Disease-drug and drug-drug interaction in COVID-19: risk and assessment

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Abstract

COVID-19 is announced as a global pandemic in 2020. The emergent outbreak of COVID-19 prompted by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) keeps spreading globally. Its mortality and morbidity rate are rapidly increasing, and medication options are still limited. A patient's immune response plays a pivotal role in the pathogenesis of COVID-19. Hyperinflammatory state may sparks significant imbalances in transporters and drug metabolizing enzymes, and subsequent alteration of drug pharmacokinetics that may result in unexpected therapeutic response. The present scenario has accounted the requirement for therapeutic opportunities to relive and overcome this pandemic. Despite the fact, the diminishing developments of COVID-19, there is no drug still approved to have significant effects with no side effect. Based on the evidence, many antiviral and anti-inflammatory drugs have been authorized by the Food and Drug Administration (FDA) to treat the COVID-19 patients even though not knowing the possible drug-drug interactions. Hydroxychloroquine is the first medicine chosen for the treatment of disease. Remdesivir, favipiravir, and molnupiravir are deemed the most hopeful antiviral agent; by improving health of infected patients. The dexamethasone saved the lives of seriously ill patients. Many randomized and controlled clinical trials are taking place to further corroborate these agent's safety and efficacy in handling COVID-19. The current review summarizes the involvement of drug transporters and drug metabolizing enzymes for the existing drugs and gives the opinion on the potential drug-drug interactions in inflammatory state. This may permit individualization of these drugs thereby enhancing the safety and efficacy.

Key Words: COVID-19, Drug transporters, CYPs, Remdesivir, Dexamethasone, Molnupiravir,

Introduction

SARS-CoV-2 was initially recognized and designated as COVID-19 infection (Helmy et al., 2020). The National Health Commission of China confirmed the information of the first appearance of COVID-19 in pneumonia patients appeared in the city of Wuhan in China in

December 2019 (WHO, 2020). Initially, pneumonia patients stated the normal respiratory infection which promptly transformed into acute respiratory syndrome (Huang et al., 2020). By the end of December 2020, almost 77 million cases have been reported, with the death toll of about 1.7 million deaths.

There is a very urgent prerequisite to discovering a novel antiviral drugs against COVID-19. Based on the evidence, Food and Drug Administration (FDA) approved some drugs that have been already used in the treatment of SARC-CoV and MERC-COV. In these, remdesivir and favipiravir showed the most promising effect against COVID-19 (Sheahan et al., 2017). The anti-retroviral (ARV) drug lopinavir, that has been used for COVID-19 in combination with ritonavir (potent anti-HIV drug). This lopinavir-ritonavir combination showed to be efficient against COVID-19 (Martinez, 2020). Anti-malarial drug hydroxychloroquine has demonstrated more promising results against COVID-19, and it is used in higher frequency. Alone and in combination with other many drugs (Mitja & Clotet, 2020), (Rismanbaf, 2020). Regardless of the antiviral drug, dexamethasone has proved little relief against COVID-19. In the initial clinical trial, it lowered the death by one-third on severe patients that were on a ventilator (Ledford, 2020). Fluvoxamine has also shown the potential in COVID-19 infected outpatients (Lenze et al., 2020). Molnupiravir is used to treat COVID-19 infection, It can block the transmission of SARS-CoV-2 within 24 hours (Cox, Wolf, & Plemper, 2020). Many drugs and peptide some under clinical trial that have been used for treating COVID-19 (N. Trivedi, Verma, & Kumar, 2020), has shown in table 1. Vaccine development is typically a long game and many more vaccines against COVID-19 are in clinical trials and few are in the final stage (N. Trivedi et al., 2020). We will have to wait and see how things play out (Mullard, 2020).

Many determinants of the pharmacokinetics of used possible COVID-19 medications, including absorption distribution metabolism and elimination can be modified disease state or during inflammatory response (Fig 1.). Chronic inflammation is produced when an antigen is persisted, and the immune system continuously acts against this antigen. This chronic inflammation is associated with alteration in the level of drug binding proteins (Don & Kaysen, 2004; Moshage, Janssen, Franssen, Hafkenscheid, & Yap, 1987; Ruot, Bechereau, Bayle, Breuille, & Obled, 2002), in addition, the downregulation of various hepatic and extrahepatic drug metabolizing enzyme (Morgan, 2009; Morgan et al., 2008). More recently inflammation-mediated changes in the expression of numerous membranes associated drug transporters have been reported (Cressman, Petrovic, & Piquette-Miller, 2012). In the case of co-administration of many drugs, the risk of drug interaction increases, nevertheless in

COVID-19, a more complicated diseases-drug-drug interaction is anticipated. The SARS-CoV-2 infection has shown an increasing frequency of hospitalization and intensive care unit (ICU) admission (Grasselli G, 2020). This is considered as a major clinical concern mainly when considering that critically ill patients are more influenced drug interaction that CYPs and efflux pumps are involved in the metabolism and transport respectively of commonly prescribed drugs in ICU (HJ., 2006). During highly prevalent acute and chronic inflammatory conditions, the alteration in the expression and activity of transporters and DMEs of these may modify the pharmacokinetic and pharmacodynamic properties of therapeutic drugs used in COVID-19 treatment.

This article will focus on the current state of knowledge and assume a pharmacokinetic disease -drug and drug-drug interaction potential of therapeutic agents used for common comorbidities, or frequently used in intensive care for COVID-19 patients. Herein, we also reviewed the updated status of the supportive roles of several antivirals, some antibiotics, and some therapeutics peptides that have tested their efficacy in the worldwide treatment of COVID-19.

Alteration of drug transporters mechanisms in response to inflammation

Inflammation is associated with various cytokines response. Cytokines are the broad class of small cell signaling proteins accountable for keeping homeostasis of the immune system. Proinflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF-α) are mainly responsible for an acute immune response (Furuta et al., 2013). During infection, these locally producing cytokines can circulate in the bloodstream and produce a systemic effect by interacting with cell membrane receptors, transporters on the vascular endothelium, and parenchymal cells of numerous organs. Inflammation and immune reaction represent a significant factor in many acute and chronic diseases which are clearly involved in changing drug clearance by altering drug transporters mechanism and drug metabolizing enzyme activity.

P-glycoprotein (Pgp) is one of the most comprehensively explored ABC transporter that has been studied against the response of inflammations. Several studies suggested the association of IL-6 as direct administration of this cytokine diminished the Pgp mRNA level and protein expression in hepatic cell lines as well as *in vivo* in mice (G. Lee & Piquette-Miller, 2001; Sukhai, Yong, Kalitsky, & Piquette-Miller, 2000). In humans, intestinal epithelium showed a decrease in Pgp expression in inflammatory conditions (Blokzijl et al., 2007). Caco-2 is

human enterocyte cell line and universal model for permeability experiment was treated with TNF-α resulted in to decrease in Pgp expression and activity (Belliard, Lacour, Farinotti, & Leroy, 2004; Buyse, Radeva, Bado, & Farinotti, 2005). Second, most comprehensively explored ABC transporter, BCRP (breast cancer resistance protein) was studied in recent years. Like Pgp, BCRP activity and expression were downregulated in primary human hepatocytes after treating with IL-6, while TNF-α treatment led to induction of BCRP (Le Vee, Lecureur, Stieger, & Fardel, 2009). The effect of IFN-γ on primary human hepatocytes, significantly decreased the mRNA expression of BCRP (Le Vee, Jouan, Moreau, & Fardel, 2011). The human brain cell line showed significant decreases in the expression and activity of BCRP after treating by IL-β1, IL-6, and TNF-α (Poller, Drewe, Krahenbuhl, Huwyler, & Gutmann, 2010). It is also believed that proinflammatory cytokines are key mediators of MRP2. It was recently revealed that IL-β1, IL-6, and TNF-α, all considerably down-regulate the mRNA and protein expression of MRP2 in hepatic cell lines of human and rat (Diao, Li, Brayman, Hotz, & Lai, 2010; Le Vee, Gripon, Stieger, & Fardel, 2008). Overall, alteration in the expression of Pgp, BCRP, MRP2, and several other key transporters is mediated by acute inflammatory response (Buyse et al., 2005; Langmann et al., 2004; Mak, Cheung, Cone, & Marks, 2006; Suzuki, Miyamoto, Yasui, Sugie, & Tanaka, 2007; van der Heijden, Dijkmans, Scheper, & Jansen, 2007; van Herwaarden et al., 2003). One study on inflammatory bowel diseases (IBD) patients revealed the effect of inflammation on SLC transporters (Wojtal et al., 2009). SLC transporters (ENT1, ENT2, CNt2, OATP2B1, OATP4A1) mRNA level was dysregulated in IBD patients, which is associated with the inflammation of the tissue and presents an indication about the inflammatory signaling in the regulation of SLC expression (Wojtal et al., 2009). Many transcription factors are also activated during inflammation and play a key role in the regulation of transporters and drug-metabolizing enzymes (Ho & Piquette-Miller, 2007; Kameyama et al., 2008; W. Pan, Yu, Hsuchou, & Kastin, 2010; Teng & Piquette-Miller, 2008; Yu et al., 2008). Many excellent reviews have been published on the molecular mechanism of the transporters regulations during inflammation have been described elsewhere (Kosters & Karpen, 2010; Teng & Piquette-Miller, 2008; Tirona, 2011).

Alteration of drug metabolizing enzymes activity in response to inflammation

CYPs are widely involved as the main contributor to metabolic biotransformation of most drugs (Harvey & Morgan, 2014). Like drug transporters, regulation of CYPs has also been associated with inflammation in several metabolic and infectious diseases including viral infection (Wu & Lin, 2019). Inflammatory induced alteration in hepatic CYPs expressions and activity are caused by signal molecules which are mainly cytokines, formed during the

inflammation process (Morgan, 1997). It has been reported that multiple cytokines may play a part in regulating a single enzyme, whereas a subclass of enzymes can be regulated by a specific cytokine. The regulation is extremely important when considering drug interactions because drug pharmacokinetics will ultimately be altered depending on disease type and its released cytokines, as well as the administered (Aitken & Morgan, 2007; Muntane-Relat, Ourlin, Domergue, & Maurel, 1995). Many studies have described cytokine induced CYPs activity alteration in different mammals (Calleja et al., 1998; Monshouwer, Witkamp, Nujmeijer, Van Amsterdam, & Van Miert, 1996; Tapner, Liddle, Goodwin, George, & Farrell, 1996) including humans (Abdel-Razzak et al., 1993; Rubin et al., 2015) using hepatocytes as well as *in vivo* in mice (J. Pan, Xiang, & Ball, 2000), rats (Morgan, 1993), and humans (Frye, Schneider, Frye, & Feldman, 2002). Inflammatory mediators also suppressed the extrahepatic CYPs (Bertilsson, Olsson, & Magnusson, 2001; Liptrott et al., 2009; Nicholson & Renton, 1999, 2001). Most proinflammatory cytokines are IL-1 (Dickmann, Patel, Wienkers, & Slatter, 2012; Iber, Chen, Cheng, & Morgan, 2000; Parmentier et al., 1993), IL-6, TNF-α, and IFN-γ that have displayed suppression of CYPs expression and activity (Bleau, Levitchi, Maurice, & du Souich, 2000; Donato, Guillen, Jover, Castell, & Gomez-Lechon, 1997; Nadin, Butler, Farrell, & Murray, 1995). Other cytokines IL-2 and IL-10 also showed the same effect (Elkahwaji et al., 1999; Gorski et al., 2000; Tinel et al., 1995). IL-6 has been identified as the major inflammatory factor that elicits a significant repressive effect on the expression and activity of different CYPs. Human recombinant IL-6 has exhibited concentration dependent inhibition of phenobarbital mediated induction of CYP2B1/2 in rat hepatocytes (Williams, Bement, Sinclair, & Sinclair, 1991) and reduced activity of different CYPs with variable levels (Y. L. Chen et al., 1992). Human recombinant IL-6 treatment markedly suppressed at mRNA level of CYP1A1, CYP1A2, and CYP3A3 in different human hepatoma cell lines (Y. L. Chen et al., 1992). Chronic inflammatory response, induced by turpentine or bacterial lipopolysaccharide, showed significant suppression in hepatic CYP1A2, CYP2A5, CYP2C1, and CYP3A11 in rats (Morgan, 1989; Siewert et al., 2000). Several studies have assessed the impact of IL-6 on CYPs, triggered by malignancies (Robertson et al., 2003). The vital role of IL-6 in cancer mediated suppression of hepatic CYP3A has been exhibited by mitigating such effect via monoclonal antibody against IL-6 (Kacevska et al., 2013) or IL-6 receptor (Mimura et al., 2015). Anti-IL-6 antibody intrusion was also tested in IL-6 treated primary human hepatocytes. CYP1A1, CYP1A2, CYP2B6, and CYP3A4 expression and activity were inhibited by IL-6, and It was also efficient of intervening CYP1A2 and CYP3A4, induced by omeprazole and rifampicin, respectively. The cytokine induced suppression of CYPs activity is not fully expounded but it is believed that strongly suggested that a decrease in the CYPs mRNA strongly recommended

a transcriptional mechanism affecting several transcriptional factors (Hayden, West, & Ghosh, 2006; Zordoky & El-Kadi, 2009). Nuclear factor Kappa B (NF-kB) and the aryl hydrocarbon receptor are the regulatory transcription factor in the inflammatory and immune response, they regulate the gene expression of many CYPs in human, rats, and mice (Hayden et al., 2006; Ke, Rabson, Germino, Gallo, & Tian, 2001; Tian, Rabson, & Gallo, 2002; Zordoky & El-Kadi, 2009). For example, pyrrolidine dithiocarbamate is an inhibitor of NF-kB that has the capability to block the inflammatory reduction in CYP1A2 activity (Kourylko, Fradette, Arcand, & du Souich, 2006; H. Yang et al., 2017). Pregnane X Receptor (PXR) is targeted to many genes most notably CYP3A4. PXR is regulated by NF-kB factors and NF-kB is regulated by inflammatory stimuli results manipulation of Hepatic CYPs expressions (Gu et al., 2006; J. Yang et al., 2010; C. Zhou et al., 2006). Activation of NF-kB outcomes in suppressing the glucocorticoid receptors (GR), thus down-regulating constitutive androsterone receptor (CAR) expression and its associated CYP genes (Assenat, Gerbal-chaloin, Maurel, Vilarem, & Pascussi, 2006). It has been described that proinflammatory cytokines such as IFN-γ, TNF-α, GM-CSF (granulocyte macrophage colony stimulating factor), MC-SF (macrophage colony stimulating factor), IL-1, IL-6, IL-12 elevated in peripheral blood of COVID-19 patients (Guo et al., 2020; Huang et al., 2020). IL-6 was found the most important target for anti-cytokine therapy as it is believed to be the key point in the process and its elevation is associated with poor prognosis (Moore & June, 2020; C. Zhang, Wu, Li, Zhao, & Wang, 2020; F. Zhou et al., 2020).

It is well known that change in the expression of a transporter and the activity of DMEs, can lead to alterations in the pharmacokinetics of prescribed drug therefore prescribed medication during inflammation may be an important contributor to interindividual variability in drug efficacy and toxicity. In the case of co-administration of multiple drugs, the risk of drug interactions is increased. Most prescribed drugs are given below, and their drug interaction potential are shown in the table 1.

Agents Used to Treat COVID-19

Remdesivir

Remdesivir (GS-5734) is an adenosine triphosphate analog and that has been put forth to treat the Ebola and Coronavirus (Li & De Clercq, 2020). Remdesivir halts the viral replication by inhibiting the essential replicating enzymes RNA dependent RNA Polymerase. It supports the premature termination of viral transcription by eluding the proofreading activity of exoribonuclease (Agostini et al., 2018). Remdesivir has broad-spectrum activity against many

viruses, including, SARS-CoV, and MERS-CoV(Martinez, 2020),(Sheahan et al., 2017). Clinical pharmacokinetics data are still unclear. Moreover, safety data on humans are available online (Mulangu et al., 2019). It is now in phase 3 clinical trial for severe and moderate COVID-19 infected patients for finding out the clinical efficacy ("Medrxiv News. from, https://times.hinet.net/mobile/news/ 22831665. [Accessed 20 March 2020]. ," 2020). Remdesivir has already shown the successful inhibition with sub micromolar concentration in tissue culture experiment against human CoV, and Zoonotic CoV (A. J. Brown et al., 2019), (Ko et al., 2020). Similar efficacy was also found in MERS-CoV infected nonhuman primate (rhesus monkey) (de Wit et al., 2020). Currently, many clinical trials are ongoing for COVID-19 patients. It may give the direction for a potential treatment for COVID-19 infected patients (NIH, 2020e).

Favipiravir

Favipiravir is an antiviral drug that was used to treat influenza infection in 2014 in Japan (Favipiravir, 2020). Favipiravir was also used against the Ebola virus, in the absence of a standard cure for Ebola (Oestereich et al., 2014). It was finally accepted for the treatment of Ebola virus infection (Bai et al., 2016),(Shiraki & Daikoku, 2020). Favipiravir also showed the immune response in viral clearance in nonhuman primates(Madelain et al., 2020). Other studies have also described that the active metabolite of favipiravir (favipiravirribofuranosyl-50-triphosphate) directly halt the transcription by inhibiting the RNA dependent RNA polymerase (Dong, Hu, & Gao, 2020), (Delang, Abdelnabi, & Neyts, 2018). The clinical evidence for the efficacy and safety was observed in open label, nonrandomized control clinical trial(Cai et al., 2020). Recently, phase-3 clinical trials for COVID-19 favipiravir with tablet was initiated in India ("Glenmark begins Phase-3 clinical trials on antiviral drug Favipiravir for COVID-19 patients in India. https://www.thehindu.com/news/national/glenmark-begins-phase-3-clinical-trials-on-antiviral-drug-favipiravir-forcovid-19-patients-in-india/article31563198.ece Accessed 25 May 2020.
," 2020). The clearance has granted Appili Therapeutics for evaluating safety and efficacy of favipiravir in the tablets form to control COVID-19 in long-term care services. FDA granted approval to Appili Therapeutics to investigate the broad-spectrum antiviral therapy for favipiravir.

Lopinavir/ritonavir

Lopinavir (LPV) is a potent anti-HIV drug that is used to treat HIV infection along with ritonavir (RTV). Ritonavir inhibits the hepatic drug metabolism of lopinavir to enhance the

half-life and activity. Infectious Diseases Society of America (IDSA) advised ritonavir-boosted combination as first line therapy for HCV patients ("Lopinavir, Ritonavir. https://www.drugbank.ca/unearth/q?utf8¼%E2%9C% 93&query¼lopinavir %2Fritonivir&searcher¼drugs Accessed 02 April 2020
", 2020). LPV/RTV has proven anti SARS-CoV-2 activity *in vitro* by preventing the protease in Vero E6 cells (Choy et al., 2020). In a comparative study (Chu et al., 2004), LPV/RTV along with ribavirin displayed a risk in SARS-CoV. Furthermore, SARS patients revealed that lopinavir-ritonavir plays an important role to explain the clinical consequences (Yao, Qian, Zhu, Wang, & Wang, 2020). Another comparative study (Yao et al., 2020), LPV/RTV treatment alone and combination with IFN enhanced clinical outcomes on some MERS patients. LPV/RTV was found to 40% decrease in the risk of MERS infection (Park et al., 2019). In India, EMR division has advised the dosing program for this drug combination for clinical management of COVID-19 ("Government of India Ministry of Health & Family Welfare Directorate General of Health Services (EMR Division). Guidelines on Clinical Management of COVID e 19 dated 17th March 2020. https://www.aiims.edu/images/pdf/ notice/Guidelines%20Clinical%20Management%20C OVID19-23-3-20.pdf," 2020). One randomized open-label clinical trial (B. Cao et al., 2020) for LPV/RTV is conducted on patients. The authors did not gain more advantage of LPV/RTV to clinical benefits outside the standard of care, while it was found to have an advantage except secondary endpoints. The efficacy of the LPV/RTV was approved, and future trials will verify the results (B. Cao et al., 2020). Currently, many clinical trials are proceeding for LPV/RTV along with other drug involvement (NIH, 2020f).

Ribavirin

Ribavirin is a guanosine analog and a broad-spectrum antiviral drug. In combination with interferon, it has been used as a treatment option for hepatitis C infected critically ill patients. It demonstrated lower risk and reduced death in ARDS (Acute respiratory distress syndrome) infection in combination LPV/RTV with than LPV/RTV only (Chu et al., 2004). Though, in recent *in-vitro* studies, ribavirin indicated a high effective concentration against COVID-19 (M. Wang et al., 2020), (Chan et al., 2015). However, ribavirin developed an unexpected adverse effect, which was very harmful to ADRS patients (Martinez, 2020).

Chloroquine, Hydroxychloroquine

The two aminoquinolines, chloroquine (CQ) and hydroxychloroquine (HCQ) are primarily used for malaria and rheumatic diseases. They showed the activity against the COVID-19 in Vero E6 cells (J. Liu et al., 2020) and recommended it as a primary treatment option for the

COVID-19 (Biot et al., 2006),(Devaux, Rolain, Colson, & Raoult, 2020; Fantini, Di Scala, Chahinian, & Yahi, 2020). CQ and HCQ have weak diprotic features and they could increase the pH of the endosome during the fusion of the virus to host cell (Mauthe et al., 2018). Several clinical trials were preceded in China for CQ and HCQ on COVID-19 infected patients. One of them disclosed that hopeful results in a reduction of the disease progression (Gao, Tian, & Yang, 2020). Temporarily, one clinical trial was performed in France for finding the efficacy of HCQ using at different doses, and along with azithromycin on COVID-19 infected patients. The clinical demonstration noticed that the treated rate was considerably higher in HQC used in combination with azithromycin (Gautret et al., 2020). Even though this study showed favorable results, large clinical data are required to confirm the efficacy and safety of HQC with azithromycin (Geleris et al., 2020). Similarly, a postexposure prophylaxis clinical trial (NCT04308668) using an oral dosing regimen has been conducted in the USA.

Umifenovir

Umifenovir, is also known as Arbidol, is a broad-spectrum antiviral drug (Pecheur et al., 2016). Umifenovir worked to prevent the fusion of endosome membrane to virus particles (Boriskin, Pecheur, & Polyak, 2006; Pecheur et al., 2007; Villalain, 2010). It was discovered to interact with the virus hemagglutinin and enhance the hemagglutinin stability, thus inhibiting the hemagglutinin transition into a functional state(Leneva, Russell, Boriskin, & Hay, 2009). Umifenovir also disclosed the immunomodulatory and macrophage activation(Q. Liu et al., 2013). LPV/RTV and umifenovir was earlier used to treat acute SARC-CoV in clinical practice. The clinical safety and efficacy of the umifenovir monotherapy were analyzed in COVID-19 patients and compared with LPV/RTV therapy. Umifenovir was found better than LVP/RTV for treating COVID-19 (Zhu et al., 2020). Central Drug Research Institute (CDRI) has acquired the approval for proceeding with the phase III clinical trial of umifenovir. In this randomized, double-blind, placebo-controlled trial, the efficacy, safety, and tolerability are going to be tested.

Nitazoxanide

Nitazoxanide is an antiparasitic and broad-spectrum antiviral drug. It has shown potential against SARS-CoV-2 and MERS-CoV in Vero E6 cells. Nitazoxanide prevents viral infection by enhancing the specific host mechanism (Jasenosky et al., 2019). The *in-vitro* activity of nitazoxanide against the SARC-CoV-2 suggested that more clinical data are required to assess the efficacy and safety against COVID-19 (Choy et al., 2020; Pepperrell, Pilkington, Owen, Wang, & Hill, 2020). While evaluating the efficacy of nitazoxanide alone and in

combination with HQ, it reduced the requirement of insidious ventilator support for COVID-19 patients. Currently, many clinical trials for nitazoxanide are proceeding with various doses to treat COVID-19 patients (Calderon, Zeron, & Padmanabhan, 2020). FDA has granted the approval to Azidus Brasil for nitazoxanide to carry on phase II clinical trial (FDA, 2020).

Ivermectin

Ivermectin is an effective antiparasitic agent that was approved by the FDA. Ivermectin has shown activity against many viruses (Ketkar, Yang, Wormser, & Wang, 2019). Recently, one *in-vitro* study revealed that ivermectin strongly impeded the replication of COVID-19 (Caly, Druce, Catton, Jans, & Wagstaff, 2020). Its antiviral activity may play a vital role and deliver as a potential candidate to treat COVID-19 (Chaccour, Hammann, Ramon-Garcia, & Rabinovich, 2020; Heidary & Gharebaghi, 2020). Finally, FDA declared a report for self-administration of ivermectin in COVID-19 patients (News, 2020d). Ivermectin is broadly offered, due to its inclusion on the WHO model list of necessary medicines.

Interferons

Interferon (IFN) is a broad-spectrum antiviral agent that inhibits viral replication via interaction with toll-like receptors (TLR) (Uematsu & Akira, 2007). It established antiviral resistance in cells (Kotenko et al., 2003; Sheppard et al., 2003). Moreover, a member of this family (IFN-λ4) was discovered for viral clearance (Prokunina-Olsson et al., 2013). IFN-λ was found to be more efficient with a slight increase in inflammation and tissue damage (Davidson et al., 2016; Galani et al., 2017), and potentially controlled viral spreading from the nasal epithelium to the upper respiratory tract (Klinkhammer et al., 2018), with efficacy as compared to IFNα-based therapies (Muir et al., 2014). IFNα and β displayed activity against the SARS-CoV in-vitro (Hensley et al., 2004; Stroher et al., 2004). IFNβ indicated the potential in inhibiting MERS-CoV replication (Chan et al., 2013; Hart et al., 2014). Mainly type I IFN showed a fast decrease of viral load in mild to moderate COVID-19 patients. In the severe COVID-19 infection, IFN revealed the antiviral response with increased lung cytokine levels, reduced the T cell response, and acute clinical relapse (Jamilloux et al., 2020).

Dexamethasone

Dexamethasone is a corticosteroid immunosuppressor. It lessens the ability of B cells to synthesize antibodies (Giles et al., 2018). Dexamethasone regulates cytokine's damaging effects by reducing the level of cytokine (H. Chen et al., 2019). Moreover, dexamethasone

prevents macrophages and natural killer cells from clearance secondary nosocomial pathogens (Cohn, 1991). Clinical evidence does not recommend the use of corticosteroids in COVID-19 infection (Russell, Millar, & Baillie, 2020). Even though corticosteroid has been associated to an increase in the viral load, it persisted in the viral load even after survival of patients from SARS-CoV (N. Lee et al., 2004). By contrast, a clinical trial proved that dexamethasone saved the life of seriously ill COVID-19 infected patients in the United kingdom (UK) (Ledford, 2020). UK government stated that dexamethasone was approved as an immediate treatment option for hospitalized patients that were seriously ill and on ventilator (Group et al., 2020). WHO added the dexamethasone in the essential medicine list that is readily available at low cost. In the USA, NIH issued the guideline to recommend dexamethasone as a treatment option for COVID-19 infected patients (Bethesda, 2020; C., 2020).

Tetracyclines

Tetracycline is an antibiotic. It can be used as a possible treatment option for COVID-19 patients because of its well-known activity to decrease the level of inflammatory cytokines such as IL-1b and IL-6 (Henehan, Montuno, & De Benedetto, 2017). Both IL-1b and IL-6 levels were significantly increased during COVID-19 infection (Yoshikawa, Hill, Li, Peters, & Tseng, 2009). Tetracycline also revealed that it lessened the inflammatory agent in the circulation and induced programmed cell death (Sandler et al., 2005). Investigators proposed that tetracycline must be a better therapeutic option to treat inflammatory disorders(Kritas et al., 2020; Sandler et al., 2005). Previously it was documented for the treatment of HIV, west nile virus (WNV), and viral encephalitis diseases (Dutta & Basu, 2011) and also used for the prevention of septic shock induced by ARDS (Griffin, Fricovsky, Ceballos, & Villarreal, 2010). It could be selected, as a potential treatment option for COVID-19 infection (Bharadwaj, Lee, Dwivedi, & Kang, 2020), and could be used as a comedication option (Gautam, Gautam, Garg, & Singh, 2020).

Teicoplanin

Teicoplanin is an antiviral drug that can inhibit the replication and transcription of the competent virus. It also worked against the MERS and SARS as well (Y. Wang et al., 2016). Mechanistic studies revealed that teicoplanin inhibits the activity of the host cell's cathepsin L and cathepsin B, these proteins are responsible for cleaving the viral glycoprotein allowing contact of the receptor binding domain of its core genome and subsequent release into the cytoplasm of the host cell (Baron, Devaux, Colson, Raoult, & Rolain, 2020; N. Zhou et al., 2016). Therefore, these studies suggested that the teicoplanin could be used as a therapeutic

option for treating COVID-19 because SARS-CoV-2 is a cathepsin L dependent virus. According to Ceccarelli et al**,** teicoplanin has shown efficacy in COVID-19 infected subjects (Ceccarelli et al., 2020). Teicoplanin was recommended as a hopeful option for the treatment of COVID-19 even though its safety and efficacy data in humans is still required.

Atazanavir

Atazanavir (ATV) is an HIV-1 protease inhibitor (PI) currently suggested as a first line treatment for naïve HIV infected patients as well as switch regimens for patients showing intolerance to other antiretroviral drugs (ARVs) ("Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. ," 2012). ATV, alone or in combination with RTV, has shown the potential to inhibit the SARS-CoV-2 replication and pro-inflammatory cytokine production (Fintelman-Rodrigues et al., 2020; Rahmani et al., 2020). ATV diminished IL-6 release in COVID-19 infected human primary monocytes. Cellular mortality and cytokine storm associated intermediaries were lowered after treatment with ATV (Fintelman-Rodrigues et al., 2020). The ATV or ATV-RTV has demonstrated new therapeutic option among clinically approved drugs that should be considered as an effective treatment for COVID-19 infected patients.

Azithromycin

Azithromycin (Pfizer, NY USA) was revealed to be active in vitro against Ebola (Madrid et al., 2015). Moreover, azithromycin is considered to have the ability in preventing severe respiratory tract infection Orally used azithromycin is distributed to a variety of tissues particularly the lungs (Bacharier et al., 2015). Azithromycin was used to treat COVID-19 patients in combination with HCQ (Arshad et al., 2020).

Darunavir

Darunavir is an HIV protease inhibitor, approved in combination with cobicistat (pharmaco-enhancer) for the treatment of both naïve and experienced patients infected with HIV-1 ("Prezcobix prescribing information. https://www.accessdata.fda.gov/drugsatfda_- docs/label/ 2016/205395s001lbl.pdf," 2020; "Rezolsta Summary of product characteristics. https://www.ema.europa.eu/en/ documents/product-information/rezolsta-epar-product-information_en.pdf. ," 2020). The safety and efficacy profile of this combination is already established based on III phase clinical trials (Orkin et al., 2013; Tashima et al., 2014). Existing data on the therapeutic effect of HIV protease inhibitors are from thorough in the COVID-19 patients. The inaccessibility of *in-vitro* activity against SARS-CoV-2, darunavir

could not be endorsed to use as the treatment option for COVID-19. Consequently, darunavir in combination with cobicistat or with RTV should remain exclusively for the treatment of HIV patients (De Meyer et al., 2020). In one study, darunavir-cobicistat combination therapy was found to be connected with considerable survival gain in critically ill patients of COVID-19 (Kim et al., 2020). Its safety and efficacy data in humans are still required.

Ruxolitinib

Ruxolitinib is routinely used for the care of myelofibrosis including polycythemia vera (Vannucchi et al., 2015; Verstovsek et al., 2012). It is a Janus kinase inhibitor and inhibits the JAK-STAT signaling (Venugopal, Bar-Natan, & Mascarenhas, 2020). Ruxolitinib is being continued to investigate against placebo for COVID-19 patients with ARDS in two randomized phase III clinical trials (NCT04363137 and NCT04377620) and which is currently evaluating the requirement of mechanical ventilation for COVID-19 patients with ARDS (El Bairi et al., 2020). Ruxolitinib might be effective against the outcomes of the elevated levels of cytokines in COVID-19 patients (Y. Cao et al., 2020). Its safety and efficacy data in humans are still required in critically ill conditions.

Baricitinib

Baricitinib is used as a therapeutic option for rheumatoid arthritis. It also a reversible JAK-inhibitor (Grasselli et al., 2020; Jin & Tong, 2020; Mehta et al., 2020). The JAK-STAT signaling intervenes in the signaling of several cytokines and interfering with this pathway may be an appealing approach to alter the immunopathology of SARS-CoV-2 (Fragoulis, McInnes, & Siebert, 2019; Jamilloux et al., 2020; Richardson, Corbellino, & Stebbing, 2020). Further, many drugs within this class exhibit antiviral effects, albeit often at supra-therapeutic concentration, by targeting host factors that viruses usurp for cell entry (Pu et al., 2018; P. Richardson et al., 2020). Baricitinib has the advantage of providing in vitro antiviral activity at concentration achieved with approved dosing (P. J. Richardson et al., 2020). Baricitinib plus remidesivir comedication was shown promise for treating COVID-19. This co-medication therapy was superior upon remdesivir alone in lowering recovery and accelerating improvement in clinical status. This combination has been shown fewer serious adverse effects (Kalil et al., 2020).

Imatinib

Imatinib is a tyrosine kinase inhibitor, used to treat chronic myelogenous leukemia, gastrointestinal stromal tumors, and the number of other malignancies. It has been pointed out as an unexplored SARS-CoV-2 infection (Gasmi et al., 2020). One case report on

COVID-19 patients exhibited that who received imatinib due to clinical relapse even with dual therapy with HCQ and lopinavir/ritonavir (Morales-Ortega et al., 2020). One study was conducted for finding the efficacy and safety of oral administration of imatinib combined with the best conventional care (BCC) versus placebo in hospitalized COVID-19 patients (Emadi, Chua, Talwani, Bentzen, & Baddley, 2020).

Fluvoxamine

Fluvoxamine is a strong S1R agonist (Cobos, Entrena, Nieto, Cendan, & Del Pozo, 2008; Hashimoto, 2015) is used as an antidepressant. It is extremely hydrophilic and has fast intracellular uptake (Hallifax & Houston, 2007). One study was conducted on adult symptomatic COVID-19 patients, Fluvoxamine was given orally to outpatients (Lenze et al., 2020). However, this study was restricted by a small sample size. This study was triggered by a hypothesis including the influence on the S1R-IRE1 pathway. Cytokine reduction resulting from S1R activation would fit with this recent finding of benefits of the other anti-inflammatory drugs for COVID-19 (Deftereos et al., 2020; Sterne et al., 2020). The potential advantage of fluvoxamine for outpatient treatment of COVID-19 includes its safety (Omori et al., 2009) widespread availability, low cost, and oral administration. QT prolongation is not promoted by Fluvoxamine like other SSRIs (Assimon, Brookhart, & Flythe, 2019). Nonetheless, fluvoxamine has adverse effects and can cause drug-drug interaction, via inhibition of CYP1A2 and CYP2C19 (Christensen et al., 2002).

Tocilizumab

Tocilizumab is a recombinant monoclonal antibody. Tocilizumab is mainly used to treat rheumatoid arthritis. It was conceived as an IL-6 receptor blocker to diminish inflammation. IL-6 drastically increases in patients when COVID-19 infection is produced (Yoshikawa et al., 2009). This's why tocilizumab is used as a therapeutic option for treating COVID-19 patients (Luo et al., 2020; News, 2020d). In COVID-19 infected patients, T-lymphocyte and macrophages generate IL-6 to cause the cytokine storm and severe inflammatory responses mainly in the lungs. Therefore, it is turned into an effective therapeutic drug for the treatment of severe COVID-19 infected patients (X. Xu et al., 2020; C. Zhang et al., 2020). Tocilizumab exhibited a trend association towards lowered mortality among ICU patients (Ip et al., 2020). The Genentech has been given approval by FDA continuing the phase III clinical trial for tocilizumab to assess the safety and efficacy of severe COVID-19 infected patients (News, 2020a).

Itolizumab

Itolizumab is a recombinant monoclonal antibody for CD6 (Cluster of Differentiation 6) of IgG1 (Immunoglobulin G1). It is basically used for the treatment psoriatic patients (Dogra, Uprety, & Suresh, 2017). Itolizumab has shown the reduction of inflammatory cytokines, such as IFN-γ, TNF-α, and IL-6 (Aira et al., 2016; Aira et al., 2014; Nair, Melarkode, Rajkumar, & Montero, 2010). It could be used as a treatment option for COVID-19 infection (Loganathan, Athalye, & Joshi, 2020). It showed the reduction of IL-6 in critically ill patients (Saavedra et al., 2020). The pharmaceutical company Biocon has acquired consent for itolizumab from the DGCI (Drugs Controller General of India) for the treatment of COVID-19 patients in emergency state (News, 2020b). Cuban regulatory agency has approved for the trial to use of itolizumab for COVID-19. Itolizumab might interrupt the hyperinflammatory cascade and stop COVID-19 morbidity and mortality (Caballero et al., 2020).

Meplazumab

Meplazumab is a humanized monoclonal antibody for CD147. It efficiently inhibited virus replication in Vero E6 cells (Ke Wang, 2020). One study has been conducted to ascertain the clinical results of meplazumab and revealed progress in the COVID-19 infected patients (Huijie Bian, 2020). It was previously reported that meplazumab exhibited activity against the Chauge-Strauss syndrome (Wechsler et al., 2017). Phase I clinical trial (NCT04369586) in the healthy volunteers of maplazumab has been achieved for finding the safety, efficacy, tolerability, PK attributes, and dosage regimen for Phase II clinical trial (NIH, 2020c). Phase II clinical trials are going in the USA to find the safety and efficacy of meplazumab injection in COVID-19 infected patients (NCT04275245). This trial will be completed in December 2020 (NIH, 2020a).

Eculizumab

Eculizumab is a monoclonal antibody for complement C5 protein. It prevents cleavage to C5a and C5b and impedes the creation of the membrane attack complex (MAC) C5b-9 to stop lysis of the cell (Jodele et al., 2020). Eculizumab was disclosed to be an effective therapeutic option for hematological and neuroinflammatory diseases (Jodele et al., 2020; Nunius, Buttner-Herold, Bertz, Schiffer, & Buchholz, 2020; Olson et al., 2018; Roselli, Karasu, Volpe, & Huber-Lang, 2018). Evermore, evidence (Wong et al., 2004) shows that complement is also a key mediator of lung damage notably during CoV infection. Therefore, eculizumab might work as an emergency therapy to treat COVID-19 patients associated with ARDS. Some studies (Diurno et al., 2020), (NIH, 2020b) supported the eculizumab use as a treatment for severe COVID-19. Studies were performed along with ruxolitinib for

confirming the efficacy of Eculizumab in severe COVID-19 patients (Giudice et al., 2020), (Risitano et al., 2020). It has been approved for continuing the clinical trial.

AMY101

AMY101 is a highly selective complement C3 inhibitor that was developed by Amyndas Pharmaceuticals (Mastellos et al., 2015; Silasi-Mansat et al., 2015; van Griensven et al., 2019). It is a small sized cyclic peptide that indicated more promising efficacy in non-human primates(Zimmerman, Dellinger, Straube, & Levin, 2000). AMY101 has effectively completed the phase I clinical trial with acceptable safety and tolerability, and now it is in phase II clinical trial (NCT04395456) (NIH, 2020d), (Reis et al., 2018). Some studies (Magro et al., 2020; Risitano et al., 2020) have shown the proinflammatory response by the activation of the compliment system (C3) in COVID-19 patients. AMY101 could be a unique therapeutic option to overcome the complement mediated inflammatory response in COVID-19 patients. The recent clinical study (Mastaglio et al., 2020), AMY101 revealed the safety and efficacy in patients with severe ARDS due to COVID-19 infection.

ARDS-003

Cannabinoid (CBD) is also a probable treatment for severe COVID-19 patients (N. Trivedi et al., 2020; N. V. Trivedi, A. Kumar, D., 2020). It was designed as an injectable form to treat a serious case of coronavirus “acute respiratory distress syndrome (ARDS)”. This syndrome generated a cytokine storm to create inflammation. It will have the advantage of impacting several pro-inflammatory signaling pathways, by enhancing the effectiveness of the drug to rapidly diminish the release of the cytokines and avert acute outcomes like ARDS. The cannabinoid drug named, ARDS-003, has been approved for the phase I clinical trial. It is still being tested by Tetra Bio-Pharma ("https://www.forbes.com/sites/emilyearlenbaugh/2020/08/20/synthetic-cannabinoid-drug-for-covid-19-approved-for-phase-1-clinical-trials/#314337063329," 2020). Firstly, the FDA emphasized that the nonclinical study results were appropriate for starting a study in COVID-19 infected patients ("https://ir.tetrabiopharma.com/newsroom/press-releases/news-details/2020/FDA-Provides-Positive-Feedback-on-Tetra-Bio-Pharmas-Pre-Investigational-New-Drug-Application-for-ARDS-003-to-Be-Studied-in-COVID-19-Patients-at-Risk-of-Developing-Acute-Respiratory-Distress-Syndrome-ARDS/default.aspx," 2020).

LCB1

LCB1 revealed as the SARS-CoV-2 neutralizing antibody. It is a computer designed mini protein that has been synthesized by the researchers of the University of Washington School of Medicine. It binds firmly to SARS-CoV-2 spikes proteins and hinders them from infecting cells. LCB1 appeared to protect the Vero E6 cells from SARS-CoV-2 infection. This synthesized antiviral candidate was conceived to overcome the infection by interfering with the mechanism that coronavirus uses to break into and enter cells. LCB1 is presently being evaluated in rodents (News, 2020c). These hyper stable mini-binders provide the starting point for COVID-19 therapeutics (Longxing Cao, 2020).

Molnupiravir

Molnupiravir (MK448/EIDD-2801) is a prodrug of synthetic nucleoside derivative N4-hydroxy-cytidine and applies its antiviral action via the introduction of copying error during viral RNA replication (Sheahan et al., 2020). Institute for Biomedical Sciences, Georgia State University, developed this antiviral drug. After being found to be active against SARC-CoV-2, MK448/EIDD-2801 was analyzed in the preliminary human study for safety, tolerability, and pharmacokinetics in healthy volunteers in the UK and US (NCT04392219). On October 19, 2020, Merck has started one-year stage 2/3 trial aimed at hospitalized patients (NCT04575584). MK448/EIDD-2801 can block the transmission of SARS-CoV-2 within 24 hours (Cox et al., 2020). Plemper's team repurposed molnupiravir against COVID-19 and applied a ferret model to test the effect of it on containing the spread of the COVID-19 (Cox et al., 2020).

Table 1. Drug-drug interaction potential of therapeutic agents used to treat COVID-19

	Drug	Drug Transporter	reference	Metabolism	reference
1	Remdesivir	$Pgp $OATPB1, IOATPB1, IOATPB3, IBSEP, IMRP4, INTCP	(K. Yang, 2020)	$CYP2C8, $CYP2D6, $CYP3A4, ICYP3A4	(K. Yang, 2020)
2	Favipiravir	IOAT1, IOAT3	(Mishima, Anzai, Miyazaki, & Abe, 2020)	$AO	(Mishima et al., 2020)
3	Ribavirin	$NT, $ENT1	(Fukuchi, Furihata, Hashizume, Iikura, & Chiba, 2010; Karbanova et al., 2019)	Phosphorylation, Deribosylation, Amide hydrolysis	(Hodge et al., 2020)
4	Interferons	$OAT2	(C. Chen, Han, Yang, & Rodrigues, 2011)	$CYP1A2, $UGT2B7, ICYP3A, ICYP2D6	(Becquemont et al., 2002; C. Chen et al., 2011)
5	Lopinavir	$Pgp, $MRP1, $MRP2, $OATP1A2, $OATP1B1 IPgp, IBCRP,	(Kiser et al., 2008; Rakhmanina et al., 2011; van Waterschoot et al., 2010) (Gupta, Zhang, Unadkat,	ICYP3A4	(Kiser et al., 2008; Rakhmanina et al., 2011; van Waterschoot et

		[I]OATP1B1, [I]OATP1B3, [I]OATP2B1	& Mao, 2004; Janneh, Jones, Chandler, Owen, & Khoo, 2007; Storch, Theile, Lindenmaier, Haefeli, & Weiss, 2007; Weiss et al., 2007)		al., 2010)
6	Ritonavir	[$]Pgp, [$]MRP1, [$]MRP2 ,[I]Pgp, [I]MRP1[I], BCRP, [I]OATP1A2, [I]OATP2B1, [I]OATP1B1, [I]OATP1B3, [I]OCT1, OCT2	(Rakhmanina et al., 2011) (Marzolini, Gibbons, Khoo, & Back, 2016) (Cvetkovic, Leake, Fromm, Wilkinson, & Kim, 1999; Gupta et al., 2004; Huisman et al., 2002; Jung et al., 2008; M. D. Perloff, von Moltke, & Greenblatt, 2002; Tirona, Leake, Wolkoff, & Kim, 2003; van der Sandt et al., 2001; Weiss et al., 2007; L. Zhang et al., 2000)	[$]CYP1A2, [$]CYP2C8, [$]CYP2C9, [$]CYP2C19, [I]CYP3A4, [I]CYP2D6	(Aungst, Nguyen, Bulgarelli, & Oates-Lenz, 2000) (Marzolini et al., 2016)
7	Chloroquine	[$]OATP1A2	(Sortica et al., 2017; C. Xu et al., 2016)	[$]CYP2C8, [$]CYP3A4 [$]CYP2D6	(Babayeva & Loewy, 2020; Elewa & Wilby, 2017)
8	Hydroxy chloroquine	[I]Pgp, [I]OATP1A2	(Sortica et al., 2017; Weiss, Bajraktari-Sylejmani, & Haefeli, 2020; C. Xu et al., 2016)	[$]CYP2C8, [$]CYP3A4 [$]CYP2D6	(Babayeva & Loewy, 2020; Elewa & Wilby, 2017; J. Y. Lee et al., 2016)
9	Dexamethasone	[$]Pgp, [$]MRP2	(Courtois, Payen, Guillouzo, & Fardel, 1999; Manceau et al., 2012)	[$]CYP3A4	(Pascussi et al., 2001)
10	Umifenovir	Unclear		[$]CYP3A4 and [$]FMOs	(Deng et al., 2013)
11	Teicoplanin	Unclear		Unclear Metabolic path	(Bernareggi et al., 1992)
12	Nitazoxanide	unclear		[$]Deacetylase, [$]UGT	(Broekhuysen, Stockis, Lins, De Graeve, & Rossignol, 2000)
13	Ivermectin	[I]Pgp, [I]BCRP, [I]MRP1, [I]MRP2, [I]MRP3	(Houshaymi, Nasreddine, Kedees, & Soayfane, 2019; Jani et al., 2011; Lespine et al., 2006)	[I]CYP2C9, [I]CYP2C19 [I]CYP2D6, [I]CYP3A4	(Neodo, Schulz, Huwyler, & Keiser, 2019)
14	Atazanavir	[$]Pgp, [$]MRP1, [$]MRP2, [I]OATP2B1	(Kis, Zastre, Hoque, Walmsley, & Bendayan, 2013; E. S. Perloff, Duan, Skolnik, Greenblatt, & von Moltke, 2005) (Bousquet et al., 2008; Storch et al., 2007; Weiss et al., 2007; Zastre et al., 2009)	[I]CYP3A4, [I]UDGT	(E. S. Perloff et al., 2005)
15	Azithromycin	[$]Pgp and [$]MRP2 [$]OATP	(Lan et al., 2009; Sugie et al., 2004)	[$]CYP3A4	(Galetin, Burt, Gibbons, &

					Houston, 2006; Westphal, 2000)
16	Darunavir	[$]Pgp, [$]OATP1A2, OATP1B1, [I]Pgp, [I]OATP2B1	(Holmstock, Mols, Annaert, & Augustijns, 2010) (K. C. Brown, Paul, & Kashuba, 2009; Fujimoto et al., 2009; Tong et al., 2007)	[I]CYP3A4	(Holmstock, Gonzalez, Baes, Annaert, & Augustijns, 2013; Vermeir et al., 2009)
17	Ruxolitinib	[$]OATP1B1, and [$]OCT1, [$]NTCP, [I]Pgp, [I]BCRP	(Holmstock et al., 2013; Vermeir et al., 2009)	[$]CYP1A2, [$]CYP2B6, [$]CYP2C9 [$]CYP3A4	(Aslanis et al., 2019; Febvre-James, Bruyere, Le Vee, & Fardel, 2018)
18	Baricitinib	[$]P-gp,[$]BCRP, [$]OAT3, [$]MATE-K	(Hodge et al., 2020; Posada et al., 2017)	[$]CYP3A4	(Hodge et al., 2020; Takahashi, Luzum, Nicol, & Jacobson, 2020)
19	Imatinib	[$]Pgp, [$]OATP1B3	(Mlejnek, Kosztyu, Dolezel, Bates, & Ruzickova, 2017; Yamakawa et al., 2011)	[$]CYP2C8, [$]CYP3A4	(Filppula, Neuvonen, Laitila, Neuvonen, & Backman, 2013; Gschwind et al., 2005)
19	Fluvoxamine	Unclear		[$]CYP1A2, [$]CYP2C19, [$]CYP2D6, [$]CYP3A4 [I]CYP1A2, [I]CYP2C19	(Iga, 2016; Kashuba et al., 1998) (Christensen et al., 2002)
20	Canabinoids	[$]Pgp, [$]BCRP, [$]MRPs	(Alsherbiny & Li, 2018)	[$]CYPs, [$]UGT	(Alsherbiny & Li, 2018; Stout & Cimino, 2014)
21	Molnupiravir	Unclear		Unclear	
22	Itolizumab	Unclear		Unclear	
23	Tocilizumab	Unclear		Unclear	
24	Meplazumab	Unclear		Unclear	
25	Eculizumab	Unclear		Unclear	
26	AMY101	Unclear		Unclear	
27	ARDS-003	Unclear		Unclear	
28	LCB1	Unclear		Unclear	

[$]-substrate of, [I]-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, CYP; Cytochrome P450, UGT, UDP-Glucuronosyltransferase, AO; Aldehyde Oxidase, FMO; Flavin-containing Monooxygenase

Conclusions

The present review pointed out the possibilities of risk of drug interaction of mentioned drug in tackling COVID-19. The inflammatory response enforces changes in the expression and activity of transporters and DMEs. Disposition of drugs used to treat COVID-19 infection involves drug metabolism CYPs enzymes and drug transported by ABC and SLC

transporters. However, it is already known that ABC and SLC transporters play a central role in the disposition of mostly antiviral drugs and can participate in many drug-drug interactions. Most importantly, the involvement of CYPs in used drug in COVID-19 infection, drug-drug interaction has been comprehensively known but some drugs are still unknown. That's why in COVID-19 infection, inflammatory responses play a key role in disease-drug or drug-drug interactions. Alteration in the transporters and DMEs can lead to changes in the pharmacokinetic parameters of used the drug. Hence, inflammation might play an important role in drug efficacy and toxicity. The risk of drug interactions should not be prohibited since they are frequently manageable and convenient. LPV/RTV is being used in combination with other drugs. HCQ in combination with azithromycin and with LPV/RTV has been used in COVID-19 Patients. These medications have been classified as having a risk of developing torsades de points (TdP). Moderate to severe QTc prolongation was observed during these pharmacological treatments (Padilla et al., 2020). The ATV-RTV have shown new option among clinically approved drugs and should be considered as an effective treatment option. Another combination of remdesivir with bericitinib has shown the serious side effect even though this combination has shown promise for COVID-19 with accelerating improvement in clinical status (Kalil et al., 2020). 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 potential of drug-drug interaction or disease-drug interaction is an important consideration when identifying optimal treatment regimens for individual patients.

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References

Abdel-Razzak, Z., Loyer, P., Fautrel, A., Gautier, J. C., Corcos, L., Turlin, B., ... Guillouzo, A. (1993). Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human hepatocytes in primary culture. *Mol Pharmacol*, *44*(4), 707-715. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/8232220

Agostini, M. L., Andres, E. L., Sims, A. C., Graham, R. L., Sheahan, T. P., Lu, X., ... Denison, M. R. (2018). Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *mBio*, *9*(2)doi:10.1128/mBio.00221-18

Aira, L. E., Hernandez, P., Prada, D., Chico, A., Gomez, J. A., Gonzalez, Z., ... Mazorra, Z. (2016). Immunological evaluation of rheumatoid arthritis patients treated with itolizumab. *MAbs*, *8*(1), 187-195. doi:10.1080/19420862.2015.1105416

Aira, L. E., Lopez-Requena, A., Fuentes, D., Sanchez, L., Perez, T., Urquiza, A., ... Mazorra, Z. (2014). Immunological and histological evaluation of clinical samples from psoriasis patients treated with anti-CD6 itolizumab. *MAbs*, *6*(3), 783-793. doi:10.4161/mabs.28376

Aitken, A. E., & Morgan, E. T. (2007). Gene-specific effects of inflammatory cytokines on cytochrome P450 2C, 2B6 and 3A4 mRNA levels in human hepatocytes. *Drug Metab Dispos*, *35*(9), 1687-1693. doi:10.1124/dmd.107.015511

Alsherbiny, M. A., & Li, C. G. (2018). Medicinal Cannabis-Potential Drug Interactions. *Medicines (Basel)*, *6*(1)doi:10.3390/medicines6010003

Arshad, S., Kilgore, P., Chaudhry, Z. S., Jacobsen, G., Wang, D. D., Huitsing, K., ... Henry Ford, C.-T. F. (2020). Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis*, *97*, 396-403. doi:10.1016/j.ijid.2020.06.099

Aslanis, V., Umehara, K., Huth, F., Ouatas, T., Bharathy, S., Butler, A. A., ... Gadbaw, B. (2019). Multiple administrations of fluconazole increase plasma exposure to ruxolitinib in healthy adult subjects. *Cancer Chemother Pharmacol*, *84*(4), 749-757. doi:10.1007/s00280-019-03907-1

Assenat, E., Gerbal-chaloin, S., Maurel, P., Vilarem, M. J., & Pascussi, J. M. (2006). Is nuclear factor kappa-B the missing link between inflammation, cancer and alteration in hepatic drug metabolism in patients with cancer? *Eur J Cancer*, *42*(6), 785-792. doi:10.1016/j.ejca.2006.01.005

Assimon, M. M., Brookhart, M. A., & Flythe, J. E. (2019). Comparative Cardiac Safety of Selective Serotonin Reuptake Inhibitors among Individuals Receiving Maintenance Hemodialysis. *J Am Soc Nephrol*, *30*(4), 611-623. doi:10.1681/ASN.2018101032

Aungst, B. J., Nguyen, N. H., Bulgarelli, J. P., & Oates-Lenz, K. (2000). The influence of donor and reservoir additives on Caco-2 permeability and secretory transport of HIV protease inhibitors and other lipophilic compounds. *Pharm Res*, *17*(10), 1175-1180. doi:10.1023/a:1026402410783

Babayeva, M., & Loewy, Z. (2020). Repurposing Drugs for COVID-19: Pharmacokinetics and Pharmacogenomics of Chloroquine and Hydroxychloroquine. *Pharmgenomics Pers Med*, *13*, 531-542. doi:10.2147/PGPM.S275964

Bacharier, L. B., Guilbert, T. W., Mauger, D. T., Boehmer, S., Beigelman, A., Fitzpatrick, A. M., ... Martinez, F. D. (2015). Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses: A Randomized Clinical Trial. *JAMA*, *314*(19), 2034-2044. doi:10.1001/jama.2015.13896

Bai, C. Q., Mu, J. S., Kargbo, D., Song, Y. B., Niu, W. K., Nie, W. M., ... Jiang, J. F. (2016). Clinical and Virological Characteristics of Ebola Virus Disease Patients Treated With Favipiravir (T-705)-Sierra Leone, 2014. *Clin Infect Dis*, *63*(10), 1288-1294. doi:10.1093/cid/ciw571

Baron, S. A., Devaux, C., Colson, P., Raoult, D., & Rolain, J. M. (2020). Teicoplanin: an alternative drug for the treatment of COVID-19? *Int J Antimicrob Agents*, *55*(4), 105944. doi:10.1016/j.ijantimicag.2020.105944

Becquemont, L., Chazouilleres, O., Serfaty, L., Poirier, J. M., Broly, F., Jaillon, P., ... Funck-Brentano, C. (2002). Effect of interferon alpha-ribavirin bitherapy on cytochrome P450 1A2 and 2D6 and N-acetyltransferase-2 activities in patients with chronic active hepatitis C. *Clin Pharmacol Ther*, *71*(6), 488-495. doi:10.1067/mcp.2002.124468

Belliard, A. M., Lacour, B., Farinotti, R., & Leroy, C. (2004). Effect of tumor necrosis factor-alpha and interferon-gamma on intestinal P-glycoprotein expression, activity, and localization in Caco-2 cells. *J Pharm Sci*, *93*(6), 1524-1536. doi:10.1002/jps.20072

Bernareggi, A., Borghi, A., Borgonovi, M., Cavenaghi, L., Ferrari, P., Vekey, K., ... Zerilli, L. F. (1992). Teicoplanin metabolism in humans. *Antimicrob Agents Chemother*, *36*(8), 1744-1749. doi:10.1128/aac.36.8.1744

Bertilsson, P. M., Olsson, P., & Magnusson, K. E. (2001). Cytokines influence mRNA expression of cytochrome P450 3A4 and MDRI in intestinal cells. *J Pharm Sci*, *90*(5), 638-646. doi:10.1002/1520-6017(200105)90:5<638::aid-jps1020>3.0.co;2-l

Bethesda, M. (2020). COVID-19 treatment guidelines: National Institutes of Health, 2020

Bharadwaj, S., Lee, K. E., Dwivedi, V. D., & Kang, S. G. (2020). Computational insights into tetracyclines as inhibitors against SARS-CoV-2 M(pro) via combinatorial molecular simulation calculations. *Life Sci*, *257*, 118080. doi:10.1016/j.lfs.2020.118080

Biot, C., Daher, W., Chavain, N., Fandeur, T., Khalife, J., Dive, D., & De Clercq, E. (2006). Design and synthesis of hydroxyferroquine derivatives with antimalarial and antiviral activities. *J Med Chem*, *49*(9), 2845-2849. doi:10.1021/jm0601856

Bleau, A. M., Levitchi, M. C., Maurice, H., & du Souich, P. (2000). Cytochrome P450 inactivation by serum from humans with a viral infection and serum from rabbits with a turpentine-induced inflammation: the role of cytokines. *Br J Pharmacol*, *130*(8), 1777-1784. doi:10.1038/sj.bjp.0703486

Blokzijl, H., Vander Borght, S., Bok, L. I., Libbrecht, L., Geuken, M., van den Heuvel, F. A., ... Faber, K. N. (2007). Decreased P-glycoprotein (P-gp/MDR1) expression in inflamed human intestinal epithelium is independent of PXR protein levels. *Inflamm Bowel Dis*, *13*(6), 710-720. doi:10.1002/ibd.20088

Boriskin, Y. S., Pecheur, E. I., & Polyak, S. J. (2006). Arbidol: a broad-spectrum antiviral that inhibits acute and chronic HCV infection. *Virol J*, *3*, 56. doi:10.1186/1743-422X-3-56

Bousquet, L., Roucairol, C., Hembury, A., Nevers, M. C., Creminon, C., Farinotti, R., & Mabondzo, A. (2008). Comparison of ABC transporter modulation by atazanavir in lymphocytes and human brain endothelial cells: ABC transporters are involved in the atazanavir-limited passage across an in vitro human model of the blood-brain barrier. *AIDS Res Hum Retroviruses*, *24*(9), 1147-1154. doi:10.1089/aid.2007.0022

Broekhuysen, J., Stockis, A., Lins, R. L., De Graeve, J., & Rossignol, J. F. (2000). Nitazoxanide: pharmacokinetics and metabolism in man. *Int J Clin Pharmacol Ther*, *38*(8), 387-394. doi:10.5414/cpp38387

Brown, A. J., Won, J. J., Graham, R. L., Dinnon, K. H., 3rd, Sims, A. C., Feng, J. Y., ... Sheahan, T. P. (2019). Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Res*, *169*, 104541. doi:10.1016/j.antiviral.2019.104541

Brown, K. C., Paul, S., & Kashuba, A. D. (2009). Drug interactions with new and investigational antiretrovirals. *Clin Pharmacokinet*, *48*(4), 211-241. doi:10.2165/00003088-200948040-00001

Buyse, M., Radeva, G., Bado, A., & Farinotti, R. (2005). Intestinal inflammation induces adaptation of P-glycoprotein expression and activity. *Biochem Pharmacol*, *69*(12), 1745-1754. doi:10.1016/j.bcp.2005.03.025

C., W. (2020). Dexamethasone in the treatment of COVID-19: Implementation and management of supply for treatment in hospitals. London: Medicines and Healthcare Products Regulatory Agency, June 16, 2020

Caballero, A., Filgueira, L. M., Betancourt, J., Sanchez, N., Hidalgo, C., Ramirez, A., ... Crombet, T. (2020). Treatment of COVID-19 patients with the anti-CD6 antibody itolizumab. *Clin Transl Immunology*, *9*(11), e1218. doi:10.1002/cti2.1218

Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., ... Liu, L. (2020). Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering (Beijing)*doi:10.1016/j.eng.2020.03.007

Calderon, J. M., Zeron, H. M., & Padmanabhan, S. (2020). Treatment with Hydroxychloroquine vs Hydroxychloroquine + Nitazoxanide in COVID-19 patients with risk factors for poor prognosis: A structured summary of a study protocol for a randomised controlled trial. *Trials*, *21*(1), 504. doi:10.1186/s13063-020-04448-2

Calleja, C., Eeckhoutte, C., Dacasto, M., Larrieu, G., Dupuy, J., Pineau, T., & Galtier, P. (1998). Comparative effects of cytokines on constitutive and inducible expression of the gene encoding for the cytochrome P450 3A6 isoenzyme in cultured rabbit hepatocytes: consequences on progesterone 6beta-hydroxylation. *Biochem Pharmacol*, *56*(10), 1279-1285. doi:10.1016/s0006-2952(98)00178-6

Caly, L., Druce, J. D., Catton, M. G., Jans, D. A., & Wagstaff, K. M. (2020). The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*, *178*, 104787. doi:10.1016/j.antiviral.2020.104787

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., ... Wang, C. (2020). A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*, *382*(19), 1787-1799. doi:10.1056/NEJMoa2001282

Cao, Y., Wei, J., Zou, L., Jiang, T., Wang, G., Chen, L., ... Zhou, J. (2020). Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*, *146*(1), 137-146 e133. doi:10.1016/j.jaci.2020.05.019

Ceccarelli, G., Alessandri, F., d'Ettorre, G., Borrazzo, C., Spagnolello, O., Oliva, A., ... Intensive Care, C.-S. G. o. S. U. (2020). Is teicoplanin a complementary treatment option for COVID-19? The question remains. *Int J Antimicrob Agents*, *56*(2), 106029. doi:10.1016/j.ijantimicag.2020.106029

Chaccour, C., Hammann, F., Ramon-Garcia, S., & Rabinovich, N. R. (2020). Ivermectin and COVID-19: Keeping Rigor in Times of Urgency. *Am J Trop Med Hyg*, *102*(f6), 1156-1157. doi:10.4269/ajtmh.20-0271

Chan, J. F., Chan, K. H., Kao, R. Y., To, K. K., Zheng, B. J., Li, C. P., ... Yuen, K. Y. (2013). Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. *J Infect*, *67*(6), 606-616. doi:10.1016/j.jinf.2013.09.029

Chan, J. F., Yao, Y., Yeung, M. L., Deng, W., Bao, L., Jia, L., ... Yuen, K. Y. (2015). Treatment With Lopinavir/Ritonavir or Interferon-beta1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. *J Infect Dis*, *212*(12), 1904-1913. doi:10.1093/infdis/jiv392

Chen, C., Han, Y. H., Yang, Z., & Rodrigues, A. D. (2011). Effect of interferon-alpha2b on the expression of various drug-metabolizing enzymes and transporters in co-cultures of freshly prepared human primary hepatocytes. *Xenobiotica*, *41*(6), 476-485. doi:10.3109/00498254.2011.560971

Chen, H., Wang, F., Zhang, P., Zhang, Y., Chen, Y., Fan, X., ... He, A. (2019). Management of cytokine release syndrome related to CAR-T cell therapy. *Front Med*, *13*(5), 610-617. doi:10.1007/s11684-019-0714-8

Chen, Y. L., Florentin, I., Batt, A. M., Ferrari, L., Giroud, J. P., & Chauvelot-Moachon, L. (1992). Effects of interleukin-6 on cytochrome P450-dependent mixed-function oxidases in the rat. *Biochem Pharmacol*, *44*(1), 137-148. doi:10.1016/0006-2952(92)90047-m

Choy, K. T., Wong, A. Y., Kaewpreedee, P., Sia, S. F., Chen, D., Hui, K. P. Y., ... Yen, H. L. (2020). Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral Res*, *178*, 104786. doi:10.1016/j.antiviral.2020.104786

Christensen, M., Tybring, G., Mihara, K., Yasui-Furokori, N., Carrillo, J. A., Ramos, S. I., ... Bertilsson, L. (2002). Low daily 10-mg and 20-mg doses of fluvoxamine inhibit the metabolism of both caffeine (cytochrome P4501A2) and omeprazole (cytochrome P4502C19). *Clin Pharmacol Ther*, *71*(3), 141-152. doi:10.1067/mcp.2002.121788

Chu, C. M., Cheng, V. C., Hung, I. F., Wong, M. M., Chan, K. H., Chan, K. S., ... Group, H. U. S. S. (2004). Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*, *59*(3), 252-256. doi:10.1136/thorax.2003.012658

Cobos, E. J., Entrena, J. M., Nieto, F. R., Cendan, C. M., & Del Pozo, E. (2008). Pharmacology and therapeutic potential of sigma(1) receptor ligands. *Curr Neuropharmacol*, *6*(4), 344-366. doi:10.2174/157015908787386113

Cohn, L. A. (1991). The influence of corticosteroids on host defense mechanisms. *J Vet Intern Med*, *5*(2), 95-104. doi:10.1111/j.1939-1676.1991.tb00939.x

Courtois, A., Payen, L., Guillouzo, A., & Fardel, O. (1999). Up-regulation of multidrug resistance-associated protein 2 (MRP2) expression in rat hepatocytes by dexamethasone. *FEBS Lett*, *459*(3), 381-385. doi:10.1016/s0014-5793(99)01295-8

Cox, R. M., Wolf, J. D., & Plemper, R. K. (2020). Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. *Nat Microbiol*doi:10.1038/s41564-020-00835-2

Cressman, A. M., Petrovic, V., & Piquette-Miller, M. (2012). Inflammation-mediated changes in drug transporter expression/activity: implications for therapeutic drug response. *Expert Rev Clin Pharmacol*, *5*(1), 69-89. doi:10.1586/ecp.11.66

Cvetkovic, M., Leake, B., Fromm, M. F., Wilkinson, G. R., & Kim, R. B. (1999). OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. *Drug Metab Dispos*, *27*(8), 866-871. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10421612

Davidson, S., McCabe, T. M., Crotta, S., Gad, H. H., Hessel, E. M., Beinke, S., ... Wack, A. (2016). IFNlambda is a potent anti-influenza therapeutic without the inflammatory side effects of IFNalpha treatment. *EMBO Mol Med*, *8*(9), 1099-1112. doi:10.15252/emmm.201606413

De Meyer, S., Bojkova, D., Cinatl, J., Van Damme, E., Buyck, C., Van Loock, M., ... Ciesek, S. (2020). Lack of antiviral activity of darunavir against SARS-CoV-2. *Int J Infect Dis*, *97*, 7-10. doi:10.1016/j.ijid.2020.05.085

de Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T., ... Feldmann, H. (2020). Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A*, *117*(12), 6771-6776. doi:10.1073/pnas.1922083117

Deftereos, S. G., Giannopoulos, G., Vrachatis, D. A., Siasos, G. D., Giotaki, S. G., Gargalianos, P., ... investigators, G.-. (2020). Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019: The GRECCO-19 Randomized Clinical Trial. *JAMA Netw Open*, *3*(6), e2013136. doi:10.1001/jamanetworkopen.2020.13136

Delang, L., Abdelnabi, R., & Neyts, J. (2018). Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. *Antiviral Res*, *153*, 85-94. doi:10.1016/j.antiviral.2018.03.003

Deng, P., Zhong, D., Yu, K., Zhang, Y., Wang, T., & Chen, X. (2013). Pharmacokinetics, metabolism, and excretion of the antiviral drug arbidol in humans. *Antimicrob Agents Chemother*, *57*(4), 1743-1755. doi:10.1128/AAC.02282-12

Devaux, C. A., Rolain, J. M., Colson, P., & Raoult, D. (2020). New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*, *55*(5), 105938. doi:10.1016/j.ijantimicag.2020.105938

Diao, L., Li, N., Brayman, T. G., Hotz, K. J., & Lai, Y. (2010). Regulation of MRP2/ABCC2 and BSEP/ABCB11 expression in sandwich cultured human and rat hepatocytes exposed to inflammatory cytokines TNF-{alpha}, IL-6, and IL-1{beta}. *J Biol Chem*, *285*(41), 31185-31192. doi:10.1074/jbc.M110.107805

Dickmann, L. J., Patel, S. K., Wienkers, L. C., & Slatter, J. G. (2012). Effects of interleukin 1beta (IL-1beta) and IL-1beta/interleukin 6 (IL-6) combinations on drug metabolizing enzymes in human hepatocyte culture. *Curr Drug Metab*, *13*(7), 930-937. doi:10.2174/138920012802138642

Diurno, F., Numis, F. G., Porta, G., Cirillo, F., Maddaluno, S., Ragozzino, A., ... Facchini, G. (2020). Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *Eur Rev Med Pharmacol Sci*, *24*(7), 4040-4047. doi:10.26355/eurrev_202004_20875

Dogra, S., Uprety, S., & Suresh, S. H. (2017). Itolizumab, a novel anti-CD6 monoclonal antibody: a safe and efficacious biologic agent for management of psoriasis. *Expert Opin Biol Ther*, *17*(3), 395-402. doi:10.1080/14712598.2017.1279601

Don, B. R., & Kaysen, G. (2004). Serum albumin: relationship to inflammation and nutrition. *Semin Dial*, *17*(6), 432-437. doi:10.1111/j.0894-0959.2004.17603.x

Donato, M. T., Guillen, M. I., Jover, R., Castell, J. V., & Gomez-Lechon, M. J. (1997). Nitric oxide-mediated inhibition of cytochrome P450 by interferon-gamma in human hepatocytes. *J Pharmacol Exp Ther*, *281*(1), 484-490. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9103535

Dong, L., Hu, S., & Gao, J. (2020). Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther*, *14*(1), 58-60. doi:10.5582/ddt.2020.01012

Dutta, K., & Basu, A. (2011). Use of minocycline in viral infections. *Indian J Med Res*, *133*, 467-470. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21623029

El Bairi, K., Trapani, D., Petrillo, A., Le Page, C., Zbakh, H., Daniele, B., ... Afqir, S. (2020). Repurposing anticancer drugs for the management of COVID-19. *Eur J Cancer*, *141*, 40-61. doi:10.1016/j.ejca.2020.09.014

Elewa, H., & Wilby, K. J. (2017). A Review of Pharmacogenetics of Antimalarials and Associated Clinical Implications. *Eur J Drug Metab Pharmacokinet*, *42*(5), 745-756. doi:10.1007/s13318-016-0399-1

Elkahwaji, J., Robin, M. A., Berson, A., Tinel, M., Letteron, P., Labbe, G., ... Pessayre, D. (1999). Decrease in hepatic cytochrome P450 after interleukin-2 immunotherapy. *Biochem Pharmacol*, *57*(8), 951-954. doi:10.1016/s0006-2952(98)00372-4

Emadi, A., Chua, J. V., Talwani, R., Bentzen, S. M., & Baddley, J. (2020). Safety and Efficacy of Imatinib for Hospitalized Adults with COVID-19: A structured summary of a study protocol for a randomised controlled trial. *Trials*, *21*(1), 897. doi:10.1186/s13063-020-04819-9

Fantini, J., Di Scala, C., Chahinian, H., & Yahi, N. (2020). Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. *Int J Antimicrob Agents*, *55*(5), 105960. doi:10.1016/j.ijantimicag.2020.105960

Favipiravir. (2020). https://www.drugbank.ca/drugs/DB12466 Accessed 26 March 2020.

FDA. (2020). https://clinicaltrials.gov/ct2/show/NCT04435314.

Febvre-James, M., Bruyere, A., Le Vee, M., & Fardel, O. (2018). The JAK1/2 Inhibitor Ruxolitinib Reverses Interleukin-6-Mediated Suppression of Drug-Detoxifying Proteins in Cultured Human Hepatocytes. *Drug Metab Dispos*, *46*(2), 131-140. doi:10.1124/dmd.117.078048

Filppula, A. M., Neuvonen, M., Laitila, J., Neuvonen, P. J., & Backman, J. T. (2013). Autoinhibition of CYP3A4 leads to important role of CYP2C8 in imatinib metabolism: variability in CYP2C8 activity may alter plasma concentrations and response. *Drug Metab Dispos*, *41*(1), 50-59. doi:10.1124/dmd.112.048017

Fintelman-Rodrigues, N., Sacramento, C. Q., Ribeiro Lima, C., Souza da Silva, F., Ferreira, A. C., Mattos, M., ... Souza, T. M. L. (2020). Atazanavir, Alone or in Combination with Ritonavir, Inhibits SARS-CoV-2 Replication and Proinflammatory Cytokine Production. *Antimicrob Agents Chemother*, *64*(10)doi:10.1128/AAC.00825-20

Fragoulis, G. E., McInnes, I. B., & Siebert, S. (2019). JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. *Rheumatology (Oxford)*, *58*(Suppl 1), i43-i54. doi:10.1093/rheumatology/key276

Frye, R. F., Schneider, V. M., Frye, C. S., & Feldman, A. M. (2002). Plasma levels of TNF-alpha and IL-6 are inversely related to cytochrome P450-dependent drug metabolism in patients with congestive heart failure. *J Card Fail*, *8*(5), 315-319. doi:10.1054/jcaf.2002.127773

Fujimoto, H., Higuchi, M., Watanabe, H., Koh, Y., Ghosh, A. K., Mitsuya, H., ... Saito, H. (2009). P-glycoprotein mediates efflux transport of darunavir in human intestinal Caco-2 and ABCB1 gene-transfected renal LLC-PK1 cell lines. *Biol Pharm Bull*, *32*(9), 1588-1593. doi:10.1248/bpb.32.1588

Fukuchi, Y., Furihata, T., Hashizume, M., Iikura, M., & Chiba, K. (2010). Characterization of ribavirin uptake systems in human hepatocytes. *J Hepatol*, *52*(4), 486-492. doi:10.1016/j.jhep.2010.01.011

Furuta, Y., Gowen, B. B., Takahashi, K., Shiraki, K., Smee, D. F., & Barnard, D. L. (2013). Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antiviral Res*, *100*(2), 446-454. doi:10.1016/j.antiviral.2013.09.015

Galani, I. E., Triantafyllia, V., Eleminiadou, E. E., Koltsida, O., Stavropoulos, A., Manioudaki, M., ... Andreakos, E. (2017). Interferon-lambda Mediates Non-redundant Front-Line Antiviral Protection against Influenza Virus Infection without Compromising Host Fitness. *Immunity*, *46*(5), 875-890 e876. doi:10.1016/j.immuni.2017.04.025

Galetin, A., Burt, H., Gibbons, L., & Houston, J. B. (2006). Prediction of time-dependent CYP3A4 drug-drug interactions: impact of enzyme degradation, parallel elimination pathways, and intestinal inhibition. *Drug Metab Dispos*, *34*(1), 166-175. doi:10.1124/dmd.105.006874

Gao, J., Tian, Z., & Yang, X. (2020). Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*, *14*(1), 72-73. doi:10.5582/bst.2020.01047

Gasmi, A., Noor, S., Tippairote, T., Dadar, M., Menzel, A., & Bjorklund, G. (2020). Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. *Clin Immunol*, *215*, 108409. doi:10.1016/j.clim.2020.108409

Gautam, S. S., Gautam, C. S., Garg, V. K., & Singh, H. (2020). Combining hydroxychloroquine and minocycline: potential role in moderate to severe COVID-19 infection. *Expert Rev Clin Pharmacol*, *13*(11), 1183-1190. doi:10.1080/17512433.2020.1832889

Gautret, P., Lagier, J. C., Parola, P., Hoang, V. T., Meddeb, L., Mailhe, M., ... Raoult, D. (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*, *56*(1), 105949. doi:10.1016/j.ijantimicag.2020.105949

Geleris, J., Sun, Y., Platt, J., Zucker, J., Baldwin, M., Hripcsak, G., ... Schluger, N. W. (2020). Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*, *382*(25), 2411-2418. doi:10.1056/NEJMoa2012410

Giles, A. J., Hutchinson, M. N. D., Sonnemann, H. M., Jung, J., Fecci, P. E., Ratnam, N. M., ... Gilbert, M. R. (2018). Dexamethasone-induced immunosuppression: mechanisms and implications for immunotherapy. *J Immunother Cancer*, *6*(1), 51. doi:10.1186/s40425-018-0371-5

Giudice, V., Pagliano, P., Vatrella, A., Masullo, A., Poto, S., Polverino, B. M., ... Selleri, C. (2020). Combination of Ruxolitinib and Eculizumab for Treatment of Severe SARS-CoV-2-Related Acute Respiratory Distress Syndrome: A Controlled Study. *Front Pharmacol*, *11*, 857. doi:10.3389/fphar.2020.00857

Glenmark begins Phase-3 clinical trials on antiviral drug Favipiravir for COVID-19 patients in India. https://www.thehindu.com/news/national/glenmark-begins-phase-3-clinical-trials-on-antiviral-drug-favipiravir-forcovid-19-patients-in-india/article31563198.ece Accessed 25 May 2020.

. (2020).

Gorski, J. C., Hall, S. D., Becker, P., Affrime, M. B., Cutler, D. L., & Haehner-Daniels, B. (2000). In vivo effects of interleukin-10 on human cytochrome P450 activity. *Clin Pharmacol Ther*, *67*(1), 32-43. doi:10.1067/mcp.2000.103860

Government of India Ministry of Health & Family Welfare Directorate General of Health Services (EMR Division). Guidelines on Clinical Management of COVID e 19 dated 17th March 2020. https://www.aiims.edu/images/pdf/ notice/Guidelines%20Clinical%20Management%20C OVID19-23-3-20.pdf. (2020).

Grasselli G, P. A., Cecconi M. (2020). Critical care utilization for the COVID-19 outbreak in lombardy, italy: early experience and forecast during an emergency response. . *JAMA*, *28*(323), 1545-1546.

Grasselli, G., Zangrillo, A., Zanella, A., Antonelli, M., Cabrini, L., Castelli, A., … Network, C.-L. I. (2020). Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA*, *323*(16), 1574-1581. doi:10.1001/jama.2020.5394

Griffin, M. O., Fricovsky, E., Ceballos, G., & Villarreal, F. (2010). Tetracyclines: a pleitropic family of compounds with promising therapeutic properties. Review of the literature. *Am J Physiol Cell Physiol*, *299*(3), C539-548. doi:10.1152/ajpcell.00047.2010

Group, R. C., Horby, P., Lim, W. S., Emberson, J. R., Mafham, M., Bell, J. L., … Landray, M. J. (2020). Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med*doi:10.1056/NEJMoa2021436

Gschwind, H. P., Pfaar, U., Waldmeier, F., Zollinger, M., Sayer, C., Zbinden, P., … Gross, G. (2005). Metabolism and disposition of imatinib mesylate in healthy volunteers. *Drug Metab Dispos*, *33*(10), 1503-1512. doi:10.1124/dmd.105.004283

Gu, X., Ke, S., Liu, D., Sheng, T., Thomas, P. E., Rabson, A. B., … Tian, Y. (2006). Role of NF-kappaB in regulation of PXR-mediated gene expression: a mechanism for the suppression of cytochrome P-450 3A4 by proinflammatory agents. *J Biol Chem*, *281*(26), 17882-17889. doi:10.1074/jbc.M601302200

Guo, Y. R., Cao, Q. D., Hong, Z. S., Tan, Y. Y., Chen, S. D., Jin, H. J., … Yan, Y. (2020). The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Mil Med Res*, *7*(1), 11. doi:10.1186/s40779-020-00240-0

Gupta, A., Zhang, Y., Unadkat, J. D., & Mao, Q. (2004). HIV protease inhibitors are inhibitors but not substrates of the human breast cancer resistance protein (BCRP/ABCG2). *J Pharmacol Exp Ther*, *310*(1), 334-341. doi:10.1124/jpet.104.065342

Hallifax, D., & Houston, J. B. (2007). Saturable uptake of lipophilic amine drugs into isolated hepatocytes: mechanisms and consequences for quantitative clearance prediction. *Drug Metab Dispos*, *35*(8), 1325-1332. doi:10.1124/dmd.107.015131

Hart, B. J., Dyall, J., Postnikova, E., Zhou, H., Kindrachuk, J., Johnson, R. F., … Hensley, L. (2014). Interferon-beta and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. *J Gen Virol*, *95*(Pt 3), 571-577. doi:10.1099/vir.0.061911-0

Harvey, R. D., & Morgan, E. T. (2014). Cancer, inflammation, and therapy: effects on cytochrome p450-mediated drug metabolism and implications for novel immunotherapeutic agents. *Clin Pharmacol Ther*, *96*(4), 449-457. doi:10.1038/clpt.2014.143

Hashimoto, K. (2015). Activation of sigma-1 receptor chaperone in the treatment of neuropsychiatric diseases and its clinical implication. *J Pharmacol Sci*, *127*(1), 6-9. doi:10.1016/j.jphs.2014.11.010

Hayden, M. S., West, A. P., & Ghosh, S. (2006). NF-kappaB and the immune response. *Oncogene*, *25*(51), 6758-6780. doi:10.1038/sj.onc.1209943

Heidary, F., & Gharebaghi, R. (2020). Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *J Antibiot (Tokyo)*, *73*(9), 593-602. doi:10.1038/s41429-020-0336-z

Helmy, Y. A., Fawzy, M., Elaswad, A., Sobieh, A., Kenney, S. P., & Shehata, A. A. (2020). The COVID-19 Pandemic: A Comprehensive Review of Taxonomy, Genetics, Epidemiology, Diagnosis, Treatment, and Control. *J Clin Med*, *9*(4)doi:10.3390/jcm9041225

Henehan, M., Montuno, M., & De Benedetto, A. (2017). Doxycycline as an anti-inflammatory agent: updates in dermatology. *J Eur Acad Dermatol Venereol*, *31*(11), 1800-1808. doi:10.1111/jdv.14345

Hensley, L. E., Fritz, L. E., Jahrling, P. B., Karp, C. L., Huggins, J. W., & Geisbert, T. W. (2004). Interferon-beta 1a and SARS coronavirus replication. *Emerg Infect Dis*, *10*(2), 317-319. doi:10.3201/eid1002.030482

HJ., M. (2006). Drug-associated disease: cytochrome P450 interactions. *Crit CareClin.*, *22*(2), 329-345. doi:10.1016/j.ccc.2006.02.004.

Ho, E. A., & Piquette-Miller, M. (2007). KLF6 and HSF4 transcriptionally regulate multidrug resistance transporters during inflammation. *Biochem Biophys Res Commun*, *353*(3), 679-685. doi:10.1016/j.bbrc.2006.12.090

Hodge, C., Marra, F., Marzolini, C., Boyle, A., Gibbons, S., Siccardi, M., … Khoo, S. (2020). Drug interactions: a review of the unseen danger of experimental COVID-19 therapies. *J Antimicrob Chemother*, *75*(12), 3417-3424. doi:10.1093/jac/dkaa340

Holmstock, N., Gonzalez, F. J., Baes, M., Annaert, P., & Augustijns, P. (2013). PXR/CYP3A4-humanized mice for studying drug-drug interactions involving intestinal P-glycoprotein. *Mol Pharm*, *10*(3), 1056-1062. doi:10.1021/mp300512r

Holmstock, N., Mols, R., Annaert, P., & Augustijns, P. (2010). In situ intestinal perfusion in knockout mice demonstrates inhibition of intestinal p-glycoprotein by ritonavir causing increased darunavir absorption. *Drug Metab Dispos*, *38*(9), 1407-1410. doi:10.1124/dmd.110.032771

Houshaymi, B., Nasreddine, N., Kedees, M., & Soayfane, Z. (2019). Oleic acid increases uptake and decreases the P-gp-mediated efflux of the veterinary anthelmintic Ivermectin. *Drug Res (Stuttg)*, *69*(3), 173-180. doi:10.1055/a-0662-5741

https://ir.tetrabiopharma.com/newsroom/press-releases/news-details/2020/FDA-Provides-Positive-Feedback-on-Tetra-Bio-Pharmas-Pre-Investigational-New-Drug-Application-for-ARDS-003-to-Be-Studied-in-COVID-19-Patients-at-Risk-of-Developing-Acute-Respiratory-Distress-Syndrome-ARDS/default.aspx. (2020).

https://www.forbes.com/sites/emilyearlenbaugh/2020/08/20/synthetic-cannabinoid-drug-for-covid-19-approved-for-phase-1-clinical-trials/#314337063329. (2020).

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., ... Cao, B. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, *395*(10223), 497-506. doi:10.1016/S0140-6736(20)30183-5

Huijie Bian, Z.-H. Z., Ding Wei, Zheng Zhang, Wen-Zhen Kang, Chun-Qiu Hao, Ke Dong, Wen Kang, Jie-Lai Xia, Jin-Lin Miao, Rong-Hua Xie, Bin Wang, Xiu-Xuan Sun, Xiang-Min Yang, Peng Lin, Jie-Jie Geng, Ke Wang, Hong-Yong Cui, Kui Zhang, Xiao-Chun Chen, Hao Tang, Hong Du, Na Yao, Shuang-Shuang Liu, Lin-Na Liu, Zhe Zhang, Zhao-Wei Gao, Gang Nan, Qing-Yi Wang, Jian-Qi Lian, Zhi-Nan Chen, Ping Zhu. (2020). Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. *medRxiv*doi:doi.org/10.1101/2020.03.21.20040691

Huisman, M. T., Smit, J. W., Crommentuyn, K. M., Zelcer, N., Wiltshire, H. R., Beijnen, J. H., & Schinkel, A. H. (2002). Multidrug resistance protein 2 (MRP2) transports HIV protease inhibitors, and transport can be enhanced by other drugs. *AIDS*, *16*(17), 2295-2301. doi:10.1097/00002030-200211220-00009

Iber, H., Chen, Q., Cheng, P. Y., & Morgan, E. T. (2000). Suppression of CYP2C11 gene transcription by interleukin-1 mediated by NF-kappaB binding at the transcription start site. *Arch Biochem Biophys*, *377*(1), 187-194. doi:10.1006/abbi.2000.1772

Iga, K. (2016). Dynamic and Static Simulations of Fluvoxamine-Perpetrated Drug-Drug Interactions Using Multiple Cytochrome P450 Inhibition Modeling, and Determination of Perpetrator-Specific CYP Isoform Inhibition Constants and Fractional CYP Isoform Contributions to Victim Clearance. *J Pharm Sci*, *105*(3), 1307-1317. doi:10.1016/j.xphs.2015.11.044

Ip, A., Berry, D. A., Hansen, E., Goy, A. H., Pecora, A. L., Sinclaire, B. A., ... Goldberg, S. L. (2020). Hydroxychloroquine and tocilizumab therapy in COVID-19 patients-An observational study. *PLoS One*, *15*(8), e0237693. doi:10.1371/journal.pone.0237693

Jamilloux, Y., Henry, T., Belot, A., Viel, S., Fauter, M., El Jammal, T., ... Seve, P. (2020). Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. *Autoimmun Rev*, *19*(7), 102567. doi:10.1016/j.autrev.2020.102567

Jani, M., Makai, I., Kis, E., Szabo, P., Nagy, T., Krajcsi, P., & Lespine, A. (2011). Ivermectin interacts with human ABCG2. *J Pharm Sci*, *100*(1), 94-97. doi:10.1002/jps.22262

Janneh, O., Jones, E., Chandler, B., Owen, A., & Khoo, S. H. (2007). Inhibition of P-glycoprotein and multidrug resistance-associated proteins modulates the intracellular concentration of lopinavir in cultured CD4 T cells and primary human lymphocytes. *J Antimicrob Chemother*, *60*(5), 987-993. doi:10.1093/jac/dkm353

Jasenosky, L. D., Cadena, C., Mire, C. E., Borisevich, V., Haridas, V., Ranjbar, S., ... Goldfeld, A. E. (2019). The FDA-Approved Oral Drug Nitazoxanide Amplifies Host Antiviral Responses and Inhibits Ebola Virus. *iScience*, *19*, 1279-1290. doi:10.1016/j.isci.2019.07.003

Jin, M., & Tong, Q. (2020). Rhabdomyolysis as Potential Late Complication Associated with COVID-19. *Emerg Infect Dis*, *26*(7), 1618-1620. doi:10.3201/eid2607.200445

Jodele, S., Medvedovic, M., Luebbering, N., Chen, J., Dandoy, C. E., Laskin, B. L., & Davies, S. M. (2020). Interferon-complement loop in transplant-associated thrombotic microangiopathy. *Blood Adv*, *4*(6), 1166-1177. doi:10.1182/bloodadvances.2020001515

Jung, N., Lehmann, C., Rubbert, A., Knispel, M., Hartmann, P., van Lunzen, J., ... Taubert, D. (2008). Relevance of the organic cation transporters 1 and 2 for antiretroviral drug therapy in human immunodeficiency virus infection. *Drug Metab Dispos*, *36*(8), 1616-1623. doi:10.1124/dmd.108.020826

Kacevska, M., Mahns, A., Sharma, R., Clarke, S. J., Robertson, G. R., & Liddle, C. (2013). Extra-hepatic cancer represses hepatic drug metabolism via interleukin (IL)-6 signalling. *Pharm Res*, *30*(9), 2270-2278. doi:10.1007/s11095-013-1042-3

Kalil, A. C., Patterson, T. F., Mehta, A. K., Tomashek, K. M., Wolfe, C. R., Ghazaryan, V., ... Beigel, J. H. (2020). Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med*doi:10.1056/NEJMoa2031994

Kameyama, N., Arisawa, S., Ueyama, J., Kagota, S., Shinozuka, K., Hattori, A., ... Wakusawa, S. (2008). Increase in P-glycoprotein accompanied by activation of protein kinase Calpha and NF-kappaB p65 in the livers of rats with streptozotocin-induced diabetes. *Biochim Biophys Acta*, *1782*(5), 355-360. doi:10.1016/j.bbadis.2008.02.005

Karbanova, S., Cerveny, L., Jiraskova, L., Karahoda, R., Ceckova, M., Ptackova, Z., & Staud, F. (2019). Transport of ribavirin across the rat and human placental barrier: Roles of nucleoside and ATP-binding cassette drug efflux transporters. *Biochem Pharmacol*, *163*, 60-70. doi:10.1016/j.bcp.2019.01.024

Kashuba, A. D., Nafziger, A. N., Kearns, G. L., Leeder, J. S., Gotschall, R., Rocci, M. L., Jr., ... Bertino, J. S., Jr. (1998). Effect of fluvoxamine therapy on the activities of CYP1A2, CYP2D6, and CYP3A as determined by phenotyping. *Clin Pharmacol Ther*, *64*(3), 257-268. doi:10.1016/S0009-9236(98)90174-6

Ke, S., Rabson, A. B., Germino, J. F., Gallo, M. A., & Tian, Y. (2001). Mechanism of suppression of cytochrome P-450 1A1 expression by tumor necrosis factor-alpha and lipopolysaccharide. *J Biol Chem*, *276*(43), 39638-39644. doi:10.1074/jbc.M106286200

Ke Wang, W. C., Yu-Sen Zhou, Jian-Qi Lian, Zheng Zhang, Peng Du, Li Gong, Yang Zhang, Hong-Yong Cui, Jie-Jie Geng, Bin Wang, Xiu-Xuan Sun, Chun-Fu Wang, Xu Yang, Peng Lin, Yong-Qiang Deng, Ding Wei, Xiang-Min Yang, Yu-Meng Zhu, Kui Zhang, Zhao-Hui Zheng, Jin-Lin Miao, Ting Guo, Ying Shi, Jun Zhang, Ling Fu, Qing-Yi Wang, Huijie Bian, Ping Zhu, Zhi-Nan Chen. (2020). SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *bioRxiv*doi:https://doi.org/10.1101/2020.03.14.988345

Ketkar, H., Yang, L., Wormser, G. P., & Wang, P. (2019). Lack of efficacy of ivermectin for prevention of a lethal Zika virus infection in a murine system. *Diagn Microbiol Infect Dis*, *95*(1), 38-40. doi:10.1016/j.diagmicrobio.2019.03.012

Kim, E. J., Choi, S. H., Park, J. S., Kwon, Y. S., Lee, J., Kim, Y., ... Choi, E. Y. (2020). Use of Darunavir-Cobicistat as a Treatment Option for Critically Ill Patients with SARS-CoV-2 Infection. *Yonsei Med J*, *61*(9), 826-830. doi:10.3349/ymj.2020.61.9.826

Kis, O., Zastre, J. A., Hoque, M. T., Walmsley, S. L., & Bendayan, R. (2013). Role of drug efflux and uptake transporters in atazanavir intestinal permeability and drug-drug interactions. *Pharm Res*, *30*(4), 1050-1064. doi:10.1007/s11095-012-0942-y

Kiser, J. J., Gerber, J. G., Predhomme, J. A., Wolfe, P., Flynn, D. M., & Hoody, D. W. (2008). Drug/Drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. *J Acquir Immune Defic Syndr*, *47*(5), 570-578. doi:10.1097/QAI.0b013e318160a542

Klinkhammer, J., Schnepf, D., Ye, L., Schwaderlapp, M., Gad, H. H., Hartmann, R., ... Staeheli, P. (2018). IFN-lambda prevents influenza virus spread from the upper airways to the lungs and limits virus transmission. *Elife*, *7*doi:10.7554/eLife.33354

Ko, W. C., Rolain, J. M., Lee, N. Y., Chen, P. L., Huang, C. T., Lee, P. I., & Hsueh, P. R. (2020). Arguments in favour of remdesivir for treating SARS-CoV-2 infections. *Int J Antimicrob Agents*, *55*(4), 105933. doi:10.1016/j.ijantimicag.2020.105933

Kosters, A., & Karpen, S. J. (2010). The role of inflammation in cholestasis: clinical and basic aspects. *Semin Liver Dis*, *30*(2), 186-194. doi:10.1055/s-0030-1253227

Kotenko, S. V., Gallagher, G., Baurin, V. V., Lewis-Antes, A., Shen, M., Shah, N. K., ... Donnelly, R. P. (2003). IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat Immunol*, *4*(1), 69-77. doi:10.1038/ni875

Kourylko, O., Fradette, C., Arcand, M., & du Souich, P. (2006). Modulation of CYP1A2 and CYP3A6 catalytic activities by serum from rabbits with a turpentine-induced inflammatory reaction and interleukin 6. *Drug Metab Dispos*, *34*(1), 27-35. doi:10.1124/dmd.105.006528

Kritas, S. K., Ronconi, G., Caraffa, A., Gallenga, C. E., Ross, R., & Conti, P. (2020). Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. *J Biol Regul Homeost Agents*, *34*(1), 9-14. doi:10.23812/20-Editorial-Kritas

Lan, T., Rao, A., Haywood, J., Davis, C. B., Han, C., Garver, E., & Dawson, P. A. (2009). Interaction of macrolide antibiotics with intestinally expressed human and rat organic anion-transporting polypeptides. *Drug Metab Dispos*, *37*(12), 2375-2382. doi:10.1124/dmd.109.028522

Langmann, T., Moehle, C., Mauerer, R., Scharl, M., Liebisch, G., Zahn, A., ... Schmitz, G. (2004). Loss of detoxification in inflammatory bowel disease: dysregulation of pregnane X receptor target genes. *Gastroenterology*, *127*(1), 26-40. doi:10.1053/j.gastro.2004.04.019

Le Vee, M., Gripon, P., Stieger, B., & Fardel, O. (2008). Down-regulation of organic anion transporter expression in human hepatocytes exposed to the proinflammatory cytokine interleukin 1beta. *Drug Metab Dispos*, *36*(2), 217-222. doi:10.1124/dmd.107.016907

Le Vee, M., Jouan, E., Moreau, A., & Fardel, O. (2011). Regulation of drug transporter mRNA expression by interferon-gamma in primary human hepatocytes. *Fundam Clin Pharmacol*, *25*(1), 99-103. doi:10.1111/j.1472-8206.2010.00822.x

Le Vee, M., Lecureur, V., Stieger, B., & Fardel, O. (2009). Regulation of drug transporter expression in human hepatocytes exposed to the proinflammatory cytokines tumor necrosis factor-alpha or interleukin-6. *Drug Metab Dispos*, *37*(3), 685-693. doi:10.1124/dmd.108.023630

Ledford, H. (2020). Coronavirus breakthrough: dexamethasone is first drug shown to save lives. *Nature*, *582*(7813), 469. doi:10.1038/d41586-020-01824-5

Lee, G., & Piquette-Miller, M. (2001). Influence of IL-6 on MDR and MRP-mediated multidrug resistance in human hepatoma cells. *Can J Physiol Pharmacol*, *79*(10), 876-884. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11697747

Lee, J. Y., Vinayagamoorthy, N., Han, K., Kwok, S. K., Ju, J. H., Park, K. S., ... Park, S. H. (2016). Association of Polymorphisms of Cytochrome P450 2D6 With Blood Hydroxychloroquine Levels in Patients With Systemic Lupus Erythematosus. *Arthritis Rheumatol*, *68*(1), 184-190. doi:10.1002/art.39402

Lee, N., Allen Chan, K. C., Hui, D. S., Ng, E. K., Wu, A., Chiu, R. W., ... Lo, Y. M. (2004). Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *J Clin Virol*, *31*(4), 304-309. doi:10.1016/j.jcv.2004.07.006

Leneva, I. A., Russell, R. J., Boriskin, Y. S., & Hay, A. J. (2009). Characteristics of arbidol-resistant mutants of influenza virus: implications for the mechanism of anti-influenza action of arbidol. *Antiviral Res*, *81*(2), 132-140. doi:10.1016/j.antiviral.2008.10.009

Lenze, E. J., Mattar, C., Zorumski, C. F., Stevens, A., Schweiger, J., Nicol, G. E., ... Reiersen, A. M. (2020). Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19: A Randomized Clinical Trial. *JAMA*doi:10.1001/jama.2020.22760

Lespine, A., Dupuy, J., Orlowski, S., Nagy, T., Glavinas, H., Krajcsi, P., & Alvinerie, M. (2006). Interaction of ivermectin with multidrug resistance proteins (MRP1, 2 and 3). *Chem Biol Interact*, *159*(3), 169-179. doi:10.1016/j.cbi.2005.11.002

Li, G., & De Clercq, E. (2020). Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov*, *19*(3), 149-150. doi:10.1038/d41573-020-00016-0

Liptrott, N. J., Penny, M., Bray, P. G., Sathish, J., Khoo, S. H., Back, D. J., & Owen, A. (2009). The impact of cytokines on the expression of drug transporters, cytochrome P450 enzymes and chemokine receptors in human PBMC. *Br J Pharmacol*, *156*(3), 497-508. doi:10.1111/j.1476-5381.2008.00050.x

Liu, J., Cao, R., Xu, M., Wang, X., Zhang, H., Hu, H., ... Wang, M. (2020). Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*, *6*, 16. doi:10.1038/s41421-020-0156-0

Liu, Q., Xiong, H. R., Lu, L., Liu, Y. Y., Luo, F., Hou, W., & Yang, Z. Q. (2013). Antiviral and anti-inflammatory activity of arbidol hydrochloride in influenza A (H1N1) virus infection. *Acta Pharmacol Sin*, *34*(8), 1075-1083. doi:10.1038/aps.2013.54

Loganathan, S., Athalye, S. N., & Joshi, S. R. (2020). Itolizumab, an anti-CD6 monoclonal antibody, as a potential treatment for COVID-19 complications. *Expert Opin Biol Ther*, 1-7. doi:10.1080/14712598.2020.1798399

Longxing Cao, I. G., Brian Coventry, James Brett Case, Lauren Miller, Lisa Kozodoy, Rita E Chen, Lauren Carter, Alexandra C Walls, Young-Jun Park, Eva-Maria Strauch, Lance Stewart, Michael S Diamond, David Veesler, David Baker (2020). De novo design of picomolar SARS-CoV-2 miniprotein inhibitors. *Science*, 1-10. doi:10.1126/science.abd9909

Lopinavir, Ritonavir. https://www.drugbank.ca/unearth/q?utf8¼%E2%9C% 93&query¼lopinavir %2Fritonivir&searcher¼drugs Accessed 02 April 2020

(2020).
Luo, P., Liu, Y., Qiu, L., Liu, X., Liu, D., & Li, J. (2020). Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol*, *92*(7), 814-818. doi:10.1002/jmv.25801
Madelain, V., Mentre, F., Baize, S., Anglaret, X., Laouenan, C., Oestereich, L., ... Guedj, J. (2020). Modeling Favipiravir Antiviral Efficacy Against Emerging Viruses: From Animal Studies to Clinical Trials. *CPT Pharmacometrics Syst Pharmacol*, *9*(5), 258-271. doi:10.1002/psp4.12510
Madrid, P. B., Panchal, R. G., Warren, T. K., Shurtleff, A. C., Endsley, A. N., Green, C. E., ... Tanga, M. J. (2015). Evaluation of Ebola Virus Inhibitors for Drug Repurposing. *ACS Infect Dis*, *1*(7), 317-326. doi:10.1021/acsinfecdis.5b00030
Magro, C., Mulvey, J. J., Berlin, D., Nuovo, G., Salvatore, S., Harp, J., ... Laurence, J. (2020). Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res*, *220*, 1-13. doi:10.1016/j.trsl.2020.04.007
Mak, R. H., Cheung, W., Cone, R. D., & Marks, D. L. (2006). Mechanisms of disease: Cytokine and adipokine signaling in uremic cachexia. *Nat Clin Pract Nephrol*, *2*(9), 527-534. doi:10.1038/ncpneph0273
Manceau, S., Giraud, C., Decleves, X., Batteux, F., Chereau, C., Chouzenoux, S., ... Treluyer, J. M. (2012). Expression and induction by dexamethasone of ABC transporters and nuclear receptors in a human T-lymphocyte cell line. *J Chemother*, *24*(1), 48-55. doi:10.1179/1120009X12Z.00000000010
Martinez, M. A. (2020). Compounds with Therapeutic Potential against Novel Respiratory 2019 Coronavirus. *Antimicrob Agents Chemother*, *64*(5)doi:10.1128/AAC.00399-20
Marzolini, C., Gibbons, S., Khoo, S., & Back, D. (2016). Cobicistat versus ritonavir boosting and differences in the drug-drug interaction profiles with co-medications. *J Antimicrob Chemother*, *71*(7), 1755-1758. doi:10.1093/jac/dkw032
Mastaglio, S., Ruggeri, A., Risitano, A. M., Angelillo, P., Yancopoulou, D., Mastellos, D. C., ... Ciceri, F. (2020). The first case of COVID-19 treated with the complement C3 inhibitor AMY-101. *Clin Immunol*, *215*, 108450. doi:10.1016/j.clim.2020.108450
Mastellos, D. C., Yancopoulou, D., Kokkinos, P., Huber-Lang, M., Hajishengallis, G., Biglarnia, A. R., ... Lambris, J. D. (2015). Compstatin: a C3-targeted complement inhibitor reaching its prime for bedside intervention. *Eur J Clin Invest*, *45*(4), 423-440. doi:10.1111/eci.12419
Mauthe, M., Orhon, I., Rocchi, C., Zhou, X., Luhr, M., Hijlkema, K. J., ... Reggiori, F. (2018). Chloroquine inhibits autophagic flux by decreasing autophagosome-lysosome fusion. *Autophagy*, *14*(8), 1435-1455. doi:10.1080/15548627.2018.1474314
Medrxiv News. from, https://times.hinet.net/mobile/news/ 22831665. [Accessed 20 March 2020]. . (2020).
Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., Manson, J. J., & Hlh Across Speciality Collaboration, U. K. (2020). COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*, *395*(10229), 1033-1034. doi:10.1016/S0140-6736(20)30628-0
Mimura, H., Kobayashi, K., Xu, L., Hashimoto, M., Ejiri, Y., Hosoda, M., & Chiba, K. (2015). Effects of cytokines on CYP3A4 expression and reversal of the effects by anti-cytokine agents in the three-dimensionally cultured human hepatoma cell line FLC-4. *Drug Metab Pharmacokinet*, *30*(1), 105-110. doi:10.1016/j.dmpk.2014.09.004
Mishima, E., Anzai, N., Miyazaki, M., & Abe, T. (2020). Uric Acid Elevation by Favipiravir, an Antiviral Drug. *Tohoku J Exp Med*, *251*(2), 87-90. doi:10.1620/tjem.251.87
Mitja, O., & Clotet, B. (2020). Use of antiviral drugs to reduce COVID-19 transmission. *Lancet Glob Health*, *8*(5), e639-e640. doi:10.1016/S2214-109X(20)30114-5
Mlejnek, P., Kosztyu, P., Dolezel, P., Bates, S. E., & Ruzickova, E. (2017). Reversal of ABCB1 mediated efflux by imatinib and nilotinib in cells expressing various transporter levels. *Chem Biol Interact*, *273*, 171-179. doi:10.1016/j.cbi.2017.06.012
Monshouwer, M., Witkamp, R. F., Nujmeijer, S. M., Van Amsterdam, J. G., & Van Miert, A. S. (1996). Suppression of cytochrome P450- and UDP glucuronosyl transferase-dependent enzyme activities by proinflammatory cytokines and possible role of nitric oxide in primary cultures of pig hepatocytes. *Toxicol Appl Pharmacol*, *137*(2), 237-244. doi:10.1006/taap.1996.0077
Moore, J. B., & June, C. H. (2020). Cytokine release syndrome in severe COVID-19. *Science*, *368*(6490), 473-474. doi:10.1126/science.abb8925

Morales-Ortega, A., Bernal-Bello, D., Llarena-Barroso, C., Frutos-Perez, B., Duarte-Millan, M. A., Garcia de Viedma-Garcia, V., ... San Martin-Lopez, J. V. (2020). Imatinib for COVID-19: A case report. *Clin Immunol*, *218*, 108518. doi:10.1016/j.clim.2020.108518

Morgan, E. T. (1989). Suppression of constitutive cytochrome P-450 gene expression in livers of rats undergoing an acute phase response to endotoxin. *Mol Pharmacol*, *36*(5), 699-707. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/2511427

Morgan, E. T. (1993). Down-regulation of multiple cytochrome P450 gene products by inflammatory mediators in vivo. Independence from the hypothalamo-pituitary axis. *Biochem Pharmacol*, *45*(2), 415-419. doi:10.1016/0006-2952(93)90078-b

Morgan, E. T. (1997). Regulation of cytochromes P450 during inflammation and infection. *Drug Metab Rev*, *29*(4), 1129-1188. doi:10.3109/03602539709002246

Morgan, E. T. (2009). Impact of infectious and inflammatory disease on cytochrome P450-mediated drug metabolism and pharmacokinetics. *Clin Pharmacol Ther*, *85*(4), 434-438. doi:10.1038/clpt.2008.302

Morgan, E. T., Goralski, K. B., Piquette-Miller, M., Renton, K. W., Robertson, G. R., Chaluvadi, M. R., ... Sinal, C. J. (2008). Regulation of drug-metabolizing enzymes and transporters in infection, inflammation, and cancer. *Drug Metab Dispos*, *36*(2), 205-216. doi:10.1124/dmd.107.018747

Moshage, H. J., Janssen, J. A., Franssen, J. H., Hafkenscheid, J. C., & Yap, S. H. (1987). Study of the molecular mechanism of decreased liver synthesis of albumin in inflammation. *J Clin Invest*, *79*(6), 1635-1641. doi:10.1172/JCI113000

Muir, A. J., Arora, S., Everson, G., Flisiak, R., George, J., Ghalib, R., ... group, E. s. (2014). A randomized phase 2b study of peginterferon lambda-1a for the treatment of chronic HCV infection. *J Hepatol*, *61*(6), 1238-1246. doi:10.1016/j.jhep.2014.07.022

Mulangu, S., Dodd, L. E., Davey, R. T., Jr., Tshiani Mbaya, O., Proschan, M., Mukadi, D., ... Team, P. C. S. (2019). A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med*, *381*(24), 2293-2303. doi:10.1056/NEJMoa1910993

Mullard, A. (2020). COVID-19 vaccine development pipeline gears up. *Lancet*, *395*(10239), 1751-1752. doi:10.1016/S0140-6736(20)31252-6

Muntane-Relat, J., Ourlin, J. C., Domergue, J., & Maurel, P. (1995). Differential effects of cytokines on the inducible expression of CYP1A1, CYP1A2, and CYP3A4 in human hepatocytes in primary culture. *Hepatology*, *22*(4 Pt 1), 1143-1153. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/7557864

Nadin, L., Butler, A. M., Farrell, G. C., & Murray, M. (1995). Pretranslational down-regulation of cytochromes P450 2C11 and 3A2 in male rat liver by tumor necrosis factor alpha. *Gastroenterology*, *109*(1), 198-205. doi:10.1016/0016-5085(95)90285-6

Nair, P., Melarkode, R., Rajkumar, D., & Montero, E. (2010). CD6 synergistic co-stimulation promoting proinflammatory response is modulated without interfering with the activated leucocyte cell adhesion molecule interaction. *Clin Exp Immunol*, *162*(1), 116-130. doi:10.1111/j.1365-2249.2010.04235.x

Neodo, A., Schulz, J. D., Huwyler, J., & Keiser, J. (2019). In Vitro and In Vivo Drug-Drug Interaction Study of the Effects of Ivermectin and Oxantel Pamoate on Tribendimidine. *Antimicrob Agents Chemother*, *63*(1)doi:10.1128/AAC.00762-18

News. (2020a). https://www.cancernetwork.com/view/fda-approves-phase-iii-clinical-trial-tocilizumab-covid-19-pneumonia.

News. (2020b). https://www.pharmaceutical-technology.com/news/biocon-itolizumab-approval/.

News. (2020c). https://www.sciencedaily.com/releases/2020/09/200909140314.htm.

News. (2020d). News. FDA approves COVACTA trial for RA drug Actemra in COVID-19 patients. From: https://www.pharmaceuticalbusiness-review.com/news/covacta-trial- actemra-covid-19/. [Accessed 28 March 2020].

Nicholson, T. E., & Renton, K. W. (1999). Modulation of cytochrome P450 by inflammation in astrocytes. *Brain Res*, *827*(1-2), 12-18. doi:10.1016/s0006-8993(99)01261-5

Nicholson, T. E., & Renton, K. W. (2001). Role of cytokines in the lipopolysaccharide-evoked depression of cytochrome P450 in the brain and liver. *Biochem Pharmacol*, *62*(12), 1709-1717. doi:10.1016/s0006-2952(01)00859-0

NIH. (2020a). https://clinicaltrials.gov/ct2/show/NCT04275245.

NIH. (2020b). https://clinicaltrials.gov/ct2/show/NCT04288713.

NIH. (2020c). https://clinicaltrials.gov/ct2/show/NCT04369586.

NIH. (2020d). https://clinicaltrials.gov/ct2/show/NCT04395456?lead=Amyndas&draw=2&rank=1.
NIH. (2020e). NIH US National Library of Medicine clinical trial database https:// clinicaltrials.gov/ct2/results? cond¼COVID&term¼remdesivir&cntry¼& state¼&city¼&dist¼ Accessed 23 May 2020.

.
NIH. (2020f). NIH US National Library of Medicine clinical trial database. https:// clinicaltrials.gov/ct2/results? cond¼COVID&term¼lopinavir-ritonavir&cntry¼ &state¼&city¼&dist= Accessed 23 May 2020.
Nunius, C., Buttner-Herold, M., Bertz, S., Schiffer, M., & Buchholz, B. (2020). Isolated thrombotic microangiopathy of the small intestine in a patient with atypical hemolytic uremic syndrome - a case report. *BMC Nephrol*, *21*(1), 104. doi:10.1186/s12882-020-01766-0
Oestereich, L., Ludtke, A., Wurr, S., Rieger, T., Munoz-Fontela, C., & Gunther, S. (2014). Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. *Antiviral Res*, *105*, 17-21. doi:10.1016/j.antiviral.2014.02.014
Olson, S. R., Lu, E., Sulpizio, E., Shatzel, J. J., Rueda, J. F., & DeLoughery, T. G. (2018). When to Stop Eculizumab in Complement-Mediated Thrombotic Microangiopathies. *Am J Nephrol*, *48*(2), 96-107. doi:10.1159/000492033
Omori, I. M., Watanabe, N., Nakagawa, A., Akechi, T., Cipriani, A., Barbui, C., ... Meta-Analysis of New Generation Antidepressants Study, G. (2009). Efficacy, tolerability and side-effect profile of fluvoxamine for major depression: meta-analysis. *J Psychopharmacol*, *23*(5), 539-550. doi:10.1177/0269881108089876
Orkin, C., DeJesus, E., Khanlou, H., Stoehr, A., Supparatpinyo, K., Lathouwers, E., ... Tomaka, F. (2013). Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. *HIV Med*, *14*(1), 49-59. doi:10.1111/j.1468-1293.2012.01060.x
Padilla, S., Telenti, G., Guillen, L., Garcia, J. A., Garcia-Abellan, J., Ding, C., ... Group, C. O.-E. (2020). Predictive factors for cardiac conduction abnormalities with hydroxychloroquine-containing combinations for COVID-19. *Int J Antimicrob Agents*, *56*(4), 106142. doi:10.1016/j.ijantimicag.2020.106142
Pan, J., Xiang, Q., & Ball, S. (2000). Use of a novel real-time quantitative reverse transcription-polymerase chain reaction method to study the effects of cytokines on cytochrome P450 mRNA expression in mouse liver. *Drug Metab Dispos*, *28*(6), 709-713. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10820145
Pan, W., Yu, C., Hsuchou, H., & Kastin, A. J. (2010). The role of cerebral vascular NFkappaB in LPS-induced inflammation: differential regulation of efflux transporter and transporting cytokine receptors. *Cell Physiol Biochem*, *25*(6), 623-630. doi:10.1159/000315081
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. . (2012). *Department of Health and Human Services*.
Park, S. Y., Lee, J. S., Son, J. S., Ko, J. H., Peck, K. R., Jung, Y., ... Shi, H. (2019). Post-exposure prophylaxis for Middle East respiratory syndrome in healthcare workers. *J Hosp Infect*, *101*(1), 42-46. doi:10.1016/j.jhin.2018.09.005
Parmentier, J. H., Kremers, P., Ferrari, L., Batt, A. M., Gielen, J. E., & Siest, G. (1993). Repression of cytochrome P450 by cytokines: IL-1 beta counteracts clofibric acid induction of CYP4A in cultured fetal rat hepatocytes. *Cell Biol Toxicol*, *9*(3), 307-313. doi:10.1007/BF00755608
Pascussi, J. M., Drocourt, L., Gerbal-Chaloin, S., Fabre, J. M., Maurel, P., & Vilarem, M. J. (2001). Dual effect of dexamethasone on CYP3A4 gene expression in human hepatocytes. Sequential role of glucocorticoid receptor and pregnane X receptor. *Eur J Biochem*, *268*(24), 6346-6358. doi:10.1046/j.0014-2956.2001.02540.x
Pecheur, E. I., Borisevich, V., Halfmann, P., Morrey, J. D., Smee, D. F., Prichard, M., ... Polyak, S. J. (2016). The Synthetic Antiviral Drug Arbidol Inhibits Globally Prevalent Pathogenic Viruses. *J Virol*, *90*(6), 3086-3092. doi:10.1128/JVI.02077-15
Pecheur, E. I., Lavillette, D., Alcaras, F., Molle, J., Boriskin, Y. S., Roberts, M., ... Polyak, S. J. (2007). Biochemical mechanism of hepatitis C virus inhibition by the broad-spectrum antiviral arbidol. *Biochemistry*, *46*(20), 6050-6059. doi:10.1021/bi700181j
Pepperrell, T., Pilkington, V., Owen, A., Wang, J., & Hill, A. M. (2020). Review of safety and minimum pricing of nitazoxanide for potential treatment of COVID-19. *J Virus Erad*, *6*(2), 52-60. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32405422
Perloff, E. S., Duan, S. X., Skolnik, P. R., Greenblatt, D. J., & von Moltke, L. L. (2005). Atazanavir: effects on P-glycoprotein transport and CYP3A metabolism in vitro. *Drug Metab Dispos*, *33*(6), 764-770. doi:10.1124/dmd.104.002931

Perloff, M. D., von Moltke, L. L., & Greenblatt, D. J. (2002). Fexofenadine transport in Caco-2 cells: inhibition with verapamil and ritonavir. *J Clin Pharmacol*, *42*(11), 1269-1274. doi:10.1177/009127002762491370

Poller, B., Drewe, J., Krahenbuhl, S., Huwyler, J., & Gutmann, H. (2010). Regulation of BCRP (ABCG2) and P-glycoprotein (ABCB1) by cytokines in a model of the human blood-brain barrier. *Cell Mol Neurobiol*, *30*(1), 63-70. doi:10.1007/s10571-009-9431-1

Posada, M. M., Cannady, E. A., Payne, C. D., Zhang, X., Bacon, J. A., Pak, Y. A., ... Hillgren, K. M. (2017). Prediction of Transporter-Mediated Drug-Drug Interactions for Baricitinib. *Clin Transl Sci*, *10*(6), 509-519. doi:10.1111/cts.12486

Prezcobix prescribing information. https://www.accessdata.fda.gov/drugsatfda_-docs/label/2016/205395s001lbl.pdf. (2020).

Prokunina-Olsson, L., Muchmore, B., Tang, W., Pfeiffer, R. M., Park, H., Dickensheets, H., ... O'Brien, T. R. (2013). A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. *Nat Genet*, *45*(2), 164-171. doi:10.1038/ng.2521

Pu, S. Y., Xiao, F., Schor, S., Bekerman, E., Zanini, F., Barouch-Bentov, R., ... Einav, S. (2018). Feasibility and biological rationale of repurposing sunitinib and erlotinib for dengue treatment. *Antiviral Res*, *155*, 67-75. doi:10.1016/j.antiviral.2018.05.001

Rahmani, H., Davoudi-Monfared, E., Nourian, A., Nabiee, M., Sadeghi, S., Khalili, H., ... Yekaninejad, M. S. (2020). Comparing outcomes of hospitalized patients with moderate and severe COVID-19 following treatment with hydroxychloroquine plus atazanavir/ritonavir. *Daru*, *28*(2), 625-634. doi:10.1007/s40199-020-00369-2

Rakhmanina, N. Y., Neely, M. N., Van Schaik, R. H., Gordish-Dressman, H. A., Williams, K. D., Soldin, S. J., & van den Anker, J. N. (2011). CYP3A5, ABCB1, and SLCO1B1 polymorphisms and pharmacokinetics and virologic outcome of lopinavir/ritonavir in HIV-infected children. *Ther Drug Monit*, *33*(4), 417-424. doi:10.1097/FTD.0b013e318225384f

Reis, E. S., Berger, N., Wang, X., Koutsogiannaki, S., Doot, R. K., Gumas, J. T., ... Lambris, J. D. (2018). Safety profile after prolonged C3 inhibition. *Clin Immunol*, *197*, 96-106. doi:10.1016/j.clim.2018.09.004

Rezolsta Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/rezolsta-epar-product-information_en.pdf. . (2020).

Richardson, P., Griffin, I., Tucker, C., Smith, D., Oechsle, O., Phelan, A., ... Stebbing, J. (2020). Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *Lancet*, *395*(10223), e30-e31. doi:10.1016/S0140-6736(20)30304-4

Richardson, P. J., Corbellino, M., & Stebbing, J. (2020). Baricitinib for COVID-19: a suitable treatment? - Authors' reply. *Lancet Infect Dis*, *20*(9), 1013-1014. doi:10.1016/S1473-3099(20)30270-X

Risitano, A. M., Mastellos, D. C., Huber-Lang, M., Yancopoulou, D., Garlanda, C., Ciceri, F., & Lambris, J. D. (2020). Author Correction: Complement as a target in COVID-19? *Nat Rev Immunol*, *20*(7), 448. doi:10.1038/s41577-020-0366-6

Rismanbaf, A. (2020). Potential Treatments for COVID-19; a Narrative Literature Review. *Arch Acad Emerg Med*, *8*(1), e29. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/32232214

Robertson, G. R., Field, J., Goodwin, B., Bierach, S., Tran, M., Lehnert, A., & Liddle, C. (2003). Transgenic mouse models of human CYP3A4 gene regulation. *Mol Pharmacol*, *64*(1), 42-50. doi:10.1124/mol.64.1.42

Roselli, F., Karasu, E., Volpe, C., & Huber-Lang, M. (2018). Medusa's Head: The Complement System in Traumatic Brain and Spinal Cord Injury. *J Neurotrauma*, *35*(2), 226-240. doi:10.1089/neu.2017.5168

Rubin, K., Janefeldt, A., Andersson, L., Berke, Z., Grime, K., & Andersson, T. B. (2015). HepaRG cells as human-relevant in vitro model to study the effects of inflammatory stimuli on cytochrome P450 isoenzymes. *Drug Metab Dispos*, *43*(1), 119-125. doi:10.1124/dmd.114.059246

Ruot, B., Bechereau, F., Bayle, G., Breuille, D., & Obled, C. (2002). The response of liver albumin synthesis to infection in rats varies with the phase of the inflammatory process. *Clin Sci (Lond)*, *102*(1), 107-114. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11749667

Russell, C. D., Millar, J. E., & Baillie, J. K. (2020). Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*, *395*(10223), 473-475. doi:10.1016/S0140-6736(20)30317-2

Saavedra, D., Añé Kourí, A., Sánchez, N., Filgueira, L., Betancourt, J., Herrera, C., ... Crombet, T. (2020). *An Anti-CD6 Monoclonal Antibody (Itolizumab) Reduces Circulating IL-6 in Severe Covid-19 Elderly Patients*.

Sandler, C., Ekokoski, E., Lindstedt, K. A., Vainio, P. J., Finel, M., Sorsa, T., ... Eklund, K. K. (2005). Chemically modified tetracycline (CMT)-3 inhibits histamine release and cytokine production in mast cells: possible involvement of protein kinase C. *Inflamm Res*, *54*(7), 304-312. doi:10.1007/s00011-005-1358-5

Sheahan, T. P., Sims, A. C., Graham, R. L., Menachery, V. D., Gralinski, L. E., Case, J. B., ... Baric, R. S. (2017). Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med*, *9*(396)doi:10.1126/scitranslmed.aal3653

Sheahan, T. P., Sims, A. C., Zhou, S., Graham, R. L., Pruijssers, A. J., Agostini, M. L., ... Baric, R. S. (2020). An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Sci Transl Med*, *12*(541)doi:10.1126/scitranslmed.abb5883

Sheppard, P., Kindsvogel, W., Xu, W., Henderson, K., Schlutsmeyer, S., Whitmore, T. E., ... Klucher, K. M. (2003). IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol*, *4*(1), 63-68. doi:10.1038/ni873

Shiraki, K., & Daikoku, T. (2020). Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. *Pharmacol Ther*, *209*, 107512. doi:10.1016/j.pharmthera.2020.107512

Siewert, E., Bort, R., Kluge, R., Heinrich, P. C., Castell, J., & Jover, R. (2000). Hepatic cytochrome P450 down-regulation during aseptic inflammation in the mouse is interleukin 6 dependent. *Hepatology*, *32*(1), 49-55. doi:10.1053/jhep.2000.8532

Silasi-Mansat, R., Zhu, H., Georgescu, C., Popescu, N., Keshari, R. S., Peer, G., ... Lupu, F. (2015). Complement inhibition decreases early fibrogenic events in the lung of septic baboons. *J Cell Mol Med*, *19*(11), 2549-2563. doi:10.1111/jcmm.12667

Sortica, V. A., Lindenau, J. D., Cunha, M. G., MD, O. O., AM, R. V., Ribeiro-Dos-Santos, A. K., ... Hutz, M. H. (2017). SLCO1A2, SLCO1B1 and SLCO2B1 polymorphisms influences chloroquine and primaquine treatment in Plasmodium vivax malaria. *Pharmacogenomics*, *18*(15), 1393-1400. doi:10.2217/pgs-2017-0077

Sterne, J. A. C., Murthy, S., Diaz, J. V., Slutsky, A. S., Villar, J., Angus, D. C., ... Marshall, J. C. (2020). Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. *JAMA*, *324*(13), 1330-1341. doi:10.1001/jama.2020.17023

Storch, C. H., Theile, D., Lindenmaier, H., Haefeli, W. E., & Weiss, J. (2007). Comparison of the inhibitory activity of anti-HIV drugs on P-glycoprotein. *Biochem Pharmacol*, *73*(10), 1573-1581. doi:10.1016/j.bcp.2007.01.027

Stout, S. M., & Cimino, N. M. (2014). Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review. *Drug Metab Rev*, *46*(1), 86-95. doi:10.3109/03602532.2013.849268

Stroher, U., DiCaro, A., Li, Y., Strong, J. E., Aoki, F., Plummer, F., ... Feldmann, H. (2004). Severe acute respiratory syndrome-related coronavirus is inhibited by interferon- alpha. *J Infect Dis*, *189*(7), 1164-1167. doi:10.1086/382597

Sugie, M., Asakura, E., Zhao, Y. L., Torita, S., Nadai, M., Baba, K., ... Hasegawa, T. (2004). Possible involvement of the drug transporters P glycoprotein and multidrug resistance-associated protein Mrp2 in disposition of azithromycin. *Antimicrob Agents Chemother*, *48*(3), 809-814. doi:10.1128/aac.48.3.809-814.2004

Sukhai, M., Yong, A., Kalitsky, J., & Piquette-Miller, M. (2000). Inflammation and interleukin-6 mediate reductions in the hepatic expression and transcription of the mdr1a and mdr1b Genes. *Mol Cell Biol Res Commun*, *4*(4), 248-256. doi:10.1006/mcbr.2001.0288

Suzuki, R., Miyamoto, S., Yasui, Y., Sugie, S., & Tanaka, T. (2007). Global gene expression analysis of the mouse colonic mucosa treated with azoxymethane and dextran sodium sulfate. *BMC Cancer*, *7*, 84. doi:10.1186/1471-2407-7-84

Takahashi, T., Luzum, J. A., Nicol, M. R., & Jacobson, P. A. (2020). Pharmacogenomics of COVID-19 therapies. *NPJ Genom Med*, *5*, 35. doi:10.1038/s41525-020-00143-y

Tapner, M., Liddle, C., Goodwin, B., George, J., & Farrell, G. C. (1996). Interferon gamma down-regulates cytochrome P450 3A genes in primary cultures of well-differentiated rat hepatocytes. *Hepatology*, *24*(2), 367-373. doi:10.1002/hep.510240213

Tashima, K., Crofoot, G., Tomaka, F. L., Kakuda, T. N., Brochot, A., Van de Casteele, T., ... Szwarcberg, J. (2014). Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial. *AIDS Res Ther*, *11*, 39. doi:10.1186/1742-6405-11-39

Teng, S., & Piquette-Miller, M. (2008). Regulation of transporters by nuclear hormone receptors: implications during inflammation. *Mol Pharm*, *5*(1), 67-76. doi:10.1021/mp700102q

Tian, Y., Rabson, A. B., & Gallo, M. A. (2002). Ah receptor and NF-kappaB interactions: mechanisms and physiological implications. *Chem Biol Interact*, *141*(1-2), 97-115. doi:10.1016/s0009-2797(02)00068-6

Tinel, M., Robin, M. A., Doostzadeh, J., Maratrat, M., Ballet, F., Fardel, N., ... et al. (1995). The interleukin-2 receptor down-regulates the expression of cytochrome P450 in cultured rat hepatocytes. *Gastroenterology*, *109*(5), 1589-1599. doi:10.1016/0016-5085(95)90648-7

Tirona, R. G. (2011). Molecular mechanisms of drug transporter regulation. *Handb Exp Pharmacol*(201), 373-402. doi:10.1007/978-3-642-14541-4_10
Tirona, R. G., Leake, B. F., Wolkoff, A. W., & Kim, R. B. (2003). Human organic anion transporting polypeptide-C (SLC21A6) is a major determinant of rifampin-mediated pregnane X receptor activation. *J Pharmacol Exp Ther*, *304*(1), 223-228. doi:10.1124/jpet.102.043026
Tong, L., Phan, T. K., Robinson, K. L., Babusis, D., Strab, R., Bhoopathy, S., ... Ray, A. S. (2007). Effects of human immunodeficiency virus protease inhibitors on the intestinal absorption of tenofovir disoproxil fumarate in vitro. *Antimicrob Agents Chemother*, *51*(10), 3498-3504. doi:10.1128/AAC.00671-07
Trivedi, N., Verma, A., & Kumar, D. (2020). Possible treatment and strategies for COVID-19: review and assessment. *Eur Rev Med Pharmacol Sci*, *24*(23), 12593-12608. doi:10.26355/eurrev_202012_24057
Trivedi, N. V., A. Kumar, D. (2020). Possible treatment and strategies for COVID-19: review and assessment. *Eur Rev Med Pharmacol Sci*, *24 (23) Ahead of print*.
Uematsu, S., & Akira, S. (2007). Toll-like receptors and Type I interferons. *J Biol Chem*, *282*(21), 15319-15323. doi:10.1074/jbc.R700009200
van der Heijden, J. W., Dijkmans, B. A., Scheper, R. J., & Jansen, G. (2007). Drug Insight: resistance to methotrexate and other disease-modifying antirheumatic drugs--from bench to bedside. *Nat Clin Pract Rheumatol*, *3*(1), 26-34. doi:10.1038/ncprheum0380
van der Sandt, I. C., Vos, C. M., Nabulsi, L., Blom-Roosemalen, M. C., Voorwinden, H. H., de Boer, A. G., & Breimer, D. D. (2001). Assessment of active transport of HIV protease inhibitors in various cell lines and the in vitro blood--brain barrier. *AIDS*, *15*(4), 483-491. doi:10.1097/00002030-200103090-00007
van Griensven, M., Ricklin, D., Denk, S., Halbgebauer, R., Braun, C. K., Schultze, A., ... Huber-Lang, M. (2019). Protective Effects of the Complement Inhibitor Compstatin CP40 in Hemorrhagic Shock. *Shock*, *51*(1), 78-87. doi:10.1097/SHK.0000000000001127
van Herwaarden, A. E., Jonker, J. W., Wagenaar, E., Brinkhuis, R. F., Schellens, J. H., Beijnen, J. H., & Schinkel, A. H. (2003). The breast cancer resistance protein (Bcrp1/Abcg2) restricts exposure to the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine. *Cancer Res*, *63*(19), 6447-6452. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/14559835
van Waterschoot, R. A., ter Heine, R., Wagenaar, E., van der Kruijssen, C. M., Rooswinkel, R. W., Huitema, A. D., ... Schinkel, A. H. (2010). Effects of cytochrome P450 3A (CYP3A) and the drug transporters P-glycoprotein (MDR1/ABCB1) and MRP2 (ABCC2) on the pharmacokinetics of lopinavir. *Br J Pharmacol*, *160*(5), 1224-1233. doi:10.1111/j.1476-5381.2010.00759.x
Vannucchi, A. M., Kiladjian, J. J., Griesshammer, M., Masszi, T., Durrant, S., Passamonti, F., ... Verstovsek, S. (2015). Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*, *372*(5), 426-435. doi:10.1056/NEJMoa1409002
Venugopal, S., Bar-Natan, M., & Mascarenhas, J. O. (2020). JAKs to STATs: A tantalizing therapeutic target in acute myeloid leukemia. *Blood Rev*, *40*, 100634. doi:10.1016/j.blre.2019.100634
Vermeir, M., Lachau-Durand, S., Mannens, G., Cuyckens, F., van Hoof, B., & Raoof, A. (2009). Absorption, metabolism, and excretion of darunavir, a new protease inhibitor, administered alone and with low-dose ritonavir in healthy subjects. *Drug Metab Dispos*, *37*(4), 809-820. doi:10.1124/dmd.108.024109
Verstovsek, S., Mesa, R. A., Gotlib, J., Levy, R. S., Gupta, V., DiPersio, J. F., ... Kantarjian, H. M. (2012). A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*, *366*(9), 799-807. doi:10.1056/NEJMoa1110557
Villalain, J. (2010). Membranotropic effects of arbidol, a broad anti-viral molecule, on phospholipid model membranes. *J Phys Chem B*, *114*(25), 8544-8554. doi:10.1021/jp102619w
Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., ... Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*, *30*(3), 269-271. doi:10.1038/s41422-020-0282-0
Wang, Y., Cui, R., Li, G., Gao, Q., Yuan, S., Altmeyer, R., & Zou, G. (2016). Teicoplanin inhibits Ebola pseudovirus infection in cell culture. *Antiviral Res*, *125*, 1-7. doi:10.1016/j.antiviral.2015.11.003
Wechsler, M. E., Akuthota, P., Jayne, D., Khoury, P., Klion, A., Langford, C. A., ... Team, E. M. S. (2017). Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med*, *376*(20), 1921-1932. doi:10.1056/NEJMoa1702079

Weiss, J., Bajraktari-Sylejmani, G., & Haefeli, W. E. (2020). Interaction of Hydroxychloroquine with Pharmacokinetically Important Drug Transporters. *Pharmaceutics*, *12*(10)doi:10.3390/pharmaceutics12100919

Weiss, J., Rose, J., Storch, C. H., Ketabi-Kiyanvash, N., Sauer, A., Haefeli, W. E., & Efferth, T. (2007). Modulation of human BCRP (ABCG2) activity by anti-HIV drugs. *J Antimicrob Chemother*, *59*(2), 238-245. doi:10.1093/jac/dkl474

Westphal, J. F. (2000). Macrolide - induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin. *Br J Clin Pharmacol*, *50*(4), 285-295. doi:10.1046/j.1365-2125.2000.00261.x

WHO. (2020). Novel coronavirus (2019-nCoV) situation reports. World Health Organization. http://www.who.int/emergencies/diseases/novel -coronavirus-2019/situation-reports/. (

).

Williams, J. F., Bement, W. J., Sinclair, J. F., & Sinclair, P. R. (1991). Effect of interleukin 6 on phenobarbital induction of cytochrome P-450IIB in cultured rat hepatocytes. *Biochem Biophys Res Commun*, *178*(3), 1049-1055. doi:10.1016/0006-291x(91)90998-m

Wojtal, K. A., Eloranta, J. J., Hruz, P., Gutmann, H., Drewe, J., Staumann, A., ... Vavricka, S. R. (2009). Changes in mRNA expression levels of solute carrier transporters in inflammatory bowel disease patients. *Drug Metab Dispos*, *37*(9), 1871-1877. doi:10.1124/dmd.109.027367

Wong, C. K., Lam, C. W., Wu, A. K., Ip, W. K., Lee, N. L., Chan, I. H., ... Sung, J. J. (2004). Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol*, *136*(1), 95-103. doi:10.1111/j.1365-2249.2004.02415.x

Wu, K. C., & Lin, C. J. (2019). The regulation of drug-metabolizing enzymes and membrane transporters by inflammation: Evidences in inflammatory diseases and age-related disorders. *J Food Drug Anal*, *27*(1), 48-59. doi:10.1016/j.jfda.2018.11.005

Xu, C., Zhu, L., Chan, T., Lu, X., Shen, W., Madigan, M. C., ... Zhou, F. (2016). Chloroquine and Hydroxychloroquine Are Novel Inhibitors of Human Organic Anion Transporting Polypeptide 1A2. *J Pharm Sci*, *105*(2), 884-890. doi:10.1002/jps.24663

Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., ... Wei, H. (2020). Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*, *117*(20), 10970-10975. doi:10.1073/pnas.2005615117

Yamakawa, Y., Hamada, A., Nakashima, R., Yuki, M., Hirayama, C., Kawaguchi, T., & Saito, H. (2011). Association of genetic polymorphisms in the influx transporter SLCO1B3 and the efflux transporter ABCB1 with imatinib pharmacokinetics in patients with chronic myeloid leukemia. *Ther Drug Monit*, *33*(2), 244-250. doi:10.1097/FTD.0b013e31820beb02

Yang, H., Sun, R., Ma, N., Liu, Q., Sun, X., Zi, P., ... Yu, L. (2017). Inhibition of nuclear factor-kappaB signal by pyrrolidine dithiocarbamate alleviates lipopolysaccharide-induced acute lung injury. *Oncotarget*, *8*(29), 47296-47304. doi:10.18632/oncotarget.17624

Yang, J., Hao, C., Yang, D., Shi, D., Song, X., Luan, X., ... Yan, B. (2010). Pregnane X receptor is required for interleukin-6-mediated down-regulation of cytochrome P450 3A4 in human hepatocytes. *Toxicol Lett*, *197*(3), 219-226. doi:10.1016/j.toxlet.2010.06.003

Yang, K. (2020). What Do We Know About Remdesivir Drug Interactions? *Clin Transl Sci*, *13*(5), 842-844. doi:10.1111/cts.12815

Yao, T. T., Qian, J. D., Zhu, W. Y., Wang, Y., & Wang, G. Q. (2020). A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. *J Med Virol*, *92*(6), 556-563. doi:10.1002/jmv.25729

Yoshikawa, T., Hill, T., Li, K., Peters, C. J., & Tseng, C. T. (2009). Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*, *83*(7), 3039-3048. doi:10.1128/JVI.01792-08

Yu, C., Argyropoulos, G., Zhang, Y., Kastin, A. J., Hsuchou, H., & Pan, W. (2008). Neuroinflammation activates Mdr1b efflux transport through NFkappaB: promoter analysis in BBB endothelia. *Cell Physiol Biochem*, *22*(5-6), 745-756. doi:10.1159/000185558

Zastre, J. A., Chan, G. N., Ronaldson, P. T., Ramaswamy, M., Couraud, P. O., Romero, I. A., ... Bendayan, R. (2009). Up-regulation of P-glycoprotein by HIV protease inhibitors in a human brain microvessel endothelial cell line. *J Neurosci Res*, *87*(4), 1023-1036. doi:10.1002/jnr.21898

Zhang, C., Wu, Z., Li, J. W., Zhao, H., & Wang, G. Q. (2020). Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents*, *55*(5), 105954. doi:10.1016/j.ijantimicag.2020.105954

Zhang, L., Gorset, W., Washington, C. B., Blaschke, T. F., Kroetz, D. L., & Giacomini, K. M. (2000). Interactions of HIV protease inhibitors with a human organic cation transporter in a mammalian expression system. *Drug Metab Dispos*, *28*(3), 329-334. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10681378

Zhou, C., Tabb, M. M., Nelson, E. L., Grun, F., Verma, S., Sadatrafiei, A., ... Blumberg, B. (2006). Mutual repression between steroid and xenobiotic receptor and NF-kappaB signaling pathways links xenobiotic metabolism and inflammation. *J Clin Invest*, *116*(8), 2280-2289. doi:10.1172/JCI26283

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., ... Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, *395*(10229), 1054-1062. doi:10.1016/S0140-6736(20)30566-3

Zhou, N., Pan, T., Zhang, J., Li, Q., Zhang, X., Bai, C., ... Zhang, H. (2016). Glycopeptide Antibiotics Potently Inhibit Cathepsin L in the Late Endosome/Lysosome and Block the Entry of Ebola Virus, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). *J Biol Chem*, *291*(17), 9218-9232. doi:10.1074/jbc.M116.716100

Zhu, Z., Lu, Z., Xu, T., Chen, C., Yang, G., Zha, T., ... Xue, Y. (2020). Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. *J Infect*, *81*(1), e21-e23. doi:10.1016/j.jinf.2020.03.060

Zimmerman, J. L., Dellinger, R. P., Straube, R. C., & Levin, J. L. (2000). Phase I trial of the recombinant soluble complement receptor 1 in acute lung injury and acute respiratory distress syndrome. *Crit Care Med*, *28*(9), 3149-3154. doi:10.1097/00003246-200009000-00004

Zordoky, B. N., & El-Kadi, A. O. (2009). Role of NF-kappaB in the regulation of cytochrome P450 enzymes. *Curr Drug Metab*, *10*(2), 164-178. doi:10.2174/138920009787522151