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REVIEW

COVID-19 drugs: potential interaction with ATP-binding cassette transporters P-glycoprotein and breast cancer resistance protein

Jaeok Lee[1] · Jihye Kim[1] · Jiyeon Kang[1] · Hwa Jeong Lee[1]

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Abstract

Background The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2, has resulted in acute respiratory distress, fatal systemic manifestations (extrapulmonary as well as pulmonary), and premature mortality among many patients. Therapy for COVID-19 has focused on the treatment of symptoms and of acute inflammation (cytokine storm) and the prevention of viral infection. Although the mechanism of COVID-19 is not fully understood, potential clinical targets have been identified for pharmacological, immunological, and vaccinal approaches.

Area covered Pharmacological approaches including drug repositioning have been a priority for initial COVID-19 therapy due to the time-consuming nature of the vaccine development process. COVID-19 drugs have been shown to manage the antiviral infection cycle (cell entry and replication of proteins and genomic RNA) and anti-inflammation. In this review, we evaluated the interaction of current COVID-19 drugs with two ATP-binding cassette transporters [P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP)] and potential drug-drug interactions (DDIs) among COVID-19 drugs, especially those associated with P-gp and BCRP efflux transporters.

Expert opinion Overall, understanding the pharmacodynamic/pharmacokinetic DDIs of COVID-19 drugs can be useful for pharmacological therapy in COVID-19 patients.

Keywords COVID-19 · ABC transporters · P-gp · BCRP · COVID-19 drug · Drug-drug interaction

Introduction

The pandemic coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses 2020), has resulted in approximately 18.3 million infectees and 24,488 deaths in Korea and 541 million infectees/6.32 million deaths worldwide (Our World in Data, accessed on 22 June 2022) since the first outbreak occurred in Wuhan on 1 December 2019 (Ritchie et al 2021). The disease presents as acute respiratory distress (ARD) and can develop into fatal systemic manifestations (extrapulmonary as well as pulmonary) and premature mortality (Yan et al. 2020; Gupta et al. 2020). Clinical management of COVID-19 patients is focused on improving symptoms, supporting lung function, remedying acute inflammation (cytokine storm), and preventing infection (Yan et al. 2020).

SARS-CoV-2, the novel coronavirus (65–125 nm in size), an enclosed and single-stranded positive-sense ribonucleic acid (RNA) (26–32 kbs) virus (Fig. 1a), belongs to the genus *Beta-coronavirus*, like SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) (Zhang and Holmes 2020; Shereen et al. 2020). SARS-CoV-2 has a similar infection cycle to SARS-CoV and MERS-CoV (V'Kovski et al. 2021), as shown in Fig. 1b. The spike glycoprotein (S-gp) of the virus binds to the human cell membrane receptor angiotensin-converting enzyme 2 (ACE2) and cell entry is enabled by priming of the S-gp by the cellular transmembrane serine protease 2 (TMPRSS2) (Hoffman et al. 2020). Once the host cell is entered, the viral infection cycle proceeds with replication of the nucleocapsid (N), envelope (E), membrane (M), S-gp proteins, RNA-dependent RNA polymerase, 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), and the RNA genome; followed by assembly; and exocytosis of mature SARS-CoV-2. Viral infection

✉ Hwa Jeong Lee
hwalee@ewha.ac.kr

[1] College of Pharmacy and Graduate School of Pharmaceutical Sciences, Ewha Womans University, Seoul 03760, Republic of Korea

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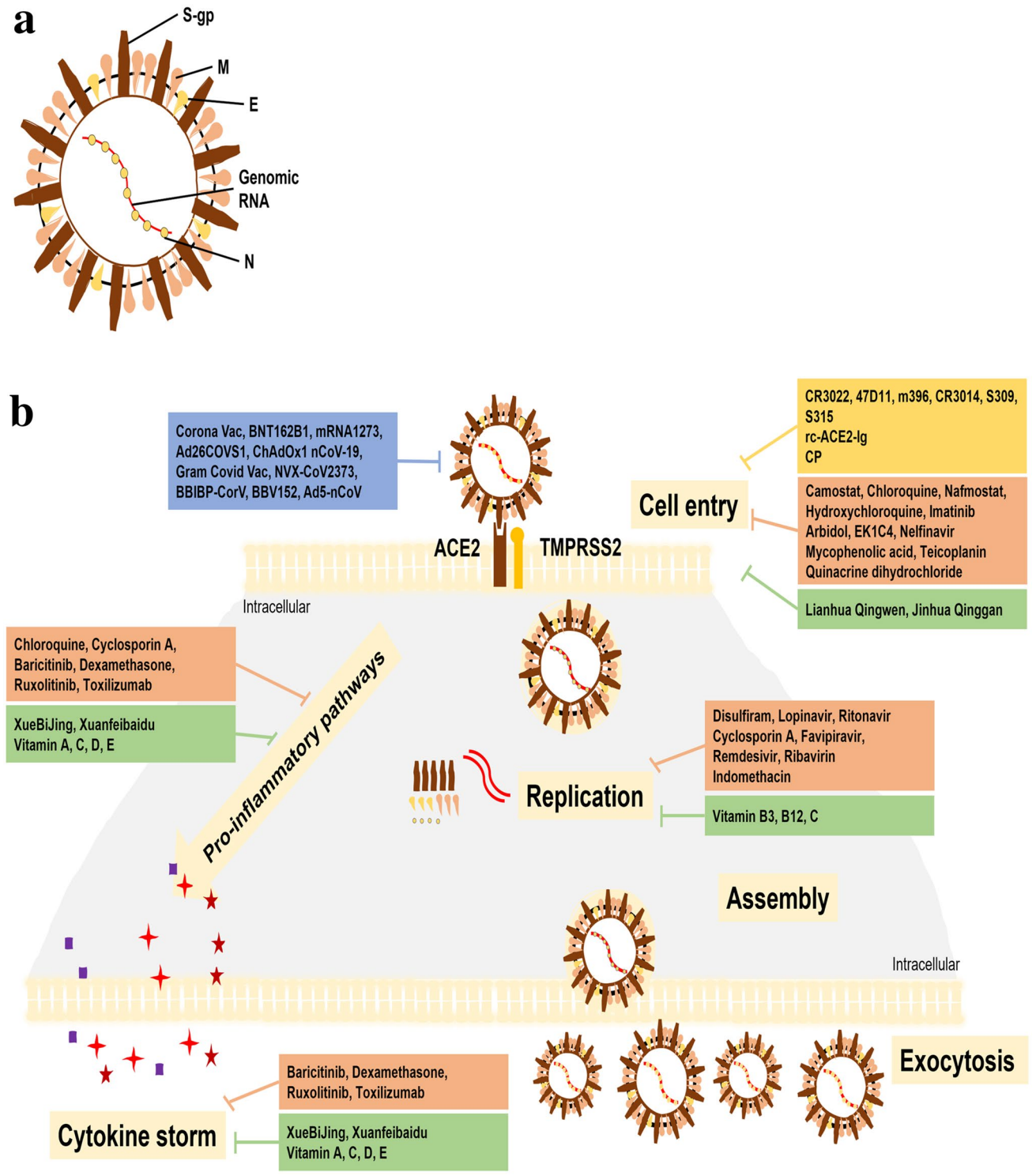

Fig. 1 SARS-CoV-2 infection. **a** SARS-CoV-2 structure. S-gp, spike glycoprotein; M, membrane protein; E, envelope protein; N, nucleocapsid protein. **b** Viral infection cycle and molecular interventions are comprised of cell entry, host cell entry by endocytosis or membrane fusion; Replication (of viral proteins and genomic RNA); Assembly; Exocytosis (of mature SARS-CoV-2); Cytokine storm, SARS-CoV-2 infection induces pro-inflammatory pathways (IL-6, TNF, CXCL 10, and cytokines) (Chen et al. 2021a, c). Blue, orange, yellow, and green boxes represent interventions of vaccines, drugs, antibodies, and traditional Chinese medicine plus and vitamins, respectively. CP, convalescent plasma

induces pathology in the respiratory tissue, liver, intestine, and kidney, among other locations, through viral toxicity, endothelial cell damage, and immunological/inflammatory responses (Gupta et al 2020; Chen et al. 2021a). Although the mechanism of COVID-19 pathology is not fully understood, potential clinical targets have been explored for pharmacological, immunological, and molecular approaches (Chen et al. 2021a; Ghareeb et al. 2021) (Fig. 1b). The pharmacological approach to COVID-19 therapy covers most steps of the viral infection cycle (cell entry, replication of proteins and genomic RNA, and assembly), while immunological approaches (antibodies and vaccines) mainly focus on the initial step (cell entry) (Fig. 1b).

Pharmacological intervention in COVID-19 therapy has investigated various possible candidates such as antiviral and anti-inflammatory drugs (Chen et al. 2021a; Ghareeb et al. 2021; Saleem et al. 2021). In pharmacological therapy, drug pharmacokinetic/pharmacodynamic issues are of great importance. P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), which are apical membrane efflux transporters, are a crucial reason for these issues. These transporters are also one of the key factors in multidrug resistance (MDR) and affect the absorption, distribution, metabolism, and excretion of drugs in patients (Choi and Yu 2014). Many drugs have been identified as substrates and/or inhibitors of efflux transporters. Moreover, drug-drug interactions (DDIs), which lead to a reduction in a therapeutic effect or an increase in the adverse effect of a drug, should be considered in pharmacological therapy for patients with comedications (Lazarou et al. 1998; Skvrce et al. 2011). In this review, we summarized therapeutic strategies for COVID-19 patients, especially those focused on pharmacotherapy and evaluated interactions of the current COVID-19 drugs with ATP-binding cassette (ABC) transporters P-gp and BCRP. We further examined the potential DDIs of COVID-19 drugs, especially those associated with P-gp and BCRP efflux transporters.

COVID-19

COVID-19 pathology

COVID-19 patients have various symptoms; fever, cough, labored breathing, muscle aches, dizziness, headache, sore throat, rhinorrhea, chest pain, diarrhea, abdominal pain, anorexia, nausea/vomiting, fever, and cough are the most common (Yan et al. 2020). Viral infection, morbidity, and mortality are influenced by intrinsic (sex, age, etc.) and extrinsic (lifestyle, underlying disease, etc.) factors. There are fewer SARS-CoV-2 infections among women than men (Conti and Younes 2020). ARD syndrome, an established COVID-19 pathology, is diagnosed at all ages, but the symptoms are more severe in adults than pediatric cases (Guan et al. 2020; Dudley and Lee 2020).

COVID-19 manifestations include not only pulmonary diseases such as pneumonia and ARD, but extrapulmonary indications including neurologic illnesses, ocular symptoms, thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, hepatocellular injury, hyperglycemia and ketosis, and dermatologic complications (Gupta et al. 2020; Moreira et al. 2021; Chen et al. 2021c; Mohamadi Yarijani and Najafi 2021).

Therapeutic strategies

Despite an incomplete understanding of the mechanisms of COVID-19 pathology, potential therapeutic strategies have been developed with various medical interventions (drugs, antibodies, vaccines, etc.) against fatal viral infection (Fig. 2).

Pharmacological therapy (drugs)

Since the initial COVID-19 outbreak, drug repositioning to target SARS-CoV-2 has included many potential drugs that are antiviral, anti-inflammatory, or have other functions (Chen et al. 2021a, b; Ghareeb et al. 2021). These COVID-19 drugs target most steps of the viral infection cycle (host cell entry, replication of proteins and genomic RNA, and assembly [Fig. 1b]) and are used for the treatment of acute inflammation (cytokine storm) and various clinical symptoms. More details about COVID-19 drugs will be presented in the next section.

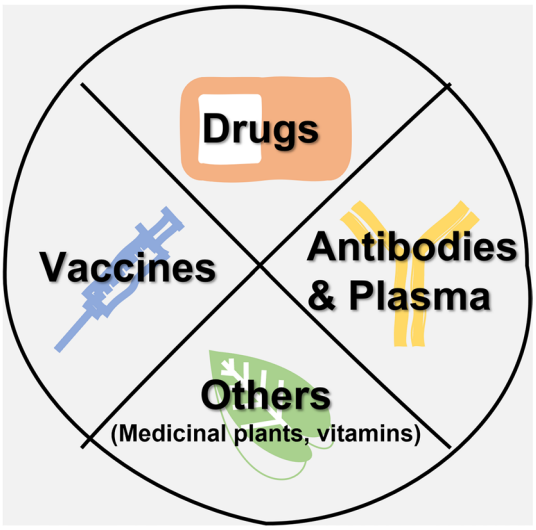

Fig. 2 Therapeutic strategies for COVID-19

Immunological therapy (neutralizing antibodies and convalescent plasma [CP])

The generation of monoclonal antibodies against vulnerable sites on viral surface proteins provides a path to neutralize the COVID-19 virus. The SARS-CoV specific antibody CR3022 can bind to the SARS-CoV-2 S-gp receptor-binding domain (RBD) (Tian et al. 2020; Wang et al. 2020). Many other monoclonal antibodies are also used for intervention with COVID-19 infection, especially those targeting viral protein-host receptor interaction (Fig. 1b); 47D11, m396, CR3014, S230, S304, S309, and S315 (Zhang and Liu 2020; Yuan et al. 2020; Chen et al. 2021a). In addition, recombinant human ACE2-Fc fusion protein (rc-ACE2-Ig) can block viral entry into the host cell (Kruse 2020). The recombinant fusion protein provides a potential treatment avenue for COVID-19 infection with cross-reactivity and high binding affinity to RBD of SARS-CoV and SARS-CoV-3 (Lei et al. 2020).

Convalescent patient plasma containing antibodies (immunoglobulins G, A, M, E, and D) to SARS-CoV-2 can be used for hospitalized COVID-19 patients (Roback and Guarner 2020). CP therapy has been recommended by the United State Food and Drug Administration (US FDA) for the treatment of certain hospitalized COVID-19 patients (21 April 2021) issued as an Emergency Use Authorization (National Institution of Health 2021).

Vaccinal therapy (COVID-19 vaccines)

Vaccines, the most effective control for acquiring immunity and preventing massive outbreaks of infectious diseases, have been developed against SARS-CoV-2a using inactivated virus, mRNA, viral vector, and other forms: SinoVac (Corona Vac, inactivated virus, 50% efficacy, China), Pfizer-BioNTech (BNT162B1, mRNA, 95% efficacy, Germany), Moderna (mRNA1273, mRNA, 94% efficacy, USA), Janssen COVID-19 Vaccine (Ad26COVS1, viral vector, 73% efficacy, The Netherlands), AstraZeneca (ChAdOx1 nCoV-19, viral vector, 70% efficacy, England), Sputnik V (Gram Covid Vac, viral vector, 91% efficacy, Russia), Novavax (NVX-CoV2373, recombinant protein, 96% efficacy, USA), Sinopharm (BBIBP-CorV, inactivated virus, 79% efficacy, China), Covaxin (BBV152, inactivated virus, 81% efficacy, India) and CanSino (Ad5-nCoV, viral vector, 66% efficacy, China) (Saleem et al. 2021).

The mRNA vaccine system that translated the S-pg protein of SARS-CoV-2 after injection was first used in the COVID-19 pandemic (Pardi et al. 2018). Studies of the vaccines/vaccinations are continuing, and current COVID-19 vaccines such as those developed by Moderna, Pfizer-BioNTech, and AstraZeneca have shown poor safety data in aged and sensitive individuals (Soiza et al. 2021).

Other therapeutic approaches (medicinal plants and vitamins)

Many studies have provided evidence that medicinal plants and phytocomponents, consisting of traditional Chinese, Indian Ayurvedic, and homeopathic medicines are effective in the prophylaxis and treatment of COVID-19 (Reche et al. 2020; Tallei et al. 2020; Chu et al. 2021; Saleem et al. 2021). The natural compounds of flavonoids (quercetin, baicalin, luteolin, hesperidin, kaempferol, and curcumin), phenols (glycyrrhizic acid and lignan), quinones (emodin and skonin), alkaloids (matrine), and diterpenoids (andrographolide) have potent activity for inhibiting the viral infection cycle and for improving clinical symptoms (Fig. 1b) (Saleem et al. 2021). However, the therapeutic effects of Ayurvedic and homeopathic treatments were exhibited in asymptomatic COVID-19 patients rather than symptomatic patients (Reche et al. 2020).

Several studies suggested that vitamins, used for antioxidative and immune responses, can also target SARS-CoV-2 infection (Fig. 1b) (Ghareeb et al. 2021). Vitamin D reduces pro-inflammatory cytokines and increases anti-inflammatory cytokines, while its deficiency increases the severity of ARD (Grant et al. 2020). Vitamin C, vitamin B3, and vitamin B12 also help to improve the symptoms of COVID patients (Rosa and Santos 2020; Kandeel and Al-Nazawi 2020).

COVID-19 drugs

Due to the time-consuming nature of vaccine development, repurposed drugs have been a top priority for initial COVID-19 treatments (Table 1). Antiviral (affecting the steps of the viral infection cycle) and anti-inflammatory activities are major targets for COVID-19 drugs. Various therapeutic drugs, their classical uses, and their target sites and actions in SARS-CoV-2 infection are illustrated in Fig. 1b and Table 1.

Antiviral drugs

Many potent COVID-19 drugs focus on antiviral activity.

Camostat, chloroquine, EK1C4, nafamostat, umifenovir, nelfinavir, quinacrine dihydrochloride and hydroxychloroquine prevent host cell entry of SARS-CoV-2 by blocking the interaction of the viral protein with the host cell receptor and blocking membrane fusion or endocytosis (Chen et al. 2021a, b; Ghareeb et al. 2021). Cyclosporin, disulfiram, favipiravir, lopinavir, remdesivir, ribavirin and ritonavir inhibit viral replication, including replication of viral protein and genomic RNA (Chen et al. 2021a, b; Ghareeb et al. 2021). Chloroquine and cyclosporin also target pro-inflammatory

Table 1 Current COVID-19 drugs; the candidate drugs and the approved drugs

Type	Name	Approval (US FDA[a])	Classical use	SARS-CoV-2 targets	Development state[b] (COVID-19)	References
Antiviral drugs	Remdesivir	Yes	Broad-spectrum antivirus (Ebola) /Adenosine analogue	RNA genome replication	FDA approval	Chen et al. (2021a;) Chen et al. (2021b;) Ghareeb et al. (2021)
	Ritonavir	Yes	HIV (AIDS)/Thiazole analogue	Protein translation and proteolysis	FDA EUA[d]	Chen et al. (2021a); Chen et al. (2021b); Ghareeb et al. (2021)
	Arbidol	No	Broad-spectrum antivirus (Influenza) /Indole analogue	Membrane fusion	Phase 4	Ghareeb et al. (2021); Chen et al. (2021b)
	Chloroquine	Yes	Broad-spectrum antivirus/ Quinoline analogue	Viral protein-host receptor interaction /Pro-inflammatory pathways	Phase 4	Chen et al. (2021a)); Chen et al. (2021b); Ghareeb et al. (2021); Saleem et al. (2021)
	Cyclosporin A	Yes	Immunosuppressant	RNA genome replication /Pro-inflammatory pathways	Phase 4	Chen et al. (2021a); Pandey et al. (2021)
	Hydroxychloroquine	Yes	Malaria, endosomal acidification inhibitor	Endocytosis	Phase 4	Chen et al. (2021a); Ghareeb et al. (2021)
	Lopinavir	Yes	HIV (AIDS)/Amide analogue	Protein translation and proteolysis	Phase 4	Chen et al. (2021a); Chen et al. (2021b); Ghareeb et al. (2021)
	Camostat	No (orphan[c])	Chronic pancreatitis, postoperative reflux, esophagitis, and liver fibrosis	Viral protein-host receptor interaction	Phase 3	Chen et al. (2021a); Ghareeb et al. (2021)
	Favipiravir	No	Broad-spectrum antivirus (Influenza) /Nucleoside analogue	RNA genome replication	Phase 3	Chen et al. (2021a); Chen et al. (2021b); Ghareeb et al. (2021)
	Nafamostat	No (orphan)	Anticoagulant, protease inhibitor	Viral protein-host receptor interaction	Phase 2	Maruyama et al. (2011); Chen et al. (2021a)
	Disulfiram	Yes	Protease inhibitor	Protein translation and proteolysis	Phase 2	Chen et al. (2021a)
	Ribavirin	Yes	Broad-spectrum antivirus (Influenza, Hepatitis C)/ Nucleoside analogue	RNA genome replication	Phase 2	Chen et al. (2021b)
	EK1C4	No	Fusion inhibitor	Membrane fusion	Preclinic	Xia et al. (2020); Chen et al. (2021a)
	Nelfinavir	Yes	HIV (AIDS)	Membrane fusion	Preclinic	Perry et al. (2005); Chen et al. (2021a)
	Quinacrine dihydrochloride	No	Malaria	Cell entry	Preclinic	Chen et al. (2021a)

Table 1 (continued)

Type	Name	Approval (US FDA[a])	Classical use	SARS-CoV-2 targets	Development state[b] (COVID-19)	References
Anti-inflammatory drugs	Baricitinib	Yes	Rheumatoid arthritis, myelofibrosis /JAK inhibitor	Pro-inflammatory pathways	FDA approval	Chen et al. (2021a)
	Tocilizumab	Yes	Rheumatic diseases /Anti-IL-6 antibody	Cytokine storm	FDA EUA	Ghareeb et al. (2021)
	Dexamethasone	Yes	Immunosuppressant	Pro-inflammatory pathways	Phase 4	Chen et al. (2021a)
	Ruxolitinib	Yes	JAK 1 and 2 inhibitors	Hyperinflammatory status	Phase 3	Ghareeb et al. (2021)
	Indomethacin	Yes	COX 1 and 2 inhibitors	Virus replication	Recruiting	Ghareeb et al. (2021)
	Mycophenolic acid	Yes	Immunosuppressant	Cell entry	Preclinic	Chen et al. (2021a)
Anticancer drug	Imatinib	Yes	Chronic myeloid leukemia, gastrointestinal stromal tumors	Endocytosis	Recruiting	Mishima et al. (2004;) Chen et al. (2021a)
Antibiotics	Teicoplanin	No	Gram-positive bacterial infection	Cathepsin L-dependent virus	Preclinic	Ghareeb et al. (2021)
Chinese medicine	Jinhua Qinggan granule	No	H1N1	Viral protein-host receptor interaction	Clinical[e]	Chu et al. (2021)
	Xuanfeibaidu granule	No		Inflammation	Clinical[e]	Chu et al. (2021)
	Lianhua Qingwen capsule/granule	No	Influenza (H1N1, H7N9)	Cell entry	Phase 4[e]	Chu et al. (2021)
	LungCleansing and detoxifying decoction	No	H1N1	Severe patients' symptoms (fever, cough, fatigue, etc.)	Phase 1[e]	Chu et al. (2021), Huang et al. (2021)
	XueBiJing injection	No	SARS, H1N1, H7N9, MERS, Ebola, Dengue	Pro-inflammatory pathways	Phase 0[e]	Chu et al. (2021), Huang et al. (2021)
	Huashibaidu formula	No			Recruiting[e]	Chu et al. (2021)

[a]Drugs@FDA: FDA-Approved Drugs search (https://www.accessdata.fda.gov/scripts/cder/daf/) (accessed on 26 May 2022)

[b]Coronavirus (COVID-10)/Drugs (https://www.fda.gov/drugs/emergency-preparedness-drugs/coronavirus-covid-19-drugs) and NIH ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) (accessed on 26 May 2022)

[c]Search Orphan Drug Designations and Approvals (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm) (accessed on 26 May 2022). Orphan drug designations. An orphan drug is intended for the diagnosis, prevention or treatment of a rare disease or condition that affects approximately 6 in 10,000 US people

[d]Paxlovid consists of nirmalrelvir and ritonavir

[e]Clinical trials in China (Chu et al. 2021)

EAU, an emergency use authorization; JAK, Janus kinase; COX, cyclooxygenase

pathways induced by SARS-CoV-2 infection (Saleem et al. 2021; Chen et al. 2021a).

Chloroquine and hydroxychloroquine, classical antimalaria drugs, have potential actions for inhibition of virus post-translational modification (protein glycosylation), production of non-functional ACE2, as well as inhibition of viral cell entry (Oscanoa et al. 2020; Chen et al. 2021a). Moreover, they can be used not only as antivirals, but also as anti-inflammatories and anticoagulants (Oscanoa et al. 2020). These drugs are widely used for COVID-19 patients; however, their side effects include gastrointestinal (GI) disturbance, cardiac toxicity, hyperglycemia, and neuropsychiatric toxicity (Saleem et al. 2021).

Lopinavir and ritonavir, an amide analogue and a thiazole analogue, respectively, are protease inhibitors and antiviral drugs for the treatment and prevention of HIV/AIDS (Chen et al. 2021b; Ghareeb et al. 2021). These drugs are used in combination for HIV/AIDS treatment (Chandwani and Shuter 2008; Cattaneo et al. 2020; Biswas 2021). The combination drug has been broadly used for COVID-19 therapy but has induced multiple adverse effects such as GI disturbance, cardiac conduction abnormality, and hepatotoxicity (Ghareeb et al. 2021; Saleem et al. 2021).

Remdesivir, a broad-spectrum antiviral drug and an adenosine analogue, is used for COVID-19 therapy in adults and pediatric (> 12 years old and weighing > 40 kg) patients and has been approved by the US FDA (Saleem et al. 2021). The drug inhibits viral RNA replication (RNA polymerase function), but transaminase elevation and kidney damage have been reported as the adverse effects of this drug (Stebbing et al. 2020).

Among the above 15 drugs, chloroquine, cyclosporin A, disulfiram, hydroxychloroquine, lopinavir, nelfinavir, remdesivir, ribavirin and ritonavir have been approved by the US FDA for other uses, while camostat and nafamostat were designated orphan drugs by the US FDA (Table 1). Only remdesivir (Veklury) has been approved by US FDA for COVID-19 treatment (the first approved drug on 22 Oct. 2020), while ritovanir packaged with nirmatrevir (Palxlovid) has an emergency use authorization (EUA). With the exception of EK1C4, nelfinavir, and quinacrine dihydrochloride, the others are under the clinical trials (Table 1).

Anti-inflammatory drugs

Due to the acute inflammation (cytokine storm) generated by viral infection, anti-inflammatory drugs are also used for COVID-19 therapy. Baricitinib, dexamethasone, ruxolitinib and tocilizumab are used to inhibit pro-inflammatory pathways (Chen et al. 2021a; Ghareeb et al. 2021). Indomethacin and mycophenolic acid target SARS-CoV-2 replication and cell entry, respectively, and have potential anti-inflammatory effects as well (Chen et al. 2021a; Ghareeb et al. 2021).

Tocilizumab, a recombinant human monoclonal anti-interlukine-6 antibody, is used in COVID-19 patients (Luo et al. 2020). This antibody effectively inhibits cytokine storm and stabilizes the condition of severe or urgent patients (Ghareeb et al. 2021; Saleem et al. 2021). GI disturbance, skin/subcutaneous infections, and altered liver enzymes have been reported as adverse effects (Luo et al. 2020).

All the drugs mentioned above are US FDA-approved for other purposes, while baricitinb (Olumiant) has been approved specifically for COVID-19 treatment (10 May 2022) and tocilizumab has EUA (Table 1). Dexamethasone and ruxolitinib are under clinical trials (Table 1).

Anticancer drugs and antibiotics

Imatinib (an anticancer drug) and teicoplanin (an antibiotic) are also potent COVID-19 drugs. Both drugs are thought to inhibit COVID-19 infection by interfering with host cell entry of the virus in vitro (Chen et al. 2021a; Ghareeb et al. 2021).

Imatinib is a US FDA-approved drug and under the recruiting state for COVID-19 trials (Table 1). Teicoplanin (Targocid) was approved by the European Medicine Agency (30 Jul. 1988) and is available in many countries around the world (Vimberg 2021), but has not been approved by the US FDA.

Traditional Chinese medicines

Traditional Chinese medicines have been used for COVID-19 therapy from the early stage of the COVID-19 outbreak in China. COVID-19 medicines were developed based on the medicines used for the treatment of pandemic SARS, MERS and H1N1 influenza (Chu et al. 2021). Table 1 shows several Chinese medicines used to treat COVID-19 that were clinically trialed in China. These medicines are composed of various herb plants such as *Isatis tinctoria L.* (Banlagen), *Lonicera japonica* Thunb. (Jinyinhua), *Paeonia lactiflora* Pall. (Chishao), and *Ephedia sinica* Stapf (Ma huang); GI disturbance (nausea or diarrhea), abnormal liver function, heart palpitation and skin problems (itchiness or rash) have been reported as adverse effects (Chu et al. 2021).

Chinese medicines, which generally have few side effects, are being used clinically as well as in clinical trials in China (Table 1) (Chu et al. 2021).

P-gp and BCRP substrate and inhibitor drugs

ABC transporters, one of the largest transporter families, act as active efflux pumps related to pathogenic conditions as well as in normal physiological roles in living organisms (Trowitzsch and Tampe 2018; Liu 2019). P-gp (ABC subfamily B member 1 [ABCB1]; Fig. 3a) and BCRP (ABCG2;

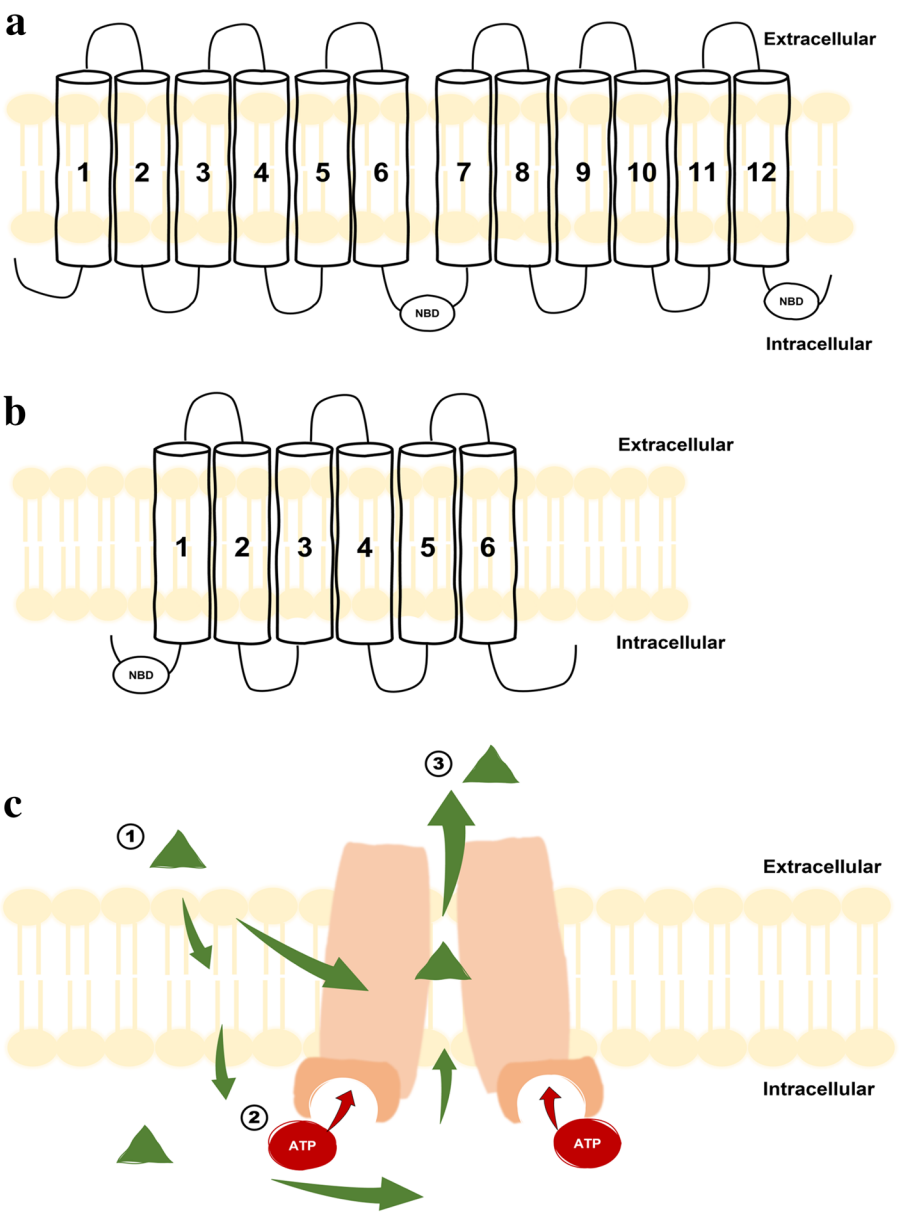

Fig. 3 ABC transporters. **a** P-gp consists of 12 transmembrane domains (TMDs) and 2 nucleotide-binding domains (NBDs) (approximately 150 kDa in size). **b** BCRP consists of 6 TMDs and 1 NBD as a monomer (approximately 72 kDa). **c** Drug efflux function of the transporters. ① A drug (substrate/inhibitor [green triangle] of the transporters) permeates into the cell membrane and binds to the affinity site in the TMD of the transporters. ② ATP binds to NBD and then it is hydrolyzed by ATP-hydrolyses. ③ The inward structure of the transporters changes to outward, and transporters efflux the drug to the extracellular region. The green arrows indicate the path of the drug

Fig. 3b), are widely expressed in important tissues such as the intestinal epithelium, the biliary canaliculi of hepatocytes, and the proximal tubules of the kidney, and are well-characterized MDR transporters among ABC transporters (Juliano and Ling 1976; Doyle et al. 1998; Robey et al. 2018; Dei et al. 2019). P-gp and BCRP are different in size and structure but are similar in their ATP-dependent function (dimerization) (Fig. 3c) (Robey et al. 2018; Dean et al. 2001). Numerous pharmacological agents are substrates and/or inhibitors of the transporters, and many drugs including antiviral and anticancer drugs are common substrates and/or inhibitors (Durmus et al. 2015; Chen et al. 2016). Efflux transporters affect drug pharmacokinetic parameters as well as MDR, and the US FDA has published guidelines for evaluation of transporter-mediated drug interactions (US FDA 2020).

It is important understand the association of current COVID-19 drugs, which are administered by an oral route (except remdesivir, nafamostat, teicoplanin and tocilizumab, which are administered via an intravenous route), with ABC transporters (P-gp and BCRP) located in the GI tract (Dei et al. 2019). We evaluated interactions of the COVID-19 drugs in Table 1 (except the traditional Chinese medicines) with P-gp and BCRP (Table 2). Thomas et al. predicted potential binding of repurposed COVID-19 drugs to P-gp via in silico studies, induced-fit docking and binding free energy calculation (Thomas et al. 2021). Remdesivir (− 2,687.21 (net binding energy)), baricitinib (− 2,471.25), indomethacin (− 2,441.04), arbidol (− 2,410.27),

Table 2 The interactions of COVID-19 drugs with P-gp and BCRP transporters

Drug type	Name	P-gp interaction	BCRP interaction	References/Sources
Antiviral	Arbidol	O[a]		Thomas et al. (2021)
	Camostat	X (inhibitor)[b]	X (inhibitor)[b]	Weiss et al. (2021)
	Chloroquine	O[a] (substrate/inhibitor)	O (inhibitor)	Rijpma et al.(2014); Thomas et al. (2021); https://go.drugbank.com/drugs/DB00608
	Cyclosporin A	O (K_M: 3.8 μM[3]/IC_{50}: 3.2 μM[d])	O (inhibitor)	Fricker et al.(1996); Angli-cheau et al. (2006); Tiberghien, et al. (2000); US FDA[e]
	Disulfiram	O (IC_{50}: 3.5, 6.3, 8.1 μM)[f]		Sauna et al. (2004)
	EK1C4			
	Favipiravir	O[a] (inhibitor)[g]		Thomas et al. (2021); https://go.drugbank.com/drugs/DB12466
	Hydroxychloroquine	O[a]		Thomas et al. (2021)
	Lopinavir	O[a] ($IC_{50:}$ 1.7, 6.3, 0.6 μM)[h]	O ($IC_{50:}$ 13.1, 4.2 μM)[h]	Vishnuvardhan et al. 2003; Telbisz et al.(2021); Biswas (2021); Thomas et al.(2021); US FDA
	Nafamostat	X (substrate)		Li et al. (2004)
	Nelfinavir	O (substrate)	O (($IC_{50:}$ 12.5 μM)[i]	Kim et al. (1998); Gupta et al. (2004)
	Quinacrine dihydrochloride	O (substrate/inhibitor)	O (inhibitor/docking)[j]	Tiberghien and Loor (1996); Huang et al. (2006); Nayak et al.(2020)
	Remdesivir	O[a] (substrate/ $IC_{50:}$ 20 μM[k])	O ($IC_{50:}$ over 50, 20 μM)[k]	Yang (2020); Telbisz et al. (2021); Thomas et al.(2021)
	Ribavirin			
	Ritonavir	O[a] (substrate/$IC_{50:}$ 8.4, 0.3 μM[l])	O (substrate/$IC_{50:}$ 19.5, 8.3, 7.5 μM[l])	Gupta et al. (2004); Bow et al. (2014); Telbisz et al. (2021); Biswas (2021); Thomas et al. (2021); US FDA
Anti-inflammatory	Baricitinib	O[a] (substrate)	O (substrate)	Posada et al.(2017); Thomas et al.(2021)
	Dexamethasone	O (substrate/inhibitor)	O (inhibitor)	Schinkel et al.(1995); Romiti et al.(2002); Elahian et al. (2010)
	Indomethacin	O[a]		Thomas et al. (2021)
	Mycophenolic acid	O (substrate)		Wang et al.(2008)
	Ruxolitinib	O[a] (inhibitor)[m]	O (substrate)	Ebert et al.(2016); Buks et al. (2021); Thomas et al. (2021)
	Tocilizumab			
Anticancer	Imatinib	O (substrate/inhibitor) [n]	O (substrate/inhibitor) [n]	Burger et al. (2004); Houghton et al.(2004); Breedveld et al. (2005); Dohse et al.(2010);
Antibiotics	Teicoplanin			

[a]In silico docking using the homology modeling of human P-gp protein PDB (id P08183 and references protein (PDB ID: 3G60) (Thomas et al. 2021)

[b]In vitro tests (Calcein-AM efflux assay in L-MDR1 cells for P-gp inhibition and Pheophorbide A efflux assay for BCRP inhibition) (Weiss et al. 2021)

[c]The kinetic parameter (K_M) of apical to basolateral permeation across Caco-2 cells monolayers (Fricker et al. 1996)

[d]Calcein-AM efflux assay in MDR-CEM cells (Tiberghien et al. 2000)

[e]Drug development and drug interaction, Table of substrates, inhibitions and inducers (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table4-1) (accessed on 26 May 2022)

[f]The binding of [^{125}I] Iodoarylazidoprazosin to P-gp (3.5 μM (ATP site protected) and 6.3 μM (ATP site free)) and the binding of [α-^{32}P]8-

Table 2 (continued)

AzidoATP to P-gp (8.1 μM)

[g]Favipiravir (5 mM) decreased P-gp efflux of the standard substrate to 81.9% of the control

[h]P-gp-mediated rhodamine 123 (Rh123) efflux in Caco-2 monolayers (1.7 μM) (Vishuvardhan et al 2003), P-gp-mediated Calcein-AM efflux in intact human PLB-985/ABCB1 cells (6.3 μM) and P-gp-mediated N-methyl quinidine (NMQ) efflux in HEK293/ABCB1 membrane vesicles (0.6 μM) (Telbisz et al 2021), and BCRP-mediated PhenGreen (PG) efflux in intact human PLB-985/ABCG2 cells (13.1 μM) and BCRP-mediated lucifer yellow (LY) efflux in HEK293/ABCG2 membrane vesicles (4.2 μM) (Telbisz et al 2021)

[i]Mitoxantrone (MX) efflux assay in BCRP-expressing HEK293 cells (Gupta et al 2004)

[j]Quinacrine (5 μM and 2 μM) decreased ATP hydrolysis and curcumin accumulation in the side population cells (sixfold higher BCRP-expressing) isolated from MCF-10A-Tr-P-EMT and predicted the binding to BCRP (-53.97 kcal/mol affinity) using the homology modeling (Nayak et al 2020)

[k]P-gp-mediated NMQ efflux in HEK293/ABCB1 membrane vesicles (20 μM), BCRP-mediated PG efflux in intact human PLB-985/ABCG2 cells (over 50 μM) and BCRP-mediated LY efflux in HEK293/ABCG2 membrane vesicles (20 μM) (Telbisz et al 2021)

[l]P-gp-mediated Calcein-AM efflux in intact human PLB-985/ABCB1 cells (8.4 μM) and P-gp-mediated NMQ efflux in HEK293/ABCB1 membrane vesicles (0.3 μM) (Telbisz et al 2021), and BCRP-mediated MX efflux in HEK293 cells (19.5 μM) (Gupta et al 2004), BCRP-mediated PG efflux in intact human PLB-985/ABCG2 cells (13.1 μM) and BCRP-mediated LY efflux in HEK293/ABCG2 membrane vesicles (4.2 μM) (Telbisz et al 2021)

[m]P-gp-mediated Rh123 efflux in JAK2 V617F-mutated cells and primary human T-cells (0.1, 0.5 and 1 μM) (Elbert et al. 2016)

[n]Imatinib (5 μM) decreased IC_{50} values of romidepsin (2.5 ng/mL) in HEK293-ABCB1 cells and topotecan (0.72 μM) in HEK293-ABCG2 as much as ninefold and 45-fold, respectively, and IC_{50} values of imatinib in K562-ABCB1 cells (1.01 μM) and K562-ABCG2 cells (0.21 μM) were reduced as much as eightfold and twofold by P-gp inhibitor and BCRP inhibitor, respectively (Dohse et al 2010)

hydroxychloroquine (− 2,148.34), ritonavir (− 2,095.04), chloroquine (− 1,965.43), lopinavir (− 1,735.14), ruxolitinib (− 1,647.90) and favipiravir (− 636.90) can be substrates or inhibitor of P-gp (Thomas et al. 2021). According to a US FDA report, 'Drug Development and Drug Interaction', cyclosporin A and ritonavir are in vitro inhibitors for P-gp (26 Sep. 2016), lopinavir and ritonavir are clinical inhibitors for P-gp (26 Sep. 2016) and cyclosporin A is a clinical inhibitor for BCRP (26 Sep. 2016). Moreover, many in vitro studies (apical to basolateral penetration assay, substrate efflux/accumulation assays, and ATP hydrolysis assay) have demonstrated that potential COVID-19 drugs are substrates and/or inhibitors of P-gp and/or BCRP (Table 2) (Fricker et al. 1996; Tiberghien et al. 2000; Romiti et al. 2002; Vishuvardhan et al. 2003; Burger et al. 2004; Gupta et al. 2004; Houghton et al. 2004; Li et al. 2004; Sauna et al. 2004; Anglicheau et al. 2006; Elahian et al. 2010; Doshe et al. 2010; Rijpma et al. 2014; Elbert et al. 2016; Nayak et al. 2020; Buks et al. 2021; Telbisz et al. 2021; Weiss et al. 2021). Furthermore, in vivo studies (pharmacokinetic study, brain distribution study) also support that these drugs interact with P-gp and/or BCRP transporters as substrates and/or inhibitors of transporters (Table 2) (Schinkel et al. 1995; Kim et al. 1998; Breedveld et al. 2005; Huang et al. 2006; Wang et al. 2008). The oral bioavailability of nelfinavir (Kim et al. 1998) and quinacrine (Huang et al. 2006) increased approximately fivefold (a dose of 6 mg/kg) and 49-fold (multiple doses of 10 mg/kg/day for 7 days) in P-gp-knockout (*Mdr1a*$^{-/-}$) mice (vs. wild-type mice), respectively. In the same animal model, brain penetration of cyclosporin A (Schinkel et al. 1995), nelfinavir (Kim et al. 1998), quinacrine (Huang et al. 2006) and dexamethasone (Schinkel et al. 1995) also increased 17-fold (a dose of 1 mg/kg), 36-fold (a dose of 3 mg/kg), 6–ninefold (a dose of 2 mg/kg) and 2.5-fold (a dose of 0.2 mg/kg), respectively, after intravenous injection. Mycophenolic acid levels in the plasma and brain after oral administration of mycophenolate mofetil (60 mg/kg), a prodrug of mycophenolic acid, were markedly increased in *Mdr1a/1b*$^{-/-}$ mice compared with wild-type mice (Wang et al. 2008). The area under the curve (AUC) of plasma imatinib after IV administration (12.5 mg/kg) was higher in *Bcrp1* knockout mice and *Mdr1a/1b* knockout mice than in wild-type mice, and clearance of the drug significantly decreased 1.6-fold in *Bcrp1* knockout mice and 1.25-fold in *Mdr1a/1b* knockout (vs. wild type), respectively. In addition, co-administration of pantoprazole (40 mg/kg) or elacridar (100 mg/kg), P-gp and BCRP inhibitors, significantly decreased imatinib clearance by 1.7-fold and 1.5-fold, respectively, in wild-type mice. Moreover, the brain penetration of imatinib following IV administration was also increased 2.5-fold in *Bcrp1* knockout mice (vs. the wild type), and co-administration with inhibitors also significantly increased brain penetration of the drug (1.8-fold by pantoprazole and 4.2-fold by elacridar) (Breedveld et al. 2005). Table 3 presents pharmacokinetic information for COVID-19 drugs that possess potential or reported interactions with P-gp and BCRP transporters.

Most drugs (19 of 23) showed interactions or potential interactions with P-gp (predominantly) and BCRP as substrates and/or inhibitors (Table 2). Among the drugs interacting with these efflux transporters, chloroquine, cyclosporin A, lopinavir, nelfinavir, quinacrine dihydrochloride, remdesivir, ritonavir, baricitinib, dexamethasone, ruxolitinib, and imatinib (11 drugs) can bind to both P-gp and BCRP

Table 3 Pharmacological or pharmacokinetic information of COVID-19 drugs related to the potential/reported interaction with P-gp and BCRP

Drug type	Name	Information	References/sources
Antiviral	Arbidol	A poor bioavailability (BA) in rat (18.8%) and human (40%)[a]	Liu et al. (2007); Answer et al. (2021)
	Camostat		
	Chloroquine	An increased serum cyclosporin A[b] level by oral chloroquine	Prescribing information (Aralen®)
	Cyclosporin A	An increased brain distribution in P-gp knockout mice an incomplete/variable absorption (C_{max} at 3.5 h) an increased plasma level by P-gp inhibitor a substrate of P-gp	Schinkel et al. (1995); Lown et al (1997); Prescribing information (Sandimmune®)
	Disulfiram		
	EK1C4		
	Favipiravir		
	Hydroxychloroquine	An increased plasma cyclosporin A level by hydroxychloroquine an increased serum digoxin[c] level by hydroxychloroquine an increased adverse reaction by co-administration with methotrexate[d] C_{max} at 3.3 ~ 3.7 h	Prescribing information (Plaquenil®)
	Lopinavir	An increased oral AUC in P-gp knockout mice (approx. ninefold)	Waterschoot et al.(2010)
	Nafamostat		
	Nelfinavir	An increased oral bioavailability and brain distribution in P-gp knockout mice	Kim et al. (1998)
	Quinacrine dihydrochloride	An increased oral bioavailability and brain distribution in P-gp knockout mice	Huang et al.(2006)
	Remdesivir	No clinical relevance about a P-gp substrate confirmed in vitro a poor BA of a prodrug (GS-441524) in rodent (12–57%) and human (13–20%)	Prescribing information (Verlury®); Rasmussen et al. (2022)
	Ribavirin	A low BA (52%) in human	Preston et al. (1999)
	Ritonavir	An increased BA of saquinavir[e], and brain and fetal distribution by high doses of ritonavir in mice an increased AUC (4 ~ sixfold) of P-gp substrates[f] by ritonavir in rats	Huisman et al. (2001); Kumar et al. (2003)

Table 3 (continued)

Drug type	Name	Information	References/sources
Anti-inflammatory	Baricitinib	A substrate of P-gp and BCRP but not clear on clinical relevance no clinically meaningful effects as an inhibitor (pharmacokinetics of digoxin or methotrexate)	Prescribing information (Olumiant®)
	Dexamethasone	An increased brain distribution in P-gp knockout mice an increased plasma level and brain level in both P-gp and BCRP knockout mice after IV injection	Schinkel et al. (1995); Hashimoto et al. (2017)
	Indomethacin	An increased serum digoxin level and its longer $t_{1/2}$ by oral indomethacin possibly increased the toxicity of cyclosporine A and methotrexate by oral indomethacin	Prescribing information (Indocin®)
	Mycophenolic acid	An increased plasma metabolite level by cyclosporin A in mice a limited enterohepatic recirculation of mycophenolic acid by cyclosporin A (a decreased plasma level)	Wang et al.(2008); Prescribing information (Myfortic®)
	Ruxolitinib		
	Tocilizumab	No effect of methotrexate on tocilizumab clearance	Prescribing information (Actemra®)
Anticancer	Imatinib	An increased AUC in P-gp knockout, BCRP knockout and P-gp/BCRP knockout mice a decreased clearance by P-gp and BCRP inhibitors[g] in mice an increased brain distribution by P-gp and BCRP inhibitors[g] in mice decreased fecal clearance and brain distribution in P-gp knockout mice	Breedveld et al. (2005); Oostendorp et al. (2009)
Antibiotics	Teicoplanin		

[a]Insolubility in aqueous media is major repercussion of the poor bioavailability in rat and human (Answer et al. 2021)

[b]P-gp substrate and inhibitor

[c]P-gp substrate

[d]P-gp and BCRP substrate

[e]P-gp substrate and inhibitor

[f]Novel antagonist of chemokine receptor 5 [2-(R)-[N-methyl-N-(1-(R)-3-(S)-((4-(3-benzyl-1-ethyl-(1H)-pyrazol-5-yl)piperidin-1-yl)methyl)-4-(S)-(3-fluorophenyl)cyclopent-1-yl)amino]-3-methylbutanoic acid (MRK-1)]

[g]Pantoprazole and elacridar

concomitantly. Remdesivir, baricitinib and ritonavir, which are US FDA-approved and FDA EUA drugs for COVID-19 treatment, require to pay a care this point when the drugs are used to treat the patients, especially, who take multiple medications. Indeed, the Liverpool Drug Interaction Group (COVID-19 Drug Interaction) recommended that ripamficin (an antibiotic), a well-known P-gp inducer, should not be co-administered with remdesivir because the strong induction of P-gp potentially reduces remdesivir level (Yang 2020). Other drugs under clinical trials (except nelfinavir and quinacrine dihydrochloride (preclinic)) also need to be considered in this light. These dual-interaction drugs control the host cell entry of SARS-CoV-2 (chloroquine, nelfinavir, quinacrine dihydrochloride, and imatinib), viral replication (cyclosporine, lopinavir, remdesivir, ritonavir and ivermectin), and acute inflammation (baricitinib, dexamethasone and ruxolitinib) in COVID-19. Camostat, EK1C4, nafamostat, ribavirin, and teicoplanin might not interact with efflux transporters. In vitro efflux assays showed that camostat was not an inhibitor of P-gp or BCRP (Weiss et al. 2021), and nafamostat was not a substrate of P-gp (Li et al. 2004) (Table 2).

In addition, P-gp polymorphisms have been associated with variability in the pharmacokinetics of lopinavir and

ritonavir (Rakhmanina et al. 2011; Biswas 2021). The *ABCB1* C3435T single nucleotide polymorphism (SNP), one of 50 SNPs in the *ABCB1* gene and one that is highly prevalent in different ethnic groups [Europe (78%), America (67%), Asia (63.5%), Africa (41.4%)], might affect the pharmacodynamics and pharmacokinetics of lopinavir and ritonavir. High expression or low expression of this SNP can lead to therapeutic failure or adverse risk of the COVID-19 drugs (Biswas 2021).

Drug-drug interactions

DDIs are another important pharmacological issue. DDIs can decrease the therapeutic effect of drug and/or increase minor or serious unexpected adverse drug reactions (Lazarou et al. 1998; Skvrce et al. 2011). COVID-19 patients, especially those who are elderly or have co-morbidities such as cancer, cardiovascular, lung, and/or kidney diseases, take multiple drugs to remedy various COVID-19 symptoms and other diseases. Therefore, COVID-19 patients with polypharmacy need to be carefully monitored.

DDIs of COVID-19 drugs with other drugs used for managing other diseases have been reported (Cattaneo et al. 2020; Baburaj et al. 2021; Thomas et al. 2021). Lopinavir/ritonavir, chloroquine, hydroxychloroquine, and dexamethasone have potential DDIs with lung cancer medications. Among these COVID-19 drugs, lopinavir/ritonavir have potentially the most severe DDIs with many anticancer drugs (afatinib, brigatinib, cabozantinib, certinib, crizotinib, cyclophosphamide, dabrafenib, docetaxel, doxorubicin, entrectinib, erlotinib, everolimus, irinotecan, larotrectinib, lorlatinib, lurbinectedin, osimertinib, selpercatinib, topotecan, vandetanib, vemurafenib, vinblastine, and vincristine) and with antitubercular drugs (rifampin, clarithromycin, levofloxacin, moxifloxacin, ofloxacin, clofazimine, delamanid, and bedaquiline) (Baburaj et al. 2021; Thomas et al. 2021). Chloroquine, hydroxychloroquine, dexamethasone, and ruxolitinib were also identified to have potential DDIs with several antitubercular drugs (rifampin, clarithromycin, levofloxacin, moxifloxacin, ofloxacin, clofazimine, delamanid and bedaquiline) (Thomas et al. 2021). Ribavirin, remdesivir, and tocilizumab might not induce DDIs with lung cancer drugs (Baburaj et al. 2021), and remdesivir, baricitinib and tocilizumab might not be related to DDIs with antitubercular drugs (Thomas et al. 2021).

Hu et al. investigated the pharmacokinetic interactions between lopinavir/ritonavir and arbidol in an animal study. An oral co-administration of lopinavir (50 mg/kg)/ritonavir (12.5 mg/kg) and arbidol (25 mg/kg) significantly enhanced the AUC of arbidol (more than twofold) and the C_{max} of lopinavir in rats (Hu et al. 2021). In northern Italy, the risk of potential DDIs was analyzed in hospitalized patients with COVID-19 ($n = 502$, mean age 61 ± 16 years (range 15–99 years) between 21 Feb. and 30 Apr. 2020) who had co-morbidities including cardiovascular, metabolic, lung, oncological, kidney, immune, and chronic infectious diseases (Cattaneo et al. 2020). Among the patients, 68% were exposed to at least one potential DDI, and 55% of patients were exposed to at least one potentially severe DDI. DDIs of co-medications, particularly with lopinavir/ritonavir, caused various and severe adverse events, and the combination of lopinavir/ritonavir and hydroxychloroquine induced a number of potentially severe DDIs resulting in a high risk of cardiotoxicity (Cattaneo et al. 2020). Remdesivir and tocilizumab were not observed to induce any potentially severe DDIs in hospitalized patients with COVID-19.

Remdesivir and tocilizumab could be safer with regard to pharmacodynamic DDIs when given with various drugs to treat co-morbidities than other COVID-19 drugs, whereas lopinavir, ritonavir, chloroquine, and hydroxychloroquine are assumed to lead to potentially severe pharmacodynamic DDIs (Cattaneo et al. 2020; Saleh et al. 2020; Baburaj et al. 2021; Biswas 2021; Thomas et al. 2021). COVID-19 drugs interacting with the P-gp and BCRP transporters (Table 2 and 3) also lead to pharmacokinetic DDIs. These pharmacokinetic DDIs, altering the absorption, distribution, metabolism, and excretion of medications, are more common than pharmacodynamic DDIs (Peng et al. 2021).

We examined the potentially severe efflux transporter-mediated DDIs between COVID-19 drugs by consulting the website of 'Drugs.com (https://www.drugs.com/drug_interactions.html)' and 'COVID-19 Drug Interactions (http://www.covid19-druginteractions.org/checker)', 'drug prescribing information (downloaded from FDA website)' as well as literature data. Major DDIs were monitored when the combination treatment of chloroquine-hydroxychloroquine, chloroquine-lopinavir, chloroquine-remdesivir, cyclosporin A-nelfinavir, cyclosporin A-ritonavir, cyclosporin A-baricitinib, disulfiram-ritonavir, hydroxychloroquine-lopinavir, hydroxychloroquine-remdesivir, lopinavir-nelfinavir, lopinavir-ritonavir, nelfinavir-ruxolotinib, ritonavir-ruxolitinib, baricitinib-dexamethasone, baricitinib-mycophenolic acid, baricitinib-ruxolitinib, baricitinib-tocilizumab, baricitinib-imatinib and ruxolotinib-tocilizumab were administered (Table 4). Combinations exhibiting major DDIs were not recommended. Although many other cases showed moderate DDIs, these combinations were also not recommended. On the other hand, the combination of cyclosporin A-lopinavir, lopinavir-imatinib, ritonavir-indomethacin and ruxolitinib-imatinib appeared to lead to only minor DDIs, which has minimal clinical significance and a low risk (Drugs.com/Drug Interactions Checker).

In addition, the combination of favipiravir-chloroquine, favipiravir-cyclosporin A, favipiravir-hydroxychloroquine, favipiravir-lopinavir/ritonavir, **favipiravir-remdesivir**, favipiravir-dexamethasone, favipiravir-mycophenolic

Table 4 Potential DDIs between COVID-19 drugs binding to P-gp and BCRP transporters

Drug type	Name	DDI drugs (possible/clinical mechanism)	Reference/Sources
Antiviral	Arbidol	Lopinavir (the increased the AUC of plasma arbidol)[a] Ritonavir[a]	Hu et al. (2021)[a]
	Chloroquine	***Hydroxychloroquine (the increased risk of an irregular heart rhythm)*** ***Lopinavir (the increased risk of an irregular heart rhythm)*** ***Remdesivir (less effect by chloroquine)*** Cyclosporin A (the increased blood level and effects) Nelfinavir (increased blood level and effects of chloroquine) Ritonavir (the increased blood level and effects of chloroquine) Imatinib (an increased blood chloroquine level) *Disulfiram (the increased risk of nerve damage)* *Baricitinib (the potential additive toxicity)* *Dexamethasone (an increased risk of myopathies)* *Tocilizumab (the increased risk of nerve damage (a potential side effect of both))*	Drugs.com[b] COVID-19 Drug Interactions[c] Prescribing information (Aralen®)
	Cyclosporin A	**Nelfinavir (the increased blood level and effects of cyclosporin A)** **Ritonavir (the increased blood level and effects of cyclosporin A)** ***Baricitinib (the increased risk of serious and potentially fatal infections as well as some cancers)*** Chloroquine (the increased blood level and effects of cyclosporin A) Hydroxychloroquine (increased blood level and effects of cyclosporin A) Mycophenolic acid (the decreased blood level and effects of mycophenolic acid) Dexamethasone (the altered blood levels and effects of both) Ruxolitinib (the increased blood level and effects of cyclosporin A) Imatinib (the increased blood level and effects of cyclosporin A) *Remdesivir (the increased risk of liver problem caused by remdesivir)* *Indomethacin (Kidney risk)* *Tocilizumab (a decreased blood cyclosporin A level and the increased risk of serious infections)* Lopinavir (a minor interaction)	Drugs.com COVID-19 Drug Interactions Prescribing information (Sandimmune®)
	Disulfiram	***Ritonavir (unpleasant side effects of disulfiram reaction by the breakdown of alcohol[d])*** *Chloroquine (the increased risk of nerve damage)* *Hydroxychloroquine (the increased risk of nerve damage)* *Remdesivir (the increased risk of liver problem caused by remdesivir)* *Tocilizumab (the increased risk of nerve damage)*	Drugs.com COVID-19 Drug Interactions
	Favipiravir	Baricitinib (an increased exposure of baricitinib)	COVID-19 Drug Interactions

Table 4 (continued)

Drug type	Name	DDI drugs (possible/clinical mechanism)	Reference/Sources
	Hydroxychloroquine	***Chloroquine (the increased risk of an irregular heart rhythm*** ***Lopinavir (the increased risk of an irregular heart rhythm)*** ***Remdesivir (less effect by hydroxychloroquine)*** Cyclosporin A (increased blood level and effects of cyclosporin A) Nelfinavir (the increased blood level and effects of hydroxychloroquine) Ritonavir (the increased blood level and effects of hydroxychloroquine) Imatinib (an increased blood hydroxychloroquine level) *Disulfiram (the increased risk of nerve damage)* *Bricitinib (the potential additive toxicity)* *Dexamethasone (an increased risk of myopathies)* *Ruxolitinib (the risk of additive immunosuppression and haematological toxicity)* *Tocilizumab (the increased risk of nerve damage)*	Drugs.com Prescribing information (Plaquenil®)
	Lopinavir	**Nelfinavir (decreased blood lopinavir level and effects)** **Ritonavir (an increased blood lopinavir level)** ***Chloroquine (the increased risk of an irregular heart rhythm)*** ***Hydroxychloroquine (the increased risk of an irregular heart rhythm)*** Arbido (an increased lopinavir C_{max})[a] Dexamethasone (the decreased blood level and effects of lopinavir) *Disulfiram (a disulfiram-like reaction)* Cyclosporine A (a minor interaction) Imatinib (a minor interaction)	Drugs.com COVID-19 Drug Interactions Prescribing information (Kaletra®) Hu et al (2021)
	Nafamostat	*ND*	
	Nelfinavir	**Cyclosporine A (the increased blood level and effects of cyclosporin A)** **Lopinavir (an increased blood nelfinavir level)** **Ruxolitinib (the increased blood level and effects of ruxolitinib)** Chloroquine (increased blood level and effects of chloroquine), Hydroxychloroquine (the increased blood level and effects of hydroxychloroquine) Ritonavir (an increased nelfinavir effect) Imatinib (an increased nelfinavir effect) *Dexamethasone (the altered effects of both and the increased risk of an irregular heart rhythm)*	Drugs.com COVID-19 Drug Interactions Prescribing information (Viracept®)
	Quinacrine dihydrochloride	*ND*	

Table 4 (continued)

Drug type	Name	DDI drugs (possible/clinical mechanism)	Reference/Sources
	Remdesivir	**Chloroquine (an interference of remdesivir activity)** **Hydroxychloroquine (an interference of remdesivir activity)** *Cyclosporin A (the increased risk of liver problem caused by remdesivir)* *Disulfiram (the increased risk of liver problem caused by remdesivir)* *Ritonavir (the increased risk of liver problem caused by remdesivir)* *Indomethacin (the increased risk of liver problem caused by remdesivir)* *Tocilizumab (the increased risk of liver problem caused by remdesivir)* *Imatinib (the increased risk of liver problem caused by remdesivir)*	Drugs.com COVID-19 Drug Interactions Prescribing information (Veklury®)
	Ritonavir	**Cyclosporine A (the increased blood level and effects of cyclosporin A)** **Disulfiram (unpleasant side effects of disulfiram reaction by the breakdown of alcohol[d])** **Ruxolitinib (the increased blood level and effects of ruxolitinib)** Chloroquine (the increased blood level and effects of chloroquine) Hydroxychloroquine (the increased blood level and effects of hydroxychloroquine) Nelfinavir (an increased nelfinavir effect) Imatinib (the increased blood level and effects of both) *Remdesivir (the increased risk of liver problem caused by remdesivir)* *Dexamethasone (the altered effects of both and the increased risk of an irregular heart rhythm)* Mycophenolic acid (an altered mycophenolic acid level) Indomethacin (a minor interaction	Drugs.com COVID-19 Drug Interactions
Anti-inflammatory	Baricitinib	***Cyclosporine A (the increased risk of serious and potentially fatal infection as well as some cancers)*** ***Dexamethasone (the increased risk of serious and potentially fatal infections as well as various types of cancers)*** ***Mycophenolic acid (the increased risk of serious and potentially fatal infections as well as various types of cancers)*** ***Ruxolitinib (the increased risk of serious and potentially fatal infections as well as some cancers)*** ***Tocilizumab (the increased risk of serious and potentially fatal infections as well as some cancers)*** ***Imatinib (the increased risk of serious ana potentially fatal infections as well as various types of cancers)*** Favipiravir (an increased exposure of baricitinib) *Chloroquine (the potential additive toxicity)* *Hydroxychloroquine (the potential additive toxicity)* *Indomethacin (additive adverse effects and the increased risk of diverticular disease or GI bleeding or perforation)*	Drugs.com COVID-19 Drug Interactions

Table 4 (continued)

Drug type	Name	DDI drugs (possible/clinical mechanism)	Reference/Sources
	Dexamethasone	***Baricitinib (the increased risk of serious and potentially fatal infections as well as various types of cancers)*** Cyclosporin A (the altered blood levels and effects of both) Lopinavir (the reduced blood level and effects of lopinavir by dexamethasone) Ruxolitinib (the reduced blood level and effects of ruxolitinib) Imatinib (the reduced blood level and effects of imatinib in some patients) *Chloroquine (an increased risk of myopathies)* *Nelfinavir (the altered effects of both and the increased risk of an irregular heart rhythm)* *Hydroxychloroquine (an increased risk of myopathies)* *Ritonavir (the altered effects of both and the increased risk of an irregular heart rhythm)* *Indomethacin (the increased risk of side effects in the GI tract)*	Drugs.com COVID-19 Drug Interactions
	Indomethacin	Imatinib (an inhibitor: the increased blood level and effects of indomethacin) *Cyclosporin A (Kidney risk)* *Remdesivir (the increased risk of liver problem caused by remdesivir)* *Baricitinib (additive adverse effects and the increased risk of diverticular disease or GI bleeding or perforation)* *Dexamethasone (the increased risk of side effects in the GI tract)* *Ruxolitinib (the increased risk of bleeding)* Ritonavir (a minor interaction)	Drugs.com COVID-19 Drug Interactions Prescribing information (Indocin®)
	Mycophenolic acid	***Baricitinib (the increased risk of serious and potentially fatal infections as well as various types of cancers)*** Cyclosporin A (the reduced blood level and effects of mycophenolic acid) Ritonavir (an altered mycophenolic acid level)	Drugs.com COVID-19 Drug Interactions Prescribing information (Myfortic®)
	Ruxolitinib	**Nelfinavir (the increased blood level and effects of ruxolitinib)** **Ritonavir (the increased blood level and effects of ruxolitinib)** ***Baricitinib (the increased risk of serious and potentially fatal infections as well as some cancers)*** ***Tocilizumab (the risk of additive immunosuppression and haematological toxicity)*** Cyclosporin A (a substrate: the increased blood level and effects of cyclosporin A) Dexamethasone (the reduced blood level and effects of ruxolitinib) Lopinavir *Chloroquine (the potential additive toxicity)* *Hydroxychloroquine (the risk of additive immunosuppression and haematological toxicity)* *Indomethacin (the increased risk of bleeding)* Imatinib (a minor interaction)	Drugs.com COVID-19 Drug Interactions

Table 4 (continued)

Drug type	Name	DDI drugs (possible/clinical mechanism)	Reference/Sources
	Tocilizumab	***Baricitinib (the increased risk of serious and potentially fatal infections as well as some cancers)*** ***Ruxolitinib (the risk of additive immunosuppression and haematological toxicity)*** *Chloroquine (the increased risk of nerve damage (a potential side effect of both))* *Cyclosporin A (a decreased blood cyclosporin A level and the increased risk of serious infections))* *Disulfiram (the increased risk of nerve damage)* *Hydroxychloroquine (the increased risk of nerve damage)* *Remdesivir (the increased risk of liver problem caused by remdesivir)* *Imatinib (a potential additive haematological toxicity)*	Drugs.com COVID-19 Drug Interactions
Anticance	Imatinib	***Baricitinib (the increased risk of serious ana potentially fatal infections as well as various types of some cancers)*** Chloroquine (an increased blood chloroquine level) Cyclosporin A (an increased blood level and effects) Hydroxychloroquine (an increased blood hydroxychloroquine level) Nelfinavir (an increased nelfinavir effect) Ritonavir (an increased blood level and effects of both) Dexamethasone (the reduced blood level and effects of imatinib in some patients) Indomethacin (the increased blood level and effects of indomethacin) *Remdesivir (the increased risk of liver problem caused by remdesivir)* *Imatinib (a potential additive haematological toxicity)* Lopinavir (a minor interaction) Ruxolitinib (a minor interaction)	Drugs.com COVID-19 Drug Interactions

ND not determined

Major interaction (bold fonts), highly clinically significant and not recommend for co-administration; moderate interactions (others), moderately clinically significant and usually not recommend for co-administration; *italic fonts,* generally not used together or induced risk; minor interactions, minimally clinically significant and minimize risk

[a]Reference

[b]Drugs.com [Internet]. 'Drug Interactions Checker' from Drugs.com; c1996-2018 [Updated: 13 February 2018, Cited: 19 June 2018]. Available from: https://www.drugs.com/drug_interactions.html (accessed on 28 May 2022). The Drugs.com 'Drug Information Database' is powered by several independent leading medical-information suppliers, including; 'American Society of Health-System Pharmacists', 'Cerner Multum' and 'IBM Watson Micromedex'. Individual drug (or drug-class) content compiled by these sources is peer reviewed and delivered by Drugs.com

[c]Interaction Checkers' of COVID-19 Drug Interactions, c1999-2022 [updated 8 March 2022], University of Liverpool, available from http://www.covid19-druginteractions.org/checker (accessed on 28 May 2022). Liverpool Drug Interaction Group established by the department of Pharmacology at the university of Liverpool provides a freely available drug-drug interaction resource for the drugs of HIV, hepatitis and cancers treatment

[d]Ritonivir is formulated with alcohol

acid, favipiravir-ruxolitinib, **favipiravir-tocilizumab**, favipiravir-imatinib, remdesivir-lopinavir, **remdesivir-baricitinib**, **remdesivir-dexamethasone**, **remdesivir-mycophenolic acid**, **remdesivir-ruxolitinib**, **baricitinib-lopinavir/ritonavir**, **baricitinib-mycophenolic acid**, dexamethasone-mycophenolic acid, dexamethasone-ruxolitinib, **dexamethasone-tocilizumab**, ruxolitinib-mycophenolic acid, **tocilizumab-lopinavir/ritonavir** and **tocilizumab-mycophenolic acid** are not expected to lead to DDIs (COVID-19 Drug Interactions/Interaction Checkers

and Drugs.com/Drug Interactions Checker). Drugs with minor or no DDIs can be considered in treatment with an adjusted regimen. Among the above DDIs, the combinations (**bold and underline**) of US FDA-approved and EUA drugs (remdesivir, baricitinib, ritonavir and tocilizumab) can be considered for the clinical trial. The possible or clinical mechanisms of DDIs between COVID-19 drugs are mentioned in Table 4. The mechanism of drug interaction has been mainly interpreted based on the activity of cytochrome P450 enzymes. However, the results from in silico, in vitro and non-clinical approaches to interactions with P-gp and BCRP provide the strong potential for the correlation of DDIs between COVID-19 drugs (Table 4, except tocilitinib) with these transporters (Schinkel et al. 1995; Fricker et al. 1996; Kim et al. 1998; Wang et al. 2008; Romiti et al. 2002; Vishuvardhan et al. 2003; Burger et al. 2004; Gupta et al. 2004; Houghton et al. 2004; Li et al. 2004; Sauna et al. 2004; Breedveld et al.2005; Huang et al. 2006; Anglicheau et al. 2006; Elahian et al. 2010; Doshe et al. 2010; Rijpma et al. 2014; Elbert et al. 2016; Tiberghien et al. 2000; Nayak et al. 2020; Buks et al. 2021; Telbisz et al. 2021; Weiss et al. 2021; Thomas et al. 2021). Overall, a better understanding of the pharmacokinetic and pharmacodynamic DDIs of COVID-19 drugs would be useful for managing pharmacological therapy in COVID-19 patients.

Conclusions

COVID-19, which is caused by SARS-CoV-2, results in ARD, fatal systemic manifestations (extrapulmonary as well as pulmonary), and premature mortality in patients. Clinical approaches to COVID-19 are the treatment of various symptoms and acute inflammation (cytokine storm) and the prevention of viral infection. Among various therapeutic strategies including immunological and vaccinal approaches, pharmacological therapy targets most steps of the SARS-CoV-2 infection cycle (cell entry, replication of proteins and genomic RNA) and inflammation (cytokine storm). Drug repositioning has been a priority due to the time-consuming nature of vaccine development for initial COVID-19 therapy.

We evaluated the interaction of current COVID-19 drugs with ABC transporters (P-gp and BCRP) and examined the potential DDIs of COVID-19 drugs, especially those associated with the efflux transporters. Most drugs interact with these transporters. Chloroquine, cyclosporin A, lopinavir, nelfinavir, quinacrine dihydrochloride, remdesivir, ritonavir, baricitinib, dexamethasone, ruxolitinib, and imatinib can bind to both efflux transporters, while EK1C4, ribavirin, tocilizumab and teicoplanin might not interact with any transporters. P-gp and BCRP-mediated COVID-19 drugs can lead to pharmacokinetic DDIs. Favipiravir may be safer than other COVID-19 drugs in terms of pharmacodynamic DDIs with various drugs to treat co-morbidities. Drug combinations of minor or no DDIs may be considered in clinical trials with an adjusted regimen. Moreover, combination therapy of remdesivir, baricitinib, ritonavir and tocilizumab (US FDA-approved and EUA drugs) with drugs which have little or no DDIs is expected to be widely used in the treatment of COVID-19, including favipiravir-remdesivir, favipiravir-tocilizumab, remdesivir-baricitinib, remdesivir-dexamethasone, remdesivir-mycophenolic acid, remdesivir-ruxolitinib, baricitinib-lopinavir/ritonavir, baricitinib-mycophenolic acid, dexamethasone-tocilizumab, tocilizumab-lopinavir/ritonavir and tocilizumab-mycophenolic acid. A better understanding of COVID-19 drugs and their potential pharmacokinetic and/or pharmacodynamic DDIs will be helpful in the management of pharmacological therapy for COVID-19.

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Declarations

Conflict of interest None of the authors (J Lee, J Kim, J Kang and HJ Lee) have potential conflicts of interest to declare.

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