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REVIEW ARTICLE

Role of Cytochrome P450 2C9 in COVID-19 Treatment: Current Status and Future Directions

Sharoen Yu Ming Lim[1] · **Basel Al Bishtawi**[1] · **Willone Lim**[2]

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Abstract

The major human liver drug metabolising cytochrome P450 (CYP) enzymes are downregulated during inflammation and infectious disease state, especially during coronavirus disease 2019 (COVID-19) infection. The influx of proinflammatory cytokines, known as a 'cytokine storm', during severe COVID-19 leads to the downregulation of CYPs and triggers new cytokine release, which further dampens CYP expression. Impaired drug metabolism, along with the inevitable co-administration of drugs or 'combination therapy' in patients with COVID-19 with various comorbidities, could cause drug–drug interactions, thus worsening the disease condition. Genetic variability or polymorphism in CYP2C9 across different ethnicities could contribute to COVID-19 susceptibility. A number of drugs used in patients with COVID-19 are inducers or inhibitors of, or are metabolised by, CYP2C9, and co-administration might cause pharmacokinetic and pharmacodynamic interactions. It is also worth mentioning that some of the COVID-19 drug interactions are due to altered activity of other CYPs including CYP3A4. Isoniazid/rifampin for COVID-19 and tuberculosis co-infection; lopinavir/ritonavir and cobicistat/remdesivir combination therapy; or multi-drug therapy including ivermectin, azithromycin, montelukast and acetylsalicylic acid, known as TNR4 therapy, all improved recovery in patients with COVID-19. However, a combination of CYP2C9 inducers, inhibitors or both, and plausibly different CYP isoforms could lead to treatment failure, hepatotoxicity or serious side effects including thromboembolism or bleeding, as observed in the combined use of azithromycin/warfarin. Further, herbs that are CYP2C9 inducers and inhibitors, showed anti-COVID-19 properties, and in silico predictions postulated that phytochemical compounds could inhibit SARS-CoV-2 virus particles. COVID-19 vaccines elicit immune responses that activate cytokine release, which in turn suppresses CYP expression that could be the source of compromised CYP2C9 drug metabolism and the subsequent drug–drug interaction. Future studies are recommended to determine CYP regulation in COVID-19, while recognising the involvement of CYP2C9 and possibly utilising CYP2C9 as a target gene to tackle the ever-mutating SARS-CoV-2.

Key Points

A cytokine storm during COVID-19 leads to downregulation of CYP2C9 that impairs drug metabolism.

A number of herbs and drugs used in patients with COVID-19 are inhibitors or inducers of CYP2C9 and may interact with CYP2C9-metabolised drugs.

COVID-19 vaccines, e.g. BTN162b2 (tozinameran), elicits an immune response that decreases CYP enzyme activity, impacting drug absorption, metabolism and excretion.

CYP2C9 is one of the potential therapeutic target genes for COVID-19.

✉ Sharoen Yu Ming Lim
sharoenlim@gmail.com

[1] Faculty of Science and Engineering, University of Nottingham Malaysia, 43500 Semenyih, Malaysia

[2] Faculty of Engineering, Computing and Science, Swinburne University of Technology, 93350 Kuching, Malaysia

1 Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a respiratory infection [1]. COVID-19 is characterised by a series of clinical symptoms including cough, flu-like symptoms, headache, hyperthermia, nausea, vomiting, anorexia, diarrhoea, dyspnoea, shortness of breath, inflammation, vascular dysfunction, coagulopathy and many other serious complications including sepsis, cardiac failure, kidney injury, acute lung injury (ALI), acute respiratory distress syndrome (ARDS) [2] and death [3]. In early 2023, the World Health Organization (WHO) announced the emergence of a new Omicron variant, XBB. 1.5, which was increasingly found in more than 25 countries [4], indicating that we are a far cry from containing the virus. Individuals with existing hypertension, diabetes mellitus, obesity or cancer are more susceptible to COVID-19 than healthy individuals, primarily due to compromised immunity [5]. Patients with COVID-19 and with primary and secondary illnesses may face derangements of drug metabolism and clearance, leading to accumulation of drugs in their body and resulting in unexpected therapeutic or toxic response and drug–drug interactions [3, 6]. Polypharmacy (co-administration of five or more medications, e.g. anti-virals, antibiotics, anti-parasitics, corticosteroids) is practiced in patients with COVID-19 that have various comorbidities, with the hope that medications working through different mechanisms could be more effective. Instead, it appeared to be one of the main causes of COVID-19 mortality due to adverse drug reactions (ADRs) [7, 8]. Repositioned drugs that are repurposed to treat a different medical condition in COVID-19 infection than that for which it was originally developed may impose an additional risk of ADRs [9]. Some of the promising repurposed drugs for COVID-19 management metabolised by cytochrome P450 2C9 (CYP2C9) include chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir, atazanavir, favipiravir, nevirapine, efavirenz, oseltamivir, remdesivir, anakinra, tocilizumab, eculizumab, heme oxygenase 1 (HO-1) regulators, renin–angiotensin–aldostetone system (RAAS) inhibitors, ivermectin and nitazoxanide [10].

Cytochrome P450s (CYPs) are important major human liver drug metabolising enzymes which are responsible for metabolism of endogenous and exogenous substances, as well as being involved in diseases including viral infections, cancer, diabetes, rheumatoid arthritis, inflammatory bowel disease and age-related disorders such as normal ageing, metabolic disorders and neurodegenerative diseases [11, 12]. Immunodeficiency and infectious disease states, especially during COVID-19 infection, could (i) modulate drug metabolism and pharmacokinetics [13], (ii) induce hyperinflammation that triggers a cytokine storm and (iii) downregulate CYP expression and activity [7, 8]. As the main contributor to the metabolic biotransformation of most drugs, CYPs are widely involved in disease–drug interactions [14]. Changes in the expression and function of CYPs, and their impact on COVID-19 pathophysiology and metabolism of therapeutic agents in COVID-19, remain to be elucidated [15]. CYP2C9, one of the most abundant CYP enzymes, metabolises 15–20% of drugs [16], some of which are extensively used by patients with COVID-19, for instance, warfarin [17, 18], sulfonylureas [19], phenytoin [20] and non-steroidal anti-inflammatory drugs (NSAIDs) [21]. Further, studies have provided evidence that cytokines such as interleukin-6 (IL-6), tumour necrosis factor α (TNF-α) and interferon gamma (IFN-γ) suppress CYP2C9 expression [22].

Surprisingly, a number of drugs and herbs [23–28] used in COVID-19 therapy are inhibitors [29–33] or inducers of [34, 35], or are metabolised by CYP2C9 [36–39]. In addition to the involvement of CYP2C9 in inflammatory processes and cytokine storms during COVID-19 infection, studies regarding CYP2C9 expression and alteration, their mechanism of actions and their impact on COVID-19 pathophysiology and metabolism of therapeutic agents are lacking. COVID-19 therapies, and inflammation and disease investigations primarily revolve around CYP2C9, and therefore, efforts are warranted to focus on CYP2C9 research, which could be a promising approach towards effective COVID-19 therapeutic development. This review aimed to document current findings regarding the involvement of CYP2C9 in the cytokine storm during COVID-19 infection; provide an update of the drugs and herbs used during COVID-19 that are inhibitors, inducers or metabolised by CYP2C9; give an overview of possible drug–drug and/or herb–drug interactions from the concurrent use of inhibitors, inducers and drugs metabolised by CYP2C9 in patients with COVID-19; highlight COVID-19 vaccinations that may downregulate CYP2C9 expression; and examine the future of CYP2C9 in COVID-19 research.

2 Literature Search and Selection Criteria

Databases including Embase, Google Scholar, MEDLINE and PubMed, and publisher websites including ASPET, BioMed Central, PLoS, Springer Nature, Elsevier, Oxford University Press, Wiley, American Chemical Society, Frontiers, Nature, Hindawi, MDPI, Royal Society of Chemistry, Taylor & Francis and SAGE Publications, were searched electronically with keywords namely 'COVID-19' and combination of terms including 'cytochrome P450', 'CYP450', 'CYPs', 'CYP2C9', 'herb-drug interaction', 'drug-drug interaction', 'cytokine storm', 'SARS-CoV-2', 'CYP2C9 inducer', 'CYP2C9 inhibitor', 'genetic variability',

'polymorphism', 'susceptibility', and drugs metabolised by CYP2C9 namely 'ibuprofen', 'celecoxib', 'phenytoin', 'sulfonylureas', 'glimepiride', 'glyburide', 'glibenclamide', 'tolbutamide', 'propofol', 'warfarin', 'irbersartan', 'ruxolitinib', 'rosuvastatin', 'sildenafil', 'nirmatrelvir-ritonavir', 'fluoxetine', 'montelukast', 'bosentan' and 'voriconazole'. Searches were restricted to papers in English only. Similar papers collected from different databases were removed. The inclusion criteria were as follows: (a) original research and/or reviews related to COVID-19 and cytochromes P450, (b) original research and/or reviews of drugs metabolised by CYP2C9 used to treat COVID-19, (c) original research and/or reviews of drugs metabolised by CYP2C9 used concurrently by patients with COVID-19 suffering from other diseases and (d) letters to the editor and case studies regarding concurrent use of combinations of drugs in patients with COVID-19. The exclusion criteria were as follows: (a) articles in non-English languages, (b) non-peer-reviewed studies, (c) research with unclear methods and (d) articles in which the full text was not available. Articles selected were the latest issues from the beginning of the COVID-19 outbreak and thereafter, recognizing the quality of evidence and contribution of all individual research. The literature search was finalised on 21 March 2023.

3 Cytochrome P450 in COVID-19

3.1 CYP2C9 and Cytokine Storms

In humans, the CYP2C9 gene is highly polymorphic, with approximately 61 variant alleles and many sub-alleles, with different allele frequencies across geographical, racial and ethnic groups [40]. Based on CYP2C9 different phenotypes, the Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) published therapeutic recommendations of NSAIDs including celecoxib, diclofenac, flurbiprofen, ibuprofen, indomethacin, lornoxicam, meloxicam, nabumetone, naproxen, piroxicam, tenoxicam and sulindac [40]. Drug–gene variant pairs could modify treatment outcomes in patients with COVID-19 [10]. Patients that carry CYP gene variants and take COVID-19 drugs or herbal products metabolised by a particular CYP isoform and inhibitors of a similar CYP, may further exacerbate drug–drug interactions (DDIs) and/or herb–drug interactions (HDIs) [41]. Mechanistically, CYP regulation and interactions with CYP gene regulators are complex, encompassing a wide variety of ligand-activated transcription factors and mediators. Cytokine-mediated changes in CYP gene expression are unique to each individual CYP enzyme and could be the major regulatory mechanism responsible for altering CYP activity during inflammation, particularly in COVID-19 infection [42]. Figure 1 illustrates an overview of the sequence of events of CYP modulation caused by SARS-CoV-2 infection triggering cytokine release.

To date, studies focusing on the effects of SARS-CoV-2 on CYP expression and activities are still lacking [15]. However, what is known is that the major human drug metabolising CYP enzymes, including CYP3A4, CYP2B6 and CYP2C9, are downregulated during the cytokine storm in COVID-19 [43]. During severe COVID-19 infection, various inflammatory pathways are activated, with the release of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukins (IL-1β, IL-6) and chemokines, termed a 'cytokine storm', which could lead to altered molecular pathophysiology and eventually multi-organ damage and death [44]. The influx of cytokines during COVID-19 infection, leading to CYP2C9 downregulation.

Data obtained from hospitalised patients with COVID-19 and autopsies revealed features of sepsis, a dysregulated immune response due to life-threatening organ dysfunction caused by bacterial, viral, parasitic or fungal infections [45], including immune cell reprogramming, cytokine storms, immunosuppression and cell death [46]. The production of inflammatory cytokines can activate new cytokine release, which subsequently causes organ damage during severe COVID-19 infections [47]. Briefly, during sepsis, glucocorticoid receptors (GR) and aryl hydrocarbon receptors (AHR) in hepatocytes are inhibited due to production of inflammatory factors such as tumour necrosis factor 1 (TNF-1) and interleukin-1β (IL-1β) [48]. Inhibition of GR expression leads to downregulation of CYP2C9 gene expression [48]. The gush of inflammatory cytokines triggering more new cytokine release reduces CYPs expression further, impairing drug detoxification, and the inevitable concurrent use of medications in patients with COVID-19 with various comorbidities would worsen the disease condition.

3.2 CYP Downregulation during Infection and Inflammation

The downregulation of hepatic and extra-hepatic CYPs and other drug-metabolising enzymes and transporters is associated with infection and inflammation [49]. Pro-inflammatory cytokines including IL-6, IL-1β, TNF-α, IFN-γ and transforming growth factor beta (TGF-β), released during inflammation or infection are thought to be the main cause of CYP downregulation. These cytokines were found to downregulate CYP expression in vivo and in hepatocyte cultures [50]. CYPs are regulated by multiple cytokines in hepatocyte cultures, and different CYP isoforms can be regulated by different cytokines resulting in the gene-specific effects of inflammatory cytokines on CYP mRNA levels [51] and differential CYP regulation in various inflammatory disease states [49]. Viral infection, inflammatory mediators and hepatic injury also influence CYP expression and activity, which is

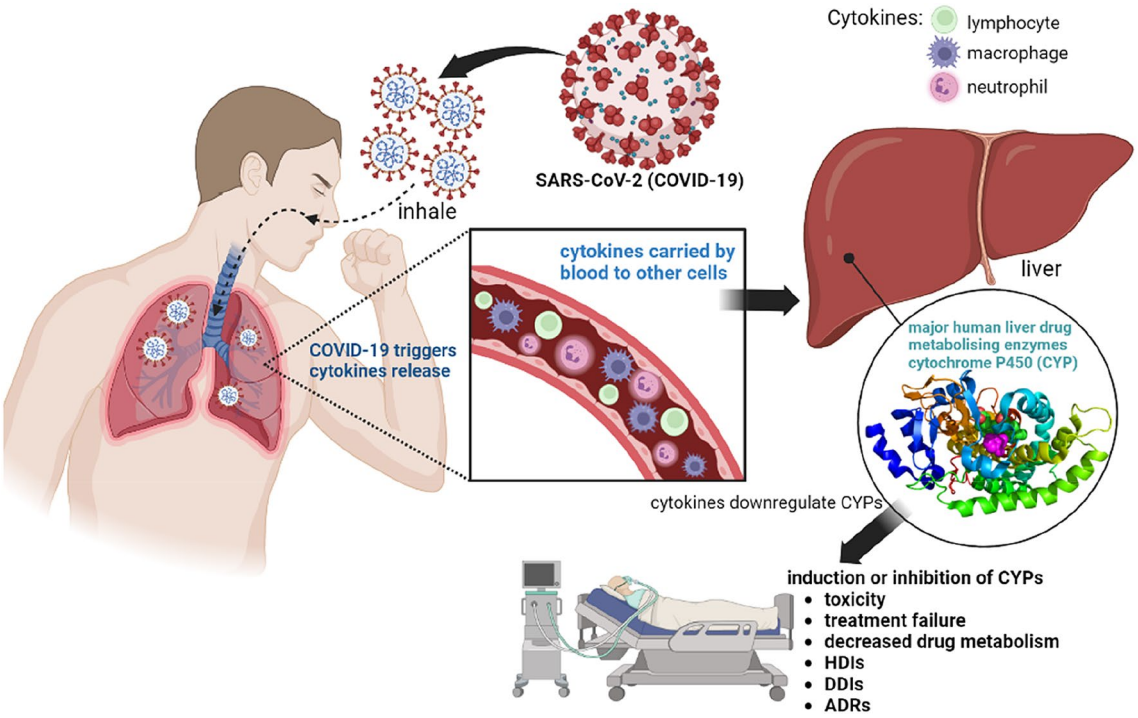

Fig. 1 Relationship of cytokines, CYPs and inflammatory processes in patients with COVID-19. *CYP* cytochrome P450, *HDI* herb-drug interaction, *DDI* drug-drug interaction, *ADR* adverse drug reaction

prevalent in patients with COVID-19 [15]. Cytokines including IL-1β, IL-6, IFNγ and TNFα are responsible for CYP enzyme suppression during viral infection; however, there is currently no strong evidence for whether this mechanism occurs during SARS-CoV-2 infection [44].

3.2.1 CYP2C9 Downregulation by Inflammatory Cytokines

Inflammation-mediated downregulation of CYP2C9 could lead to lower metabolism of drugs and decreased clearance and increased plasma concentrations of COVID-19 CYP2C9 substrate drugs. With the presence of both IL-6 at high concentrations and IL-1β, the constitutive androstane receptor (CAR) is downregulated [52], leading to downregulation of CYP2C9 expression. A study using the Geneva cocktail, in which subjects were simultaneously administered rifampin and fluconazole, a CYP2C9 inducer and inhibitor respectively, to assess the impact of COVID-19 on CYP activity hypothesized that CYP2C9 activity levels (increased by 56%) measured after infection could be associated with long COVID-19 metabolic disturbances [53].

IL-6 is one of the main regulators of inflammatory processes. Several studies have demonstrated that IL-6 induces a reduction in CYP2C9 mRNA levels in human hepatocytes. IL-6 was found to decrease rifampicin- and phenobarbital-mediated induction of CYP2C9 by negatively regulating PXR and CAR gene expression [54]. In addition, inhibition of IL-6 signalling by the monoclonal antibody sirukumab reversed suppression of CYP2C9 activity in patients with rheumatoid arthritis [55]. The cytokine-mediated downregulation of CYPs during inflammation suppresses patients' ability to metabolise CYP substrate drugs [56]. TNF-α is another of the main cytokines in the liver involved in inflammation. TNF-α treatment showed no effect on CYP2C9 mRNA levels but CYP2C9 protein levels were reduced by >95% after 24 hours of treatment [51]. The effects of inflammation, assessed by measuring metabolite formation of probe substrates of CYP2C9 (tolbutamide), showed reduced metabolite formation upon cytokine IL-6 treatment [57]. Exposure of differentiated hepatoma HepaRG cells or primary human hepatocytes to 10 ng/mL interleukin-22 (IL-22) was found to suppress mRNA expression of several major drug-metabolising CYPs including CYP2C9 [58]. Downregulation of hepatic drug-metabolising enzymes, notably CYP2C9, by inflammatory cytokines may contribute to the alteration of pharmacokinetics in patients suffering from acute and chronic inflammatory diseases in the event of COVID-19 infection, and may be the source of drug–drug interactions (Fig. 2).

3.3 CYP Genetic Variability and Susceptibility to COVID-19

Host genetic variability or polymorphisms play a key role in the susceptibility or resistance to viral infections, including COVID-19 [59]. The variation in symptoms and severity

of COVID-19 could be partially explained by known risk factors including age, sex and existing comorbidities such as diabetes, obesity, hypertension and cardiovascular diseases. However, severe COVID-19 observed in young adults hints that factors such as genetic variability may control the risk and severity [60]. Prevalence of infection was highest in patients of Black ethnicity, who are twice as likely to be infected with COVID-19 as compared with white patients, followed by patients of Hispanic and Asian ethnicity, with pooled adjusted risk ratios (RR) of 2.02, 1.77 and 1.50, respectively [61]. An observational cohort study in the UK found that the likelihood of being COVID-19 positive was slightly higher in South Asians, with an adjusted hazard ratio (HR) of 1.99, followed by Black with an HR of 1.69, mixed ethnicity with HR of 1.49 and other ethnicities with an HR of 1.20, as compared with White people [62].

CYP2C9 is a highly polymorphic enzyme, with 62 allelic variants identified and named thus far by the PharmVar Consortium, and the recently identified novel CYP2C9 variant (I213V) [63]. The most well-studied *CYP2C9* alleles are *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910), associated with the reduced metabolism of CYP2C9 substrates in vivo, such as warfarin and phenytoin [64]. *CYP2C9*2* is most prevalent in Middle Eastern populations (up to 18.1%) followed by South European populations (up to 16.5%), whereas *CYP2C9*3* is most abundant in Emiratis (21.3%) and South Asian populations (up to 11.9%), followed by South European populations (up to 10.1%) [64]. CYP genetic variances encompass intra-individual, inter-individual, intra-ethnic or inter-ethnic genetic polymorphisms [13]. It is well known that CYP polymorphisms determine the pharmacokinetic status of drugs (e.g. rate of metabolism, efficacy, production of metabolites and ADRs) and CYP variants result in either ultra-rapid or slow metabolisers [65]. However, whether CYP genetic variances determine susceptibility to SARS-CoV-2 infection and the correlation with COVID-19 severity is unknown.

Genetic variants of CYPs involved in pathologic processes, including the entrance of viruses into cells, anti-viral immunity and inflammatory response of COVID-19, are not entirely understood. What is known is that genetic variants of *ACE1*, *ACE2*, *TMPRSS2* and *GSTT1* are associated with a higher susceptibility to COVID-19. However, contradicting findings have not identified a connection between *ACE1* [66] or *ACE2* [67] and COVID-19. Considering the involvement of CYP2C9 and other CYPs in COVID-19 infection and drug metabolism, and the association of infection and inflammation with downregulation of hepatic and extrahepatic CYPs, the genetic variability of CYPs across ethnicities could play a role in COVID-19 resistance and/or susceptibility.

4 Drugs Used to Treat COVID-19

The majority of drugs used to treat COVID-19 are inducers or inhibitors of CYP2C9 (Table 1). Understanding the possible interactions of drugs and whether they induce or inhibit CYP2C9 is essential, especially where a combination of drugs is inevitable to combat severe COVID-19 infection and existing comorbidities in critically ill patients. This development of polypharmacy understanding would be beneficial to minimise potential complications, adverse drug reactions and therapeutic failure.

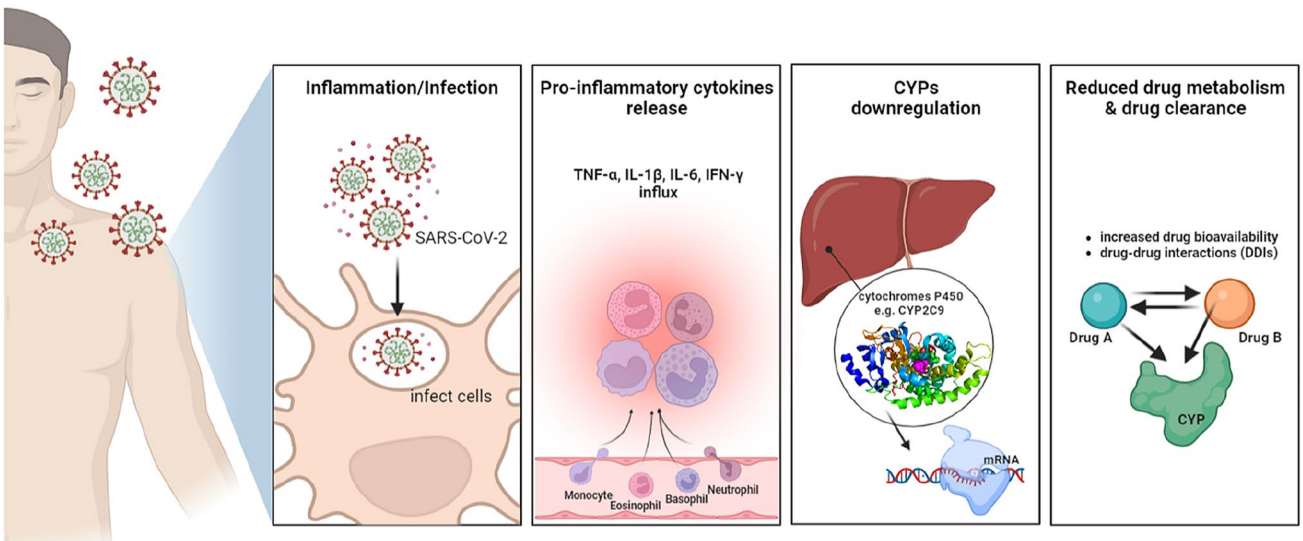

Fig. 2 Downregulation of hepatic cytochrome P450s responsible for drug metabolism and detoxification results in reduced clearance, elevated plasma drug concentrations and possible drug–drug interactions. *CYP* cytochrome P450, *TNF* tumor necrosis factor, *IFN* interferon

4.1 Inducers and Inhibitors of CYP2C9

4.1.1 Antibiotics

Isoniazid, an antibiotic and CYP2C9 inhibitor, and rifampin or rifampicin are standard anti-tuberculosis therapy to treat COVID-19 and *Mycobacterium tuberculosis* (MBT) co-infection [68]. Due to the combination of isoniazid and rifampin as the standard strategy for tuberculosis treatment and COVID-19 co-infection, the prospect of drug-induced liver injury is inevitable [69]. Therefore, patients taking both rifampin and isoniazid should be monitored closely for hepatotoxicity. Concurrent administration of isoniazid with the anti-seizure drug, valproate, which are both CYP2C9 inhibitors, could result in increased serum levels and decreased metabolism [70].

4.1.2 Anti-depressants

Fluoxetine and fluvoxamine are serotonin reuptake inhibitors (SSRIs) used to fight COVID-19 [30]. Fluoxetine is a weak CYP2C9 inhibitor [71] while fluvoxamine is a moderate CYP2C9 inhibitor. Fluoxetine showed anti-inflammatory activities in mouse models with SARS-CoV-2 infection, with significantly reduced lung tissue viral titres and inflammatory cytokines [72]. Dexamethasone, a widely used medication in patients with COVID-19 that have pneumonia, could cause pharmacodynamic interactions with fluoxetine as concurrent administration led to confusion, psychosis and agitation [30]. Fluoxetine deserves special attention due to its CYP inhibitory effects that could last for several weeks after discontinuation due to its long half-life and its metabolite norfluoxetine [73]. SSRI-like fluoxetine may potentially interfere with dexamethasone metabolism as the long half-life of fluoxetine means it would take a longer time for plasma concentrations to fall below clinically relevant concentrations and be eliminated from the system, possibly increasing the chances of drug–drug interactions [74]. Co-administration of fluvoxamine is contraindicated with drugs including linezolid, phenelzine and tranylcypromine which raise serotonin levels leading to elevated blood pressure, tremor, coma and death [75]. Based on the National Institutes of Health (NIH), fluvoxamine use could enhance serotonergic effects resulting in serotonin syndrome [76], which is commonly observed in patients with COVID-19 who exhibited hyper-reflexia or myoclonus, signs relatively specific for serotonin toxicity, that carries a significant risk of morbidity and mortality if left undiagnosed and untreated [77]. However, there is insufficient evidence to recommend either for or against fluvoxamine use in COVID-19 treatment [76].

4.1.3 Anti-seizure Drugs

Valproate, an anti-seizure drug (anti-epileptic or anti-convulsant), inhibits CYP2C9 enzyme activity. Lopinavir/ritonavir, a combination of repurposed drugs used in treatment of COVID-19, are CYP2C9 inducers that could increase metabolism of valproate, a CYP2C9 inhibitor, by inducing valproate glucuronidation [34]. Hepatoxicity is one of the adverse effects of valproate use and therefore, it is recommended to avoid administering valproate in patients with COVID-19 with abnormal liver functions [34]. Isoniazid is an antibiotic used for the treatment of tuberculosis and COVID-19 co-infection [68]. The metabolism of valproate could be inhibited by isoniazid, an antibiotic used for tuberculosis treatment, producing high serum levels of valproate leading to toxicity, especially in patients with epilepsy [78]. Both valproate and isoniazid inhibit CYP2C9 and concomitant use of both drugs could result in competition for the active sites of CYP2C9, resulting in decreased metabolism and increased serum levels of these drugs. Besides that, phenytoin, an anti-epileptic drug, could reduce lopinavir/ritonavir serum levels by 30%, and therefore patients with COVID-19 suffering from epilepsy who receives phenytoin may require an increase dosage of lopinavir/ritonavir of about 50% to maintain unaltered serum concentrations [20].

4.1.4 Anti-viral Drugs

Lopinavir/ritonavir is a combined anti-retroviral therapy used in COVID-19 therapy. Lopinavir/ritonavir use has drawbacks including its ability to modify hepatic metabolism of other drugs, its interaction/inhibition of CYP3A4, and induction of CYP2C9 and CYP2C19 [79]. Lopinavir/ritonavir, a CYP2C9 inducer, could interact with anti-depressants including fluoxetine, a CYP2C9 inhibitor [80]. Therefore, co-administration of a CYP2C9 inducer and inhibitor could alter the drug clearance, plasma concentration and the resulting clinical efficacy [80]. Ritonavir, a pharmaceutical enhancer used in nirmatrelvir–ritonavir (NMVr or Paxlovid, manufactured by Pfizer), was claimed to be an inducer of CYP2C9 [81, 82] as well as an inhibitor of CYP2C9 [83]. NMVr is used to treat symptomatic, non-hospitalised patients with COVID-19 who are at high risk of amplified severity, especially individuals with cardiovascular diseases [81]. Drugs that are CYP3A4 inducers (e.g. rifampicin, carbamazepine) may led to a decrease in nirmatrelvir and ritonavir concentrations, causing treatment failure against SARS-CoV-2 [84]. Similarly, remdesivir, one of the first anti-viral agent that the US Food and Drug Administration (FDA) approved for treatment of COVID-19, inhibits CYP2C9 activity [31]. Combination therapy with the CYP3A (and potential CYP2C9) inhibitor cobicistat and remdesivir showed a synergistic effect on the inhibition of

Table 1 Potential drug–drug interactions (DDIs) of inducers and inhibitors of CYP2C9 and interactions due to alteration of CYP3A4 activity

Classification	Drug(s)	CYP2C9 inhibitor or inducer	IC_{50} or K_i values	Pharmacodynamic or pharmacokinetic changes	References
Antibiotics	Isoniazid	Inhibitor	Isoniazid inhibited CYP2C9 with a K_i of 500 µM (in vitro)	Concurrent administration with valproate result in increased serum levels and decreased metabolism Combination of isoniazid and rifampin associated with liver injury and hepatotoxicity	[69, 70, 89]
Anti-depressants	Fluoxetine	Inhibitor	Fluoxetine inhibited CYP2C9, with the following K_i values: R-fluoxetine (13 µM), norfluoxetine (17 µM), RS-fluoxetine (19 µM), S-fluoxetine (62 µM) (in vitro)	Dexamethasone–fluoxetine interaction causes confusion, psychosis and agitation Fluoxetine may interfere with dexamethasone metabolism due to the long half-life of fluoxetine meaning it takes a longer time for plasma concentrations of fluoxetine to fall below clinically relevant concentrations	[30, 71, 73, 74]
	Fluvoxamine	Inhibitor	Fluvoxamine inhibited CYP2C9 with a K_i of 6.4–18.7 µM (in vitro)	Co-administration with linezolid, phenelzine and tranylcypromine raises serotonin levels, leading to elevated blood pressure, tremor, coma and death	[75, 90]
Anti-seizure drugs	Valproate	Inhibitor	Valproate inhibited CYP2C9 with a K_i of 600 µM (in vitro)	Isoniazid inhibits the metabolism of valproate, producing high serum levels of valproate, resulting in potential clinical toxicity in patients with epilepsy Rifampin or rifampicin, a CYP2C9 inducer, counteracts valproate's anti-epileptic effects, reducing valproate plasma concentrations and effectiveness	[34, 70, 78, 91]
Anti-virals	Lopinavir/ritonavir	Inducer	–	Administration of the anti-seizure drug, primidone, decreases serum concentrations of lopinavir/ritonavir Lopinavir/ritonavir, a CYP2C9 inducer, could interact with antidepressants including fluoxetine, a CYP2C9 inhibitor Co-administration of CYP2C9 inducers and inhibitors could alter the drug clearance, plasma concentration and resulting clinical efficacy	[34, 79, 80]
	Ritonavir (NMVr or Paxlovid)	Both inhibitor and inducer	K_i 4 µM (in vitro)	Co-administration with CYP3A4 inducers (e.g. rifampicin, carbamazepine) decreases nirmatrelvir and ritonavir concentrations, resulting in treatment failure against SARS-CoV-2	[81–84, 92]
	Remdesivir	Inhibitor	Remdesivir inhibited SARS-CoV-1 with an IC_{50} value of 0.069 µmol/L	Administration of the anti-seizure drug, primidone, decreased the serum concentration of remdesivir Patients with epilepsy and COVID-19 under primidone treatment are not recommended to use remdesivir concurrently	[31, 34, 93]

Table 1 (continued)

Classification	Drug(s)	CYP2C9 inhibitor or inducer	IC_{50} or K_i values	Pharmacodynamic or pharmacokinetic changes	References
Proton pump inhibitors (PPIs)	Omeprazole	Inhibitor	Omeprazole inhibit SARS-CoV-2 with an IC_{50} of 17.06 µmol/L	Omeprazole could enhance the anti-SARS-CoV-2 effects of aprotinin and remdesivir Co-administration increase voriconazole trough concentration PPI-mediated inhibition of CYPs increases plasma concentrations of voriconazole	[33, 85, 86, 94]
Steroids	Dexamethasone	Inducer	–	Reduced trough concentration when co-administered with voriconazole which is metabolised by CYP2C9	[33, 35]

IC_{50} Half-maximal inhibitory concentration, indicates how much drug is needed to inhibit a biological process by half, *K_i* dissociation constant, binding affinity between the inhibitor and the enzyme, e.g. the smaller the K_i, the smaller the amount of medication needed to inhibit the activity of that enzyme, *CYP* cytochrome P450, *NMVr* nirmatrelvir/ritonavir

SARS-CoV-2 replication in vitro, and decreased viral titres and COVID-19 progression in rodents in vivo [32]. Administration of the anti-seizure drug, primidone, was shown to decrease serum concentrations of remdesivir and lopinavir/ritonavir [34]. Patients with epilepsy and COVID-19 under primidone treatment are therefore not recommended to use remdesivir concurrently [34].

4.1.5 Proton Pump Inhibitors

Omeprazole, a proton pump inhibitor (PPI) originally used to suppress gastric acid production, was found to inhibit viral replication by interfering with the acidification of lysosomes and viral formation of SARS-CoV-2 beyond therapeutic plasma concentration at 8 µM [85]. At therapeutic concentrations, omeprazole could enhance anti-SARS-CoV-2 effects of aprotinin and remdesivir by 2.7-fold and 10-fold, respectively [85]. Proton pump inhibitors, except pantoprazole, are CYP2C9 inhibitors that could increase voriconazole trough concentration upon co-administration in patients with COVID-19 [33]. PPI-mediated inhibition of CYPs may lead to increased plasma concentrations of voriconazole, and patients with COVID-19 on concomitant use of PPI should be monitored for side effects [86].

4.1.6 Steroids

Steroids, such as dexamethasone, an inducer of CYP2C9, are widely used in patients with COVID-19 due to their anti-inflammatory and immunosuppressing effects [35]. Moreover, they have been reported to possibly reduce voriconazole trough concentration when co-administered with voriconazole, which is metabolised by CYP2C9 [33]. Since voriconazole is metabolised by CYP2C9 [87], any medication that affects this pathway can alter its plasma concentration. Moreover, given the narrow therapeutic window of voriconazole [88] and the relationship between efficacy and plasma concentration of voriconazole, drug monitoring of voriconazole in patients receiving a high dose of dexamethasone is recommended to achieve optimal response to treatment and minimal toxicity.

CYP2C9, CYP1A2, CYP2C8 and CYP3A4 are among the most shared enzymes, linked with approximately 77 COVID-19 drugs, indicating possible interactions upon co-administration [95]. Inhibitor drugs compete with other substrate drugs to bind with CYPs, leading to an increase of plasma area under the curve (AUC) values and a > 80% decrease in their clearance [95]. This review focuses on CYP2C9 but it is worth mentioning that some of the drug interactions described in Table 1 are due to induction and inhibition of CYP3A4. Inhibition of one or both CYP2C9

and CYP3A4 and/or other CYP isoforms, for instance, is the likely mechanism by which one drug slows the elimination of co-administered drugs and other drugs metabolised by these two enzymes [89]. A single drug could be an inducer, inhibitor or both, for one or more CYP isoforms. Lopinavir/ritonavir combination therapy used in COVID-19 treatment was designed in a way that a low dose of ritonavir is added to protease inhibitors to take advantage of the potent inhibition of CYP3A4, thereby raising the plasma concentration of the co-administered lopinavir [82]. Ritonavir is both an inducer and inhibitor of CYP2C9 and CYP3A4, inhibits CYP2D6 and induces CYP2B6, CYP2C19 and CYP1A2; therefore, co-administration of multiple drug substrates, e.g. rifampin or rifampicin, would lead to drug interactions. CYP3A4 inducers (e.g. rifampicin, carbamazepine) cause a reduction of ritonavir concentrations, resulting in treatment failure against SARS-CoV-2 [84].

4.2 CYP2C9-Metabolised Drugs

Many medications authorized for emergency use to treat COVID-19 are CYP2C9-metabolised drugs including anaesthetic drugs, antibiotics, anti-coagulants, anti-diabetics, anti-fungals, anti-hypertensives, anti-inflammatory and lipid-lowering drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) and phosphodiesterase (PDE) inhibitors (Table 2). Concurrent use of CYP2C9-metabolised drugs with CYP2C9 inducers or inhibitors could trigger drug–drug interactions as well as therapeutic failure. Furthermore, potential interactions between CYP2C9-metabolised drugs and other drugs sharing similar metabolic pathways are recommended to consider the context of CYP2C9 polymorphisms [96].

4.2.1 Anaesthetics

Propofol, an anaesthetic agent, is commonly administered to achieve ventilator synchrony in critically ill patients with COVID-19, but its safety profile is undetermined [97]. Propofol is formulated in a phospholipid emulsion and may lead to hypertriglyceridaemia at high doses and/or long duration of use [97]. COVID-19 may lead to hypertriglyceridaemia development more often and at low cumulative doses of propofol, indicating that COVID-19 may impact the metabolism and utilisation of triglycerides [97]. Propofol is metabolised by CYP2C9 and the concurrent use of a CYP2C9 enzyme inducer (e.g. lopinavir/ritonavir) might lead to decreased serum concentrations, which then complicates atrial fibrillation management in patients with COVID-19 [36].

4.2.2 Anti-coagulants

Patients with severe COVID-19 have a high risk of thromboembolism, and individuals with lower vitamin K levels are prone to pro-thrombotic conditions [18]. This may lead to poorer outcomes among patients with COVID-19 on warfarin treatment, which works by antagonising vitamin K [18]. The clinical evidence on the impact of regular use of warfarin on COVID-19-related thromboembolism observed in patients with severe COVID-19 is lacking. The S-enantiomer of warfarin is metabolised by CYP2C9 and is five times more potent than the R-isomer, and the R-isomer is metabolised by CYP1A2 and CYP3A4. Drugs that inhibit CYP2C9, CYP1A2 and/or CYP3A4, such as remdesivir, can increase the international normalized ratio (INR) by increasing exposure to warfarin [98]. Decreased levels of R-warfarin may cause reduced anti-coagulation in patients with COVID-19, leading to a higher risk of arterial or venous thromboembolism (VTE) [37].

Azithromycin, a macrolide antibiotic used in patients with COVID-19 to reduce the risk of secondary infection [29], was thought to be unlikely to interact with warfarin, but azithromycin–warfarin interaction was captured, with a resultant increase in the international normalized ratio (INR) in some patients ranging from 1.75–3.03 to 8.32 [99]. The infectious process may exert effect on the functioning of CYPs that are responsible for warfarin's biotransformation. The inflammatory cytokines released during COVID-19 infection downregulate CYP2C9 expression and could be the culprits in slowing the metabolism of warfarin, leading to increased INRs with warfarin in patients taking antibiotics such as azithromycin [99]. Due to the long half-life of azithromycin of about 2–4 days, interactions may persist even days after discontinuation [100]. Despite studies suggesting that azithromycin may potentiate warfarin activity, clinical events due to excessive anti-coagulation caused by warfarin are controversial because of different patient factors and study designs [100]. Patient factors refer to individuals living with diabetes mellitus and cardiovascular (e.g. atrial fibrillation, ischemic stroke, prosthetic heart valve, venous thromboembolism and anti-phospholipid antibody syndrome) and respiratory illnesses that require periodic check-ups to ensure the effectiveness of warfarin therapy as the INR of these patients needs to be monitored regularly, especially in patients with COVID-19 [101]. Patients with genetic variants of CYP2C9 require lower doses of warfarin and a longer time to reach a stable dose, accompanied by a higher risk of over-anti-coagulation and serious bleeding [102], which healthcare providers should consider, especially in patients with COVID-19. The gene-based warfarin dosing [102] approach is therefore recommended for patients with COVID-19 on warfarin therapy.

Table 2 Cytochrome P450 (CYP) 2C9-metabolised drugs for treating COVID-19 and their respective drugs that may cause drug–drug interactions (DDIs)

Classification	Drug(s)	Co-administered drug(s) that may cause DDIs	Pharmacodynamic or pharmacokinetic changes	References
Anaesthetics	Propofol	Lopinavir/ritonavir	Concurrent use decreases serum concentration, which then complicates atrial fibrillation management in patients with COVID-19	[36]
Anti-coagulants	Warfarin	Ritonavir, Remdesivir	Drugs that inhibit CYP2C9, CYP1A2 and/or CYP3A4, such as remdesivir, can increase INR by increasing exposure to warfarin Decreased levels of warfarin may reduce anti-coagulation leading to higher risk of arterial or venous thromboembolism (VTE)	[37, 98]
		Azithromycin	Slowing the metabolism of warfarin leading to increased INRs with warfarin in patients taking antibiotics such as azithromycin Long half-life of azithromycin of about 2–4 days, interactions may persist even after days of discontinuation Azithromycin–warfarin interaction based on patient factors	[99–101]
Anti-diabetics	Glibenclamide, glimepiride, glipizide and glyburide	Bosentan	Higher incidence of hepatic injury in patients who concomitantly use bosentan and glyburide (glibenclamide)	[2, 44, 103]
Anti-fungals	Voriconazole	Lopinavir/ritonavir, atazanavir and hydroxychloroquine	Voriconazole can induce severe hyperkalaemia in patients with COVID-19 with severe inflammation, when serum voriconazole level was elevated or when voriconazole–drug interactions occur Co-administration with atazanavir would lead to significant drug–drug interactions and elevated plasma concentrations, commonly observed in patients with hepatic impairment.	[105–107]
Anti-hypertensives	Irbersartan, losartan and azilsartan	Ritonavir (nirmatrelvir/ritonavir [NMVr] or Paxlovid)	Co-administration led to hypotension	[81]
	Bosentan	Ritonavir	Increased the concentration of bosentan by 48-fold, bosentan was recommended to be discontinued for at least 36 hours before administration of NMVr	[81]

Table 2 (continued)

Classification	Drug(s)	Co-administered drug(s) that may cause DDIs	Pharmacodynamic or pharmacokinetic changes	References
Anti-inflammatory drugs	Montelukast	Levocetirizine	Remarkable synergistic anti-inflammatory effects, preventing COVID-19 progression Could interact with CYP2C8 substrates such as rifampin/rifampicin, an inducer of CYP2C8, which was also used to treat COVID-19 co-infection	[68, 112]
	Ruxolitinib	Fluconazole	Fluconazole inhibits CYP2C9, altering drug clearance and toxicity of ruxolitinib	[114]
	Ruxolitinib, colchicine	Anti-neoplastic drugs	Ruxolitinib co-administration with alectinib, brigatinib or ceritinib may cause increased bradycardiac effect and increased ruxolitinib serum concentration Co-administration of colchicine with abiraterone, ceritinib and cisplatin led to increased serum concentration and uricemia	[5]
Lipid-lowering drugs	Rosuvastatin	Ritonavir (NMVr or Paxlovid)	Decrease in plasma levels of statins	[81]
NSAIDs	Ibuprofen	Warfarin	Co-administration triggered bleeding independently or because of drug–drug interactions when used concurrently	[119]
	Celecoxib		Bleeding, especially in patients with CYP2C9 gene variant	[117]
Phosphodiesterase inhibitors	Sildenafil (Viagra)	Bosentan	Patients with pulmonary arterial hypertension (PAH) may experience drug–drug interactions, with reduced sildenafil plasma concentrations and increased bosentan plasma concentrations	[122]

4.2.3 Anti-diabetic Drugs

COVID-19 infections are linked to cytokine storms that may cause blood–brain barrier (BBB) injury, where activated immune cells and severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) can pass into the brain, activating glial cells and leading to neuroinflammation [2]. Glibenclamide, an anti-diabetic drug metabolised by CYP2C9, could reduce neuroinflammation and BBB injury by inhibition of nod-like receptor pyrin 3 (NLRP3) inflammasome, microglial activation, oxidative stress and reducing the release of pro-inflammatory cytokines [2]. Other anti-diabetic agents metabolised by CYP2C9 used in patients with COVID-19 include sulfonylureas such as glimepiride, glipizide and glyburide [44]. Glyburide (glibenclamide) has been shown to downregulate pro-inflammatory cytokine expression, reduce mRNA expression of macrophages and inhibit NLRP-3 inflammasome which is indicative of the anti-inflammatory properties of sulfonylureas in reducing the mortality risk of patients with COVID-19 [19]. There is a higher incidence of hepatic injury in patients who concomitantly use bosentan and glyburide [103].

4.2.4 Anti-fungals

Voriconazole is metabolised by CYP2C9, and concurrent use with lopinavir/ritonavir that induces CYP2C9 is not recommended [104]. However, there are contradicting findings on concurrent use of voriconazole and lopinavir/ritonavir, as some studies have found that the area under the concentration-time curve (AUC) and maximum concentration (C_{max}) of voriconazole decreased; while, other studies have shown

Table 3 Herbs and phytochemicals that inhibits CYP2C9 and their anti-COVID-19 properties

Herb(s)/phytochemical(s)	Effects on CYP2C9	Anti-COVID-19 properties	References
Boswellia serrata (Indian olibanum), *Citrus paradisi* (grapefruit), *Echinacea purpurea*, *Eschscholzia california* (California poppy or golden poppy), *Matricaria chamomilla* (*Matricaria recutita*, German or wild chamomile), *Panax ginseng*, *Rhodiola rosea* (golden root, rose root, roseroot, Arctic root, lignum rhodium and orpin rose)	Inhibitor	Not specified, but these herbs have been used during the COVID-19 pandemic	[23]
Eleutherococcus senticosus (devil's bush or Siberian ginseng)	Inducer		
Tangeretin (TAN)	Inhibitor	Anti-viral properties	[24]
		In silico prediction: binds to M^{pro} SARS-CoV-2 receptors and carries out a nucleophilic attack on the amino acids of the receptor	
Gallic acid, quercetin, ribavirin, resveratrol, naringenin, benzoic and ellagic acids	Inhibitor	Binds to SARS-CoV-2 polymerase	[25]
Ginger	Inhibitor	Not specified, but commonly used among self-isolating patients with COVID-19 concurrently with clinically used drugs	[26]
Amentoflavone (found in St. John's wort, *Gingko biloba*, *Selaginella tamariscina*, and *Torreya nucifera*)	Inhibitor	In silico prediction: binds strongly to the active site of the main protease (M^{pro}) of the COVID-19 virus	[27]
Herbal extract of Jinyin granules (HEJG)	Inhibitor	Co-administered with anti-viral (e.g. remdesivir, lopinavir/ritonavir) and anti-inflammatory drugs	[123]
Qingfei Paidu (QPD)	Inhibitor		

an unexpected increase in voriconazole concentration when co-administered with lopinavir/ritonavir in patients with COVID-19 [104]. Voriconazole can induce severe hyperkalaemia in patients with COVID-19 with severe inflammation, when serum voriconazole level was elevated or when voriconazole–drug interaction occurs [105]. Among the experimental COVID-19 therapies, voriconazole was found to interact with atazanavir and hydroxychloroquine [106]. Voriconazole is a substrate and inhibitor of CYP2C9 and co-administration with atazanavir, for instance, would lead to significant drug–drug interaction [107] and elevated plasma concentrations, commonly observed in patients with hepatic impairment.

4.2.5 Anti-hypertensive Drugs

Angiotensin-receptor blockers such as irbersartan, losartan and azilsartan, are metabolised by CYP2C9. Co-administration of these blood pressure lowering drugs with NMVr [81] can lead to hypotension, since NMVr induces CYP2C9 and thus enhances metabolism of these anti-hypertensives. Bosentan, a pulmonary hypertension drug, is also metabolised by CYP2C9. Co-administration of bosentan with ritonavir was found to increase the concentration of bosentan by 48-fold, and therefore, concomitant use of bosentan and NMVr is contraindicated [81]. As a result, bosentan was recommended to be discontinued for at least 36 hours before administration of NMVr [108]. Angiotensin receptor blocker such as valsartan are also used in patients with COVID-19 [109]. CYP2C9 is the only CYP isoform responsible for 4-hydroxylation of valsartan in human liver microsomes, and therefore, CYP-mediated drug–drug interactions between valsartan and other co-administered drugs would be negligible [110].

4.2.6 Anti-inflammatory Drugs

Montelukast, a bronchodilator and anti-inflammatory drug used in asthma patients, is extensively metabolised by CYP2C9 and, could reduce pro-inflammatory cytokines in patients with COVID-19 [38]. Montelukast is also a strong inhibitor of CYP2C8 [111], and therefore could interact with CYP2C8 substrates such as rifampin/rifampicin, an inducer of CYP2C8, which was also used to treat COVID-19 coinfection [68]. Despite the possible risk of drug–drug interactions and complications in patients with COVID-19, a combination of montelukast and levocetirizine, a third-generation antihistamine, exhibits remarkable synergistic anti-inflammatory effects, preventing COVID-19 progression [112]. Multi-drug therapy including ivermectin, azithromycin, montelukast and acetylsalicylic acid, called TNR4 therapy, showed improved recovery and prevented hospitalisation and death in patients with COVID-19 [113]. Similarly, ruxolitinib, a Janus kinase inhibitor, is also metabolised by CYP2C9 [114]. Ruxolitinib use in patients with COVID-19 could be affected by fluconazole that inhibits CYP2C9,

leading to compromised drug clearance and toxicity [114]. Anti-neoplastic drugs (e.g. alectinib, brigatinib, ceritinib, abiraterone and cisplatin) were found to have potential interactions with anti-inflammatory drugs including ruxolitinib and colchicine [5].

4.2.7 Lipid-Lowering Drugs

Statins could be useful in COVID-19 treatment as statins could bind to the key virus protease (M^{pro}), suppress activation of NF-κB and exert anti-inflammatory effects [115]. Rosuvastatin is metabolised by CYP2C9. Since ritonavir induces CYP2C9, co-administration of NMVr would be expected to decrease plasma levels of rosuvastatin, but the mechanism remains to be explored [81]. Therefore, patients with COVID-19 with cardiovascular diseases are recommended to discontinue rosuvastatin or to increase the dosage if co-administered with NMVr [81].

4.2.8 NSAIDs

CYP2C9 is known to be involved in the metabolism of NSAIDs, such as ibuprofen, that are commonly prescribed drug for the management of pain and fever. CYP2C9 varies substantially across ethnic groups, influencing drug responses and toxicity, where European populations are more likely to show impaired ibuprofen metabolism than Sub-Saharan and East Asian populations [116]. NSAIDs could be harmful to patients with COVID-19 as it upregulates angiotensin-converting enzyme 2 (ACE2) receptors in multiple organs, which serve as COVID-19 virus entry points into cells [21]. WHO, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) did not advocate against ibuprofen use for COVID-19, but recommended careful monitoring [21].

NSAIDs such as celecoxib, a cyclooxygenase-2 (COX-2) inhibitor, have given a glimmer of hope in COVID-19 therapy by inhibiting viral replication and inflammasomes [39]. However, celecoxib exhibited cardiovascular toxicity, primarily in patients with autoimmune diseases [39]. Celecoxib is primarily metabolised by CYP2C9, and patients who lack CYP2C9 activity have an increased exposure to celecoxib and its side effects [117]. Targeting celecoxib to alveolar macrophages in the lungs via inhalation could offer superior efficacy at a lower dose as compared with higher doses administered via other routes, and reduces the side effects [118]. Exposure to warfarin and ibuprofen was found to trigger the occurrence of bleeding independently or as a result of drug–drug interaction when used concurrently [119]. Metabolism of warfarin was perturbed and led to bleeding with co-administration of celecoxib, especially in patients with variant CYP2C9 genes [117].

4.2.9 PDE Inhibitors

Sildenafil is metabolised by CYP2C9 and its administration in patients with COVID-19 and pneumonitis and acute respiratory distress syndrome (ARDS) showed improved oxygen delivery and cardiac output as a result of reduced pulmonary vascular resistance [120]. Moreover, sildenafil specifically targets pulmonary vasodilation, which has emerged as an effective first-line oral therapeutic agent in infants and in all age groups with severe COVID pneumonia-causing pulmonary arterial hypertension (PAH) [121]. Concomitant use of sildenafil and bosentan in patients with PAH is associated with substantial drug–drug interactions, with a reduction in plasma concentrations of sildenafil and increased bosentan concentrations [122].

5 Herbs with Anti-COVID-19 Properties: CYP2C9 Inhibitors, Inducers

A study in Italy documented herbs and/or botanicals used during the COVID-19 pandemic, based on the analysis carried out by the National Association of Health Products Manufacturers and Distributors (Federsalus) and IQVIA data (from 8000 pharmacies and 400 parapharmacies) collected between October 2019 and October 2022 [23]. The following botanicals showed inhibitory effects on CYP2C9: *Boswellia serrata* (Indian olibanum), *Citrus paradisi* (grapefruit), *Echinacea purpurea*, *Eschscholzia californica* (California poppy or golden poppy), *Matricaria chamomilla* (*Matricaria recutita*, German or wild chamomile), *Panax ginseng* and *Rhodiola rosea* (golden root, rose root, roseroot, Arctic root, lignum rhodium, and orpin rose), while inducing effects on CYP2C9 were seen with *Eleutherococcus senticosus* (devil's bush or Siberian ginseng) [23]. Tangeretin (TAN), a citrus polymethoxyflavone with anti-viral properties and a CYP2C9 inhibitor, was found to penetrate the central nervous system (CNS) with zero drug residues accumulating in blood and lumen of the gastrointestinal tract and without toxicological risk in rats [24]. An in silico study predicted that TAN could bind to M^{pro} SARS-CoV-2 receptors and carry out a nucleophilic attack on the amino acids of the receptor, suggesting the viability of including TAN in COVID-19 treatment plans [24].

Molecular docking simulations predicted that polyphenolic compounds such as gallic acid and quercetin exhibited higher binding affinity than ribavirin towards SARS-CoV-2 polymerase along with high drug similarities and pharmacokinetic properties [25]. Likewise, resveratrol, naringenin, benzoic and ellagic acid all showed efficacy as polymerase inhibitors [25]. These polyphenols, including resveratrol, quercetin and naringenin, are known to inhibit CYP2C9. Therefore, development of these compounds to

inhibit SARS-CoV-2 polymerase would need to consider the CYP2C9 inhibition and metabolism of drugs by CYP2C9, especially in patients with COVID-19 with secondary illnesses that require combinations of drugs. Ginger, a known CYP2C9 inhibitor, was a common herb used among self-isolating patients with COVID-19 with a combination of clinically used drugs, leading to herb–drug interactions [26].

Amentoflavone is a bio-flavonoid found in herbs such as St. John's wort, *Gingko biloba*, *Selaginella tamariscina* and *Torreya nucifera*, and acts as a potent inhibitor of CYP2C9 [27]. Molecular docking studies have shown that amentoflavone binds strongly to active site of the main protease (M^{pro}) of the COVID-19 virus. However, administration of amentoflavone should be adjusted with other CYP2C9 inhibitors, e.g. warfarin, to avoid the risk of toxicity due to increased bioavailability during concurrent use [27]. A combination of traditional Chinese medicine (TCM) with clinically used drugs was considered as an effective approach to fight COVID-19 infection. Jinyin granules are recurrently co-administered with anti-viral (e.g. remdesivir, lopinavir/ritonavir) and anti-inflammatory drugs [123]. A herbal extract of Jinyin granules (HEJG) [123] and Qingfei Paidu (QPD) that comprises 21 herbs showed inhibitory effects on CYP2C9 in a dose-dependent manner [28]. Inhibition of CYP2C9 by these herbs may lead to HDIs [123]. Table 3 shows herbs and phytochemicals that inhibits CYP2C9 and their anti-COVID-19 properties.

6 COVID-19 Vaccines: CYP2C9 Downregulation

Most COVID-19 vaccines are designed to elicit immune responses, ideally neutralizing antibodies (NAbs), against the SARS-CoV-2 spike protein [124]. Once stimulated, the immune system sets off a complex series of innate immune events encompassing phagocytosis, release of inflammatory mediators, e.g. chemokines and cytokines, and cellular recruitment [125]. The activated innate immune response generally decreases CYP enzyme activity, and these interactions extend to drug transporters and organs, impacting drug absorption, distribution, metabolism and excretion (ADME) [126]. Therefore, altered ADME is predicted after SARS-CoV-2 (COVID-19) vaccination [126].

A patient with colorectal cancer on long-term anti-programmed death 1 (anti-PD-1) monotherapy was found to experience cytokine release syndrome (CRS) 5 days after vaccination with BTN162b2 (tozinameran)—the Pfizer/BioNTech mRNA COVID-19 vaccine [127]. The CRS was demonstrated by raised inflammatory markers, thrombocytopaenia, elevated cytokine levels (IFN-γ/IL-2R/IL-18/IL-16/IL-10) and steroid responsiveness [127]. Adenovirus-based vaccines expressing mouse-adapted H1N1 influenza viruses were found to suppress CYP3A activity by 55% in mice after 24 hours [128]. These findings suggest that vaccinations leading to immune response activation and cytokine release could suppress CYP expression. Autopsies and RNA sequencing performed on patients who died 1–10 days after receiving their second COVID-19 vaccination found an abnormal secretion of cytokines, suggesting a cytokine storm could be triggered following vaccination, resulting in systemic immune response syndrome (SIRS) and death [129].

The involvement of interferons has been found to greatly reduce CYP-dependent drug biotransformation since the 1980s [130]. The associated decrease in CYP mRNAs strongly suggests a transcriptional mechanism, possibly involving transcription factors, in the inflammatory and immune response [131]. Activation of transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), represses the glucocorticoid receptor (GR), thereby downregulating expression of the constitutive androstane receptor (CAR) and its associated genes, including CYPs [132]. Figure 3 illustrates the possible mechanism of vaccine-induced cytokine release leading to the activation of transcription factors and downregulation of associated genes, including CYPs.

The concurrent use of drugs metabolised by CYP2C9, both inducers and inhibitors, should be taken into consideration by healthcare providers, particularly in patients with COVID-19 who received vaccines. As mentioned earlier, CYP2C9 is responsible for anti-seizure or anti-epileptic drug metabolism. Potential interactions between COVID-19 vaccines and anti-epileptic drugs could occur after vaccination [133]. The serum concentration of anti-epileptic drugs would significantly increase, as CYP2C9 may be downregulated with cytokine release after vaccination, leading to drug–vaccine interactions and possible hyper-toxicity. Interactions between vaccines and drugs are likely to be caused by interactions of inflammatory cytokines and CYPs, leading to a reduction in drug metabolism. As the clinical evaluation of vaccines for COVID-19 are on the rise, studies to evaluate the impact of emerging vaccines on CYP2C9 and other metabolic enzymes are necessary to circumvent therapeutic failures that could further compromise public health during infectious disease emergencies.

7 Future Directions and Conclusions

The present review summarised current evidence of the relationship between CYP expression and cytokine storms during COVID-19 infections, with a specific focus on CYP2C9; CYP gene variances that make certain ethnicities more susceptible to COVID-19 infection; drug–drug interactions and the subsequent side effects including treatment failure, hepatotoxicity or delayed metabolism resulting

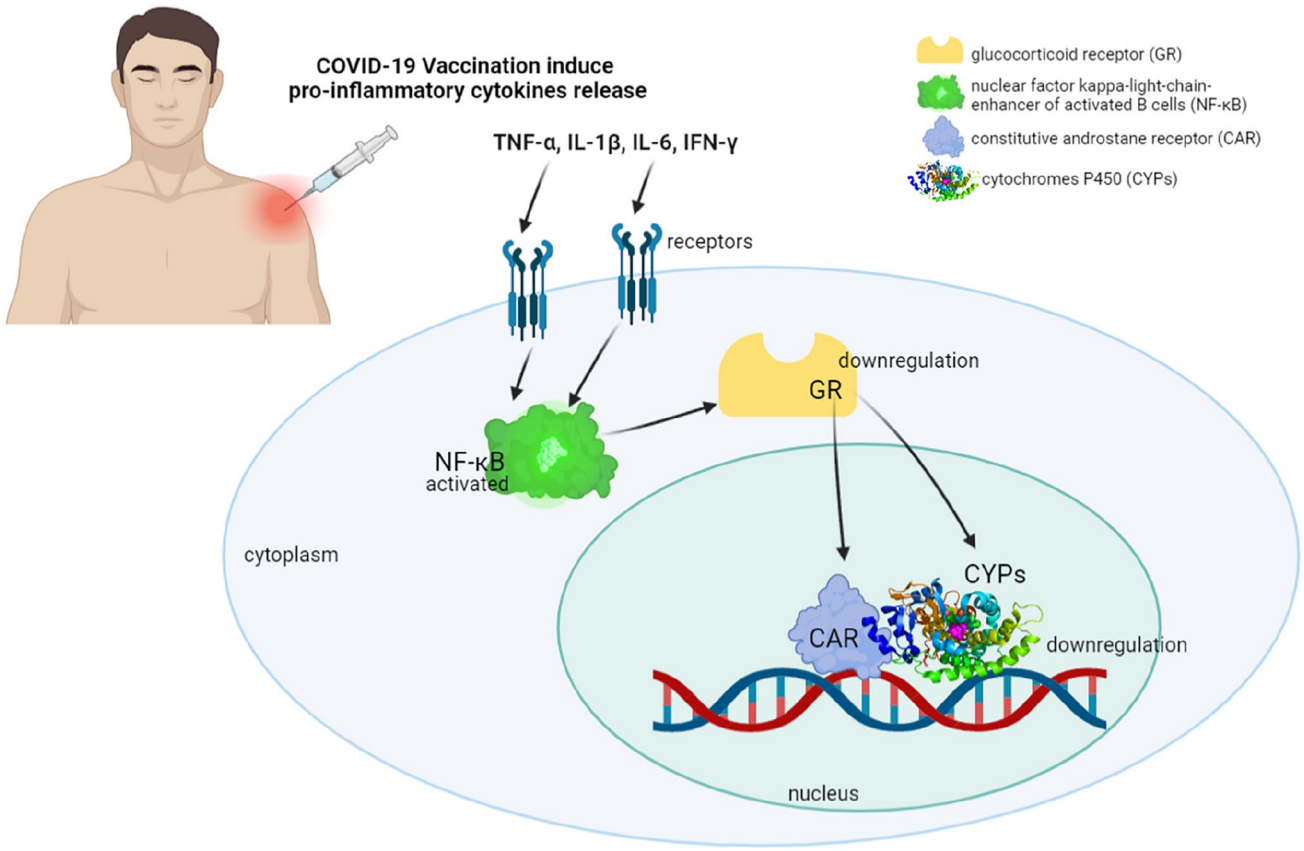

Fig. 3 COVID-19 vaccine-induced cytokine release activates transcription factor, NF-κB, repressing GR and thereby downregulating CAR and CYPs. *IFN* interferon, *TNF* tumor necrosis factor

from the co-administration of drugs; and combination or multi-drug therapy, including CYP2C9 inhibitors, inducers or CYP2C9-metabolised drugs, relative to any interactions due to the alteration of other CYPs including CYP3A4. Further, we reviewed herbs and phytochemical compounds with anti-COVID-19 properties that showed inhibition of the virus in silico, and the closely associated cytokine storm after COVID-19 vaccination that downregulates CYPs, impacting drug metabolism, efficacy and outcome of CYP2C9 substrate drugs. Genetic variability or polymorphisms determine the susceptibility or resistance of an individual to viral infections, including COVID-19. However, studies on CYP2C9 polymorphism that may determine the degree of COVID-19 susceptibility of different ethnicities with different genetic makeup are lacking. So far, studies have targeted the gene variances of cell surface receptors, including TMPRSS2 and ACE2, which SARS-CoV-2 binds to and enters the cell, but there are hardly any published experimental data validating variations in CYPs or CYP2C9 that may impact COVID-19 susceptibility. A recent study using unsupervised learning algorithms identified CYP2C9 as a potential therapeutic target for COVID-19, with highest scores selected by the Structure Preserving Nonnegative Feature Self-Representation (SPNFSR) algorithm [134]. In view of the involvement of CYPs during the early stages of COVID-19 inflammation and even after COVID-19 vaccination, plus CYP-driven drug interactions, metabolism and efficacy, CYPs, especially CYP2C9, could be a distinctive target gene to reduce COVID-19 fatalities.

Drugs used to combat COVID-19 infection could be metabolised by, inhibit, or induce different CYP isoforms, e.g. CYP1A2 and CYP3A4, at the same time. This adds to the complexity and challenge for drug prescription and finding the best therapeutic regimen. The studies and case reports collected in this review compare varied types and dosages of COVID-19 medications, and hence may not be generalized to the entire population. The present review on CYP2C9 and COVID-19 makes deductions from case reports and limited experimental data. Future studies are recommended to explore CYP2C9 genetic variabilities which could be the forefront of innovation for gene therapies that modify patients' DNA to alleviate a genetic condition that may make them more susceptible to COVID-19, as existing mRNA vaccines does not enter the cells or interact with DNA, hence does not constitute gene therapy.

Studies targeting the COVID-19 virus protease may be useful for containing the COVID-19 endemic, but this effort may be futile as the virus evolves continuously and develops variants that are capable of escaping the immune system. These COVID-19 variants may efficiently hijack cells, allowing them to spawn mutations that escape immunity more easily, and leading to cytokine storms. SARS-CoV-2 Omicron, for instance, is an immune escape variant with an altered cell entry pathway which exhibited a shift from cell surface fusion to cathepsin-dependent fusion within the endosome, taking the COVID-19 challenge to the next level [135]. Multi-factorial drug–gene interactions (DGIs) that incorporate clinical considerations of DDIs and HDIs, along with pharmacogenetic and herbo-genetic interventions, are warranted to develop personalised COVID-19 therapies. Concerted efforts could turn the current unprecedented COVID-19 challenge into a unique opportunity to find a cure for current or future viral respiratory diseases, possibly by targeting cytochrome P450s.

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