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EFFECT OF SARS-CoV-2 ON CYTOCHROME P450-DEPENDENT METABOLISM OF DRUG: A REVIEW

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Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a virus that has spread worldwide. In addition to affecting respiratory cells, SARS-CoV-2 also impacts the organs of the digestive system, particularly the liver. It has been established that COVID-19, caused by SARS-CoV-2, significantly affects liver function in infected patients, which is critical for drug pharmacokinetics and safety. SARS-CoV-2 can affect liver cells both directly (via the viral receptor angiotensin-converting enzyme 2 (ACE2)) and indirectly, including through cytokine release and the so-called "cytokine storm." Viral activity leads to elevated liver enzyme levels (ALT, AST, GGT, ALP), decreased albumin levels, and disruption of the metabolism of endogenous substances and xenobiotics. It has been shown that liver injury impairs the function of the system responsible for metabolizing xenobiotics (the monooxygenase system or cytochrome P450 (CYP) system). Dysfunction of the monooxygenase system, in turn, leads to altered drug metabolism and additional toxicity, particularly in cases of drug–drug interactions. This review highlights the main potential mechanisms of liver injury in COVID-19, raising awareness of drug metabolism pathways. Analysis of the metabolism of anti-coronavirus drugs by different CYP isoforms may help prevent drug interactions in patients with comorbidities.

SARS-CoV-2 infection also alters CYP expression, including CYP3A4, CYP2B6, and CYP2C9, via cytokine-mediated regulation, resulting in reduced drug metabolism, increased plasma drug concentrations, and higher risk of toxicity. Polypharmacy in COVID-19, including antiviral drugs, hydroxychloroquine, anti-inflammatory agents, and medications for comorbidities, further increases the risk of drug interactions and liver injury. Anti-cytokine therapy (e.g., tocilizumab) and supportive agents such as melatonin and vitamin D may help restore CYP activity, reduce inflammation, and improve drug clearance. Understanding the mechanisms of SARS-CoV-2-induced liver dysfunction and CYP modulation is essential for optimizing pharmacotherapy, minimizing drug-related toxicity, and improving clinical outcomes in patients with COVID-19.

Keywords: virus; liver; COVID-19; cytochrome P450; SARS-CoV-2 infection; xenobiotic

Introduction. Coronavirus disease 2019 (COVID-19) has become a global problem for human health. Inflammatory processes are intensively increased on the basis of the body's immune response in patients with this pathology, along with fever, cough, headache and shortness of breath, that is the basis of severe acute respiratory syndrome in coronavirus infection (SARS-CoV-2) (Panigrahy et al., 2020). The increase in inflammatory mediators, which in severe cases of coronavirus infection reach their peak during the "cytokine storm", can provoke significant disturbances in the metabolic mechanisms of cytochrome P450 in the liver and further modulation of drug clearance. This will lead to an unexpected therapeutic-toxic response (Christmas, 2015). Patients with COVID-19 are potentially vulnerable to drug interactions (Hosseini et al., 2020). All this makes the analysis of therapeutic drug monitoring relevant, which will ensure optimal clinical results.

The pathophysiological processes occurring in COVID-19 may have an indirect effect on the metabolism of drugs through changes in the cytochrome P450 system of infected patients. It is believed that the virus is tropic to the angiotensin-converting enzyme 2 (ACE2) receptor of the oropharyngeal tract in the upper respiratory tract, which is the main route of transmission of the virus in humans (Ni et al., 2020). These receptors are intensively expressed in the epithelial cells of the lungs, and are also found in the digestive tract, which correlates with another form of virus transmission (Kang et al., 2019).

Today, the impact of the pathophysiology of COVID-19 on liver function, drug metabolism, and pharmacokinetics in patients with SARS-CoV-2 remains unclear.

The fact that patients with concomitant diseases (for example, hypertension, diabetes, hyperlipidemia) are more sensitive to coronavirus infection than the general population (Yang et al., 2020; Emami et al., 2020) indicates the importance of drug metabolism in the liver in order to minimize

their toxicity under conditions of polypharmacy in patients with COVID-19.

Given the above, the aim of this artical was analyze the mechanisms of the impact of COVID-19 on liver dysfunction and evaluate the cytochrome P450-dependent metabolism of antiviral drugs.

Materials and methods. In this work, an analysis of contemporary scientific literature, clinical reports, regulatory documents, and authoritative international guidelines related to the impact of the SARS-CoV-2 virus on liver function and CYP-dependent metabolism of antiviral drugs was conducted. The literature search was performed using leading international scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, which ensured access to peer-reviewed studies, systematic reviews, meta-analyses, pharmacological reports, and experimental research. Additionally, information from reputable professional organizations was used, such as the World Health Organization (WHO), the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), as well as clinical pharmacology recommendations provided by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the International Society for the Study of Xenobiotics (ISSX).

Search queries were carried out using a set of English keywords related to the topic of the study: “SARS-CoV-2”, “COVID-19”, “cytochrome P450”, “CYP450 isoenzymes”, “drug metabolism”, “xenobiotic biotransformation”, “inflammation-mediated metabolic changes”, “cytokine storm”, “drug interactions in COVID-19”, “CYP inhibition”, “CYP induction”, “pharmacokinetics”, “metabolism of antiviral therapy”, as well as names of clinically significant isoenzymes (e.g., CYP3A4, CYP2D6, CYP1A2, CYP2C9, CYP2C19). Additional search queries included terms associated with coronavirus and its metabolic pathways, such as “viral replication”, “effect of coronavirus on the liver”, and “virus-induced CYP modulation”.

The inclusion criteria covered peer-reviewed articles and official reports published from 2019 to 2025 that examined: 1) molecular and physiological mechanisms by which SARS-CoV-2 influences CYP450 enzyme expression and activity; 2) the impact of the virus on systemic inflammation, cytokine dysregulation, and the development of liver dysfunction; 3) pharmacokinetic changes in antiviral, anti-inflammatory, and supportive medications used in COVID-19 treatment; 4) drug–drug interactions associated with CYP450-modulated pathways; 5) regulatory authority recommendations and pharmacovigilance data regarding medication safety in patients with COVID-19.

Special attention was given to high-quality experimental studies on CYP450 regulation during viral infections, clinical trials involving COVID-19 therapy, and translational research exploring virus-induced suppression or induction of hepatic metabolic enzymes. Reviews and meta-analyses were included to summarize accumulated data and identify consistent trends. Case reports and small observational studies were used selectively, mainly to illustrate specific examples of altered pharmacokinetics in COVID-19 patients.

All identified sources were critically evaluated for methodological validity, relevance to the topic, publication type, and the level of clinical or experimental evidence. The information was systematically organized into thematic sections, allowing the formation of a comprehensive overview of current knowledge regarding the impact of SARS-CoV-2 on CYP450-dependent drug biotransformation.

Results and their discussion. ***Mechanisms of the SARS-CoV-2 effect on the functional state of the liver in infected patients.*** In the absence of a proven therapy for COVID-19, scientists are trying to find an effective drug that can eradicate this infection. During the study of drugs against COVID-19, it is necessary to take into account their pharmacokinetics, which is an important aspect of the drug metabolism of in the body. Biotransformation of drugs can significantly affect the clearance, effectiveness and/or their toxicity.

Since the liver is the main organ involved in drug metabolism, it is necessary to analyze its functional state in patients with COVID-19. It is known that the liver is one of the main organs exposed to the virus during SARS-CoV-2 infection (Bertolini et al., 2020).

Angiotensin-converting enzyme 2 (ACE2) receptor expresse in the liver also (Li et al., 2020). This indicates that the liver is affected by two factors - direct viral attack and systemic inflammation (the actions of inflammatory immunogenic proteins directed at the liver).

Changes of liver enzymes in the blood is confirmed of liver dysfunction in patients with COVID-19. Thus, in patients with COVID-19, similar to other coronavirus infections, the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), bilirubin and albumin change in the blood serum. Changes in the activities of these enzymes are associated with liver damage (Nardo et al., 2021; Li et al., 2020). As a rule, ALT and AST levels are at least twice the upper limit of normal, which should be noted in patients with COVID-19 (Li et al., 2020; Bertolini et al., 2020). In addition, the ratio of AST

to ALT (> 1) changes in the direction of progressive fibrosis or cirrhosis of the liver (Hundt et al., 2020).

In some cases, ALT levels rise to 7590 U/L in patients with COVID-19. Approximately 30% of patients with COVID-19 have AST and ALT values higher than normal, which correlates with the severity of the disease (Musa, 2020). Since the liver is one of the main organs of protein synthesis, even minor changes in metabolism during COVID-19 will have a significant impact on the functioning of hepatocytes. Biosynthesis of endogenous substances and biotransformation of xenobiotics will be disturbed due to changes in enzyme systems. At the same time, a decrease in albumin and an increase of liver enzymes level indicate that the inflammatory process in patients with COVID-19 damages the liver (Feng et al., 2020; Lei et al., 2020).

The exact mechanisms of the COVID-19 impact on the liver are *inexplicable*. However, viral hepatotropic can be attributed to the relatively high expression of ACE2 in liver cells. ACE2 expression is more pronounced in cholangiocytes than in hepatocytes, which makes them more vulnerable to viral attack (Guan et al., 2020; Chai et al., 2020). This assumption is supported by an increase in GGT in patients with COVID-19 (Zhang et al., 2020). COVID-19 can exert an indirect effect on the liver, the mechanism of which is the development of inflammatory reactions in the target organs. Thus, severe acute respiratory syndrome coronavirus 2 leads to severe tissue damage that initiates a stress response in the endoplasmic reticulum (ER) and regulates its inflammatory enzymes, including microsomal prostaglandin E synthase-1 (mPGES-1) and prostaglandin endoperoxide synthase 2 (cyclooxygenase 2 (COX-2)). These enzymes catalyze the synthesis reactions of eicosanoids, including prostaglandins (PG), leukotrienes (LT) and thromboxanes (TX) (Hammock et al., 2020). The formed pro-inflammatory lipid derivatives cause a "cytokine storm" in the body, which contributes to organ damage in a severe form of coronavirus disease, and in particular the liver (Fig. 1).

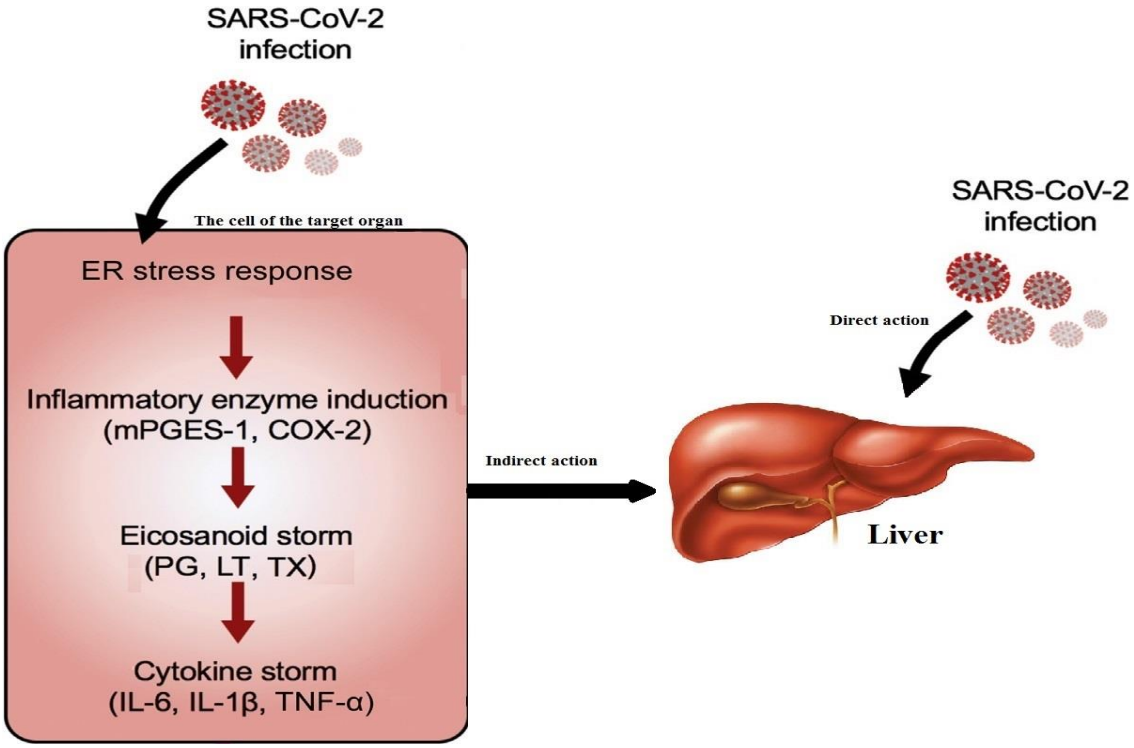

Fig. 1. Mechanisms of SARS-CoV-2 effects on the liver

Note: ER – endoplasmic reticulum; mPGES-1 – microsomal prostaglandin E synthase-1; COX-2 – cyclooxygenase-2; PG – prostaglandins; LT – leukotrienes; TX – thromboxanes; IL – interleukin; TNF – tumor necrosis factor.

Systemic inflammatory response caused by SARS-CoV-2 may be the cause of multi-organ dysfunction, including liver damage (despite the absence of viral antigens in the liver) (Papic et al., 2012). Inflammatory processes in the body can cause multiple organ failure. The systemic inflammatory response syndrome caused by SARS-CoV-2 infection is strongly associated with the activation of both humoral and cellular immunity. In fact, the virus is capable of directly inducing multiple pro-inflammatory signals through Toll-like receptors and activation of T-lymphocytes, particularly T-killers (Biswas et al., 2020; Felsenstein et al., 2020). Then, T-lymphocytes attack

the infected cells of the body, which leads to their apoptosis and necrosis. Molecules released from dead infected cells can further amplify inflammatory signals through Toll-like receptors (Biswas et al., 2020). At the same time, T-lymphocyte depletion cannot control viral and bacterial infections, thereby activating multiple inflammatory signaling pathways that lead to macrophage activation and secondary inflammatory responses (Felsenstein et al., 2020).

After infection with SARS-CoV-2, activated T cells produce granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-6, and other proinflammatory factors (Fig. 2).

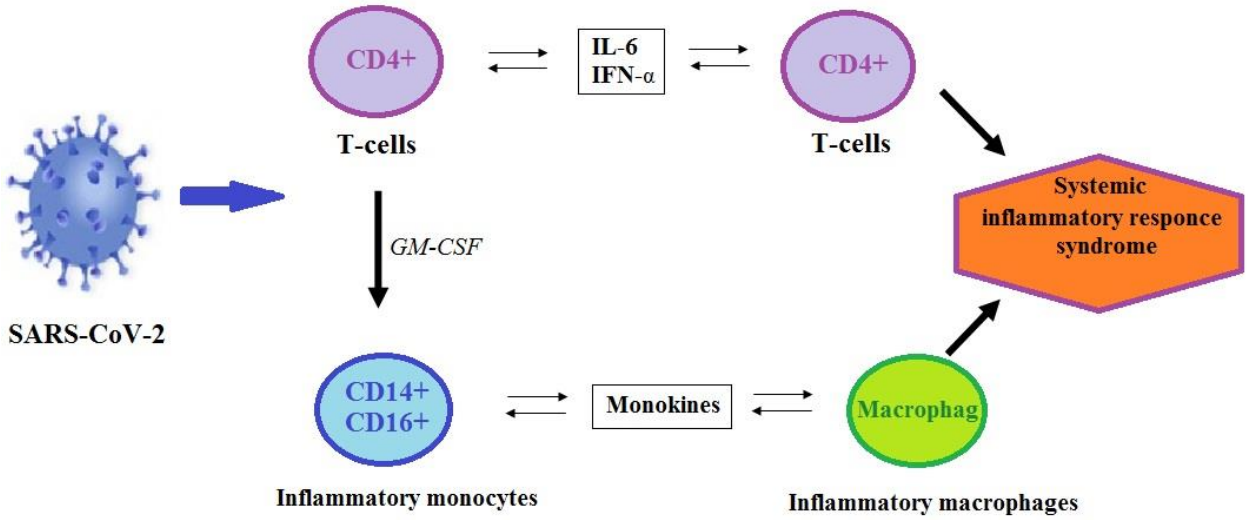

Fig. 2. Development of the systemic inflammatory response syndrome in patients with COVID-19
Note: IL – interleukin; TNF – tumor necrosis factor; GM-CSF – granulocyte-macrophage colony-stimulating factor

GM-CSF additionally activates CD14+ and CD16+ inflammatory monocytes, which produce more IL-6 and other pro-inflammatory factors, thereby causing a systemic inflammatory reaction syndrome that leads to immune damage of liver cells (Fig. 2).

Such a vicious cycle can cause numerous injuries not only to the liver, but also to the heart and kidneys. Liver abnormalities can be caused of treatment start disease under the conditions of the use of hepatotoxic agents: antipyretics (for example, acetaminophen); antiviral drugs (for example, oseltamivir and lopinavir); antibiotics and steroids (Feng et al., 2020; Sun et al., 2020).

Therefore, hepatocellular damage can occur both due to the direct effect of SARS-CoV-2 on liver cells and through pro-inflammatory molecules, which will negatively affect the metabolism of endogenous substances and xenobiotics in the body, including altered physiological, therapeutic and toxic consequences.

Inflluance of COVID-19 on cytochrome P450 expression and drug metabolism.

The cytochrome P450 system plays an important role in the biotransformation and pharmacokinetics of most drugs. The inflammatory process observed in COVID-19 can inhibit or induce some isoforms of cytochrome P450, which will lead to a change in the profile of the drug in the blood plasma and its excretion from the body. These changes will increase the side effects and toxicity of drugs, leading to a fatal outcome (Zhang et al., 2021).

One of the possible mechanisms of the COVID-19 effect on the cytochrome P450 system may be increased synthesis of cytokines in the body. Immunogenic proteins such as IL-1, IL-6, IFNγ, and TNFα can inhibit CYP enzymes during viral infection (Knudsen et al., 2018). Today, there is limited data on CYP regulation during SARS-CoV-2 infection. However, CYP regulation, which is controlled by cytokines and other inflammatory proteins, has been studied in other viral infections other than SARS-CoV-2. The mechanism of CYP regulation in other viral infections may be similar in patients with COVID-19. *In vitro* studies with hepatocytes showed that IL-6 decreased the expression of the main CYP isoforms to 40%. Differential IL-6-mediated downregulation of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 expression was observed. It was shown that during the inflammatory process in the body, the most sensitive isoforms are CYP2B6 and CYP3A4, as their expression decreases to the greatest extent (Fig. 3) (Kim et al., 2012).

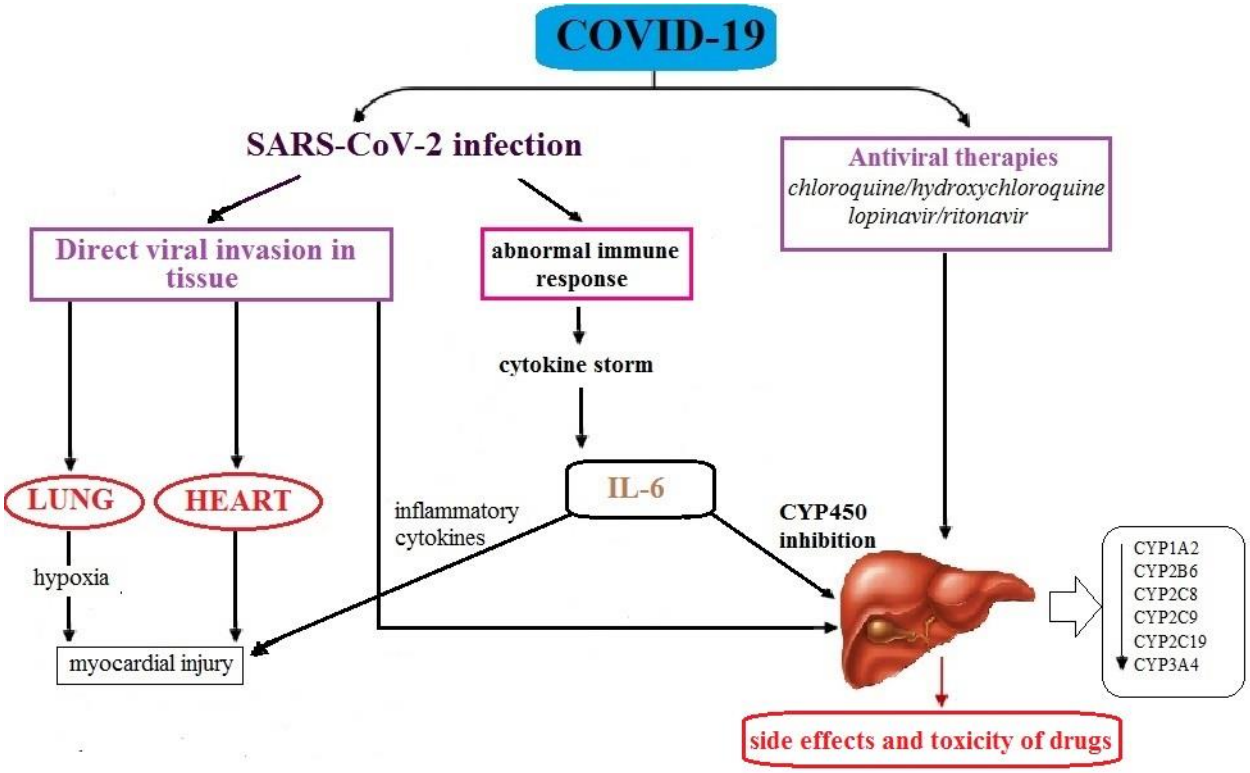

Fig. 3. Risk mechanisms of drug hepatotoxicity in patients with COVID-19

Currently, acute damage lung, heart, liver injury and antiviral therapy are considered to be the main factors of complications observed in patients with COVID-19 (Ejaz et al., 2020; Azevedo et al., 2021). Damage to the liver and myocardium can be the result of direct viral invasion of these organs, as well as an indirect consequence of severe lung damage (mediated by hypoxia and inflammatory processes in the body) (Hammock et al., 2020).

Simultaneous pharmacological load on the body with drugs used to combat viral invasion/replication (chloroquine/hydroxychloroquine), protease inhibitors (lopinavir/ritonavir) and macrolides (azithromycin) may increase the risk of liver complications (Ali et al., 2020). Inflammatory cytokines, in particular IL-6, increase the half-life of drugs due to a decrease in CYP activity. A study in human hepatocytes demonstrated that IL-6-mediated reduction of CYP enzymes depends on the concentration of IL-6 (Darakjian et al., 2021).

The cytokines such as TNFα, IFNγ, TGF, IL-6, and IL-1 are most often present in COVID-19 patients. Have been shown that these cytokines to significantly reduce CYP3A4 expression (Darakjian et al., Khan, 2021; et al., 2024; Shukla et al., 2024). It is not known whether the effect of cytokines on CYP enzymes is additive or synergistic under the conditions of the "cytokine storm" that occurs in patients with COVID-19. The type of inflammation commonly experienced by patients with COVID-19 can be greatly affected on drug metabolism. Mechanisms of CYP downregulation associated with inflammation can be very diverse. The main regulators of CYP1, CYP2 and CYP3 enzymes are aryl hydrocarbon receptors (AhR), constitutive androstane receptors (CAR) and pregnane X receptors (PXR), respectively (Danek et al., 2024). Inhibition of AhR, CAR, and PXR with subsequent reduction of CYP mRNA transcription and protein expression is the most common pathway of cytokine exposure in inflammation (Danek et al., 2024; Zhang et al., 2023). For example, IL-1β downregulates CAR expression (Danek et al., 2024). Anti-IL-1b monoclonal antibodies inhibit CYP enzymes. Another mechanism of CYP3A4 inhibition of inflammation involves the C/EBPβ protein (Nwabufo et al., 2023).

The decrease in CYP expression during coronavirus infection may occur due to free radical mechanisms that initiate oxidative stress. this is common during infection and inflammation in patients with COVID-19. It was shown that these changes were corrected during the addition of a vitamin E analogue, which quenches free radicals (Wieczfinska et al., 2022).

The main function of CYP enzymes is to increase the hydrophilicity of the drug by hydroxylation. Therefore, the decrease in CYP expression associated with viral infection and cytokines has a direct impact on drug distribution and pharmacokinetics in humans.

Today, the influence of several viruses (hepatitis A virus, influenza virus A and B, adenovirus, herpes simplex virus, and human immunodeficiency virus

(HIV)) on CYP-dependent drug metabolism has been studied in detail (Thomas et al., 2025; Schneide et al., 2023). As for the impact of SARS-CoV-2 on enzyme systems that metabolize drugs, these issues are only being studied. Different results are shown when researching different drugs against COVID-19. It has been shown that during the use of cyclosporine, as a substrate for the CYP3A4 isoform, the level of this drug in the blood plasma increases and its elimination decreases. This fact may be due to the high levels of IL-6 in patients with COVID-19 (McGonagle et al., 2020). Similar interactions between drugs and simvastatin were confirmed for cyclosporine using physiologically based pharmacokinetic modeling (Mahmood et al., 2023). Metabolism of midazolam, as a CYP3A substrate, was reduced 12 hours after induction of inflammatory states by glucose-6-phosphate isomerase. Increase in serum of IL-6 and TNFα levels led to inhibition of CYP3A mRNA synthesis (Denisov et al., 2022). Hepatic clearance of theophylline, mediated by CYP1A2, decreases under conditions of adenovirus or influenza virus presence in the body (Drozdzik et al., 2023). Similarly, inflammatory effects reduced of CYP3A4 protease inhibitors metabolism in patients with HIV (Schneider et al., 2023).

Therefore, the analysis of the viral infections effect on the expression of various CYP forms showed that immunogenic proteins suppress the clearance and other pharmacokinetic parameters of drugs. Such proteins include cytokines, which are synthesized in the body in response to the presence of a viral pathogen. Such changes in the body directly influence on the individual variability of the therapeutic and toxic effects of the drugs used.

Pharmacokinetics of drugs used in COVID-19 patients. Treatment regimens for patients with COVID-19 are combined because they target both the pathophysiology of the disease and the symptoms. The pharmacokinetic profile of the studied drugs in patients with COVID-19 primarily concerns antiviral and antiprotozoal agents. Remdesivir, which is the only drug approved by the USFDA for the treatment of COVID-19, has very limited studies on its pharmacological effects in patients with COVID-19. Only 10% of remdesivir is metabolized by CYP enzymes (Chang et al., 2025). So, it is unclear whether the renal failure that can be observed with this drug is specifically related to its metabolism by CYP.

Lopinavir/ritonavir and darunavir, which belong to the antiretroviral drugs approved for the treatment of HIV, are increasingly used in patients with SARS-CoV-2 today (Le et al., 2020).

Studies have shown that lopinavir plasma concentrations were six times higher in patients with COVID-19 compared to HIV patients (Le et al., 2020). At the same time, the level of lopinavir in the blood was correlated with the level of serum C-reactive protein (CRP). Thus, patients with higher CRP (>75 mg/L) had lower lopinavir concentrations compared to patients with CRP <75 mg/L. Age (<65 or >65 years) did not effect on lopinavir concentrations when compared between patients with similar CRP values (Marzolini et al., 2020).

Interestingly, lopinavir levels were lower after administration of monoclonal antibodies against the IL-6 receptor. The established fact indicates that the downregulation of drug metabolism is associated with inflammation. At the same time, hepatic clearance decreases, which plays an important role in disrupting the metabolism of drugs against COVID-19 (Marzolini et al., 2020). This supports the concept that the expression of certain CYP isoforms is suppressed by inflammatory proteins during active infection or inflammation (Nwabufo et al., 2023; Denisov et al., 2022). Indeed, lopinavir and darunavir are predominantly metabolized by CYP3A4, but equally the enzyme plays a minor role in the metabolism of hydroxychloroquine (HCQ). This suggests that infection-mediated downregulation of CYP3A4 may lead to decreased metabolism, decreased clearance, and increased plasma concentrations of the drug in patients with COVID-19. Therefore, when using drugs that are substrates for CYP3A4, it is necessary to combine them with anti-inflammatory drugs. Thus, the anti-inflammatory effect of tocilizumab can reduce cytokine levels and drug levels in blood plasma, thereby protecting patients from increased toxicity (AlOmeir et al., 2025).

As already mentioned above, HCQ-based drugs are one of the most promising in the treatment of coronavirus infection (Corrêa et al., 2023). Previously, several studies found HCQ's antiviral activity against some strains of HIV and the influenza virus. Recently been shown that HCQ prevent of SARS-CoV-2 reproduction in several ways (Paniri et al., 2020): 1) the effect of HCQ on enzymes involved in glycosylation and activation of angiotensin-converting enzyme, including glycosyltransferases and sugar-modifying enzymes; 2) blocks the fusion of the virus and the membrane; 3) interferes with the glycosylation of the adhesion protein (S-protein) and disrupts the fusion of viral particles mediated by endosomes; 4) HCQ prevents the cleavage of the S-protein, which is a key point for the fusion of SARS-CoV-2 with cells. This happens by increasing of lysosome pH level and inhibiting their proteases (Fig. 4) (Gautret et al., 2020; Yao et al., 2020).

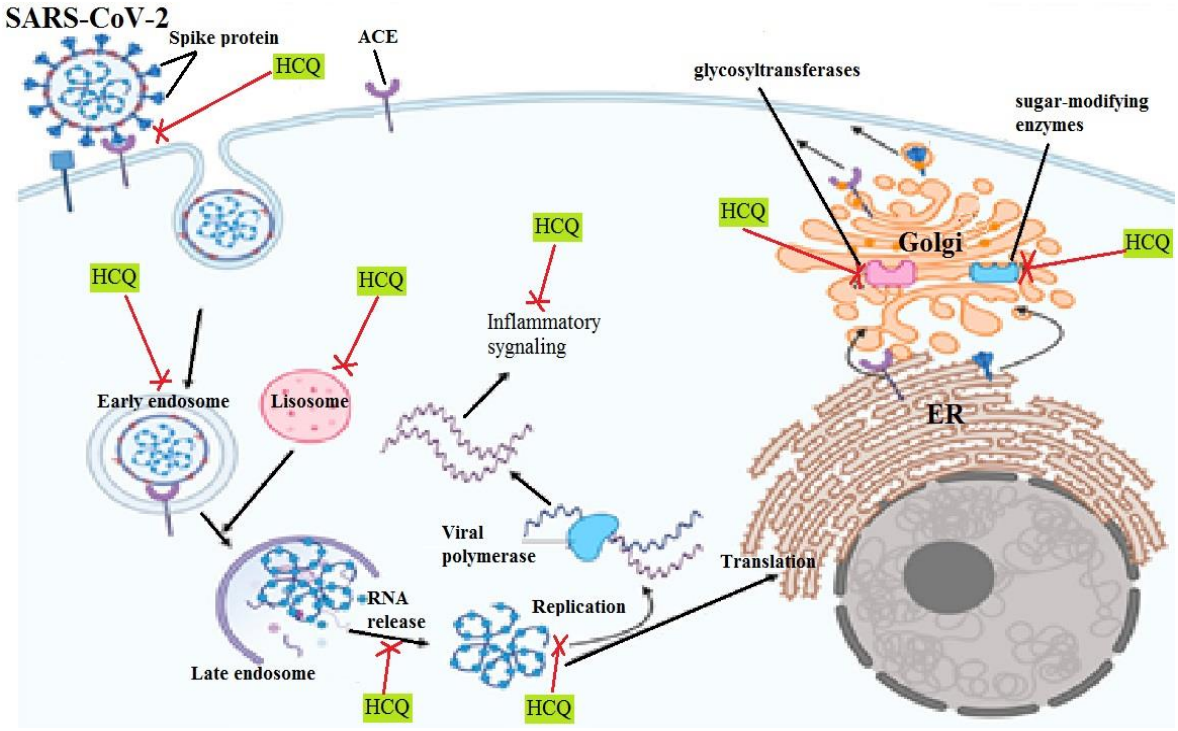

Fig. 4. Mechanism of the anti-coronavirus action of hydroxychloroquine

HCQ prevents activation of inflammatory cascades during SARS-CoV-2 virus propagation through increasing endosomal and lysosomal pH. In addition, HCQ may exert its antiviral effect through interfering with SARS-CoV-2 replication. It was shown that HCQ inhibit viral genome release through altering the number, size, and morphology of early endosomes or endolysosomes (Roldan et al., 2020). HCQ can reduce of the inflammatory response through inhibiting of major histocompatibility complex (MHC) II-mediated activation of T cells. At the same time, the release of such cytokines as IL-1, IL-6, TNF-α are inhibited. The anti-inflammatory mechanism of HCQ action is manifested precisely due to a decrease of the cytokine level. Such changes in the body will lead to reduced damage of organs, especially the lungs and possibly the liver, in patients with COVID-19 (Tripathy et al., 2020).

Inhibition of metabolism and excretion of drugs in patients with COVID-19 should be considered with other drugs that are intended for the treatment of concomitant diseases. For example, the immunosuppressive drug everolimus, used in transplant patients, may decrease its activity when CYP3A4 expression is decreased (Nagy et al., 2022).

Therefore, in patients with COVID-19, liver dysfunction is sharply increased. This confirms the increase of liver enzymes level in blood serum. In this regard, it becomes clear that the liver is under severe stress during SARS-CoV-2 infection (Feng et al., 2020; Sun et al., 2020; Qiu et al., 2025). However, the acute phase of the disease is relatively short, so it remains unknown what happens to the liver after recovery. Depending on the severity of inflammatory and infectious liver damage, patients may experience long-term liver abnormalities, including necrosis and organ failure (Sun et al., 2020; Qiu et al., 2025; Stasi, 2025). Regardless of the prognosis of liver dysfunction through increasing cytokine levels patients will experience an acute suppressive effect on CYP expression. These changes are less pronounced in other viral infections of the respiratory tract. At the same time, the metabolism of drugs, the excretion of drugs will be decrease, and eventually, local and systemic toxicity of drugs will appear already 48-72 hours after an active infection (Seifert et al., 2017). Similar to other viral infections, local and systemic inflammation as well as the “cytokine storm” during the progression of COVID-19 can potentially cause downregulation of major CYP enzymes including CYP3A4, CYP2B6, and CYP2C9 (Paniri et al., 2020).

Drug-drug interactions in patients with COVID-19. Increasing of toxic drug concentration is one of the most common causes of drug-induced liver injury. Destruction of liver parameters during SARS-CoV-2 infection can be caused both viral events and hepatotoxicity from drugs used during treatment against concomitant diseases (Pollmann et al., 2025). Patients with existing concomitant

diseases are most sensitive to SARS-CoV-2 infection. These patients often take drugs for concomitant diseases (along with drug therapy for COVID-19) (Emami et al., 2020). So, drug-drug interactions occur in patients with COVID-19 and comorbidities compared to patients with COVID-19 without comorbidities. In a meta-analysis of patients with COVID-19 and comorbidities, the three most common underlying diseases were 16% of patients with hypertension, 12% of patients with cardiovascular disease, and 8% of patients with type 2 diabetes (Emami et al., 2020). These patients usually take drugs that are metabolized by CYP enzymes. The CYP3A4 isoform metabolizes antihypertensive agents, including most dihydropyridine calcium channel blockers (amlodipine and nifedipine), all non-dihydropyridine calcium channel blockers (verapamil and diltiazem), and propranolol (Chen et al., 2025). Irbesartan and losartan are antihypertensive drugs that are metabolized by CYP2C9 (Park et al., 2021) [61].

Cholesterol-lowering drugs such as statins (except pravastatin and rosuvastatin) are also often used in patients with arterial hypertension and are metabolized by CYP3A4 (Chen et al., 2025). Antidiabetic agents such as glimepiride, glipizide, and glyburide are metabolized by CYP2C9 also (Becker et al., 2013).

In patients with COVID-19, cytokines produced during the inflammatory response, particularly IL-6, downregulate major drug-metabolizing CYP enzymes (eg, CYP2B6, CYP2C9, and CYP3A4). Therefore, the administration of drugs to treat comorbidities may be harmful to COVID-19 patients. Thus, even a small increase of IL-6 suppresses of the CYP3A4 expression. In higher concentrations of IL-6 reduces of the CYP2C9 expression. IL-1β downregulates CAR, which leads to a decrease in CYP2C9 expression (Zhang et al., 2023). These changes will lead to a decrease of antihypertensive drugs metabolism, which can lead to hypotension and other associated side effects. This can exacerbate the hypotension already caused by systemic infection with the SARS-CoV-2 virus. Similarly, higher concentrations of statins may lead to rhabdomyolysis, which will exacerbate fever-induced muscle pain in COVID-19 patients (Maor et al., 2025). Plasma concentrations of antidiabetic drugs, especially sulfonylureas, above minimally toxic concentrations can cause dangerous hypoglycemia, which in patients with COVID-19 is exacerbated by difficulty with eating and intubation (Maor et al., 2025).

Along with drug-drug interactions of therapeutic agents used in comorbidities, it is extremely important to understand that experimental therapy of COVID-19 also modulates CYP functionality. When administering drugs for COVID-19, drug interactions with drugs for concomitant diseases can be predicted. For example, ritonavir is a strong inhibitor of CYP3A4. At the same time, the expression of CYP3A4 is already decreased under the influence of cytokines in patients with COVID-19. The elimination of antihypertensive and antidiabetic drugs can be blocked also (Cao et al., 2020). Similar metabolic changes of drugs for concomitant diseases can also occur with the use of antiviral drugs against COVID-19 - lopinavir and tocilizumab, which also change the expression of CYP3A4 and CYP2C9 (Huang et al., 2023). Due to CYP dysregulation, the excretion of hypotensive, antidiabetic, and other drugs used to treat comorbidities in patients with COVID-19 will decrease. This can be fatal for these patients if they are not properly monitored.

CYP is an important modulator of HCQ metabolism, and its isoforms play a crucial role in HCQ metabolism. CYP isomers convert HCQ into active metabolites through dealkylation (Fig. 5) (Giri et al., 2020).

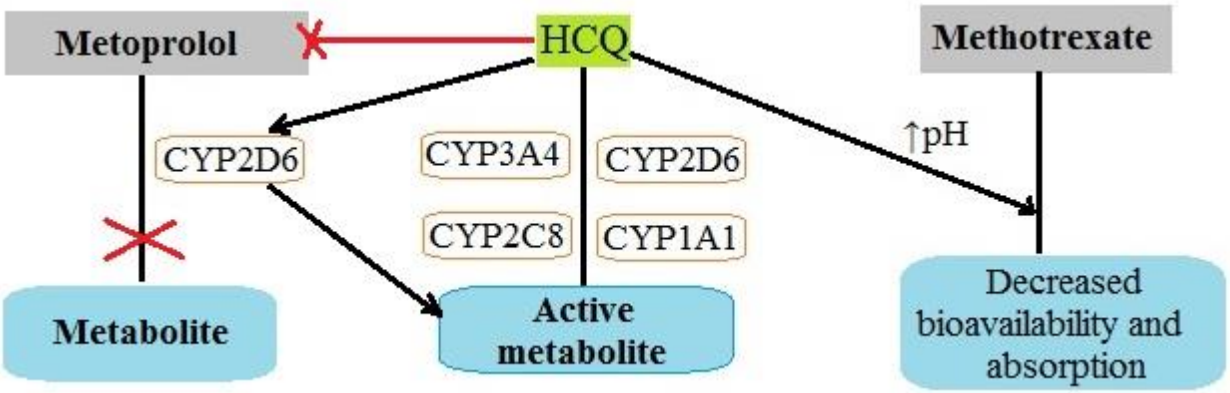

Fig. 5. Effect of hydroxychloroquine on the metabolism of metoprolol and methotrexate in the body of patients with COVID-19

CYP2C8, CYP3A4, CYP2D6 and CYP1A1 are isoforms involved in HCQ metabolism. first three of them are more important compared to CYP1A1 (Fig. 5) (Giri et al., 2020).

It was shown, that administration of HCQ to affect the metabolism of other drugs biotransformed by CYP. metoprolol is one of these drugs. metoprolol is a beta-blocker used to prevent angina and control high blood pressure. In the body, this drug is metabolized by the CYP2D6 isoform. During the combined administration of metoprolol and HCQ, the latter interferes with the metabolism of metoprolol through competing for CYP2D6 (Fig. 5) (Paludetto et al., 2023).

Another drug-drug interaction may occur during concomitant use of HCQ and methotrexate in patients with COVID-19 and rheumatoid arthritis. HCQ reduces the gastrointestinal absorption and bioavailability of methotrexate through modulating the pH level (Fig. 5) (Giri et al., 2020; Paludetto et al., 2023). HCQ may be a potential antiviral drug for the treatment of patients with COVID-19, as this drug is relatively safe and exhibits high antiviral activity (Gautret et al., 2020), as shown for HIV and influenza viruses.

Today, more and more researchers are trying to find plant-based antiviral agents for the treatment of COVID-19 in clinical settings (Khazir et al., 2024; Föderl-Höbenreich et al., 2025). In addition, it is believed that in the fight against COVID-19, a more effective way is a combination of drugs, which is always used in the therapy of COVID-19. However, the simultaneous use of several drugs can cause clinically significant drug/herb-drug interactions. Concomitant use of the antiviral agent lopinavir with the herbal extract of Qingfei paidu (recommended for the treatment of COVID-19 in China) may also have adverse effects. It was shown inhibition of CYP 1A, 2A6, 2C8, 2C9, 2C19, 2D6 and 2E1, CYP3A isoforms in a dose-dependent manner of extract. An in vivo test showed that Qingfei paidu prolongs the half-life of lopinavir (a CYP3A substrate). Thus, when a plant extract (6 g/kg) is administered to rats simultaneously with lopinavir (160 mg/kg), the concentration of lopinavir in the blood plasma of animals increases in 2.04 times. It was shown that an extract of Qingfei paidu contributes to a significant loss of CYP3A activity in the NADPH-generating system (Zhang et al., 2021).

Therefore, the plant extract of Qingfei paidu significantly inactivates CYP3A, which can reduce the pharmacokinetics of CYP3A substrate drugs. This fact must be taken into account when treating patients with COVID-19 to avoid potential risks of drug interactions. In conclusion, it should be noted that the main strategies of SARS-CoV-2 treatment should be to reduce the viral load and eliminate the source of inflammation. However, the use of anti-inflammatory drugs to neutralize inflammatory proteins may be an indirect but effective way to alleviate several pathophysiological symptoms, including up-regulation of CYP isoforms. Currently, two monoclonal antibody drugs (LY-CoV555, REGN-COV2) are designed to neutralize SARS-CoV-2 in an emergency situation in patients with COVID-19 (U.S. National Library of Medicine, 2020). Similarly, the use of anti-TNFα antibodies (infiximab, adalimumab) may also be promising for drug metabolism against COVID-19 and co-morbidities, as it would promote normal CYP expression (Hamaguchi et al., 2025). Supplements such as melatonin and vitamin D can be used as adjuvant therapy because they have the ability to reduce inflammation, attenuate the "cytokine storm," and restore expression and metabolism of CYP. Melatonin also helps to dispose of reactive oxygen species that are formed as a result of tissue damage (Zhang et al., 2020). Therefore, COVID-19 patients with impaired drug metabolism may demonstrate improved drug clearance after treatment with anti-inflammatory agents. Thus, tocilizumab (an anti-inflammatory antibody to the IL-6 blocker) helps to reduce the concentration of lopinavir in the blood plasma of patients with COVID-19. This fact indicates an increase of clearance and a decrease of inflammation, which will improve the work of CYP (Marzolini et al., 2020).

Along with this, alternative drugs can be used in patients with COVID-19 and related diseases. The comorbidities often associated with COVID-19 have many therapeutic opportunities. Patients with hypertension and heart failure can use ACE2 inhibitors, which are hardly metabolized by CYP enzymes (Fakhouri et al., 2020). Blocking of the ACE2 receptor can minimize the entry of the infectious agent into the body because the virus spreads through the ACE2 receptor. Such blocking may have some prophylactic benefit for patients. If patients have angioedema, hyperkalemia, or risk of acute heart failure, they can use thiazide diuretics, which have very low CYP metabolism (Ellison et al., 2019). Most beta-blockers metabolize by CYP2D6. simultaneous use of beta-blockers with hydroxychloroquine may inhibit of CYP2D6 (Stoll et al., 2024).

Rosuvastatin is mainly not metabolized by CYP in case of use of cholesterol-lowering drugs. 90% of the drug is excreted with feces. Therefore, this drug is better used in comparison with atorvastatin/simvastatin and other CYP3A4 substrates. Among antidiabetic drugs that are not metabolized in the liver, attention should be paid to liraglutide or semaglutide (Knudsen et al., 2019).

Therefore, patients with COVID-19 have liver dysfunction and impaired metabolic capacity, regardless of the duration and severity of the disease. In addition, liver dysfunction may increase due to the hepatotoxicity of antiviral drugs and drugs used for comorbidities in COVID-19 patients under the conditions of a cytokine storm. However, hepatocytes have high regenerative capabilities, except in a small percentage of patients who may have severe liver damage. Therefore, CYP enzymes usually recover very quickly after discontinuation of the agents.

In the case of simultaneous use of several drugs, there is a risk of drug interaction, which increases in COVID-19 patients. This fact should be considered as a serious clinical problem considering that seriously ill patients are more prone to drug interaction. It is necessary to take into account the fact that CYP is involved in the metabolism of many prescribed drugs. Moreover, a demographic analysis of patients with COVID-19 has shown that the elderly with comorbidities are the most vulnerable population group (Grasselli et al., 2020). Therefore, concomitant drug therapy makes elderly patients a high-risk group, who may experience negative consequences under the conditions of combined use of drugs.

Suppressed CYP metabolism and impaired drug metabolism may contribute to organ damage and contribute to higher mortality rates in patients with COVID-19. Knowledge of the COVID-19 pathophysiology and an understanding of CYP expression status, metabolism, and drug pharmacokinetics will minimize drug-related toxicity. This optimize pharmacotherapy of individuals infected with COVID-19.

Conclusion. The SARS-CoV-2 virus causes liver dysfunction and reduces the activity of the cytochrome P450 system, leading to impaired drug metabolism and an increased risk of toxic reactions, especially in cases of polypharmacy. Inflammatory cytokines (IL-6, TNFα, IL-1β) suppress major CYP isoforms (CYP3A4, CYP2B6, CYP2C9), altering the pharmacokinetics of antiviral, antihypertensive, antidiabetic, and other medications. The use of anti-inflammatory agents, monoclonal antibodies, melatonin, and vitamin D can help restore CYP activity and reduce drug toxicity. Understanding the mechanisms of COVID-19's impact on drug metabolism is crucial for optimizing pharmacotherapy and improving treatment safety.

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ВПЛИВ SARS-CoV-2 НА ЦИТОХРОМ Р450-ЗАЛЕЖНИЙ МЕТАБОЛІЗМ ЛІКАРСЬКИХ ПРЕПАРАТІВ: ОГЛЯД

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Коронавірусна хвороба 2019 року (COVID-19) спричинена важким гострим респіраторним синдромом коронавірусу 2 (SARS-CoV-2) – вірусом, поширеним у всьому світу. Окрім ураження клітин дихальної системи, SARS-CoV-2 уражає органи травної системи, зокрема печінку. Встановлено, що COVID-19, спричинений SARS-CoV-2, суттєво впливає на функцію печінки у інфікованих пацієнтів, що є критично важливим для фармакокінетики та безпеки ліків. На клітини печінки SARS-CoV-2 може впливати як безпосередньо (через вірусний рецептор ангіотензинперетворюючого ферменту 2 (АПФ2)), так і опосередковано, включаючи вивільнення цитокінів та «цитокіновий шторм». Дія вірусу призводить до підвищення рівня печінкових ферментів (АЛТ, АСТ, ГТТ, ЛФ), зниження рівня альбуміну та порушення метаболізму ендогенних речовин та ксенобіотиків. Показано, що внаслідок пошкодження печінки порушується функціонування системи, яка метаболізує ксенобіотики (монооксигеназної системи або системи цитохрому Р450 (CYP)). Дисфункціонування монооксигеназної системи, у свою чергу, призведе до зміни метаболізму ліків та додаткової інтоксикації організму, особливо у разі лікарської взаємодії. В огляді висвітлено основні потенційні механізми пошкодження печінки при COVID-19, що підвищить усвідомлення напрямку метаболізму ліків. Проаналізовані шляхи метаболізму протикоронавірусних препаратів різними ізоформами цитохрому Р450 допоможуть запобігти взаємодії ліків у пацієнтів із супутніми захворюваннями.

Показано, що інфекція SARS-CoV-2 також змінює експресію CYP, зокрема CYP3A4, CYP2B6 та CYP2C9, через цитокін-опосередковану регуляцію, що призводить до зниження метаболізму ліків, підвищення їх концентрації у плазмі та вищого ризику токсичності. Поліпрагмазія при COVID-19, включаючи противірусні препарати, гідроксихлорохін, протизапальні засоби та препарати від супутніх захворювань, ще більше підвищує ризик взаємодії ліків та ураження печінки. Антицитокінова терапія (наприклад, тоцилізумаб) та допоміжні засоби, такі як мелатонін та вітамін D, можуть допомогти відновити активність CYP, зменшити запалення та покращити кліренс ліків. Розуміння механізмів дисфункції печінки, спричиненої вірусом SARS-CoV-2, та модуляції CYP є важливим для оптимізації фармакотерапії, мінімізації токсичності, пов'язаної з ліками, та покращення клінічних результатів у пацієнтів з COVID-19.

Ключові слова: вірус; печінка; COVID-19; цитохром Р450; інфекція SARS-CoV-2; ксенобіотики

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