

# Immunomodulation may Affect the Efficacy of COVID-19 Medication by Changing Drug Metabolism and Pharmacokinetics

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## Abstract

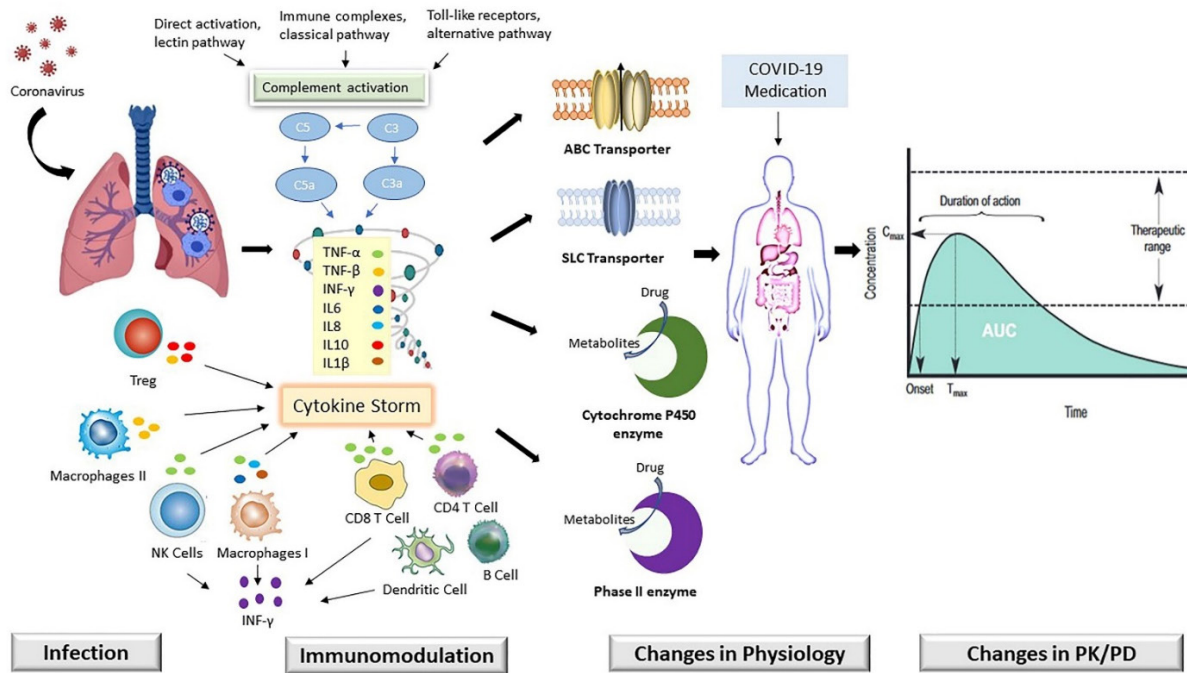
The COVID-19 outbreak, which was prompted by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, continues to spread over the world. In the pathophysiology of COVID-19, the immunological response of the patient is crucial. The immunological changes occur when the immune system is fighting against SARS-CoV-2 and the signal becomes hyperactive. In drug metabolism and transport mechanism, a hyperimmune state can cause severe abnormalities. As a result, inter-individual variability in drug pharmacokinetics may occur, potentially leading to unexpected treatment responses. The physiology of drug transporters and drug-metabolizing enzymes are also affected in COVID-19 patients with autoimmune and metabolic disorders. The Food and Drug Administration (FDA) has approved several antiviral and anti-inflammatory drugs to treat COVID-19 patients based on the evidence, despite the fact without knowing any possible interactions with each other. Inflammation directs the altered expression of drug-metabolizing enzymes and drug transporters, shown by preclinical and clinical research. A deeper understanding of the impact of immune responses on drug metabolism and transport, as well as the therapeutic implications of this knowledge, would aid in the personalization of drug treatment. The current review summarizes the effect of inflammation and the complement system on the pharmacokinetics of COVID-19 medications by altering the expression and activity of drug transporters and drug-metabolizing enzymes, as well as offers an opinion on possible drug-drug interactions in disease states. More studies, including control PK trials, are needed to determine the clinical significance in the COVID-19 infected population. The results of future studies will facilitate us to better predict concentrations in individuals who have hyperimmune responses so that we can provide them personalized medicine.

**Keywords:** COVID-19; Inflammation; IL-6; Complement Systems; Drug transporters; CYP450

## 1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection emerged as a pandemic in early 2020 year and is commonly known as COVID-19 [1]. The first case of COVID-19 in pneumonia patients was detected in Wuhan city, China in December 2019. In the beginning, pneumonia patients showed normal respiratory infection, which rapidly transformed into acute respiratory syndrome [2]. Acute respiratory syndrome was associated with chronic inflammation. Chronic inflammation occurs when an antigen is constantly present in the body, and the immune system is continuously activated to remove the infection. This constant inflammation causes some degree of alteration in the drug-binding proteins [3-5]. Recent studies have been suggested that inflammation can modulate transporters and drug-metabolizing enzymes (TDMs) [6]. The downstream

regulation of various hepatic and extrahepatic drug-metabolizing enzymes (DMEs) was already shown by some studies [7, 8]. Inflammation-induced alterations in the expression of a variety of membrane-associated drug transporters have recently been described [9]. Therefore, a better understanding of the impact of inflammation on TDMs and its associated clinical outcomes would help to recognize the individual pharmacokinetic (PK) and pharmacodynamic (PD) variability of drugs. The SARS-CoV-2 infection resulted in increased frequency of hospitalization and intensive care unit (ICU) admission [9]. This is considered a major clinical concern that critically ill patients are more affected by drug interaction that TDMs are involved in the transport and metabolism of commonly prescribed drugs [10]. The high prevalence of acute and chronic inflammatory conditions, the modulation in the expression and activity of TDMs may modify the PK/PD of drugs used in COVID-19 treatment (Figure 1).



**Figure 1:** Modification in the expression of key transporters (ABC: ATP binding cassette and SLC: Solute carrier) and drug metabolizing enzyme (Cytochrome P450 and Phase II) mediated by acute immune response in SARC-CoV-2 (COVID-19) infection play a role in alteration of drug absorption distribution metabolism and excretion (ADME).

Based on the evidence, the Food and Drug Administration (FDA) approved some drugs that have been already used (Table 1) for the treatment of SARC-CoV-2 [11, 12]. In these drugs, remdesivir and favipiravir have been proven most promising against COVID-19 treatment. The lopinavir-ritonavir combination showed to be effective against COVID-19. Other antiretroviral drugs atazanavir and darunavir were also used. Anti-malarial drug hydroxychloroquine (HCQ) showed good results against COVID-19, and it has been used frequently in combination with other drugs [13], [14]. Irrespective of the antiviral drugs, dexamethasone showed little relief against COVID-19 but involved the increased risk of hyperglycemia. The initial clinical trial showed that Dexamethasone lowered the death of one-third of severe patients that were on a ventilator [15]. Sofosbuvir plus Daclatasvir in combination with Ribavirin was shown promising results to fight COVID-19 infection [16]. Fluvoxamine has also shown the potential in COVID-19 infected outpatients [17]. Molnupiravir, which can block the transmission of SARS-CoV-2 within 24 hours, is used to treat COVID-19 infection [18]. Some anti-inflammatory and anti-complement drugs were also used either in combination or alone for the treatment of COVID-19 patients.

This article will emphasize on the current state of knowledge and assume a PK and drug-drug interaction (DDI) potential of therapeutic agents used for co-morbidities and frequently used in intensive care for COVID-19 patients. Here, we present the subscription of inflammation on modulating the expression and

activities of TDMEs and discuss its related clinical consequences of DDI based on drug metabolism and pharmacokinetics (DMPK) and finally provide the opinion on how to incorporate inflammation in pharmacological treatment.

## 2. Cytokine storm in COVID-19 patients

Cytokine storm is a complex and robust inflammatory phenomenon initiated by a group of cytokines mainly pro-inflammatory cytokines that are produced by the uncontrolled immune function. Adequate evidence showed very high levels of cytokines in severe COVID-19 patients. This cytokine storm is a range of cytokines, including interleukins (IL-1, IL-2, IL-6, IL-7, IL-8, IL-10, IL-12, IL-17, IL-18), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and monocyte chemoattractant protein-1 (MCP-1) [19-27]. Cytokine targeted treatment in critical COVID-19 patients confirmed the presence of cytokine storm and showed the clinical advantages in hemophagocytosis [28, 29]. The COVID-19 cytokine storm has shown variability as normal cytokine storms in several aspects [19, 28, 30]. Cytokine storm in COVID-19 consists of more inflammatory cytokines as well as have an abnormally low level of lymphocytes (lymphopenia), suggesting that attributed to the innate immunity rather than adaptive immune cells [28]. This treatment approach is to manage ongoing inflammatory response by specifically or non-specifically targeting inflammatory cytokines or associated signaling pathways to resume the host immune regulatory system.

### 3. Immunomodulation in COVID-19

#### 3.1. COVID-19 association with inflammation

Cytokines are the distinct class of small cell-signaling proteins responsible for maintaining the homeostasis of the immune system. Many studies have shown that, in addition to direct viral damage, unrestrained inflammation causes disease severity in COVID-19 patients [31, 32]. The high expression of inflammatory components, including C-reactive protein (CRP), ferritin, and increased levels of inflammatory cytokines and chemokines were noticed in COVID-19 infected patients [33-35]. One study was conducted to measure serum interleukin IL-6, IL-8, IL-1 $\beta$ , tumor necrosis factor (TNF) in hospitalized COVID-19 patients (n = 1484) for 41 days. Study results showed a high level of TNF- $\alpha$ , IL-6, and IL-8 at the time of hospitalization. Particularly, when adjusting for disease severity, IL-6 and TNF- $\alpha$  serum levels were constantly independent and significant predictors of severity and death [36]. Some proinflammatory cytokines such as interferon-gamma (IFN- $\gamma$ ), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), IL-12 were elevated in COVID-19 patients [2]. The cytokine profile in severe COVID-19 patients showed similarities like cytokine release syndromes, such as macrophage activation syndrome, with augmented production of cytokines and of chemokines including CCL2 (CC-chemokine ligand -2), CCL3 and CCL10 (CXC-chemokine ligand -10) as well as the  $\alpha$ -chain of the IL-2 receptor. This phenomenon has driven the hypothesis that dysregulated stimulation of the phagocytes is accountable to COVID-19 associated hyper inflammation [35, 37]. Inflammation is normal in reaction to damage or pathogenic illness, but it seems that patients with noncommunicable diseases reveal pre-heightened inflammatory levels. This can produce them subject to unrestrained inflammation when infected by the SARS-CoV-2, leading to a cytokine storm [38]. This is an excessive release of the cytokine in response to COVID-19 infection due to loss of regulation on the production of pro-inflammatory cytokines. Additionally, cytokine storm is anticipated to be the cause of acute respiratory distress syndrome (ARDS) and multiple organ failure [39, 40]. Obstructing these inflammatory elements can alter the developed immune response and stop lung destruction. IL-6 is the important target for anti-cytokine therapy and its elevation is mediated with a terrible diagnosis [29, 41, 42]. A monoclonal antibody against the IL-6 receptor named tocilizumab was used for the treatment of COVID-19 and demonstrated significant improvement in COVID-19 patients [43]. Another IL-6 receptor antagonist, sarilumab currently considered for COVID-19 treatment [44].

#### 3.2. COVID-19 association with the complement system

The Complement system performs as immune surveillance and responds rapidly against infection. However, when dysregulation of these powerful machineries (C3a, C3b, iC3, C3c, C3dg, C5),

can become harmful and incriminate as a pathogenic effector in various diseases including viral infection [45]. Initially, it was reported that complement activation is attenuated by poxviruses by secreting a protein that showed structural and functional homology to the complement regulatory protein [46]. Flavivirus also hijacks the same and HIV-1 conscripts host complement system into their virion [45]. In all these scenarios, C3 attached to the surface of viruses and virus perform the cleavage of C3 that may affect the host antiviral response [47]. Whether SARS-CoV-2 exhibits such antiviral strategies remains to be answered.

#### COVID-19 mediated complement system activation

Promising, in-vitro, and in-vivo data analysis suggest that complement activation plays a crucial part in the pathogenesis and diseases seriousness of SARS-CoV and SARS-CoV-2. Gralinski LE, et al. (2018) found the effect of SARS-CoV infection using C3-/- mice and showed complement activation [48]. Mice after getting infected by SARS-CoV, in a 24-hour C3 activation product (C3a, C3b, iC3, C3c, and C3dg) were examined in the lungs. In the absence of C3, lung grievance and weight loss were significantly reduced, without altering the viral load, and cytokine and chemokine levels were found low as well in the C3 -/- mice. Moreover, factor B -/- or C4-/- mice also showed less weight loss [48]. These results showed that pulmonary pathology and SARS-CoV infection-associated illness can be improved by activating the complement system [49]. Nucleoprotein (secreted N protein) dimer of SARS-CoV-1, SARS-CoV-2 and MERS-CoV activate the MASP-2 enzyme (mannan-binding lectin-associated serine protease -2). This is a primary enzymatic inhibitor of the lectin pathway [50]. Auto activation of MASP-2 starts to generate C3 convertase and membrane attack complex (MAC). The interaction of MSP-2 and N protein attenuates lung injury. Human proteomic and metabolomics studies [51] along with these data suggest that coronavirus infection involves the activation of various pathways of the complement system.

In Italy, a single-center case series study showed that elevated level of plasma complements protein C5a and sC5b-9 were observed in patients with mild illness (patients requiring continuous positive airway pressure) and serious critical illness (mechanically ventilated) COVID-19 [52]. In COVID-19 patients, complement fragment deposition has been found in multiple organs. Extensive deposition of C5b-9, C4d, and MASP-2 in the microvasculature induced septal capillary damage in the lungs of COVID-19 patients who died because of respiratory failure [53]. Reports have been demonstrated that the absence of complement regulation in the kidney, mainly in the proximal convoluted tubule (PCT) cells makes these cells more responsive to complement-mediated injury [54, 55]. Recently, one study published a kidney autopsy report with strong C5b-9 staining and demonstrated that C5b-9 staining was prominent on the apical brush border of tubular epithelial

kidney cells along with deposition on glomeruli and capillaries and nucleocapsid as well as the spiked protein of SARS-CoV-2 [56].

This hypothesis also supported that SARS-CoV infection is associated with complement regulators of two genetic variants, CD55 (known as DAF) and FH [57]. Earlier it has been allied to the atypical haemolytic uremic syndrome (aHUS), age-related macular degeneration (AMD), and haploinsufficiency of complement regulatory protein [58]. Even though these associations are required to be assessed in independent cohort studies, they must be proposed the lectin activation and alternative pathways of the complement system in COVID-19 patients. Complement inhibition has offered an effective medication in COVID-19 patients.

### 3.3. Auto-immune and metabolic disorders may affect the prophylaxis of COVID-19 patients

Some types of diseases like autoimmune & metabolic disorders, cancers, and infection have inflammatory conditions already. Elderly individuals, along with those pre-existing conditions, have shown in table 2, have demonstrated a higher possibility for developing severe COVID-19 conditions in addition to suffering a high risk of mortality and facing more chance of developing long-term complications. This pre-existing immunomodulation may affect the COVID-19 treatment by interfering with the DMPK of drugs in the COVID-19 medication. Results suggested, genetically and chemically induced model of various diseases mentioned in table 2, and analysis of transporters and CYPs in disease state is highly reasonable that dysregulation of intestinal and hepatic transporters expression and CYPs contribute to inconstant absorption and disposition of xenobiotics. That may be responsible for interpatient vulnerability in drug PK and therapeutic reaction [59, 60].

**Table 1:** Drugs that have been used for the treatment of COVID-19 patients.

Drug used in COVID-19 treatment	
Anti-Inflammatory drugs	Dexamethasone, Ruxolitinib, Baricitinib, Imatinib, Tocilizumab, Itolizumab, Maplazumab, Sarilumab
Anti-Complement drugs	Eculizumab, AMY101
Antiviral-drugs	Remdesivir, Favipiravir, Ribavirin, Interferon, Lopinavir, Ritonavir, Darunavir, Atazanavir, Umifenovir, Sofosbuvir, Daclatasvir, Molnupiravir, Teicoplanin, LCB1

Antibiotics	Tetracyclines, Azithromycin
Others	Chloroquine, Hydroxy chloroquine, Ivermectin, ARDS-003, Fluvoxamine

**Table 2:** Pre-existing immunomodulatory diseases may affect the COVID-19 treatment.

Diseases	Immunomodulatory effect	References
Rheumatoid Arthritis (RA)	IL-1 $\beta$ , IL-6, TNF- $\alpha$ and IFN- $\gamma$	[61]
Inflammatory bowel disease (IBD)	IL-1 $\beta$ , IL-6, TNF- $\alpha$ and IFN- $\gamma$	[62, 63]
Chronic renal failure (CRF)	IL-1 $\beta$ , IL-6, TNF- $\alpha$ and IFN- $\gamma$	[64]
Diabetes (T1DM, T2DM)	IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IFN- $\gamma$ and CRP	[65-68]
Obesity	IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IFN- $\gamma$ and CRP	[65-68]
Human Immune Virus (HIV)	IL-1 $\beta$ , IL-6, TNF- $\alpha$ , IFN- $\gamma$	[59]
Cancer	IL-1 $\beta$ , IL-6, IL-23 and TNF- $\alpha$ ,	[69]
Age related macular degeneration	TNF- $\alpha$ , IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-10 and Complement protein	[70]
atypical hemolytic uremic syndrome (aHUS)	IL-6 and Complement proteins	[71]
Paroxysmal Nocturnal Hemoglobinuria (PNH)	IL-6 and Complement proteins	[71]

### 4. Alteration of drug transporters in response to immunomodulation

In the acute immune response, proinflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  play an important role [72]. These locally forming immunomodulators disseminate in the circulatory system and generate a systemic effect by binding to cell membrane receptors on the vascular endothelium and parenchymal cells of the various tissues of the human body. During infection, the immune reaction represents a significant effect in chronic diseases, which are clearly involved in modifying drug elimination (clearance) by changing the absorption and metabolism activity of therapeutic drugs. Recently, some pre-clinical model studies also reviewed the absorption, downregulation of ATP binding cassette



(ABC) and solute carrier (SLC) in certain chronic inflammatory conditions [73].

P-glycoprotein (Pgp)/ABC and BCRP (breast cancer resistance protein) efflux transporters are vital proteins involved in the efflux of drugs. In addition, Pgp/ABC has been widely studied against the response of immunomodulation or inflammation. In humans, Pgp expression has been shown downregulated in intestinal epithelium cells in inflammatory conditions [74]. Human enterocyte cell line Caco-2 is used as a universal model for permeability research. It has been shown that Caco-2 was treated in conjunction with TNF- $\alpha$  showed downregulation of expression as well as Pgp activity [75, 76]. It is well documented about the association of Pgp mRNA level and protein expression diminished on the administration of IL-6 directly in vivo in mice or hepatic cell lines [77, 78]. Similar to Pgp, primary human hepatocytes cells also showed downregulation of BCRP expression as well as activity upon treatment with IL-6, and when these cells were treated with TNF- $\alpha$  this leads to the production of BCRP [79]. The treatment of IFN- $\gamma$ , substantially decreased the mRNA expression of BCRP in primary human hepatocytes [80]. The human brain cell line showed a significant decrease in the BCRP expression and activity after treatment with IL-1 $\beta$ , IL-6, and TNF- $\alpha$  [81]. Proinflammatory cytokines are also thought to be important mediators of MRP2, as evidenced by the fact that IL-1 $\beta$ , IL-6, and TNF- $\alpha$  all significantly downregulate mRNA and protein expression of MRP2 in rat and human hepatic cell lines [82, 83]. The acute inflammatory response arbitrates changes in the expression of Pgp, BCRP, MRP2, and a few other important transporters [64, 76, 84-87].

The human repertoire of solute carrier (SLC) transporters as a means of tackling the immune-mediated disease. A study on inflammatory bowel diseases (IBD) patients showed that SLC transporters were altered due to inflammation [82], and mRNA expression level of SLC transporters (OATP2B1, OATP4A1, ENT1, ENT2, CNT2) in IBD patients was found dysregulated [82]. SLC expression is linked with the inflammation of the tissue and gives an indication that inflammatory signaling is involved in the regulation of disease [82]. Other than intestinal, the hepatic transporters are also involved in drug clearance. Considerable downregulation has been reported in hepatic transporters such as OATP1, OCTN1, as well as Pgp and BCRP, after *Citrobacter rodentium* infection in mice as compared to control at mRNA levels [83]. This effect was not shown IL-6 or TNF- $\alpha$  lacking infected mice [83], again indicating the key role of these proinflammatory cytokines in controlling the expression and function of hepatic ABC and certain SLC transporters. Human hepatocytes have shown the downregulation of various transporters after facing the exposure of IL-6 [84]. These findings suggested that chronic inflammation can inhibit the expression and function of Pgp, ABC, MRP, and SLC transporters involved in drug pharmacokinetics and may occur in the intestine and in

the liver as well, leading to decreased absorption [85]. Due to the inflammation, several transcription factors get activated and play a crucial role in the alteration of DMEs and transporters [86-90]. Several reviews have already available which explained the role of inflammation in the molecular mechanism of the transporters have been explained in the literature [88, 91, 92].

### 5. Alteration of drug-metabolizing enzymes in response to immunomodulation

In DMEs, CYPs are extensively engaged as the leading contributor to metabolic biotransformation of more than 60% of drugs [93]. Like drug transporters, reduced expression of CYPs and UDPGT has also been reported with the inflammatory response [73]. Immunomodulatory induced changes in hepatic CYPs expressions and activity are affected by signal molecules which are mainly cytokines, produced while progressing inflammation [94]. The regulation is an important factor in drug interactions because drug PK eventually will be altered based on disease type and produced immune response components, as well as the administered drugs [95, 96]. Many studies have described the immunomodulation (especially cytokine) induced CYPs activity modulation in different mammals [97-99] including humans [100, 101] in vitro in hepatocytes as well as in vivo in mice [102], rats [103], and humans [104]. Various diseases models like colitis [105, 106], and arthritis [107-109] have exhibited the reduction in the expression and activity of various hepatic CYPs. This inhibition exists to correlate with the rise in the concentration of proinflammatory cytokines (IL-6, TNF- $\alpha$ , IL-1 $\beta$ , IFN- $\gamma$ , IL-2, and IL-1 $\alpha$ ) [105, 106, 108, 110]. Most proinflammatory cytokines are IL-1 [111-113], IL-6, TNF- $\alpha$ , and IFN- $\gamma$  that have displayed suppression of CYPs expression and activity [114-116]. Other cytokines IL-2 and IL-10 also showed the same effect [117-119].

IL-6 is most abundantly present in the blood circulation of infected mice [105] and represses CYP3A4 expression [120] and reduces CYP3A-dependent clearance of substrate drugs in the in vitro culture of human hepatocyte cells [121]. To prove this hypothesis, human hepatocytes cells were treated with an IL-6 monoclonal antibody that prevented the decrease in IL-6 induced CYP3A clearance [121] and delivered the proof of IL-6 dependent CYP3A inhibition. Another study confirmed the inhibition after deletion of IL-6 encoding gene to prevent the downregulation of CYP2D and CYP3A in *Clostridium rodentium* infected mice [122]. One study showed that in rat hepatocytes, human recombinant IL-6 has shown concentration-dependent inhibition of phenobarbital mediated induction of CYP2B1/2 [123] and significantly suppressed the expression of CYP1A1, CYP1A2, and CYP3A4 at mRNA levels in different human hepatoma cell lines [124]. Chronic inflammatory response, either induced by turpentine or bacterial lipopolysaccharide, in rats, showed significant inhibition in hepatic CYP1A2, CYP2A5, CYP3A11, and CYP2C1 enzymes [125, 126]. Several studies have shown

that malignancies also have impacted the action of IL-6 on CYPs [127]. The role of IL-6 in cancer-mediated inhibition of hepatic CYP3A has been shown by producing such effect via monoclonal antibody against IL-6 [128] or IL-6 receptor [129] and this was also confirmed in IL-6 treated primary human hepatocytes by using IL-6 monoclonal antibody. Expression and activity of CYP1A1, CYP1A2, CYP2B6, and CYP3A4 enzymes were inhibited by IL-6, and it was also significant in intervening CYP1A2 and CYP3A4, induced by omeprazole and rifampicin, respectively. IL-6 also downregulates most phase II enzymes like UDPGT [84].

TNF- $\alpha$  is also released abundantly in the blood of infected mice. Like IL-6, similar experimentation has suggested that TNF- $\alpha$  also plays role in CYP downregulation, when treated with biological medication that deactivates soluble TNF- $\alpha$  [130] and deletion of TNF- $\alpha$  receptor gene in mice infected with *Citrobacter rodentium* [131], prohibited the downregulation of CYP3A11 and CYP3A25. Infliximab, an immunosuppressive drug is generally used for the treatment of rheumatoid arthritis. Pre-adjuvant arthritic rats were treated with infliximab, which resulted in a significant increase in total protein content of CYP than in untreated rats [132]. These results along with hepatic in-vitro experiments were demonstrated that TNF- $\alpha$  significantly regulated CYPs levels (Kinloch 2011, Nygode 2010) [122, 131] and provides strong evidence in CYP downregulation.

IL-1 $\beta$  has demonstrated the inhibition of CYP3A1 protein expression by 60 % in-vitro rat hepatocyte and reduced its activity within 6 hours [133]. Numerous studies have shown that the downregulation of CYPs due to pro-inflammatory cytokines is impeded by NO synthase inhibitors [134] and proteasome inhibitors (Lee CM, et al. (2009)) [133]. Stimulation of the NO synthase [135] is promoted by pro-inflammatory cytokines such as IFN- $\gamma$ , IL-1 $\beta$ , and TNF- $\alpha$  during inflammatory responses that precede to increase NO synthesis which inhibits CYPs expression and activity. NO prompts proteasome-based CYP3A1 inhibition [133]. These results suggest that the IL-1 $\beta$  inhibits the functional

activity of CYP in the early stage of the inflammatory process. Authors [95] investigated the effects of IL-1 $\beta$ , IFN- $\gamma$ , TNF- $\alpha$ , and TGF- $\beta$  on the mRNA expression level of CYP2B6 and CYP2C9 in human hepatocytes comparing with response to control. The expression of CYP2C9 and CYP2C19 are decreased while in the presence of IL-6 and TGF- $\beta$ . CYP2C8 and CYP3A4 were downregulated by all cytokine treatments.

Extrahepatic CYPs were also inhibited by pro-inflammatory mediators [142-145]. Although the cytokine-induced inhibition of CYPs is not fully demonstrated, it is anticipated and strongly recommended that a decrease in CYPs mRNA strongly insisted on a transcriptional mechanism that altered various transcriptional factors [146, 147]. Aryl hydrocarbon and nuclear factor kappa B (NF- $\kappa$ B) receptor are the regulatory transcription factors. In humans, rats, and mice, they are actively involved in controlling the gene expression of various CYPs in response to inflammation [146-149]. Pyrrolidine dithiocarbamate is a well-known example of an NF- $\kappa$ B inhibitor that has the capacity to prevent the inflammatory reduction in CYP1A2 activity [150, 151]. Inflammatory stimuli influence NF- $\kappa$ B, which further regulates the CYPs expressions. PXR (Pregnane X Receptor) targets a variety of genes, including CYP3A4. PXR is regulated by NF- $\kappa$ B factors, with NF- $\kappa$ B activation suppressing glucocorticoid receptors (GR) and decreasing the expression of the constitutive androsterone receptor (CAR) and its related CYP gene expression [126, 152, 153]. Highly elevated cytokines and downregulation of their targets during COVID-19 infection have been shown in table 3. It is established that alteration in pharmacokinetics of the prescribed drug can alter the activity of DMEs and the expression of drug transporters, which can contribute to interindividual heterogeneity in drug efficacy and toxicity. Generally approved drugs for COVID-19 medication, and their drug interaction targets for transporters and drug-metabolizing enzymes have been shown in Tables 4 and 5, respectively.

**Table 3:** The regulation of transporters and drug metabolizing enzymes by proinflammatory cytokines.

Proinflammatory Cytokines	Species	Downregulation		References
		Transporters	DMEs	
IL-1 $\beta$	Mouse	MRP2, OATP1, OATP2, BSEP	CYP1A, CYP2B, CYP2C9, CYP2C19, CYP2D, CYP3A, UGT1A	[95, 135]
	Human		CYP2C8, CYP3A4	[95, 121, 136]
IL-6	Mouse	P-gp, MRP2, OATP1, OATP2, BSEP	CYP1A2, CYP2A5, CYP2E1, CYP3A11	[78, 125, 135, 137]
	Human	-	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4	[95, 121, 138]
IFN- $\gamma$	Mouse	-	CYP1A, CYP2B, CYP2C9, CYP2C19, CYP2D, CYP3A, UGT1A	[135]
	Human	-	CYP2B6, CYP2C8, CYP2C9, CYP3A4	[95]

TGF- $\beta$	Mouse	-	CYP1A, CYP2B, CYP2C9, CYP2C19, CYP2D, CYP3A, UGT1A	[139]
	Human	-	CYP2C8, CYP2C9, CYP2C19, CYP3A4	[95]
TNF- $\alpha$	Mouse	MRP2, MRP3, OATP2	CYP1A, CYP2B, CYP2C9, CYP2C19, CYP2D, CYP3A, UGT1A	[135, 137]
	Human	-	CYP2C8, CYP3A4	[95, 137]

**Table 4:** Transporter mediated drug-drug interaction of therapeutic agents used to treat COVID-19.

	Drug	Involvement of Drug Transporter	Reference
1	Remdesivir	<sup>\$</sup> Pgp, <sup>\$</sup> OATPB1, <sup>1</sup> OATPB1, <sup>1</sup> OATPB3, <sup>1</sup> BSEP, <sup>1</sup> MRP4, <sup>1</sup> NTCP	[140]
2	Favipiravir	<sup>1</sup> OAT1, <sup>1</sup> OAT3	[141]
3	Ribavirin	<sup>\$</sup> NT, <sup>\$</sup> ENT1	[142, 143]
4	Interferons	<sup>\$</sup> OAT2	[144]
5	Lopinavir	<sup>\$</sup> Pgp, <sup>\$</sup> MRP1, <sup>\$</sup> MRP2, <sup>\$</sup> OATP1A2, <sup>\$</sup> OATP1B1 <sup>1</sup> Pgp, <sup>1</sup> BCRP, <sup>1</sup> OATP1B1, <sup>1</sup> OATP1B3, <sup>1</sup> OATP2B1	[145-147] [148-151]
6	Ritonavir	<sup>\$</sup> Pgp, <sup>\$</sup> MRP1, <sup>\$</sup> MRP2, <sup>1</sup> Pgp, <sup>1</sup> MRP1 <sup>1</sup> , BCRP, <sup>1</sup> OATP1A2, <sup>1</sup> OATP2B1, <sup>1</sup> OATP1B1, <sup>1</sup> OATP1B3, <sup>1</sup> OCT1, OCT2	[147] [152] [148, 151, 153-159]
7	Chloroquine	<sup>\$</sup> OATP1A2	[160, 161]
8	Hydroxy chloroquine	<sup>1</sup> Pgp, <sup>1</sup> OATP1A2	[160-162]
9	Dexamethasone	<sup>\$</sup> Pgp, <sup>\$</sup> MRP2	[163, 164]
10	Umifenovir	Data Unavailable	
11	Teicoplanin	Data Unavailable	
12	Nitazoxanide	Data Unavailable	
13	Ivermectin	<sup>\$</sup> Pgp, <sup>1</sup> BCRP, <sup>1</sup> MRP1, <sup>1</sup> MRP2, <sup>1</sup> MRP3	[165-167]
14	Atazanavir	<sup>\$</sup> Pgp, <sup>\$</sup> MRP1, <sup>\$</sup> MRP2, <sup>1</sup> OATP2B1	[168, 169] [150, 151, 170, 171]
15	Azithromycin	<sup>\$</sup> Pgp and <sup>\$</sup> MRP2, <sup>\$</sup> OATP	[172, 173]
16	Darunavir	<sup>\$</sup> Pgp, <sup>\$</sup> OATP1A2, OATP1B1, <sup>1</sup> Pgp, <sup>1</sup> OATP2B1	[174] [175-177]
17	Ruxolitinib	<sup>\$</sup> OATP1B1, and <sup>\$</sup> OCT1, <sup>\$</sup> NTCP, <sup>1</sup> Pgp, <sup>1</sup> BCRP	[178, 179]
18	Baricitinib	<sup>\$</sup> P-gp, <sup>\$</sup> BCRP, <sup>\$</sup> OAT3, <sup>\$</sup> MATE-K	[180, 181]
19	Imatinib	<sup>\$</sup> Pgp, <sup>\$</sup> OATP1B3	[182, 183]
19	Fluvoxamine	Unclear	
20	Canabinoids	<sup>\$</sup> Pgp, <sup>\$</sup> BCRP, <sup>\$</sup> MRPs	[184]
21	Sofosbuvir	<sup>\$</sup> Pgp, <sup>\$</sup> BCRP	[185]
22	Daclatasvir	<sup>\$</sup> Pgp, <sup>1</sup> Pgp, <sup>1</sup> BCRP, <sup>1</sup> OAT1B1, <sup>1</sup> OAT1B3	[186]
23	Molnupiravir	Data Unavailable	

22	Itolizumab	Data Unavailable	
23	Tocilizumab	Data Unavailable	
24	Meplazumab	Data Unavailable	
25	Sarilumab	Data Unavailable	
25	Eculizumab	Data Unavailable	
26	AMY101	Data Unavailable	
27	ARDS-003	Data Unavailable	
28	LCB1	Data Unavailable	

<sup>§</sup>-substrate of, <sup>⊖</sup>Inhibitor of, Pgp; P-glycoprotein, OAT; Organic Anion Transporter, OATP; Organic Anion Transporter Protein, BCRP; Breast Cancer Resistance Protein, MRP, Multidrug Resistance Associated Protein, OCT; Organic Cation Transporter, NT; Nucleotide Transporter, ENT; Equilibrative Nucleoside Transporter, NTCP; Sodium/Taurocholate Co-transporting polypeptide, BSEP; Bile Salt Export Pump.

**Table 5:** CYP mediated drug-drug interaction of therapeutic agents used to treat COVID-19.

	Drug	Metabolism	Reference
1	Remdesivir	<sup>§</sup> CYP2C8, <sup>§</sup> CYP2D6, <sup>§</sup> CYP3A4, <sup>⊖</sup> CYP3A4	[140]
2	Favipiravir	<sup>§</sup> AO, <sup>⊖</sup> CYP2C8	[141], [187]
3	Ribavirin	Phosphorylation, Deribosylation, Amide hydrolysis	[181]
4	Interferons	<sup>§</sup> CYP1A2, <sup>§</sup> UGT2B7, <sup>⊖</sup> CYP3A, <sup>⊖</sup> CYP2D6	[144, 188]
5	Lopinavir	<sup>⊖</sup> CYP3A4	[145-147]
6	Ritonavir	<sup>§</sup> CYP1A2, <sup>§</sup> CYP2C8, <sup>§</sup> CYP2C9, <sup>§</sup> CYP2C19, <sup>⊖</sup> CYP3A4, <sup>⊖</sup> CYP2D6	[189] [152]
7	Chloroquine	<sup>§</sup> CYP2C8, <sup>§</sup> CYP3A4 <sup>§</sup> CYP2D6	[190, 191]
8	Hydroxy chloroquine	<sup>§</sup> CYP2C8, <sup>§</sup> CYP3A4 <sup>§</sup> CYP2D6	[190-192]
9	Dexamethasone	<sup>§</sup> CYP3A4	[193]
10	Umifenovir	<sup>§</sup> CYP3A4 and <sup>§</sup> FMOs	[194]
11	Teicoplanin	Unclear Metabolic path	[195]
12	Nitazoxanide	<sup>§</sup> Deacetylase, <sup>§</sup> UGT	[196]
13	Ivermectin	<sup>⊖</sup> CYP2C9, <sup>⊖</sup> CYP2C19 <sup>⊖</sup> CYP2D6, <sup>⊖</sup> CYP3A4	[197]
14	Atazanavir	<sup>⊖</sup> CYP3A4, <sup>⊖</sup> UDGT	[168]
15	Azithromycin	<sup>§</sup> CYP3A4	[198, 199]
16	Darunavir	<sup>⊖</sup> CYP3A4	[178, 179]
17	Ruxolitinib	<sup>§</sup> CYP1A2, <sup>§</sup> CYP2B6, <sup>§</sup> CYP2C9 <sup>§</sup> CYP3A4	[200, 201]
18	Baricitinib	<sup>§</sup> CYP3A4	[181, 202]
19	Imatinib	<sup>§</sup> CYP2C8, <sup>§</sup> CYP3A4, <sup>⊖</sup> CYP3A4	[203, 204]



19	Fluvoxamine	<sup>§</sup> CYP1A2, <sup>§</sup> CYP2C19, <sup>§</sup> CYP2D6, <sup>§</sup> CYP3A4 <sup>1</sup> CYP1A2, <sup>1</sup> CYP2C19	[205, 206] [207]
20	Canabinoids	<sup>§</sup> CYPs, <sup>§</sup> UGT	[184, 208]
21	Sofosbuvir	<sup>§</sup> Hydrolases	[209]
22	Daclatasvir	<sup>§</sup> CYP3A4	[186]
<sup>§</sup> -Substrate of, <sup>1</sup> Inhibitor of, CYP; Cytochrome P450, UGT, UDP-Glucuronosyltransferase, AO; Aldehyde Oxidase, FMO; Flavin-containing Monooxygenase			

## 6. Consequences of DDI of a used drug in COVID-19 treatment.

CYP isoforms, particularly CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, are responsible for approximately 80% of all drug metabolism [228]. Several CYP450 isoenzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, have had their mRNA expression reduced by the inflammatory response suggested by in-vitro data [45]. As a result, theoretically, inflammation may have an impact on their pharmacokinetics. For medications with a restricted therapeutic index, such as HCQ and chloroquine CQ, this point is critical for clinical relevance.

Inflammation effect on the PK of antiretrovirals, which are primarily metabolized by CYP3A4, would be expected. For COVID-19 treatment lopinavir, ritonavir, atazanavir, and darunavir drugs have been used. These drugs are either substrate or inhibitor of different transporters (P-gp, OATP1B1, and BCRP) and their metabolism is mediated by CYP3A4. In HIV-positive patients, CYP3A activity was approximately 50% lower than in healthy volunteers [229]. In HIV patients, there was no significant association between inflammatory biomarker concentration and atazanavir clearance [230]. Later in this study authors also showed that the presence of booster ritonavir, which is consistently connected with atazanavir to limit its clearance, may have reduced the effect of inflammation. Two recent short reports found increased plasma lopinavir concentrations in severe COVID-19 patients [231, 232], relative to those found in HIV patients, and in relation to inflammation [231]. Additional evidence supporting changes in PK of medication based on HIV-serostatus includes lower concentrations of atazanavir in HIV patients compared to healthy subjects and higher concentrations of darunavir in HIV patients compared to healthy volunteers [233].

Remdesivir has a linear PK profile. In COVID-19 patients, an intravenous administration, exhibited a peak at the end of infusion, while its phosphorylated metabolite GS-441524 reached a peak and then remained detectable with a half-life of more than 35 hours until the next remdesivir administration [210]. While there was no significant variation in the half-life of remdesivir in healthy adults, the nucleoside metabolite GS-441524 had a half-life of 24 hours [211]. Remdesivir is significantly metabolized by CYP2C8, CYP2D6, and CYP3A4 according to primary data from healthy human donors [158]. Remdesivir is a substrate of

P-gp, active efflux in the lungs and CNS could potentially be involved. Remdesivir was found below the detection range in all the compartments tested, although GS-441524 was found in bronchoalveolar aspirate and a low concentration was also detected in CSF [210]. When CQ or HCQ is used with remdesivir, the antiviral activity of remdesivir may be reduced [236]. Co-treatment of remdesivir with baricitinib, a CYP3A4 substrate, resulted in a significant adverse effect despite a rapid improvement in clinical status [237]. Although no scientific studies on remdesivir's DDI have been completed, a mathematical predication of DDI liability has been made utilizing current phase I and in-vitro data [238]. Valuation for the remdesivir potential to prevent transporters and DMEs in-vivo, a physiologically based pharmacokinetic (PBPK) model is developed to capture the in vitro inhibition potency of remdesivir and in vivo PK using SimCYP software. Because of the high to moderate extraction ratio (0.6 to 0.8) and IV route of administration, when remdesivir had a low hepatic extraction ratio the effect of inducer/inhibitor on the PK of remdesivir will be significantly reduced [239]. The variance in midazolam (CYP3A), rosuvastatin (OATP/BCRP), metformin (MATE1), and pravastatin (OATP) probe exposure (AUC) was predicted using in vitro unbound inhibition constants for CYP3A, BCRP, OATP1B3, and MATE1. For these PBPK simulations, the time of remdesivir delivery relative to prob drug was optimized to predict the maximum DDI, which was roughly related to the administration of remdesivir, so the infusion ended at the probe maximum observed plasma concentration. At therapeutic remdesivir doses, co-administration of remdesivir is thought to enhance probing drug AUC by transporters. Previous studies showed that a 200 mg loading dose followed by 100 mg maintenance doses for roughly 5 to 10 days resulted in a stable PK for the COVID-19 medication [212].

Favipiravir is an antiviral prodrug that is converted to an active metabolite through phosphorylation by the intracellular enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT). It shows non-CYPs facilitated biotransformation by aldehyde oxidase (AO) and xanthine oxidase (XO). Variants of AO are frequently linked to pharmacodynamics (PD) in other medications that are AO's substrate. Because of the genetic variability of AO, elevated plasma levels of favipiravir must be indicated in Asian populations. Based on AO, the DDI of zaleplon and cimetidine is already known.

Cimetidine co-administration inhibits AO-catalyzed oxo-zaleplon formation, and the Zaleplon level is cautiously included. Clinicians should be aware that co-administration of the medicine with an AO inhibitor, such as cimetidine, tamoxifen phenothiazines, verapamil, amlodipine, nifedipine, loratadine, cyclobenzaprine, ondansetron, or ketoconazole, could theoretically increase plasma levels of favipiravir active metabolites because of possible drug-drug interactions. Its metabolite inhibits OAT1 and OAT3 in a moderate way [141]. It is also a moderate inhibitor of various CYPs, but its effect on CYP2C8 must be clinically significant to enhance exposure [187] to drugs like rosiglitazone (hypoglycemic), repaglinide, torasemide, paclitaxel, and buprenorphine.

The HCQ metabolism is hepatic but not been precisely characterized and the effect CYP2C8 CYP2D6 and CYP3A4/5 being extrapolated from CQ data. The half-life of HCQ elimination is approximate 40 days. Both CQ and HCQ transform into active metabolites by CYP isomers through the dealkylation process [213, 214].

Systemic Lupus Erythematosus (SLE) patients demonstrated that HCQ and CQ both have variability in metabolism and the effect of CYP2D6 SNPs on blood HCQ level [215]. The gene polymorphisms of CYP2C8 CYP2D6 and CYP3A4/5 may also alter the disposition. As immunologically challenged patients frequently developed more severe COVID-19 clinical complications. HCQ medication treatment for COVID-19 infection was contested by various side effects among individual variability in CYP genotypes. Specifically, CYP2D6 genotyping may be helpful to decide the best possible HCQ dosage in the context of personalized medicine. CQ and HCQ are both inhibitors of P-gp. Both drugs also increase cyclosporine levels, with HCQ increasing digoxin levels. The multiple DDI that are now known, as well as the potential use of these agents in combination with other drug therapies, requires consideration for the safety of the patients.

Azithromycin is an antibiotic belonging to the macrolide group, used to prescribe COVID-19 patients who developed the risk of secondary infection. It has high tissue affinity with wide distribution in the body. The elimination half-life of azithromycin is between 2-4 days. It is primarily eliminated via the liver. It is noticed mainly in the bile and urine as a parental form. It inhibits CYP3A4 [198], OATP1A2 and OATP2B1 [173] moderately. Azithromycin and HCQ both drugs are both metabolized by CYP3A4. This combination was revealed to decrease the mortality associated with COVID-19 infection [216]. Co-medication of azithromycin heightened the QT of HCQ results enhance the chances of cardiac failure and cardiovascular mortality [217]. The possibility of a probable interaction is not PK but PD while recommending azithromycin as co-medication in connection with its effect on QT prolongation. Risks should be evaluated when azithromycin is administered to COVID patients with impaired

hepatic function.

Dexamethasone is a synthetic glucocorticoid. It is 6-hydroxylated (6 $\alpha$ - and 6 $\beta$ -hydroxy dexamethasone) by CYP3A4 and reversibly metabolized to dexamethasone by 11 $\beta$ -dehydrogenase isozyme. Dexamethasone is an agonist of nuclear pregnane X receptor (PXR) [218] and It is a weak inducer of CYP3A4 [219, 220] through PXR, with most data indicating that it decreases the exposure of sensitive CYP3A4 substrates by approximately 20%. PXR also changed the expression of other drug-metabolizing enzymes and transporters, such as CYP3A11, CYP2B10, and OATP2 [221-223]. Drug metabolizing enzyme variants (CYP3A4, CYP3A5, CYP3A7, and GSTT1) and transporters (ABCB1 and MDR1) have been associated with response to corticosteroids in several diseases [224]. Overdoses of corticosteroids are considered sufficiently immunosuppressive to warrant unease about probably lessening the effectiveness of vaccines. Corticosteroids also have a high risk of producing or aggravating hyperglycemia and may diminish the efficacy of antidiabetic drugs.

Ivermectin is presented as necessary medicine of the WHO model list. Ivermectin is mostly metabolized by CYP3A4, and it inhibits CYP2C9, CYP2C19, CYP2D6, and CYP3A4 [197]. In animals, Ivermectin DDIs begin mainly at the level of P-gp (ABCB1). It is a substrate for P-gp [225] that enables ivermectin intestinal and biliary excretion and prevents it from entering the CNS (Central Nervous System) [226, 227]. Other transporters might also be involved in ivermectin DDIs like MRPs and BCRP [228]. Pgp and CYP3A4 inhibitors may increase the ivermectin level in the plasma. Ideally, metabolism might decrease with age leading to higher exposure of ivermectin in aged patients [229].

Umifenovir is also described in the publication as Arbidol. It was mainly excreted in urine as phase II conjugates with glucuronide and glucuronide sulfinyl as major metabolites. Arbidol is a substrate for CYP3A4 and FMOs in vitro, insinuating that use with CYP3A4 inducer and inhibitors may lead to possibly significant increases and decreases in arbidol exposure. Total 33 arbidol metabolites were found in human plasma, urine, and feces by engaging the different CYPs including CYP1A1, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, FMO1, FMO3, and FMO5 [194]. Three major metabolites (M5, M6-1, and M8) were detected in the plasma following oral treatment of umifenovir to healthy individuals. M6-1 is critical to assess for safety and efficacy because of its high exposure and extended elimination half-life. CYP3A4 was the most active enzyme in the arbidol metabolism in the liver and gut, followed by other CYPs and FMOs [194]. However, concern and close monitoring are advisable when it is on medication, and medical practitioners are reassured to inform presumed DDI that they observe concerning arbidol.

Ruxolitinib and baricitinib, the Janus kinase inhibitor that has been used to treat COVID-19. Ruxolitinib is mostly metabolized by CYP3A4 and CYP2C9, with CYP1A2 and CYP2B6 playing a

minor role [200, 201]. Following inhibition of both CYP2C9 and CYP3A4 enzymes, fluconazole may increase plasma exposure. On the basis of the PBPK model, the importance of this interaction was validated in healthy subjects [230]. Fluconazole simulation findings were used as a foundation for ruxolitinib dose correction when perpetrator drugs were co-administered. Baricitinib clinical drug-drug interaction still needs to be known. It is metabolized in part by CYP3A4 and is a substrate of P-gp, BCRP, OAT3, multidrug, and toxin extrusion protein (MATE) 2K. OCT1 is likewise inhibited by baricitinib. Probenecid is used for treating gout disease, increasing the exposure of baricitinib following inhibition of OAT3, and lowering the renal clearance in healthy participants. The renal clearance and inhibitory effect of probenecid on baricitinib were reproduced in vitro using PBPK modelling [180]. Both have immunosuppressive effects and associated interactions concerns regarding other immunosuppressants and live vaccines.

Imatinib is the tyrosine kinase inhibitor and is solely metabolized by CYP3A4 and CYP2C8 [204]. It was also shown that CYP3A4 inhibition occurs through an irreversible mechanism [231]. The time-dependent auto inhibition of its own CYP3A4 metabolism leads to an important role for CYP2C8 in the elimination of imatinib. The auto inhibition of its own CYP3A4 metabolism in a time-dependent manner resulted in a significant involvement for CYP2C8 in imatinib elimination. Interactions with other drugs and pharmacogenetic polymorphisms both impact CYP2C8 activity during many administrations, resulting in apparent interindividual variability in imatinib exposure. Dexamethasone is a potent inducer of CYP3A4 and significantly reduces the plasma level of imatinib. However, there is no literature available to find DDI with imatinib and dexamethasone. Imatinib is a known substrate of ABC transporters [232, 233], they have been reported to antagonize these transporters. This effect could manipulate the PK properties of imatinib, perhaps lessening its absorption subsequently causing imatinib concentration to drop below therapeutic levels [234, 235].

Fluvoxamine is a serotonin reuptake inhibitor with a half-life of approximately 30 hours. It has anti-inflammatory properties. It is known that it inhibits the enzyme CYP1A2. It is, however, a strong inhibitor of CYP2C19. A case study of a 48-year-old lady with a psychiatric disorder has died following treatment of multiple drugs along with fluvoxamine. After the autopsy, femoral and cardiac blood, urine, and bile were collected for toxicological kinetics. Fluvoxamine, propranolol, clotipine, gabapentin, 7-aminoclonazepam, and haloperidol drugs were detected after the examination. Fluvoxamine levels in the blood exceeded the upper limit of therapeutic blood level by approximately ten times. The relevant cause of death was due to multiple drug use [236]. Fluvoxamine has a minor effect on medications that are metabolized by CYP3A4. It is classified as a potent inhibitor of CYP1A2 and CYP2C19 by the FDA. It is commonly used for

clinical DDI [237]. PBPK model was created to characterize the CYP1A2 and CYP2C19 for interaction between fluvoxamine and other drugs [238]. As a result, it can be used to support prospective dose adaptation suggestions, labelling, and clinical DDI trial design.

Sofosbuvir is a substrate of Pgp and BCRP [185]. Hydrolases metabolize sofosbuvir extensively, and GS-331007 metabolite accounts for more than 90 % of overall drug exposure [209]. The metabolizing enzymes and drug transporters are not inhibited or induced by sofosbuvir or its metabolites. Daclatasvir is a substrate for CYP3A4 Pgp and also the inhibitor of Pgp, BCRP, OATP1B1, and OATP1B3 [186]. The feces are the predominant route of elimination for daclatasvir, followed by the kidneys. Sofosbuvir and daclatasvir have exhibited good safety profiles with minimum drug interaction and widely available therapeutic options for COVID-19 treatment.

Some of the drugs included in Table 1 lack pharmacogenomic data and are still in clinical trials for the treatment of COVID-19 infection, therefore more research is needed to determine drug metabolism and disposition in the inflammatory and immunomodulatory state.

## Conclusion

COVID-19 is classified as a multisystemic disease. The elementary pathogenesis involves distinct components; immune deficiency and severe lung inflammation, which leads to increased production of cytokines and is related to inappropriate immune response. Timely management of the cytokine storm in its early stage through immunomodulators, cytokine antagonists as well as the reduction of lung inflammatory cell infiltration, are the key to reducing the mortality rate and improving the treatment success rate of COVID-19 patients. In consequence, treatment approaches at present include anti-infectious, anti-viral, anti-proinflammatory cytokines, and life support therapies. The potential of disease-drug or drug-drug interaction is an essential concern while providing optimal treatment regimens for individual patients. Hence, the present review expounded the probability of drug interaction in COVID-19 patients while reaching inflammatory conditions and or having comorbidity like autoimmune and metabolic diseases. This point is highly clinical relevance for drugs with a narrow therapeutic index like HCQ and CQ. As the mechanism underlying the observed alteration in the plasma binding proteins, drug transporters, and DMEs comes to be clear, the next step is to address the clinical importance to better predict the drug concentration in the inflammatory state of the disease condition. Proinflammatory cytokines impede the expression and activity of drug transporters and DMEs (hepatic and extrahepatic). Alteration in the transporters and DMEs can lead to changes in the PK parameters of used drugs. The risk of drug interactions should not be prohibited since they are frequently manageable and convenient. The consumption of a single drug may possibly



not be more effective, but during co-medication of multiple drugs, the risk of drug interaction must be increased. The impact of inflammation on the PK of the drug remains and alternated an important field of research.

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