells clear viruses from the body by activating cytotoxic pathways [17]. CD4+ cells are involved in synthesizing and releasing chemokines and cytokines from the immune cells by differentiating into T-helper 1 cell (Th1) [18]. Cytokines and various compounds such as interleukins (ILs)-1  $\alpha/\beta$ , IL-2, IL-4, IL-6, IL-10, IL-17 and TNF- $\alpha$ . [19], are produced when cells get infected by SARS-CoV-2, culminating in the migration of lymphocytes and leukocytes to the lesion site [20]. This mechanism can lead to the overproduction of cytokines (known as cytokine storm), damage to normal lung cells, destruction of lung tissue, and even critical condition or death [13, 18]. A detailed account of COVID-19 impacts on the immune system as well as its immunopathology ramifications is illustrated in Fig. 1.

It is hypothesized that the application of immunomodulatory drugs can neutralize these cytokines or prevent critical conditions in patients by inhibiting the function of harmful molecules [21]; for this reason, these drugs have been considered for the treatment of COVID-19. So far, only one particular antiviral drug called Molnupiravir is suggested for COVID-19 treatment [22]. However, various antiviral agents with different mechanisms of action have been used for COVID-19 patients in clinical trials, which sometimes have been effective and sometimes ineffective [23]. This review paper is aimed at summarizing the immunomodulatory drugs administered to treat COVID-19 or alleviate its

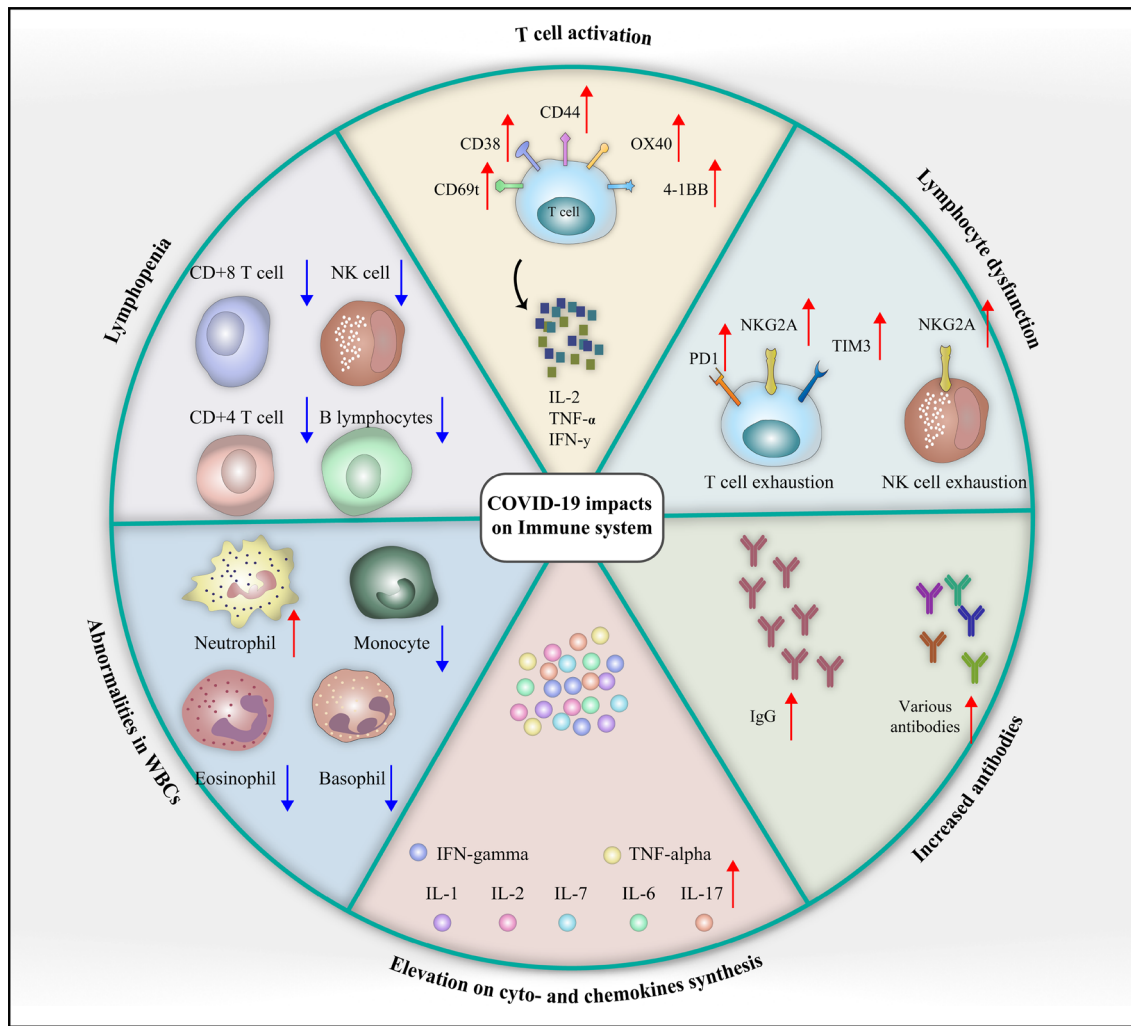
symptoms. It also tries to investigate the possible mechanism of action and clinical trials implemented to express their effectiveness or ineffectiveness. In the following section, the most critical immunomodulatory agents from different drug families are reviewed.

## Main text

The following describes the possible mechanism of action and pharmacological properties of some critical agents from various family drugs, which are discussed or seem to be effective for modulating immune system responses after SARS-CoV-2 infection.

## Anakinra

Anakinra is an anti-inflammatory drug that is primarily applied to treat Rheumatoid arthritis (RA). Interleukin-I and other cytokines are involved in the development of RA [24]. This issue has drawn the attention of scientists and researchers to anti-rheumatoid medications because in COVID-19 infection, like RA [25], over activation of the immune system and overproduction of cytokines such as IL-1 worsen the patient's condition [26]. In 1980, after discovering Interleukin-I Receptor Antagonist (IL-I Ra)—which is naturally present in the synovial membrane—various proteins and antagonistic compounds were adopted for RA treatment via inhibiting the function of interleukins or other pathways [27, 28]. After the detection of endogenous IL-1Ra, it was isolated. After the purification and determination of its amino acid sequence, its mRNA and synthesized cDNA were inserted into the *Escherichia coli* (*E. coli*) genome for protein expression [29]. This produced human recombinant protein in *E. coli*, which had IL-1R antagonistic properties, was called Anakinra. This therapeutic protein with a molecular weight of about 17 kDa can exert its effect by binding to Interleukin-I Receptors (IL-1Rs) that are present on the surface of T cell membranes [30]. It is primarily capable of inhibiting the function of both IL-1 $\alpha$  and IL-1 $\beta$ . Anakinra's mechanism of action against IL-1 is conducted by suppressing the natural binding of IL-1 to IL-1Rs and IL-1 accessory portion (IL-1Acp) that are present on the exterior of T cell membranes. In fact, in the absence of Anakinra, IL-1 binds to IL-1R and IL-1Acp to activate intracellular signaling pathways and stimulates T cells [28]. IL-1 can also stimulate the production of Prostaglandin E2 (PEG2) or metalloprotease enzymes and the degradation of peptidoglycans [28, 31]. Anakinra also inhibits IL-1-induced hyaluronic acid (HA) production in cartilage [32]. It is hypothesized that these positive effects of Anakinra can effectively block the destruction of lung tissue and its harmful heterogeneous regeneration. Various cohort studies have been conducted



**Fig. 1** The investigation of COVID-19 immunopathology indicated that the infected individuals' immune patterns include increased activation of T cells, which is accomplished by the higher expression of some receptors in the T cell membrane. Lymphopenia is a critical immune pattern in COVID-19 patients. Overproduction of some

cytokines and chemokines caused by SARS-CoV-2 infection may result in cytokine storm and even ARDS. Lymphocytes dysfunction, abnormalities in WBCs, and increased antibodies are also other important immunopathological patterns in COVID-19 that can be observed in detail

on the application of this drug in COVID-19 patients. In one of these studies, the utilization of Anakinra reduced the requirement of mechanical ventilation in patients and also decreased the demand for ICU hospitalization and fatality rate [33]. This cohort study [33], along with available information on the mechanism of action in this therapeutic agent as well as other studies, has set forth Anakinra as an appropriate candidate to hinder the destructive effects of the cytokine storm.

### Tocilizumab

As noted before, Interleukin 6 (for short, IL-6) is a significant pro-inflammatory protein and cytokine that can be freely present in serum [34]. The concentration of this

cytokine in a normal situation is not high in a healthy person. Its concentration, however, increases following an infection or inflammation. This interleukin has an influential role in initiating and inducing biochemical reactions and can regulate inflammation and the immune response in two ways [35]: Classical and Trans pathways. In the classical pathway, IL-6 attaches to the membrane-bound receptor for IL-6 (mbIL-6), which is present on various immune cells' membranes. Then this complex acts as a ligand and binds to a glycoprotein structure called Glycoprotein-130 (gp-130) [36]. Next, it stimulates the innate immune response (via macrophages and neutrophils) and acquired immunity (through T and B cell stimulation) [37]. In the Trans pathway, IL-6 can cause the production of large volumes of pro-inflammatory agents by attachment to a structure called soluble

receptor for IL-6 (srIL-6), which is amply present on the surface of endothelial cells (rather than immune cells) [38]. Tocilizumab, a humanized monoclonal antibody, can act as an antagonist against IL-6 and bind to both mL-6R and sIL-6R receptors to prevent IL-6 from attaching to them. This attachment ultimately results in the prevention of signaling pathways leading to inflammation. The United States Food and Drug Administration (US-FDA) approved phase III of Tocilizumab's clinical trial for COVID-19 patients [39]. Nevertheless, extensive studies are still required to evaluate the effectiveness of Tocilizumab and its mechanism of action.

### Infliximab

Infliximab is a chimeric monoclonal antibody with the molecular formula  $C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$ , which is capable of binding to either soluble or membrane-bound TNF- $\alpha$  [40]. The attachment of Infliximab to soluble TNF- $\alpha$  prevents it from binding to the cellular receptors and suppresses the initiation of signaling cascades caused by this binding. The attachment of this therapeutic agent to membrane-bound TNF- $\alpha$  has also been proved to cause cell lysis through different immunological mechanisms such as antibody-dependent cellular cytotoxicity (ADCC) [40, 41]. This medication is vastly applied for treating RA via suppressing the harmful effects of cytokines [42]. The utilization of Infliximab can also reduce the concentration of C-Reactive Protein (CRP) as well as IL-6 in the patients' blood [43] and appears to be able to prevent cytokine storms in COVID-19 patients. The synovial biopsy also indicated that consumption of Infliximab could reduce TNF- $\alpha$  production followed by a reduction in IL-1 synthesis [44, 45]. These findings suggest that Infliximab may be a viable option for preventing cytokine storm incidence and the patients' severe condition. Finally, Mohsen Farrokhpour et al. [46] investigated the impact of Infliximab prescription for COVID-19 patients. All patients in this study were in severe condition and admitted to the ICU. This study revealed that the patients who received Infliximab survived more than the ones in the control group (63% vs. 37.2%, respectively) [46]. In this study, the mortality rate was reported to be only 37% in the Infliximab group, while it was 62.8% for the control group [46]. However, further studies are warranted to determine the precise efficacy of this drug in the treatment of COVID-19 patients.

### Baricitinib

As mentioned earlier, SARS-CoV-2 results in cytokine storm and severe inflammation by stimulating the secretion of pro-inflammatory factors [26, 47]. Baricitinib, under the commercial name of Olumiant, is a Janus kinase (JAK) 1/2 inhibitor drug applied to treat RA. It has potent

anti-inflammatory properties and is hypothesized to have off-target antiviral impacts against SARS-CoV-2. For this reason, it has been introduced as a suitable candidate for treating COVID-19 [48, 49].

In a clinical trial conducted by Boghuma K. Titanji et al. [50], 2 to 4 mg of Baricitinib with 200 to 400 mg of Hydroxychloroquine were administered to 13 out of 15 patients daily. The inflammatory factors' levels were monitored in all patients. The results demonstrated that in 13 out of 15 patients, the levels of inflammatory factors such as CRP, IL-6, and erythrocyte sedimentation rate (ESR) diminished. Moreover, the fever in these patients disappeared during the treatment period, and their body temperature decreased [50]. The Baricitinib action mechanism in COVID-19 may be such that it interferes with the entry of the virus into the host cell. This drug disrupts the process of virus endocytosis into the cell by acting on two numb-associated kinase enzymes, thus preventing SARS-CoV-2 from penetrating the host cell [50, 51]. However, the utilization of this agent in COVID-19 patients has been associated with concerns. Interferon is one of the essential proteins and a practical component of the innate immune system that prevents the virus from replicating in the cell and spreading in the body. By activating the JAK-STAT signaling pathway (in which JAK-1 and JAK-2 enzymes play a significant role), the expression of interferon genes increases, resulting in viral clearance [52]. Baricitinib, as a Janus kinase (JAK) inhibitor, can disrupt the JAK-STAT pathway and prevent an adequate antiviral response; thus, it potentially can increase the severity of COVID-19 in patients [50, 53]. Therefore, the consumption of this agent must be done very cautiously.

### Interferon I- $\beta$ 1a

Interferon- $\beta$  is type-1 interferon that is utilized for multiple sclerosis (MS) treatment. It is indicated that it can positively influence the elimination of the virus from nasopharyngeal sampling swabs in phase II clinical trials [54, 55]. It can be utilized subcutaneously (S.C.) and intravenously (I.V.). Recent studies have determined that the use of IFN- $\beta$ 1a and IFN- $\beta$ 1b has the same promising effects on COVID-19 patients because, in both states, it launches specific and identical pathways against SARS-CoV-2 [56]. However, S.C and I.V. administration of interferon results in entirely different outcomes in patients. The utilization of IFN intravenously increases its serum concentration. Studies have revealed that this drug's subcutaneous injection reduces its bioavailability and serum concentration and thus decreases its effectiveness. The IFN serum concentration in people receiving the subcutaneous administration has been approximately 1/3 of the patients who have had the intravenous injections [57]. Elimination of interferon- $\beta$ 1a occurs by its binding to the interferon- $\alpha/\beta$  receptor (IFNAR). Subcutaneous



administration of this drug reduces the rate of its uptake by the lymphatic system. This reduction causes this drug's plasma concentration to remain high for an extended period. In comparison, intravenous infusion causes rapid removal of IFN from the blood and body fluid [58]. Nevertheless, the main reason for utilizing type-1 interferons intravenous injection instead of subcutaneous in some patients is its higher bioavailability. The best and golden time of interferon beta 1a injection to the patients with COVID-19 is immediately after the diagnosis and at the beginning of the infection. Studies have shown that subcutaneous injection is effective in mild condition patients, while intravenous injection is recommended in patients in critical condition [54]. Interferon-beta 1a increases the concentration of CD73 in the pulmonary capillaries. CD73 is an enzyme that plays a vital role in modulating lung vessel diameter, especially in hypoxic conditions, and affects pulmonary vascular integrity. This enzyme also cleaves pro-inflammatory ATP and pre-thrombotic ADP. It converts ATP and ADP into the anti-inflammatory adenosine monophosphate (AMP), clearing them (which causes inflammation) from the blood and thus preventing ARDS [59]. This drug can reduce the secretion of IL-6 and IL-8. It also strengthens the immune system while reducing the tissue damage (by decreasing neutrophil migration) [60, 61].

Recent studies have demonstrated that corticosteroids block the function of IFN and reduce the severity of CD73 expression [62]. These investigations suggest that interferon beta and corticosteroids should not be used concomitantly as their functional pathways may have unintended drug interactions [63].

## Statins

Statins are among the most well-known and accessible [64] therapeutic agents applied to the lower blood lipids that inhibit cholesterol synthesis. These medications have pleiotropic effects on inflammation and its pathways, which, along with the lipid-lowering impact, improve the patient's cardiovascular condition. These drugs also have immunomodulatory consequences, exerting these lipid-lowering effects through influencing some mechanisms. The mechanisms include the antigen presentation and production of chemokines and cytokines, as well as the impact on the migration and maturation of the immune cells [65]. The primary action mechanism of this drug is inhibiting the synthesis of isoprenoids. Isoprenoids are essential constituents of GTPase enzymes. Statins cause a reduction in the concentration of Rho and Rac enzymes by inhibiting isoprenoids' production, which leads to the downregulation of pro-inflammatory factors' genes like NF- $\kappa$ B [66]. As stated, Beta-coronaviruses, like influenza viruses, stimulate the production of large amounts of pro-inflammatory factors, which

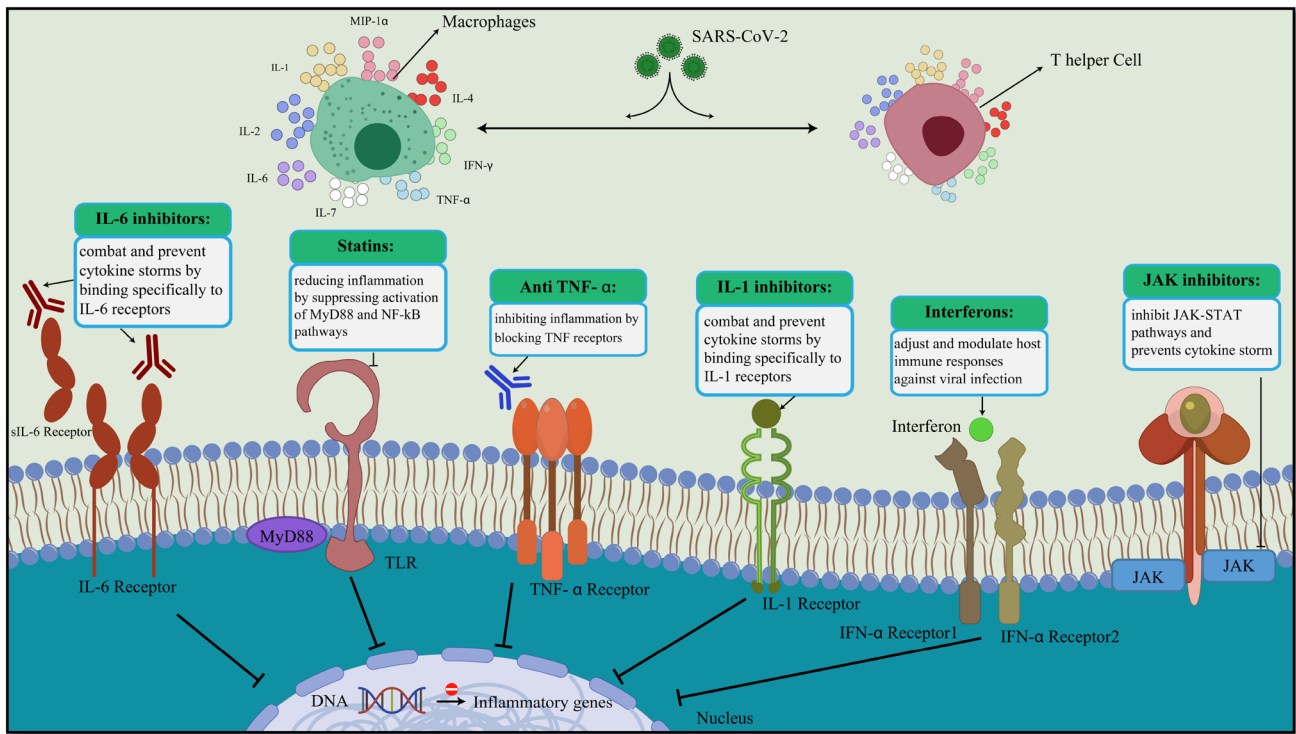
cause cytokine storms, weakening the immune system and ARDS [65]. Statins, in addition to reducing the production of pro-inflammatory factors via the above-mentioned mechanism, prevent severe pneumonia and hypoxia by stabilizing the expression of the MYD88 gene. MYD88 gene codes a protein that activates the NF- $\kappa$ B gene [67]. Research has demonstrated that the presence of atorvastatin—a drug from the statins family—at a concentration of 0.1  $\mu$ M in plasma for 48 h intensely reduces the activation of NF- $\kappa$ B and suppresses inflammation. In order to reach the concentration of 0.1  $\mu$ M in atorvastatin of the blood, about 40 mg of oral consumption of atorvastatin once a day is required [68]. After penetrating the cell via ACE2 receptor, SARS-CoV-2 reduces the expression of this receptor on the cell membrane, which can increase the concentration of angiotensin-II in the extracellular fluid and cause tissue damage. Atorvastatin enhances the intensity of ACE2 expression in the cell membrane and prevents the accumulation of angiotensin-II and tissue damages [69]. From a pharmacokinetic point of view, statins have hepatic metabolism and are affected by the CYP3A4 enzyme complex. The half-life of these drugs is about 1.4 h, and they are finally excreted through the kidneys or intestines [70]. These medications are safe, inexpensive and affordable, making them suitable treatments for COVID-19 patients. Their immunomodulatory influences on COVID-19 themselves require proper and sufficient *in vitro* and *in vivo* investigations.

The six drugs discussed so far each has a specific receptor on different cells membrane, enabling them to bind to these receptors to exert their effects. This issue is schematically illustrated in Fig. 2.

## Dexamethasone

Recently, many studies have reported the efficacy of Dexamethasone in treating patients with severe COVID-19, resulting in reduced mortality and morbidity among these patients [71]. As mentioned, SARS-CoV-2 causes respiratory infection, and this disease can involve other organs [72]. A substantial number of activated T cells and cytokine-mediated antibody extraction are required in order to clear the virus from tissues [73].

The US-FDA approved Dexamethasone in 1958 as a synthetic drug from the corticosteroid family. As a broad-spectrum immunosuppressant, it reduces inflammation and decreases immune system activity [74]. Dexamethasone, which is 30 times more immunosuppressant and active than cortisone, reduces the overproduction of cytokines. On the other hand, Dexamethasone may increase the risk of secondary infection by suppressing the T and B mature cells, which are vital to fighting the pathogens. It also interferes with NK cells and macrophages' functions, which are responsible for clearing the body from pathogens [74, 75]. The



**Fig. 2** Various mAbs or antagonists are utilized for COVID-19 treatment. These agents have different receptors on the host cell surface. The binding of these therapeutic agents to their cellular receptors is usually accompanied by the activation of intracellular pathways,

which ultimately reduces the expression of pro-inflammatory genes such as NF- $\kappa$ B. Macrophages and T cells are vastly impacted by immunomodulatory drugs administration

greatest randomized control trial (RCT) in the world, called the RECOVERY trial, was performed on 2104 patients in the United Kingdom. The elicited results demonstrated a reduction in mortality in critical cases and patients [76]. Crucial producers of pro-inflammatory cytokines that cause cytokine storms are mast cells, which together with macrophages cause overproduction of pro-inflammatory factors such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  and may also result in blood agglutination and organ failure [77]. By suppressing this mechanism, Dexamethasone can prevent critical conditions in COVID-19 patients and reduce the mortality rate. Despite all this, it is advised to use Dexamethasone in the short term and severe patients. However, further research is required to understand the exact action mechanism of Dexamethasone [71].

### Famotidine

As mentioned, labrocytes (mast cells) are absolutely crucial in developing hyper-inflammation in patients with COVID-19 [78]. These cells trigger other molecular pathways by secreting histamines. Histamines are effective in causing inflammation, increasing the volume and blood flow in the arteries, and enhancing capillaries' permeability. Histamines

are divided into two subgroups: H1 and H2. Famotidine is prescribed as a Histamine-2 receptor antagonist to reduce gastric acid secretion that causes pain and burning [79]. Histamines are related to inflammation in patients with SARS-CoV-2 infection and exert their effect by influencing the activated T cells [80]. Histamines as biological molecules can also impact leukocytes and result in the secretion of cytokines and inflammation, thus causing damages to the lungs [81]. Famotidine can prevent the occurrence of cytokine storms and death in patients by blocking these signaling pathways. A cohort study on 1,620 patients has documented that 84 of the patients who received famotidine demonstrated that this agent could efficiently block histamine-mediated inflammation and reduce mortality rate and intubation demand in the patients [82].

### Naproxen

Non-steroidal anti-inflammatory drugs (NSAIDs) are therapeutic agents that reduce inflammation by acting on the molecular pathways [83]. The liver mainly metabolizes these drugs. Naproxen is a non-selective COX inhibitor and is one of the compounds related to propionic acid. Propionic acid is essential in inflammation incidence because it triggers the

molecular pathways that reduce prostaglandin production from arachidonic acid, thus resulting in inflammation reduction via this mechanism [84, 85]. As a non-selective inhibitor, Naproxen effectively affects both COX-1 and COX-2 complex enzymes and shows its effect by reducing particular biological molecules synthesis [86]. As mentioned, this drug is metabolized in the liver by the CYP1A2 and CYP2C9 enzyme complexes. Some studies have reported that Naproxen is safe for patients with COVID-19. Its administration is accompanied by no particular or severe adverse effects [87]. This drug's precise mechanism on COVID-19, however, is not particularly known and requires further studies and clinical trials. Nonetheless, it is speculated that Naproxen is effective in decreasing ARDS and reducing patient mortality.

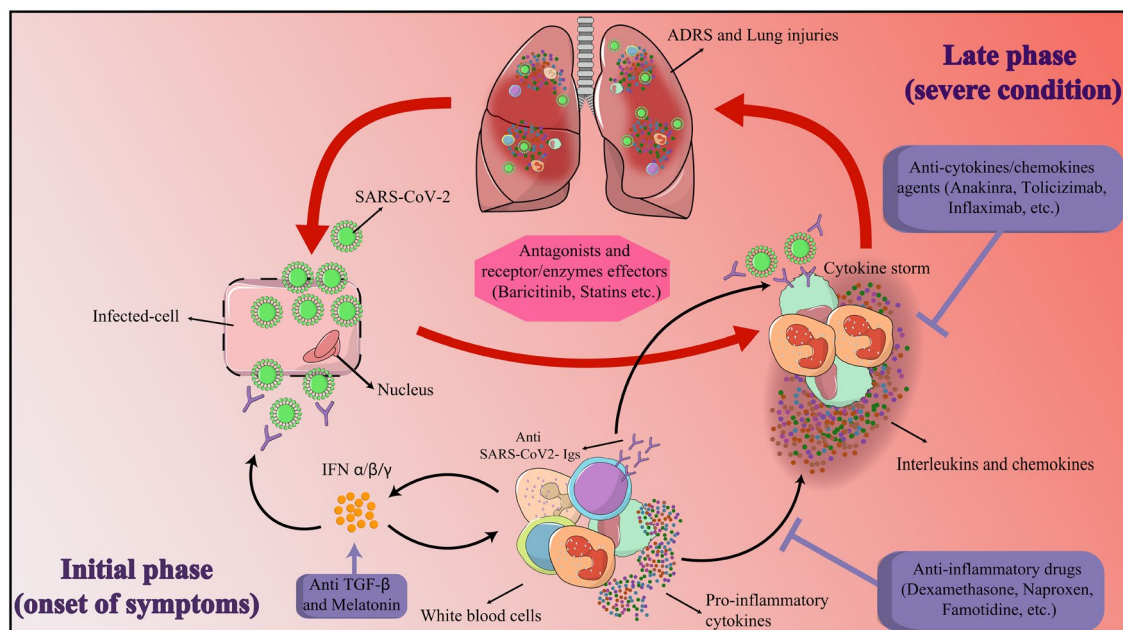
Figure 3 exhibits the occurrence of COVID-19 and its different phases in SARS-CoV-2 infected individuals. The mechanism of cytokine storm incidence and promising therapeutic agents that can influence this condition are demonstrated in Fig. 3.

### Colchicine

Colchicine is an alkaloid chemical compound with the molecular formula  $C_{22}H_{25}NO_6$ , naturally synthesized by *Colchicum* genus plants. It is clinically utilized because of its anti-inflammatory impacts on various diseases such as

gout, familial Mediterranean fever, Behcet's disease, and other inflammatory diseases and fibrotic disorders [88]. Colchicine has diverse mechanisms of action that ultimately reduce the inflammation and prevent acute conditions. Colchicine manifests its anti-inflammatory effects by acting on the immune system [89]. One function of Colchicine in the innate immune system is the suppression of neutrophil chemotaxis. In fact, Colchicine suppresses neutrophil chemotaxis by inhibiting the release of crystal-derived chemotactic factors from cell lysosomes [90].

On the other hand, in animal studies, Colchicine has been shown to stimulate the maturation of dendritic cells into various kinds of T cells by activating signaling pathways and increasing antigen presentation [91]. The stimulation of dendritic cells by Colchicine has also been reported in different studies [92, 93]. Colchicine also has anti-fibrotic influences, affecting intestinal tissue by triggering the expression of Bcl-2 genes and silencing caspase-3 genes [94]. In addition, it also suppresses lung inflammation and fibrosis by inhibiting the differentiation and growth of myofibroblasts via the Rho/Serum response factor (SRF)-dependent signaling pathway [95]. It can also block NLRP3 inflammasome and caspase-1 activity by impacting the ROS system [96]. Recently, a study examined the effect of Colchicine on non-hospitalized COVID-19 patients [97]. The elicited outcomes of this study indicated that Colchicine could reduce hospitalization or mortality rates among non-hospitalized



**Fig. 3** After the initiation of COVID-19, which is caused by infection of lung epithelial cells by SARS-CoV-2, some antiviral responses such as IFN- $\alpha/\beta/\gamma$  were started. These primary antiviral responses result in the apoptosis of infected cells and the production of pro-inflammatory cytokines, which cause virus elimination. Excessive

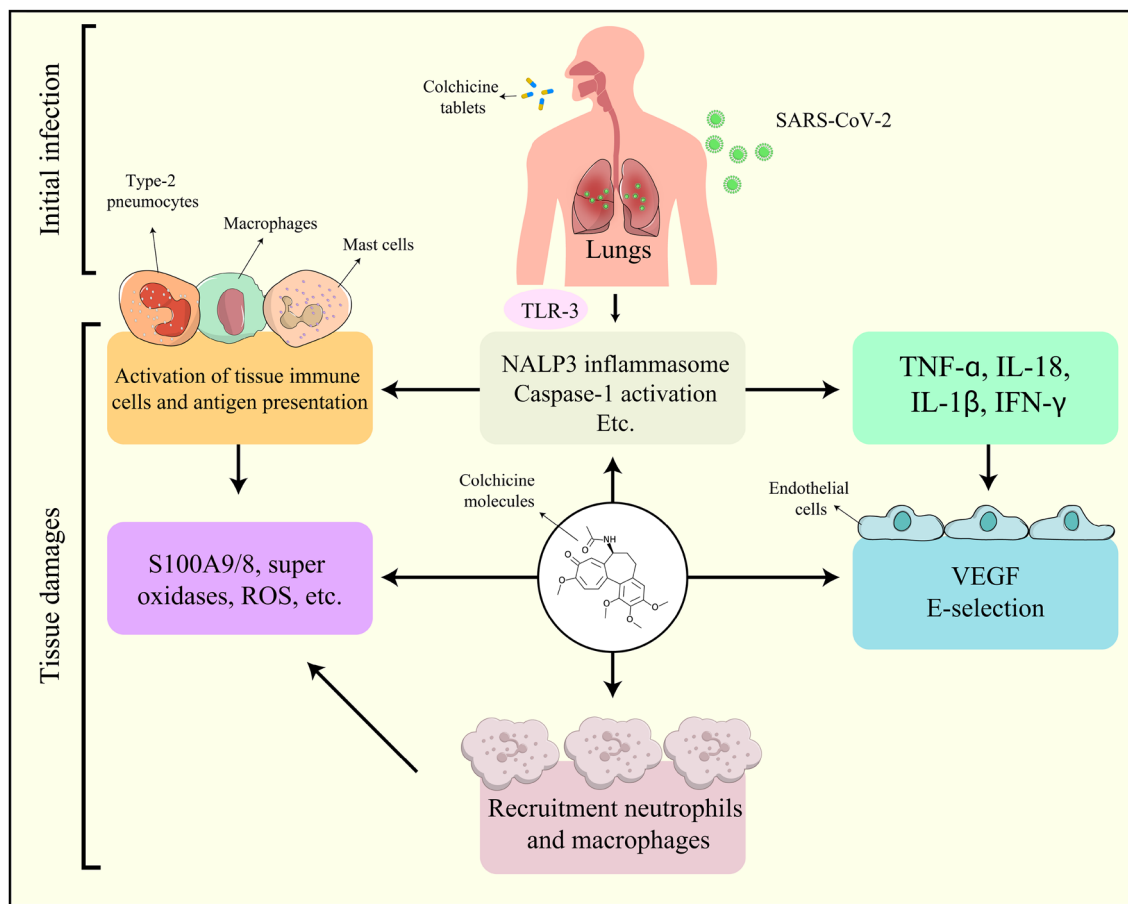
synthesis of cytokines and chemokines may lead to critical conditions like ARDS and lung injuries. The application of immunomodulatory drugs can adjust immune system responses and impede critical conditions in COVID-19 patients

patients [97]. However, at the beginning of the SARS-CoV-2 pandemic, Medine Cumhuri Cur et al. [98] noted that administering Colchicine may not have positive influences, and it could be even harmful [98]. Therefore, more clinical trials in this area are needed to understand the colchicine mechanism of action. The possible action mechanism and various functions of Colchicine are illustrated in Fig. 4.

## Melatonin

Melatonin or N-acetyl-5-methoxytryptamin is a monomeric tryptophan-derived neurotransmitter-like compound that has hormonal activities [99]. The chemical formula of Melatonin, which is mainly secreted from the enigmatic pineal gland in the brain, is  $C_{13}H_{16}N_2O_2$  [100]. It has an influential role in regulating the wake-sleep cycle, circadian rhythm, and body's biological clock [101, 102]. Melatonin is synthesized from tryptophan through a cascade of enzymatic reactions in four steps, which contains hydroxylation,

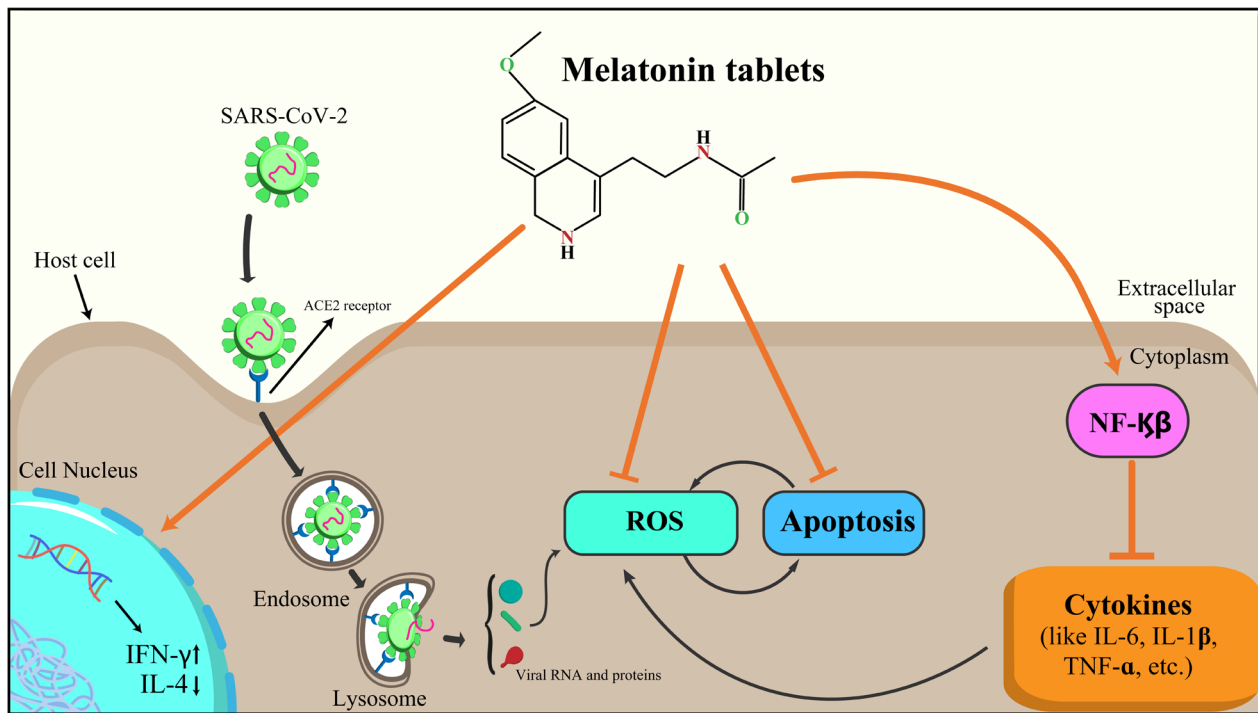
decarboxylation, N-acetylation, and methylation reactions, respectively [100, 103]. Melatonin secretion and its nexus with age were surveyed in a study by Haruo Iguchi et al. [104], which observed a reverse correlation between melatonin secretion and age. Thus, the brain-immune system axis and its interactions have been indicated to be required for appropriate body responses to pathogens' invasions [105]. Melatonin can play a significant role in the interactions of the brain-immune system. For example, this protein can increase IFN- $\gamma$  synthesis but not IL-4 by affecting peripheral mononuclear blood cells [106]. It has been proved that interferon-gamma has a prominent role in combating viral agents [107]. It has also been unveiled that viral infections can be associated with an elevation in reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) [108]. Oxidative stress in respiratory viral infections can cause extensive damage to lung tissue [109]. Melatonin has cogent antioxidant properties, and each melatonin molecule can bind to 10 oxidant agents; other antioxidant compounds



**Fig. 4** SARS-CoV-2 is recognized by innate immunity receptors such as TLR3 when it enters the body. The recognition of 2019-nCoV by TLR3 results in the activation of other immune components. Colchicine can influence various inflammatory cascades and inhibit inflam-

ation via a different process. It also affects leucocytes' recruitment, reduces ROS synthesis, and positively affects endothelial cells, alleviating tissue damage to the lungs





**Fig. 5** As stated, Melatonin as an Acetamide hormone can be consumed orally in COVID-19 patients. Melatonin molecules are capable of influencing various pathways after entering the cell. It can decrease ROS/RNS synthesis and impact host cell apoptosis. It is also able to

modulate the expression of pro-inflammatory genes such as NF- $\kappa$ B and thus affect cytokines synthesis. It also exerts its anti-inflammatory effects through other mechanisms

(e.g., vitamins C and E) usually can bind to only one oxidant molecule [110]. Furthermore, melatonin prescription in MS patients has been reported to be beneficial as Melatonin can act as an antagonist and reduce the activity of cell-mediated immunity [105, 111]. These cases, along with the regulation of sleep time and relief of insomnia symptoms in COVID-19 patients, have led to the hypothesis that melatonin consumption can be effective in SARS-CoV-2 patients. However, more clinical trials are needed to exactly evaluate the mechanism of action and efficacy of Melatonin in COVID-19 patients [112]. Diverse fates which may occur for Melatonin when interacting with host cells are exhibited in Fig. 5.

The most important information on the discussed immunomodulatory drugs used for COVID-19 treatment, along

with the possible mechanism of action, their adverse effects, etc. is presented in Table 1.

## Conclusion

COVID-19 as a respiratory disease has been continuously evolving, highlighting the need for constant research and proper measures. Recently, having been caused by mutations in SARS-CoV-2, new variants are being discovered [159]. Although vaccines can be successful in immunizing individuals against COVID-19, they seem to be not suitable for hospitalized patients with severe and critical conditions. Immune dysfunction and especially over activation of the

**Table 1** The most important information on immunomodulatory agents for COVID-19 treatment

Drug term	Drug category	Possible mechanism of action against COVID-19	Adverse and side effect (s)	Route of administration	Bioavailability (and elimination half-life)	Metabolism or elimination	Mainly prescribed for treating	Status (for COVID-19)	Reference(s)
Anakinra	Human interleukin-1 receptor antagonist	Suppressing immune system's over activation by blocking IL-1 attachment to its receptors	Diarrhea, nausea, and vomiting	Intravenous and subcutaneous bolus injection	80–95% (~4–6 h)	Mostly renal	Rheumatoid arthritis	Non-approved	[28, 113–119]
Tocilizumab	IL-6 blocker from humanized monoclonal antibody family	Binding to mIL-6R and sIL-6R receptors and blocking IL-6 from attaching to them, preventing inflammatory responses	Headache, hypertension, hepatotoxicity, injection-related reactions	Intravenous and subcutaneous injection	100% (in I.V.) and 77.9–81.1% (in S.C.) (8–14 days, concentration-dependent)	Unknown, presumably by proteolytic enzymes in the reticuloendothelial system	Rheumatoid arthritis, Juvenile idiopathic arthritis (JIA), or Castleman's disease	Emergency approval by WHO	[36, 39, 120–124]
Infliximab	Tumor necrosis factor- $\alpha$ (TNF- $\alpha$ ) inhibitors	Suppressing harmful effects of cytokines, Reducing IL-6 and CPR synthesis	Headaches, dizziness, flushing, a rash, stomach pain	Intravenous injection	100% (in I.V.) (9.5 days)	Unknown, presumably by proteolytic enzymes in the reticuloendothelial system	Rheumatoid arthritis and ulcerative colitis	Non-approved	[40, 42, 43, 122, 125–128]
Baricitimib	Janus kinase 1/2 inhibitor family	Disrupting the downstream JAK-STAT pathway and inhibiting the synthesis of inflammatory factors (CRP, IL-6, ESR, etc.)	Blurred vision, Infection, cytopenias, nausea, thrombosis, and herpes zoster	Tablet for oral administration	Approximately 79% (12.5 h)	Mainly extracted unchanged (undue 10% hepatic metabolism)	Rheumatoid arthritis	Non-approved	[48–50, 129–132]

Table 1 (continued)

Drug term	Drug category	Possible mechanism of action against COVID-19	Adverse and side effect (s)	Route of administration	Bioavailability (and elimination half-life)	Metabolism or elimination	Mainly prescribed for treating	Status (for COVID-19)	Reference(s)
Interferon I-β1a	Immunomodulatory drugs	Increasing the concentration of CD73 in the pulmonary capillaries, converting prothrombin and pro-inflammatory compound to anti-inflammatory molecules	Headache, tight muscles, weakness	Subcutaneous, Intramuscular and Intravenous injection	30% and 27% in S.C. and I.M injection, respectively (22 to 66 h dependent on route of administration)	Unknown	Multiple sclerosis	Non-approved	[55, 56, 59, 133, 134]
Atorvastatin (as a member of statins)	HMG-CoA reductase inhibitors from lipid-lowering medications	Inhibiting isoprenoids production and down-regulating genes of inflammatory pathways	Headache, Dizziness, feeling sick	Tablet and pill for oral consumption	14% (around 7 h)	Metabolized in gut and liver through oxidation	Reduction of cholesterol and Dyslipidemia	Non-approved	[65, 66, 135–137]
Dexamethasone	Immunosuppressive drug from corticosteroids family	Anti-inflammatory and immunosuppressive corticosteroids	Psychosis, mood changes, cognitive dysfunction, and behavioral disturbance	Tablet for oral usage, Intravenous, Intramuscular, and subcutaneous injection	81% in oral consumption (36 to 72 h)	Metabolized in human liver by CYP3A4	Inflammation, asthma, and pain reduction	Emergency authorization and approval by FDA	[74, 75, 138–141]
Famotidine	Histamine-2-receptor antagonists	Prevention of cytokine storm by blocking H2 histamine and inflammatory factors' production	Tablet for oral administration	Headache, Thrombocytopenia, and dry mouth	Among 40–50% (2 to 4 h)	Metabolized by the hepatic cytochrome P450 enzymes	Reflux and gastric acid overproduction and its-related pain and burning	Non-approved	[79–81, 142–145]
Naproxen	Non-steroidal anti-inflammatory drugs	Affecting COX-1 and COX-2 enzymes and reducing the synthesis of inflammatory molecules	Headache, drowsiness, dizziness, and rashes	Tablet for oral administration	Higher than 80% (average 13 h (11–17 h))	Extracted unchanged through urine	Inflammation and pain management	Non-approved	[85, 86, 146–148]

Table 1 (continued)

Drug term	Drug category	Possible mechanism of action against COVID-19	Adverse and side effect (s)	Route of administration	Bioavailability (and elimination half-life)	Metabolism or elimination	Mainly prescribed for treating	Status (for COVID-19)	Reference(s)
Colchicine	Anti-gout agent	Immunomodulation by anti-fibrotic and anti-inflammatory influences, blocking NLRP3	Diarrhea, nausea, cramping, abdominal pain, and vomiting	Often oral consumption, also I.V injection or gel type	24 to 88% (20 to 40 h)	Mostly by the liver	Gout, familial Mediterranean fever, Behcet's disease	Non-approved	[88, 149–153]
Melatonin	Acetamide hormone	Antiviral effects by enhancing IFN- $\gamma$ and not IL-4, Antioxidant impacts	Daytime sleepiness, Dizziness and Headaches	Tablet for oral consumption or I.V. injection	Approximately 15% ( 1.8 to 2.1 h)	Mainly in the liver by cytochrome P450 enzyme	Adjusting sleep time and day-night cycle	Non-approved	[106, 110, 154–158]

immune system and lymphopenia are two significant problems in COVID-19 patients [160]. In this regard, the application of immunomodulatory drugs has been considered to reduce the mortality rate in COVID-19 patients. In the present review article, the mechanism of action for several pivotal immunomodulatory and immunosuppressant agents pertaining to different drug groups was examined and discussed. More studies and extensive trials are warranted to ensure the extent of effectiveness or ineffectiveness of these medications. The outcomes of this study, however, can assist physicians and scientists in designing future studies and having better treatment guidelines.

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## Declarations

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