Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Cytochrome P450-mediated drug interactions in COVID-19 patients: Current findings and possible mechanisms

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ABSTRACT

At the end of 2019, the entire world has witnessed the birth of a new member of coronavirus family in Wuhan, China. Ever since, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has swiftly invaded every corner on the planet. By the end of April 2020, almost 3.5 million cases have been reported worldwide, with a death toll of about 250,000 deaths. It is currently well-recognized that patient's immune response plays a pivotal role in the pathogenesis of Coronavirus Disease 2019 (COVID-19). This inflammatory element was evidenced by its elevated mediators that, in severe cases, reach their peak in a cytokine storm. Together with the reported markers of liver injury, such hyperinflammatory state may trigger significant derangements in hepatic cytochrome P450 metabolic machinery, and subsequent modulation of drug clearance that may result in unexpected therapeutic/toxic response. We hypothesize that COVID-19 patients are potentially vulnerable to a significant disease-drug interaction, and therefore, suitable dosing guidelines with therapeutic drug monitoring should be implemented to assure optimal clinical outcomes.

Introduction

Coronavirus Disease 2019 (COVID-19) is an infectious disease that was first reported as pneumonia of ambiguous etiology in a cluster of patients in the Chinese city of Wuhan by the end of December 2019 [1]. The causative organism was identified several days later as a novel coronavirus (2019-nCoV). Later, its name was changed to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as it was found to be genetically related to the coronavirus responsible for the SARS outbreak of 2003 [2]. The infection broke out of China to spread to every continent around the world and was declared as an emerging pandemic by WHO in March 2020 [3]. Full-length genome sequences have revealed that SARS-CoV-2 is 96% identical to a bat coronavirus, thus providing a clue about its original reservoir host [4].

Human-to-human transmission of SARS-CoV-2 is evident and, as a respiratory infectious disease, COVID-19 primarily spreads with close contact through respiratory droplets and secretions. Controlling the disease is based mainly on directing the public towards reducing the transmission [5]. The disease is contagious, but people are reacting differently upon exposure to the virus. The virus may get eliminated by immune system and the infection can pass unnoticed. However, after an asymptomatic incubation period of up to 14 days, infected persons may develop mild flu-like symptoms, including fever, dry cough, fatigue, and shortness of breath [6]. Other reported manifestations include upper respiratory symptoms as sneezing, runny nose and sore throat, in addition to gastrointestinal symptoms as nausea, vomiting and diarrhea [7]. Anosmia or ageusia have been also reported as characteristic signs of infection [8]. While most cases develop mild symptoms, some may progress rapidly to a more severe stage that necessitates admission to an intensive care unit and probably mechanical ventilation [9]. The complications of this critical stage include severe pneumonia, acute respiratory distress syndrome (ARDS), respiratory failure, multiple organ failure, and ultimately death [10].

In the absence of a proven therapy for COVID-19, scientists are currently endeavoring to find an effective drug capable of eradicating this infection. Several agents are currently under extensive laboratory and clinical investigations. Some of these agents are investigational new drugs while the others are repurposed drugs which are already approved for other ailments [11]. When it comes to medications, pharmacokinetics should be strongly considered especially when dealing with such critical illnesses. Drug metabolism is a highly important aspect of its pharmacokinetics that may significantly influence its clearance and, eventually, its efficacy and/or toxicity. Cytochromes P450 (CYPs) are a superfamily of heme-containing monooxygenase enzymes that have been identified in all kingdoms of life [12]. They represent the major enzyme family involved in the oxidative biotransformation of

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most drugs and other lipophilic xenobiotics [13]. In mammals, these enzymes are found primarily in microsomes of the liver, the dominant metabolizing organ, in addition to other extrahepatic tissues [14].

In humans, there are 57 functional members in CYPs families, most of which have specific endogenous functions including the metabolism of arachidonic acid, cholesterol, bile-acids, steroid hormones, vitamin D, and others [15]. The biotransformation of the majority of hepatically cleared drugs and other foreign chemicals involves members belonging to the CYP1, CYP2, and CYP3 families. Pathways involving CYP3A4/5, CYP2C9, CYP2C19 and CYP2D6 are the most common, and responsible for about 80% of the phase I oxidation system reactions [16,17]. Through their profound contribution to xenobiotic biotransformation, CYPs can significantly modulate the overall body exposure to a drug. The metabolic activity of the CYPs may result in decreasing efficacy and/or toxicity of a drug by enhancing the clearance of its active form. For another drug, such metabolic activity may lead to increased efficacy or toxicity by activating its inert prodrug or generating toxic metabolites, respectively. Understanding CYPs activity in relation to the target drug is crucial in predicting its behavior inside the body and the consequences of its exposure [18].

Statement of the hypothesis

We hypothesize a pharmacokinetic disease-drug interaction in which hepatic CYPs metabolizing capacity, and eventually drug response, is altered in COVID-19 patients. Based on the conclusions drawn from the currently rapidly evolving knowledge about COVID-19, our hypothesis is built on the potential modulation of CYPs activity by the inflammatory environment provoked by SARS-CoV-2 infection, as well as the pathologic involvement of the liver which harbors the majority of the drug metabolizing enzymes (DMEs). Patient characteristics are also believed to increase the likelihood of the incidence of such interaction.

Supporting evidence for the hypothesis

Susceptibility of CYPs to the immune response in COVID-19

CYPs alteration in the state of inflammation

Systemic inflammation and immune response represent a substantial element in many acute and chronic diseases which is strongly implicated in altering drug pharmacokinetics through, mainly, modulating the expression and activity of DMEs. As a main contributor to the metabolic biotransformation of most drugs, CYPs are widely involved in such disease-drug interactions [19]. Regulation of CYPs has been linked to inflammation in several disease states such as infectious diseases (including viral infections), cancer, type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease, in addition to age-related disorders such as normal aging, metabolic disorders, and neurodegenerative diseases [20].

Alterations in hepatic CYPs expression and activity are caused by the mediators produced during the inflammation process which are mainly cytokines [21]. Cytokines are a broad category of small cell signaling proteins responsible for keeping homeostasis of the immune system and its components. The immune response is driven by a complex interplay between pro- and anti-inflammatory signals mediated by different cytokines [22]. It has been reported that different CYPs are regulated differently, that is, multiple cytokines may participate in regulating single enzymes, while a subset of enzymes can be regulated by individual cytokines. This fact about specificity of regulation is highly important when considering drug interactions because drug pharmacokinetics will ultimately vary depending on disease type and its released cytokines, as well as the administered drug and its involved metabolizing enzymes [23,24].

Since the 1990s, cytokine-induced changes in hepatic CYPs activity have been described using hepatocyte cultures from different mammals including rats [25], rabbits [26], pigs [27], and humans [28,29]. A strong evidence has been also provided through in vivo studies in mice [30], rats [31], and humans [32]. Some studies have also demonstrated the suppression of extrahepatic CYPs by inflammatory mediators [33–36]. Interleukin 1 (IL-1) [37–39], interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon gamma (IFN-γ) [40–42] are the most prominent proinflammatory cytokines that have exhibited suppression of CYPs expression and activity, in addition to other cytokines such as interleukin 2 (IL-2) [43,44] and interleukin 10 (IL-10) [45].

El-Kadi et al have assessed the effect of serum from humans with an acute upper respiratory tract viral infection on CYPs-mediated theophylline metabolism using hepatocytes from rabbits with turpentine-induced acute inflammatory reaction. Theophylline is metabolized by several CYPs isoforms (including CYP1A1, CYP1A2, and CYP3A) yielding different metabolites. Serum treatment resulted in reducing the formation of all theophylline metabolites as well as the amount of total CYPs, indicating a significant down-regulation of these metabolizing enzymes [46]. In a later study using the same experimental model, the down-regulatory effect was mainly attributed to IL-6, interleukin 1β (IL-1β), and IFN-γ [42]. CYPs down-regulation was also proven to be subsequent to the reduction of their activity. Additionally, the inflammatory mediators in human serum provoked varying degrees of suppression to different CYPs with the CYP3A being more vulnerable than CYP1A to such effect [47].

For decades, IL-6 has been recognized as the major inflammatory element that provokes a significant repressive effect on the expression and activity of different CYPs. Human recombinant interleukin 6 (rhIL-6) has shown concentration-dependent blocking of phenobarbital-mediated induction of CYP2B1/2 mRNA and activity in rat hepatocytes [48]. In Fischer 344 rats, rhIL-6 resulted in reducing different CYPs activities with variable degrees [49]. The mRNA levels of CYP1A1, CYP1A2, and CYP3A3 were markedly suppressed in three human hepatoma cell lines (HepG2, HepG2f, and Hep3f3) because of rhIL-6 treatment [50]. Acute-phase inflammatory reaction provoked by turpentine or purified bacterial lipopolysaccharide (LPS) administration to male rats resulted in significant suppression of hepatic CYP2C11 [51], an effect that was later confirmed to be transcriptional, involving CYP2C11 promoter sequences, using rhIL-6 treatment [52,53].

IL-6-knockout (IL-$6^{-/-}$) mouse was adopted in several studies as a model to assess the extent of IL-6 contribution to the suppression of different CYP isoenzymes during inflammatory response generated by various stimuli. In turpentine-induced inflammation, the inhibitory effect observed in wild-type (WT) mice on CYP1A2, CYP2A5, and CYP3A11 mRNAs was revoked in IL-6-deficient mice [54]. Induction of immune response by Bacillus Calmette-Guérin (BCG) has led to down-regulation of transcriptional expression of both CYP3A11 and CYP2C29, but only CYP3A11 in IL-1α/β-knockout mice and TNF-α-knockout mice, respectively. However, tuberculosis vaccine had non-significant effect on these enzymes in IL-6-knockout mice [55]. In a disease model, *Citrobacter rodentium* infection was used to elicit inflammatory response in IL-$6^{-/-}$ mice, where CYP3A11 mRNA suppression seen in WT mice was abolished [56]. The mentioned studies have shown that the role of IL-6 is usually critical and can't be played by another cytokine or mediator, however, sometimes IL-$6^{-/-}$ mice may react similarly as WT mice, i.e. show down-regulation too, for certain CYPs in certain inflammation models. This can be explained by the functional redundancy existing among the released cytokines which, sometimes, may replace IL-6 [54–56]. Interestingly, sometimes the suppression of CYPs may happen only in IL-$6^{-/-}$ mice, but not WT mice, thus indicating that IL-6 may have an opposing signal with inductive effect [56,57].

Several studies have evaluated the impact of IL-6 triggered by malignancies. In an interesting study by Charles et al, the hepatic levels of both human CYP3A4 as well as its murine orthologue CYP3A11 were simultaneously assessed in a tumor-derived inflammation model using transgenic mice loaded with genetic constructs containing the upstream

regulatory elements of the human CYP3A4 gene linked to the lacZ reporter gene. The tumor generated a systemic inflammatory response with high levels of circulating IL-6 resulting in down-regulation of CYP3A11 orthologue at mRNA, protein, and activity levels as well as CYP3A4 transgene product which was assessed through measuring β-galactosidase enzyme activity [58,59]. Different tumor types have also demonstrated a significant suppressive effect on hepatic CYP3A11 with an accompanying increase in IL-6, and such effect was progressively promoted by tumor growth [60]. The pivotal role of IL-6 in cancer-mediated repression of hepatic CYP3A has been further demonstrated by attenuation of such effect via Anti-IL-6 monoclonal antibody treatment [61], or interleukin-6 receptor blocking [62]. Anti-IL-6 antibody intervention was also tested in IL-6-treated primary human hepatocytes. The inhibitory effect of IL-6 affected CYP1A1, CYP1A2, CYP2B6, and CYP3A4; and it was also capable of overriding CYP1A2 and CYP3A4 induction mediated by omeprazole and rifampicin, respectively. Anti-IL-6 antibody partially abrogated enzyme activity suppression [63].

The basis of cytokine-induced down-regulation of CYPs activity is not fully elucidated; however, the associated decrease in their respective mRNAs strongly suggests a transcriptional mechanism involving a number of transcriptional factors [64,65]. Nuclear factor kappa B (NF-κB), a pivotal regulatory transcription factor in the inflammatory and immune response, has been shown to regulate gene expression of many hepatic CYP enzymes in humans, rats, and mice [66,67]. The aryl hydrocarbon receptor (AhR) is a gene battery that regulates a group of DMEs including CYP1A1, CYP1A2, and CYP1B1. Both NF-κB and AhR have a mutual inhibitory effect thus repressing each other's functions [68,69]. For instance, pyrrolidine dithiocarbamate (PDTC), an inhibitor of NF-κB signal, has demonstrated partial blocking of the inflammatory reduction in CYP1A2 activity [70,71]. The reported inhibitory effect of NF-κB activators on the pregnane X receptor (PXR) and its target genes (most notably of which is CYP3A4) on one hand, and enhanced PXR activity by inhibiting NF-κB on the other hand, indicates how inflammatory stimuli can manipulate hepatic CYPs expression [72–74]. Activation of NF-κB results in repressing glucocorticoid receptor (GR), thus down-regulating constitutive androstane receptor (CAR) expression and its associated genes such as CYP2B, CYP2C, and CYP3A [75]. Other studies have shown that NF-κB can interfere with CYPs expression, such as CYP2C11 and CYP2E1, by binding directly to their respective genes [38,76].

Immunopathological aspects of COVID-19

The immune system plays a crucial role in resolving COVID-19 infection, but it also can go out of control and contribute to its progression. After invading the alveolar cells, the host body starts mounting an immune response during the incubation period and the mild stage to exterminate the virus and hamper disease progression to the severe stage. However, if body defenses are impaired, the suboptimal antiviral immune reaction will allow viral proliferation resulting in lung damage and dissemination to other angiotensin-converting enzyme 2 (ACE2)-expressing cells such as enterocytes [77–79]. The initial containment of the infection by innate immune response generates a strong local inflammatory reaction with a myriad of inflammatory cytokines. Upon failure of this attempt, the highly specific adaptive immune cells are summoned, by systemically disseminated cytokines, to augment the immune response and clear the increasing viral load [80]. If coordinated recruitment of innate and adaptive immunity fails to effectively control the pathogen, more immune cells will get activated, with subsequent release of more cytokines, in a positive feedback loop of pathogenic inflammation. This state of systemic inflammation is called cytokine storm syndrome (CSS) and it has been reported in severe cases as an important cause of ARDS and multiple organ failure [81]. At this point, the immune system is doing more harm than good to the body and becoming a major cause of lung damage and subsequent mortality, thus suppressing such hyperinflammation is strongly recommended together with symptomatic treatment [82,83]. It is noteworthy that the immune system starts its response upon viral exposure and continues to reinforce it till, in most cases, it effectively diminishes viral burden. Premature halting of immune response may delay virus clearance and perpetuate the infection, therefore the use of immunosuppressants should be the last resort and only for severe cases with profound inflammatory lung injury [84].

It has been reported that a wide range of proinflammatory cytokines are elevated in peripheral blood of COVID-19 patients such as interferon gamma (IFN-γ), tumor necrosis factor-α (TNF-α), granulocyte–macrophage colony stimulating factor (GM-CSF), macrophage colony-stimulating factor (MCSF), and interleukins IL-1, IL-6, and IL-12; and many more [7,85]. Interfering with these inflammatory mediators can modulate the amplified immune response that ends up with lung damage. Interleukin-6 is one of the important targets for anti-cytokine therapy as it is believed to be a key player in the process and its elevation is associated with poor prognosis [86–88]. Tocilizumab is a monoclonal antibody against the interleukin-6 receptor (IL-6R) approved for the treatment of rheumatoid arthritis. It has been reported that a single dose of tocilizumab significantly improved the clinical outcomes in COVID-19 patients [89,90]. Sarilumab is another IL-6R antagonist which is also approved for treating rheumatoid arthritis and is currently assessed for its efficacy against COVID-19 [11].

Impact of COVID-19 on the hepatic metabolizing efficiency

Different organs, such as lung, kidney, and intestine, contribute to drug biotransformation in the body; however, the liver is generally regarded as the major metabolizing organ responsible for drug clearance [91]. Through several enzyme systems, the most prominent of which is CYPs, the liver can drive numerous metabolic reactions. Acute as well as chronic insults to the liver will eventually hamper its metabolic machinery resulting ultimately in inefficient drug clearance [92,93]. Regardless of the cause, it is believed that the severity of liver disease is correlated to the extent of metabolism alteration [94,95].

Lungs represent the hot spot for the pathogenesis of COVID-19, however, potential involvement of other organs, such as the liver, has been also reported [96,97]. The hepatic involvement can be tied to the incidence of other extrapulmonary, or more specifically gastrointestinal, manifestations [98,99], and it has been reported in COVID-19 patient with or without underlying liver disease [100]. Reported findings of hepatic dysfunction in COVID-19 cases include elevated aminotransferases [101] and bilirubin [102], hypoalbuminemia [6], in addition to microvesicular steatosis with mild lobular activity [77]. It is worth mentioning that hepatic impairment has been also associated with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) [103], which is highly homologous to SARS-CoV-2 [104], as well as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [105].

The exact mechanism behind liver function deterioration is not fully understood, however, it has been proposed that SARS-CoV-2 causes direct liver injury. Viral hepato-tropism can be attributed to the relatively high expression of its cellular entry gate, i.e. ACE2, in cholangiocytes, rather than hepatocytes, rendering them vulnerable to viral attack [106,107]. This assumption is supported by the increase in circulating levels of serum gamma-glutamyl transferase (GGT) in COVID-19 patients [108]. Hepatic abnormalities can be also a secondary effect induced after initiating disease management by consumption of hepatotoxic antipyretic agents (e.g. acetaminophen), antiviral medications (e.g. oseltamivir and lopinavir), antibiotics, and steroids [109,110]. Despite the absence of viral antigens in the liver, the overwhelming systemic inflammatory reaction elicited by SARS-CoV-2 can be also a major cause of multiple organ dysfunction including liver damage as seen in other respiratory viral infections [111–113].

Drug outcome alteration in a vulnerable patient population

CYPs have been implicated in mediating clinically relevant drug interactions in several disease states [114]. Such metabolic interactions have been regarded as a major reason behind revising and updating safety profiles of pharmaceutical products [115]. Disease-drug interactions are commonly observed in inflammatory conditions with drugs whose clearance is predominantly CYPs-mediated [116]. Examples of such conditions include rheumatoid arthritis [117], hepatitis [118], Crohn's disease [119], acquired immunodeficiency syndrome (AIDS) [120], influenza [121], congestive heart failure [122], and cancer [123].

As a central inflammatory regulator, agents interfering with IL-6 actions have led to regaining the inhibited CYPs activity, thus normalizing drug disposition pattern. Blocking IL-6 receptor by the monoclonal antibodies; tocilizumab [124] and sarilumab [125] in rheumatoid arthritis patients co-administering simvastatin has reversed CYP3A4 activity suppression as demonstrated by a clinically significant decrease in simvastatin exposure. Halting IL-6 signaling by direct binding with the monoclonal antibody sirukumab has also proven effective in rheumatoid arthritis patients who received a CYPs probe cocktail consisting of midazolam (CYP3A), omeprazole (CYP2C19), and warfarin (CYP2C9). Area under the plasma concentration–time curve (AUC) for probe substrates was reduced after sirukumab administration indicating that the activity of their respective metabolizing enzymes was recovered [126]. As an attempt to predict the risk of such interactions, physiologically based pharmacokinetic (PBPK) models were developed to assess the impact of anti-IL-6 agents on the metabolism of concomitant medications [127–129].

The immune response, with IL-6 in the core of its network of mediators, is a hallmark of COVID-19 pathogenesis. Based on the aforementioned examples, it is strongly postulated that CYPs metabolic activity will be inevitably altered, mostly down-regulated, during the course of SARS-CoV-2 infection in a similar manner, resulting in a clearance-related pharmacokinetic interaction with the administered drugs. Additionally, liver involvement in COVID-19 may further complicate the picture. In May 2020, the investigational antiviral agent, remdesivir, has received U.S. food and drug administration (FDA) emergency use authorization for the treatment of COVID-19. According to its manufacturer, remdesivir undergoes extensive metabolism by CYPs especially CYP3A4 [130]. Moreover, other potential candidates for treating COVID- 19 such as chloroquine [131] and colchicine [132] are also hepatically metabolized, so understanding the nature of such interaction is highly essential as it can influence the therapeutic/toxic response of patients to the agents intended for managing the disease [133,134]. Full attention should be paid when anti-cytokine therapy comes into play. In this case, partial or complete regain of normal metabolic status can be achieved as a result of the immunomodulatory effect.

In case of co-administration of multiple drugs, the risk of drug interactions increases, however, a more complex disease-drug-drug interaction is expected in COVID-19. SARS-CoV-2 infection has resulted in high rates of hospitalization and intensive care unit (ICU) admission [135,136]. This can be regarded as a major clinical concern especially when considering that critically ill patients are more predisposed to drug interactions, and that CYPs are involved in the metabolism of commonly prescribed drugs in the ICUs [137]. Moreover, demographic analysis of COVID-19 patients has revealed that older people with comorbidities are the most affected group [98,138] who also represent the potential candidates for advancing to severe stages and inevitable ICU admission [85]. Medical comorbidities in elderly patients warrant concomitant drug therapies, thus rendering them the most vulnerable group for both drug-drug and disease-drug interactions [139,140]. Therefore, the utmost level of caution is required to deliver the optimal dose for these patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382. https://doi.org/10.1056/NEJMoa2002032.
[2] Wu Y, Ho W, Huang Y, et al. SARS-CoV-2 is an appropriate name for the new coronavirus. Lancet (London, England) 2020;395(10228):949–50. https://doi.org/10.1016/S0140-6736(20)30557-2.
[3] Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed 2020;91(1):157–60. https://doi.org/10.23750/abm.v91i1.9397.
[4] Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579(7798):270–3. https://doi.org/10.1038/s41586-020-2012-7.
[5] Li Q, Guan X, Wu P, et al. Early transmission dynamics in wuhan, china, of novel coronavirus–infected pneumonia. N Engl J Med 2020;382. https://doi.org/10.1056/NEJMoa2001316.
[6] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395(10223):507–13. https://doi.org/10.1016/S0140-6736(20)30211-7.
[7] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.
[8] Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020. https://doi.org/10.1007/s00405-020-05965-1.
[9] Namendys-Silva SA. Respiratory support for patients with COVID-19 infection. Lancet Respir Med. 2020;8(4):e18https://doi.org/10.1016/S2213-2600(20)30110-7.
[10] Hui DS, Madani TA, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis 2020;91:264–6. https://doi.org/10.1016/j.ijid.2020.01.009.
[11] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. JAMA 2020. https://doi.org/10.1001/jama.2020.6019.
[12] Lamb DC, Lei L, Warrilow AG, et al. The first virally encoded cytochrome p450. J Virol 2009;83(16):8266–9. https://doi.org/10.1128/JVI.00289-09.
[13] Guengerich FP. Cytochrome p450 and chemical toxicology. Chem Res Toxicol 2008;21(1):70–83. https://doi.org/10.1021/tx700079z.
[14] Ding X, Kaminsky LS. Human extrahepatic cytochromes P450: function in xenobiotic metabolism and tissue-selective chemical toxicity in the respiratory and gastrointestinal tracts. Annu Rev Pharmacol Toxicol 2003;43:149–73. https://doi.org/10.1146/annurev.pharmtox.43.100901.140251.
[15] Nebert DW, Russell DW. Clinical importance of the cytochromes P450. Lancet 2002;360(9340):1155–62. https://doi.org/10.1016/s0140-6736(02)11203-7.
[16] Zanger UM, Turpeinen M, Klein K, Schwab M. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. Anal Bioanal Chem 2008;392(6):1093–108. https://doi.org/10.1007/s00216-008-2291-6.
[17] Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther 2013;138(1):103–41. https://doi.org/10.1016/j.pharmthera.2012.12.007.
[18] McDonnell AM, Dang CH. Basic review of the cytochrome p450 system. J Adv Pract Oncol. 2013;4(4):263–8. https://doi.org/10.6004/jadpro.2013.4.4.7.
[19] Harvey RD, Morgan ET. Cancer, inflammation, and therapy: effects on cytochrome p450-mediated drug metabolism and implications for novel immunotherapeutic agents. Clin Pharmacol Ther. 2014;96(4):449–57. https://doi.org/10.1038/clpt.2014.143.
[20] Wu KC, Lin CJ. The regulation of drug-metabolizing enzymes and membrane transporters by inflammation: Evidences in inflammatory diseases and age-related

disorders. J Food Drug Anal 2019;27(1):48–59. https://doi.org/10.1016/j.jfda.2018.11.005.
[21] Morgan ET. Regulation of cytochromes P450 during inflammation and infection. Drug Metab Rev 1997;29(4):1129–88. https://doi.org/10.3109/03602539709002246.
[22] Zhang J-M, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin 2007;45(2):27–37. https://doi.org/10.1097/AIA.0b013e318034194e.
[23] Muntane-Relat J, Ourlin JC, Domergue J, Maurel P. Differential effects of cytokines on the inducible expression of CYP1A1, CYP1A2, and CYP3A4 in human hepatocytes in primary culture. Hepatology 1995;22(4 Pt 1):1143–53.
[24] Aitken AE, Morgan ET. Gene-specific effects of inflammatory cytokines on cytochrome P450 2C, 2B6 and 3A4 mRNA levels in human hepatocytes. Drug Metab Dispos 2007;35(9):1687–93. https://doi.org/10.1124/dmd.107.015511.
[25] Tapner M, Liddle C, Goodwin B, George J, Farrell GC. Interferon gamma down-regulates cytochrome P450 3A genes in primary cultures of well-differentiated rat hepatocytes. Hepatology 1996;24(2):367–73. https://doi.org/10.1002/hep.510240213.
[26] Calleja C, Eeckhoutte C, Dacasto M, et al. 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 1998;56(10):1279–85. https://doi.org/10.1016/s0006-2952(98)00178-6.
[27] Monshouwer M, Witkamp RF, Nujmeijer SM, Van Amsterdam JG, Van Miert AS. 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 1996;137(2):237–44. https://doi.org/10.1006/taap.1996.0077.
[28] Abdel-Razzak Z, Loyer P, Fautrel A, et al. Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human hepatocytes in primary culture. Mol Pharmacol 1993;44(4):707–15.
[29] Rubin K, Janefeldt A, Andersson L, Berke Z, Grime K, Andersson TB. HepaRG cells as human-relevant in vitro model to study the effects of inflammatory stimuli on cytochrome P450 isoenzymes. Drug Metab Dispos 2015;43(1):119–25. https://doi.org/10.1124/dmd.114.059246.
[30] Pan J, Xiang Q, Ball S. 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 2000;28(6):709–13.
[31] Morgan ET. Down-regulation of multiple cytochrome P450 gene products by inflammatory mediators in vivo. Independence from the hypothalamo-pituitary axis. Biochem Pharmacol 1993;45(2):415–9. https://doi.org/10.1016/0006-2952(93)90078-b.
[32] Frye RF, Schneider VM, Frye CS, Feldman AM. 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. 2002;8(5):315–9. https://doi.org/10.1054/jcaf.2002.127773.
[33] Nicholson TE, Renton KW. Modulation of cytochrome P450 by inflammation in astrocytes. Brain Res 1999;827(1–2):12–8. https://doi.org/10.1016/s0006-8993(99)01261-5.
[34] Bertilsson PM, Olsson P, Magnusson KE. Cytokines influence mRNA expression of cytochrome P450 3A4 and MDRI in intestinal cells. J Pharm Sci 2001;90(5):638–46. https://doi.org/10.1002/1520-6017(200105)90:5<638::aid-jps1020>3.0.co;2-l.
[35] Nicholson TE, Renton KW. Role of cytokines in the lipopolysaccharide-evoked depression of cytochrome P450 in the brain and liver. Biochem Pharmacol 2001;62(12):1709–17. https://doi.org/10.1016/s0006-2952(01)00859-0.
[36] Liptrott NJ, Penny M, Bray PG, et al. The impact of cytokines on the expression of drug transporters, cytochrome P450 enzymes and chemokine receptors in human PBMC. Br J Pharmacol. 2009;156(3):497–508. https://doi.org/10.1111/j.1476-5381.2008.00050.x.
[37] Parmentier JH, Kremers P, Ferrari L, Batt AM, Gielen JE, Siest G. Repression of cytochrome P450 by cytokines: IL-1 beta counteracts clofibric acid induction of CYP4A in cultured fetal rat hepatocytes. Cell Biol Toxicol 1993;9(3):307–13. https://doi.org/10.1007/bf00755608.
[38] Iber H, Chen Q, Cheng PY, Morgan ET. Suppression of CYP2C11 gene transcription by interleukin-1 mediated by NF-kappaB binding at the transcription start site. Arch Biochem Biophys 2000;377(1):187–94. https://doi.org/10.1006/abbi.2000.1772.
[39] Dickmann LJ, Patel SK, Wienkers LC, Slatter JG. 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 2012;13(7):930–7. https://doi.org/10.2174/138920012802138642.
[40] Nadin L, Butler AM, Farrell GC, Murray M. Pretranslational down-regulation of cytochromes P450 2C11 and 3A2 in male rat liver by tumor necrosis factor alpha. Gastroenterology 1995;109(1):198–205. https://doi.org/10.1016/0016-5085(95)90285-6.
[41] Donato MT, Guillen MI, Jover R, Castell JV, Gomez-Lechon MJ. Nitric oxide-mediated inhibition of cytochrome P450 by interferon-gamma in human hepatocytes. J Pharmacol Exp Ther 1997;281(1):484–90.
[42] Bleau AM, Levitchi MC, Maurice H, du Souich P. 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 2000;130(8):1777–84. https://doi.org/10.1038/sj.bjp.0703486.
[43] Tinel M, Robin MA, Doostzadeh J, et al. The interleukin-2 receptor down-regulates the expression of cytochrome P450 in cultured rat hepatocytes. Gastroenterology 1995;109(5):1589–99. https://doi.org/10.1016/0016-5085(95)90648-7.
[44] Elkahwaji J, Robin MA, Berson A, et al. Decrease in hepatic cytochrome P450 after interleukin-2 immunotherapy. Biochem Pharmacol 1999;57(8):951–4. https://doi.org/10.1016/s0006-2952(98)00372-4.
[45] Gorski JC, Hall SD, Becker P, Affrime MB, Cutler DL, Haehner-Daniels B. In vivo effects of interleukin-10 on human cytochrome P450 activity. Clin Pharmacol Ther 2000;67(1):32–43. https://doi.org/10.1067/mcp.2000.103860.
[46] El-Kadi AO, Maurice H, Ong H, du Souich P. Down-regulation of the hepatic cytochrome P450 by an acute inflammatory reaction: implication of mediators in human and animal serum and in the liver. Br J Pharmacol 1997;121(6):1164–70. https://doi.org/10.1038/sj.bjp.0701232.
[47] Bleau AM, Fradette C, El-Kadi AO, Cote MC, du Souich P. Cytochrome P450 down-regulation by serum from humans with a viral infection and from rabbits with an inflammatory reaction. Drug Metab Dispos 2001;29(7):1007–12.
[48] Williams JF, Bement WJ, Sinclair JF, Sinclair PR. Effect of interleukin 6 on phenobarbital induction of cytochrome P-450IIB in cultured rat hepatocytes. Biochem Biophys Res Commun 1991;178(3):1049–55. https://doi.org/10.1016/0006-291x(91)90998-m.
[49] Chen YL, Florentin I, Batt AM, Ferrari L, Giroud JP, Chauvelot-Moachon L. Effects of interleukin-6 on cytochrome P450-dependent mixed-function oxidases in the rat. Biochem Pharmacol 1992;44(1):137–48. https://doi.org/10.1016/0006-2952(92)90047-M.
[50] Fukuda Y, Ishida N, Noguchi T, Kappas A, Sassa S. Interleukin-6 down regulates the expression of transcripts encoding cytochrome P450 IA1, IA2 and IIIA3 in human hepatoma cells. Biochem Biophys Res Commun 1992;184(2):960–5. https://doi.org/10.1016/0006-291X(92)90684-D.
[51] Morgan ET. Suppression of constitutive cytochrome P-450 gene expression in livers of rats undergoing an acute phase response to endotoxin. Mol Pharmacol 1989;36(5):699–707.
[52] Morgan ET, Thomas KB, Swanson R, Vales T, Hwang J, Wright K. Selective suppression of cytochrome P-450 gene expression by interleukins 1 and 6 in rat liver. BBA 1994;1219(2):475–83. https://doi.org/10.1016/0167-4781(94)90074-4.
[53] Chen JQ, Strom A, Gustafsson JA, Morgan ET. Suppression of the constitutive expression of cytochrome P-450 2C11 by cytokines and interferons in primary cultures of rat hepatocytes: comparison with induction of acute-phase genes and demonstration that CYP2C11 promoter sequences are involved in the suppressive response to interleukins 1 and 6. Mol Pharmacol 1995;47(5):940–7.
[54] Siewert E, Bort R, Kluge R, Heinrich PC, Castell J, Jover R. Hepatic cytochrome P450 down-regulation during aseptic inflammation in the mouse is interleukin 6 dependent. Hepatology 2000;32(1):49–55. https://doi.org/10.1053/jhep.2000.8532.
[55] Ashino T, Oguro T, Shioda S, et al. Involvement of interleukin-6 and tumor necrosis factor alpha in CYP3A11 and 2C29 down-regulation by Bacillus Calmette-Guerin and lipopolysaccharide in mouse liver. Drug Metab Dispos 2004;32(7):707–14. https://doi.org/10.1124/dmd.32.7.707.
[56] Nyagode BA, Lee CM, Morgan ET. Modulation of hepatic cytochrome P450s by Citrobacter rodentium infection in interleukin-6- and interferon-{gamma}-null mice. J Pharmacol Exp Ther 2010;335(2):480–8. https://doi.org/10.1124/jpet.110.171488.
[57] Warren GW, van Ess PJ, Watson AM, Mattson MP, Blouin RA. Cytochrome P450 and antioxidant activity in interleukin-6 knockout mice after induction of the acute-phase response. J Interferon Cytokine Res 2001;21(10):821–6. https://doi.org/10.1089/107999001753238060.
[58] Robertson GR, Field J, Goodwin B, et al. Transgenic mouse models of human CYP3A4 gene regulation. Mol Pharmacol 2003;64(1):42–50. https://doi.org/10.1124/mol.64.1.42.
[59] Charles KA, Rivory LP, Brown SL, Liddle C, Clarke SJ, Robertson GR. Transcriptional repression of hepatic cytochrome P450 3A4 gene in the presence of cancer. Clin Cancer Res 2006;12(24):7492–7. https://doi.org/10.1158/1078-0432.Ccr-06-0023.
[60] Sharma R, Kacevska M, London R, Clarke SJ, Liddle C, Robertson G. Downregulation of drug transport and metabolism in mice bearing extra-hepatic malignancies. Br J Cancer 2008;98(1):91–7. https://doi.org/10.1038/sj.bjc.6604101.
[61] Kacevska M, Mahns A, Sharma R, Clarke SJ, Robertson GR, Liddle C. Extra-hepatic cancer represses hepatic drug metabolism via interleukin (IL)-6 signalling. Pharm Res 2013;30(9):2270–8. https://doi.org/10.1007/s11095-013-1042-3.
[62] Mimura H, Kobayashi K, Xu L, et al. 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 2015;30(1):105–10. https://doi.org/10.1016/j.dmpk.2014.09.004.
[63] Dickmann LJ, Patel SK, Rock DA, Wienkers LC, Slatter JG. Effects of interleukin-6 (IL-6) and an anti-IL-6 monoclonal antibody on drug-metabolizing enzymes in human hepatocyte culture. Drug Metab Dispos 2011;39(8):1415–22. https://doi.org/10.1124/dmd.111.038679.
[64] Ruminy P, Gangneux C, Claeyssens S, Scotte M, Daveau M, Salier JP. Gene transcription in hepatocytes during the acute phase of a systemic inflammation: from transcription factors to target genes. Inflamm Res 2001;50(8):383–90. https://doi.org/10.1007/pl00000260.
[65] Morgan ET. Regulation of cytochrome p450 by inflammatory mediators: why and how? Drug Metab Dispos 2001;29(3):207–12.
[66] Hayden MS, West AP, Ghosh S. NF-kappaB and the immune response. Oncogene 2006;25(51):6758–80. https://doi.org/10.1038/sj.onc.1209943.
[67] Zordoky BN, El-Kadi AO. Role of NF-kappaB in the regulation of cytochrome P450 enzymes. Curr Drug Metab 2009;10(2):164–78. https://doi.org/10.2174/138920009787522151.
[68] Ke S, Rabson AB, Germino JF, Gallo MA, Tian Y. Mechanism of suppression of cytochrome P-450 1A1 expression by tumor necrosis factor-alpha and

lipopolysaccharide. J Biol Chem 2001;276(43):39638–44. https://doi.org/10.1074/jbc.M106286200.
[69] Tian Y, Rabson AB, Gallo MA. Ah receptor and NF-kappaB interactions: mechanisms and physiological implications. Chem Biol Interact 2002;141(1–2):97–115. https://doi.org/10.1016/s0009-2797(02)00068-6.
[70] Kourylko O, Fradette C, Arcand M, du Souich P. Modulation of CYP1A2 and CYP3A6 catalytic activities by serum from rabbits with a turpentine-induced inflammatory reaction and interleukin 6. Drug Metab Dispos 2006;34(1):27–35. https://doi.org/10.1124/dmd.105.006528.
[71] Yang H, Sun R, Ma N, et al. Inhibition of nuclear factor-kappaB signal by pyrrolidine dithiocarbamate alleviates lipopolysaccharide-induced acute lung injury. Oncotarget 2017;8(29):47296–304. https://doi.org/10.18632/oncotarget.17624.
[72] Zhou C, Tabb MM, Nelson EL, et al. Mutual repression between steroid and xenobiotic receptor and NF-kappaB signaling pathways links xenobiotic metabolism and inflammation. J Clin Invest 2006;116(8):2280–9. https://doi.org/10.1172/jci26283.
[73] Gu X, Ke S, Liu D, et al. 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 2006;281(26):17882–9. https://doi.org/10.1074/jbc.M601302200.
[74] Yang J, Hao C, Yang D, et al. Pregnane X receptor is required for interleukin-6-mediated down-regulation of cytochrome P450 3A4 in human hepatocytes. Toxicol Lett 2010;197(3):219–26. https://doi.org/10.1016/j.toxlet.2010.06.003.
[75] Assenat E, Gerbal-chaloin S, Maurel P, Vilarem MJ, Pascussi JM. Is nuclear factor kappa-B the missing link between inflammation, cancer and alteration in hepatic drug metabolism in patients with cancer? Eur J Cancer 2006;42(6):785–92. https://doi.org/10.1016/j.ejca.2006.01.005.
[76] Tindberg N, Bengtsson I, Hu Y. A novel lipopolysaccharide-modulated Jun binding repressor in intron 2 of CYP2E1. J Neurochem 2004;89(6):1336–46. https://doi.org/10.1111/j.1471-4159.2004.02449.x.
[77] Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8(4):420–2. https://doi.org/10.1016/s2213-2600(20)30076-x.
[78] Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395(10224):565–74. https://doi.org/10.1016/s0140-6736(20)30251-8.
[79] Zhang H, Kang Z, Gong H, et al. The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. 2020.01.30.927806 bioRxiv 2020;2020(01). https://doi.org/10.1101/2020.01.30.927806.
[80] Shi Y, Wang Y, Shao C, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020;27(5):1451–4. https://doi.org/10.1038/s41418-020-0530-3.
[81] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395(10229):1033–4. https://doi.org/10.1016/s0140-6736(20)30628-0.
[82] Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV- 2): anti-inflammatory strategies. J Biol Regul Homeost Agents 2020;34(2). 10.23812/conti-e.
[83] Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020;20(4):400–2. https://doi.org/10.1016/s1473-3099(20)30132-8.
[84] Ritchie AI, Singanayagam A. Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? Lancet 2020;395(10230):1111. https://doi.org/10.1016/s0140-6736(20)30691-7.
[85] Guo YR, Cao QD, Hong ZS, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020;7(1):11. https://doi.org/10.1186/s40779-020-00240-0.
[86] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395(10229):1054–62. https://doi.org/10.1016/s0140-6736(20)30566-3.
[87] Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020::105954https://doi.org/10.1016/j.ijantimicag.2020.105954.
[88] Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science 2020;368(6490):473–4. https://doi.org/10.1126/science.abb8925.
[89] Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences. 2020:202005615. 10.1073/pnas.2005615117.
[90] Guo C, Li B, Ma H, et al. Tocilizumab treatment in severe COVID-19 patients attenuates the inflammatory storm incited by monocyte centric immune interactions revealed by single-cell analysis. bioRxiv. 2020:2020.04.08.029769. 10.1101/2020.04.08.029769.
[91] De Kanter R, De Jager MH, Draaisma AL, et al. Drug-metabolizing activity of human and rat liver, lung, kidney and intestine slices. Xenobiotica 2002;32(5):349–62. https://doi.org/10.1080/00498250110112006.
[92] Elbekai RH, Korashy HM, El-Kadi AO. The effect of liver cirrhosis on the regulation and expression of drug metabolizing enzymes. Curr Drug Metab 2004;5(2):157–67. https://doi.org/10.2174/1389200043489054.
[93] Villeneuve JP, Pichette V. Cytochrome P450 and liver diseases. Curr Drug Metab 2004;5(3):273–82. https://doi.org/10.2174/1389200043335531.
[94] Adedoyin A, Arns PA, Richards WO, Wilkinson GR, Branch RA. Selective effect of liver disease on the activities of specific metabolizing enzymes: investigation of cytochromes P450 2C19 and 2D6. Clin Pharmacol Ther 1998;64(1):8–17. https://doi.org/10.1016/s0009-9236(98)90017-0.
[95] Frye RF, Zgheib NK, Matzke GR, et al. Liver disease selectively modulates cytochrome P450–mediated metabolism. Clin Pharmacol Ther 2006;80(3):235–45. https://doi.org/10.1016/j.clpt.2006.05.006.
[96] Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol. 2020. https://doi.org/10.1016/s2468-1253(20)30084-4.
[97] Rismanbaf A, Zarei S. Liver and Kidney Injuries in COVID-19 and Their Effects on Drug Therapy; a Letter to Editor. Archives of academic emergency medicine. 2020;8(1):e17-e.
[98] Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2019;2020. https://doi.org/10.1001/jama.2020.1585.
[99] Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929–36. https://doi.org/10.1056/NEJMoa2001191.
[100] Mantovani A, Beatrice G, Dalbeni A. Coronavirus disease (COVID-19) and prevalence of chronic liver disease: A meta-analysis. Liver International. 2019;2020. https://doi.org/10.1111/liv.14465.
[101] Omrani-Nava V, Maleki I, Ahmadi A, et al. Evaluation of Hepatic Enzymes Changes and Association with Prognosis in COVID-19 Patients. Hepat Mon. 2020;20(4):e103179https://doi.org/10.5812/hepatmon.103179.
[102] Paliogiannis P, Zinellu A. Bilirubin levels in patients with mild and severe Covid-19: a pooled analysis. Liver Int 2020. https://doi.org/10.1111/liv.14477.
[103] Chau TN, Lee KC, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. Hepatology 2004;39(2):302–10. https://doi.org/10.1002/hep.20111.
[104] Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. Gastroenterology 2020. https://doi.org/10.1053/j.gastro.2020.02.054.
[105] Alsaad KO, Hajeer AH, Al Balwi M, et al. Histopathology of Middle East respiratory syndrome coronovirus (MERS-CoV) infection - clinicopathological and ultrastructural study. Histopathology 2018;72(3):516–24. https://doi.org/10.1111/his.13379.
[106] Guan G, Gao L, Wang J, et al. Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia. Zhonghua gan zang bing za zhi = Zhonghua ganzangbing zazhi. Chin J Hepatol 2020;28:E002. https://doi.org/10.3760/cma.j.issn.1007-3418.2020.02.002.
[107] Chai X, Hu L, Zhang Y, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. bioRxiv. 2020:2020.02.03.931766. 10.1101/2020.02.03.931766.
[108] Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 2020;5(5):428–30. https://doi.org/10.1016/s2468-1253(20)30057-1.
[109] Feng G, Zheng KI, Yan Q-Q, et al. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. J Clin Transl Hepatol 2020;8(1). pp. 18–24. 10.14218/JCTH.2020.00018.
[110] Sun J, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. Liver Int 2020. https://doi.org/10.1111/liv.14470.
[111] Adams DH, Hubscher SG. Systemic viral infections and collateral damage in the liver. Am J Pathol 2006;168(4):1057–9. https://doi.org/10.2353/ajpath.2006.051296.
[112] Polakos NK, Cornejo JC, Murray DA, et al. Kupffer cell-dependent hepatitis occurs during influenza infection. pp. 1169–78; quiz 404–5 Am J Pathol 2006;168(4). https://doi.org/10.2353/ajpath.2006.050875.
[113] Papic N, Pangercic A, Vargovic M, Barsic B, Vince A, Kuzman I. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. Influenza Other Respi Viruses 2012;6(3):e2–5. https://doi.org/10.1111/j.1750-2659.2011.00287.x.
[114] Storelli F, Samer C, Reny JL, Desmeules J, Daali Y. Complex drug-drug-gene-disease interactions involving cytochromes P450: systematic review of published case reports and clinical perspectives. Clin Pharmacokinet 2018;57(10):1267–93. https://doi.org/10.1007/s40262-018-0650-9.
[115] Yoshida N, Yamada A, Mimura Y, Kawakami J, Adachi I. Trends in new drug interactions for pharmaceutical products in Japan. Pharmacoepidemiol Drug Saf 2006;15(6):421–7. https://doi.org/10.1002/pds.1197.
[116] Leung JG, Nelson S, Takala CR, Goren JL. Infection and inflammation leading to clozapine toxicity and intensive care: a case series. Ann Pharmacother 2014;48(6):801–5. https://doi.org/10.1177/1060028014526701.
[117] Mayo PR, Skeith K, Russell AS, Jamali F. Decreased dromotropic response to verapamil despite pronounced increased drug concentration in rheumatoid arthritis. Br J Clin Pharmacol 2000;50(6):605–13. https://doi.org/10.1046/j.1365-2125.2000.00314.x.
[118] Morcos PN, Moreira SA, Brennan BJ, Blotner S, Shulman NS, Smith PF. Influence of chronic hepatitis C infection on cytochrome P450 3A4 activity using midazolam as an in vivo probe substrate. Eur J Clin Pharmacol 2013;69(10):1777–84. https://doi.org/10.1007/s00228-013-1525-5.
[119] Sanaee F, Clements JD, Waugh AW, Fedorak RN, Lewanczuk R, Jamali F. Drug-disease interaction: Crohn's disease elevates verapamil plasma concentrations but reduces response to the drug proportional to disease activity. Br J Clin Pharmacol 2011;72(5):787–97. https://doi.org/10.1111/j.1365-2125.2011.04019.x.
[120] Jones AE, Brown KC, Werner RE, et al. Variability in drug metabolizing enzyme activity in HIV-infected patients. Eur J Clin Pharmacol 2010;66(5):475–85. https://doi.org/10.1007/s00228-009-0777-6.
[121] Kraemer MJ, Furukawa CT, Koup JR, Shapiro GG, Pierson WE, Bierman CW. Altered theophylline clearance during an influenza B outbreak. Pediatrics

1982;69(4):476–80.
[122] Glassman AH, Johnson LL, Giardina EG, et al. The use of imipramine in depressed patients with congestive heart failure. JAMA 1983;250(15):1997–2001.
[123] Coutant DE, Kulanthaivel P, Turner PK, et al. Understanding disease-drug interactions in cancer patients: implications for dosing within the therapeutic window. Clin Pharmacol Ther 2015;98(1):76–86. https://doi.org/10.1002/cpt.128.
[124] Schmitt C, Kuhn B, Zhang X, Kivitz AJ, Grange S. Disease-drug-drug interaction involving tocilizumab and simvastatin in patients with rheumatoid arthritis. Clin Pharmacol Ther 2011;89(5):735–40. https://doi.org/10.1038/clpt.2011.35.
[125] Lee EB, Daskalakis N, Xu C, et al. Disease-Drug Interaction of Sarilumab and Simvastatin in Patients with Rheumatoid Arthritis. Clin Pharmacokinet 2017;56(6):607–15. https://doi.org/10.1007/s40262-016-0462-8.
[126] Zhuang Y, de Vries D, Xu Z-h, et al. Evaluation of disease-mediated therapeutic protein-drug interactions between an anti-Interleukin-6 monoclonal antibody (Sirukumab) and cytochrome P450 activities in a phase I study in patients with rheumatoid arthritis using a cocktail approach. J Clin Pharmacol 2015;55.. https://doi.org/10.1002/jcph.561.
[127] Machavaram KK, Almond LM, Rostami-Hodjegan A, et al. A physiologically based pharmacokinetic modeling approach to predict disease-drug interactions: suppression of CYP3A by IL-6. Clin Pharmacol Ther 2013;94(2):260–8. https://doi.org/10.1038/clpt.2013.79.
[128] Jiang X, Zhuang Y, Xu Z, Wang W, Zhou H. Development of a physiologically based pharmacokinetic model to predict disease-mediated therapeutic protein-drug interactions: modulation of multiple cytochrome P450 enzymes by interleukin-6. AAPS J 2016;18(3):767–76. https://doi.org/10.1208/s12248-016-9890-5.
[129] Xu Y, Hijazi Y, Wolf A, Wu B, Sun YN, Zhu M. Physiologically based pharmacokinetic model to assess the influence of blinatumomab-mediated cytokine elevations on cytochrome P450 enzyme activity. CPT Pharmacometrics Syst Pharmacol. 2015;4(9):507–15. https://doi.org/10.1002/psp4.12003.
[130] Summary on compassionate use of Remdesivir Gilead [Internet]. European Medicines Agency. 2020 [cited May 5, 2020]. Available from: https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf.
[131] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14(1):72–3. https://doi.org/10.5582/bst.2020.01047.
[132] Deftereos SG, Siasos G, Giannopoulos G, et al. The Greek study in the effects of colchicine in COvid-19 complications prevention (GRECCO-19 study): Rationale and study design. Hellenic J Cardiol 2020. https://doi.org/10.1016/j.hjc.2020.03.002.
[133] Projean D, Baune B, Farinotti R, et al. In vitro metabolism of chloroquine: identification of CYP2C8, CYP3A4, and CYP2D6 as the main isoforms catalyzing N-desethylchloroquine formation. Drug Metab Dispos 2003;31(6):748–54. https://doi.org/10.1124/dmd.31.6.748.
[134] Leung YY, Yao Hui LL, Kraus VB. Colchicine-Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum 2015;45(3):341–50. https://doi.org/10.1016/j.semarthrit.2015.06.013.
[135] Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in lombardy, italy: early experience and forecast during an emergency response. JAMA 2020. https://doi.org/10.1001/jama.2020.4031.
[136] Murray CJL. Forecasting COVID-19 impact on hospital bed-days, ICU-days, ventilator-days and deaths by US state in the next 4 months. medRxiv. 2020:2020.03.27.20043752. 10.1101/2020.03.27.20043752.
[137] Mann HJ. Drug-associated disease: cytochrome P450 interactions. pp. 329–45, vii Crit CareClin. 2006;22(2). https://doi.org/10.1016/j.ccc.2006.02.004.
[138] Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020. https://doi.org/10.1001/jama.2020.5394.
[139] Gnjidic D, Johnell K. Clinical implications from drug-drug and drug-disease interactions in older people. Clin Exp Pharmacol Physiol 2013;40(5):320–5. https://doi.org/10.1111/1440-1681.12081.
[140] Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. Expert Opin Drug Saf 2018;17(12):1185–96. https://doi.org/10.1080/14740338.2018.1546841.