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REVIEW

CYP2C8-Mediated Drug–Drug Interactions and the Factors Influencing the Interaction Magnitude

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Background: Older adults often have multiple morbidities that may lead to polypharmacy. Cytochrome P450 (CYP) 2C8 has shown significant contributions in the metabolism of various medications; however, its related drug–drug interactions (DDIs) appear to be underrecognized in clinical practice compared to the major CYP enzymes (eg, CYP3A4, CYP2D6). This review summarizes the progress of CYP2C8-mediated DDIs and factors influencing the interaction magnitude.

Methods: Using CYP2C8 and drug interactions as the search terms, literature was searched through PubMed, Web of Science, and Embase as of January 2025. Eligible studies were identified following PRISMA guidelines. Screening and inclusion were assessed by two independent reviewers and 57 studies met inclusion/exclusion criteria.

Results: Based on authoritative sources (FDA, EMA, DrugBank), and literature, this review identified 5 inducers, 53 strong/moderate inhibitors, and 32 major/intermediate substrates of CYP2C8. Typical examples were illustrated to predict DDIs by in vitro-in vivo extrapolation. The factors influencing DDI magnitude include genetic polymorphisms (CYP2C8, SLCO1B1, UDP-glucuronosyltransferase, and pregnane X receptor), hepatic and renal function, properties of CYP2C8 perpetrators (dose, treatment course, systemic concentrations, time after discontinuation, inhibitory potency, inhibitory abilities of metabolites on CYP2C8), properties of object drugs (whether the active metabolite of object drug is a CYP2C8 substrate, therapeutic index, stereoselectivity), differences in DDI risk for drugs from similar therapeutic classes, and whether multiple interaction mechanisms are involved. Some botanical supplements showed potential to influence CYP2C8 in vitro or in animal experiments.

Conclusion: CYP2C8 is an important but underrecognized DME. This article reviewed its main substrates, perpetrators, DDIs, and methods for predicting interactions, and provided the first comprehensive summary of the factors influencing the interaction magnitude. Such knowledge will enhance the awareness of clinical professionals regarding safe medication for older adults. Further advances will emerge if the gaps in current knowledge and priorities for future research are recognized.

Keywords: cytochrome P450 2C8, drug interactions, older adults, pharmacokinetics, safety

Introduction

Cytochrome P450 (CYP) enzymes, mainly expressed in the liver and gut mucosa, are involved in the metabolism of various drugs, and their activity can significantly affect the pharmacokinetics and pharmacodynamics of these drugs.[1] Zanger et al investigated the elimination pathways of the 200 most commonly sold prescription drugs in the United States. The majority of hepatically eliminated drugs involve family 1, 2 or 3 CYP enzymes. The most common are CYP3A4/5, CYP2C9, CYP2D6, and CYP2C19, accounting for approximately 79% of the oxidative metabolism of these drugs.[2] As for CYP2C8, it metabolizes weakly acidic compounds with relatively large molecular weights (eg, cerivastatin, paclitaxel and pioglitazone).[3] A number of drugs are CYP2C8 inhibitors (eg, gemfibrozil, clopidogrel) and inhibiting this isozyme could cause drug–drug interactions (DDIs). Since cervastatin was withdrawn from the world

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market in 2001 due to fatal rhabdomyolysis partially associated with CYP2C8-mediated DDIs,[4] CYP2C8 has gradually emerged as an important drug-metabolizing enzyme (DME). In addition, the clinical significance of CYP2C8 was highlighted when clopidogrel, one of the most commonly used antiplatelet drugs used to prevent heart attack or stroke, was found to be a potent inhibitor of CYP2C8 via its acyl-β-D-glucuronide in 2014,[5] which led to concerns about its mediated DDIs. Also, there is substantial inter-individual variability in the protein expression and catalytic activity of CYP2C8, which leads to significant differences in drug metabolism and therapeutic effects among subjects with different variants of *CYP2C8*.[6]

Older adults often suffer from multiple morbidities that may lead to polypharmacy, that is, frequent use of at least five drugs. These situations will increase the likelihood of adverse outcomes and healthcare costs. It is very important to find out potential DDIs in geriatric care.[7] Hewitt et al summarized the relative content of CYP isoforms in human liver and the contribution of each CYP to drug metabolism.[8] It is generally believed that CYP3A4 is the most important enzyme. On the one hand, it is the most abundant enzyme in the liver, accounting for approximately 30% of the total CYP enzymes. On the other hand, it participates in the metabolism of more than 50% of drugs. CYP2D6 accounts for only 2% of the total CYP enzymes. However, this enzyme is particularly important because 30% of clinically used drugs need to be metabolized through it, and it also has the characteristic of significant genetic polymorphism. As for CYP2C8, its relative content in the liver is approximately 7%.[3] Meanwhile, as the Zanger's investigation found,[2] CYP2C8 only contributes to the drug metabolism of 6% of the best-selling prescription drugs, so there may not be sufficient attention paid to CYP2C8 in clinical practice.

Medication reconciliation is a part of the medication management process that aims to avoid medication errors (eg, omissions, duplications, dosing errors, or drug interactions). When performing medication reconciliation upon hospital admission, we identified two potentially inappropriate medications (PIMs) in a 78-year-old patient who was receiving eight medications (metformin, pioglitazone, sitagliptin, acarbose, glimepiride, clopidogrel, atorvastatin, and amlodipine). First, glimepiride was identified as a PIM based on the Beers criteria because this long-acting antidiabetic agent had a higher risk of prolonged hypoglycemia than short-acting sulfonylureas.[9] Secondly, pioglitazone in combination with clopidogrel was inappropriate because clopidogrel could double the plasma exposure to pioglitazone due to inhibiting CYP2C8 by its acyl glucuronide metabolite.[10] In other words, it is equivalent to doubling the dosage of pioglitazone, which may lead to an increased risk of congestive heart failure, a severe adverse drug reaction that may occur after pioglitazone initiation or dose escalation. We discontinued pioglitazone and acarbose for this patient and switched to dapagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor. This case reminds us that in the real world of complex patients with polypharmacy, CYP2C8-related DDIs are still insufficiently recognized.

The aim of this review is to summarize the latest progress regarding CYP2C8-mediated DDIs and the factors that influence the magnitude of their interactions and highlight the importance of CYP2C8 in ensuring that medications are effective and safe for individual patients.

Methods

Search Strategy

Potentially relevant literature published from January 1, 1990, to January 31, 2025, was searched through PubMed (PubMed Advanced Search Builder: select "all fields", and enter a search term "CYP2C8 and drug interaction"), Web of Science Core Collection (advanced search interface: "abstract" containing "CYP2C8 and drug interaction"), and Embase (broad search "CYP2C8 and drug interaction", add field "title or abstract" containing "CYP2C8 and drug interaction", and select "Embase" from several sources options).

Selection Criteria

YLY and WYH independently retrieved the papers and screened the relevant studies. If there were differences regarding the inclusion or exclusion of relevant papers, consult ZLL and QZ. A total of 663, 510 and 300 papers were retrieved from PubMed, Web of Science Core Collection and Embase, respectively. After excluding duplicates, 667 literatures were further assessed. After careful reading of the abstracts, 536 documents were removed based on the inclusion criteria

(the abstract demonstrating CYP2C8-mediated DDIs and/or whether the investigated influencing factor had an impact or not on the degree of DDI), and the initial exclusion criteria [conference papers, chapters, erratum, notes (n=6), language not in English (n=3), the abstract did not specifically describe the CYP2C8-mediated DDI, or lacked experimental data on the interactions mediated by CYP2C8 such as inhibitory constant (K_i), the concentration causing half-maximal inhibition (IC_{50}), pharmacokinetic parameters, or induction capabilities, or the entire study failed to produce any positive findings related to CYP2C8 and only made a brief mention of CYP2C8 while concentrating on other DMEs] (n=527). The full text of the remaining articles was assessed to see whether they were qualified. Seventy-four documents were further excluded due to article types of reviews, meta-analyses, and systematic reviews. Fifty-seven articles were finally selected (Figure 1). The methodological quality of the included articles were examined. Totally, the in vitro experiments were well designed according to the research guidelines at that time. Clinical studies on pharmacokinetic interactions have all employed randomized controlled trial designs. There have been a limited number of observational studies, cohort studies, and case reports. Key messages from these articles were summarized and discussed.

Results and Discussion

Substrates and Perpetrators of CYP2C8

Drug Regulatory Requirements

US Food and Drug Administration (FDA) website lists numerous drugs closely related to CYP isoenzymes and transporter.[11] As for CYP2C8, repaglinide is a sensitive substrate which refers to a drug whose area under the concentration–time curve (*AUC*) increases by at least 5 times in the presence of strong inhibitors of a given metabolic

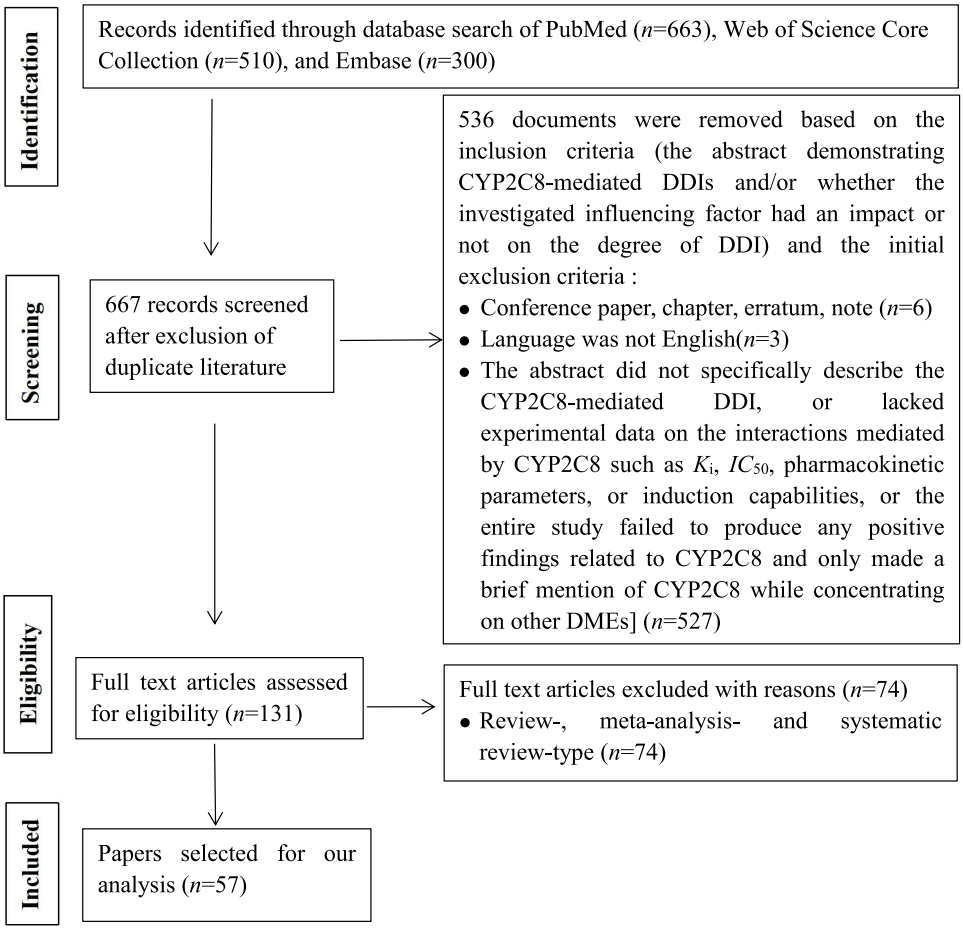

Figure 1 Flow chart showing selection of literature.
Abbreviations: DDI, drug–drug interactions; DMEs, drug-metabolizing enzymes; IC50, the concentration causing half-maximal inhibition; Ki, inhibitory constant.

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pathway, whereas montelukast, pioglitazone and rosiglitazone are moderate sensitive substrates (*AUC* increase: ≥2 to <5-fold). Rifampicin is a CYP2C8 moderate inducer, which means it can reduce the *AUC* of sensitive substrates by ≥50% to <80%. Strong or weak CYP2C8 inducers were not found on the FDA website, ie, the *AUC* of CYP2C8 substrates decreased by ≥80% and ≥20% to <50%, respectively. Based on the fold increase in the *AUC* of sensitive probe substrates, there are three types of CYP2C8 inhibitors: gemfibrozil is a strong inhibitor (≥5-fold); clopidogrel, deferasirox, and teriflunomide are moderate inhibitors (≥2-fold to <5-fold); and trimethoprim is a weak inhibitor (≥1.25-fold to <2-fold).

According to the European Medicines Agency (EMA) guidelines for drug interaction studies,[12] paclitaxel and amodiaquine are in vitro probe substrates of CYP2C8, whereas repaglinide is an index substrate for CYP2C8 in clinical studies. Examples of CYP2C8 inhibitors (in vitro studies) include gemfibrozil glucuronide, montelukast, and phenelzine, whereas gemfibrozil is an index CYP2C8 inhibitor (clinical studies). Rifampicin is a CYP2C8 inducer both in vitro and in clinical studies.

DrugBank Online

The DrugBank database includes 3 strong CYP2C8 inducers (phenytoin, rifampicin, and secobarbital), 11 strong CYP2C8 inhibitors for systemic use, and 32 moderate CYP2C8 inhibitors for systemic use.[13] Also, it lists 188 drugs as CYP2C8 substrates, including those with a narrow therapeutic index; however, it does not provide details on the extent to which CYP2C8 contributes to drug metabolism of these substrates.

Other Resources

There is considerable variation in the contribution of CYP2C8 in the clearance of its substrates. Among the 77 clinically used CYP2C8 substrates,[6] the estimated contribution of CYP2C8 to drug metabolism ($f_{mCYP2C8}$) ranges from 5 to 90%. Parmentier et al divided the ranges of in vivo f_{mCYP} values into three categories, ie, low ($f_{mCYP} \leq 30\%$), intermediate ($30\% \geq f_{mCYP} < 75\%$) and high ($f_{mCYP} \geq 75\%$).[14] Therefore, the drugs with high $f_{mCYP2C8}$ in Lai et al's review include amodiaquine and repaglinide, whereas drugs with intermediate $f_{mCYP2C8}$ include cerivastatin, chloroquine, fluvastatin, loperamide, pioglitazone, rosiglitazone, and troglitazone.[6] In Backman et al's review, CYP2C8 substrates were classified according to the contribution of CYP2C8 to their elimination [ie, major (>70%), intermediate (20–70%), and minor (<20%)].[3]

Taken together, based on authoritative sources (FDA, EMA, DrugBank), and recent literature, this review identified 5 inducers, 53 strong/moderate inhibitors, 32 major/intermediate substrates of CYP2C8, and 22 CYP2C8 substrates with a narrow therapeutic index (Table 1).

Table 1 Perpetrators and Substrates of CYP2C8

Categories	Details
CYP2C8 inducers (strong/moderate)	• Rifampicin (FDA: moderate; DrugBank: strong) • Phenytoin, secobarbital (DrugBank: strong) • Flucloxacillin, multiple-dose Ginkgo leaf (literature)
CYP2C8 inhibitors	• Gemfibrozil (FDA: strong) • Clopidogrel, deferasirox, teriflunomide (FDA: moderate) • Trimethoprim (FDA: weak; DrugBank: moderate) • Gemfibrozil glucuronide, montelukast, phenelzine (EMA: in vitro inhibitors) • Candesartan cilexetil, dabrafenib, erlotinib, felodipine, ketoconazole, ritonavir, sorafenib, trametinib, zafirlukast (DrugBank: systemic strong CYP2C8 inhibitors) • Abiraterone, amitriptyline, amlodipine, bexarotene, diltiazem, efavirenz, eltrombopag, enzalutamide, fluvoxamine, fluvastatin, genistein, irbesartan, losartan, lenvatinib, levothyroxine, loratadine, medroxyprogesterone acetate, nicardipine, nilotinib, oxybutynin, pioglitazone, pirtobrutinib, quinine, rabeprazole, rosiglitazone, saquinavir, spironolactone, tamoxifen, topiroxostat, troglitazone (DrugBank: systemic moderate CYP2C8 inhibitors) • Febuxostat, *Hedera helix* extracts, honokiol, myricetin, raloxifene, total flavonoid extracts of *Daphne genkwa* (literature)

(*Continued*)

Table 1 (Continued).

Categories	Details
CYP2C8 substrates	• Repaglinide (FDA: sensitive substrate; EMA: index substrate) • Montelukast, pioglitazone, rosiglitazone (FDA: moderate sensitive substrate) • Amodiaquine, paclitaxel [EMA: in vitro probe substrates; literature: high $f_{mCYP2C8}$ (amodiaquine), intermediate substrate (paclitaxel)] • Cerivastatin, chloroquine, fluvastatin, loperamide, troglitazone (literature: intermediate $f_{mCYP2C8}$) • Daprodustat, dasabuvir, enzalutamide (literature: major substrates) • Acotiamide, alitretinoin, amiodarone, dabrafenib, fluoxetine, *R*-ibuprofen, imatinib, irosustat, isotretinoin, olanzapine, paritaprevir, simvastatin acid, treprostinil, verapamil, zopiclone (literature: intermediate substrates) • Desloratadine, selexipag, tucatinib (literature) • Amiodarone, amitriptyline, brigatinib, cabazitaxel, carbamazepine, cyclophosphamide, dabrafenib, enasidenib, erlotinib, fluorouracil, fosphenytoin, ifosfamide, ixazomib, mycophenolic acid, paclitaxel, pazopanib, phenprocoumon, phenytoin, ponatinib, sorafenib, tegafur, warfarin (DrugBank: CYP2C8 substrates with narrow therapeutic index)

Abbreviations: FDA, US Food and Drug Administration; EMA, European Medicines Agency; $f_{mCYP2C8}$, the estimated contribution of CYP2C8 to drug metabolism.

Prediction of CYP2C8-Mediated DDIs

The EMA and FDA have issued guidelines on in vitro studies of drug interactions, which outline the general requirements and describe how study results can be interpreted and predicted to check whether the investigational drug carries a risk of DDIs in clinical practice.[12,15] The sponsor should routinely use in vitro phenotyping experiments to evaluate which enzymes metabolize the investigational drug and whether the tested drug has the ability to inhibit the CYP enzymes in a reversible and time-dependent manner. If the investigational drug has the ability to induce CYP3A4 and the data indicate the necessity of conducting clinical studies, it is necessary for the sponsors to further evaluate the risk of inducing CYP2C (CYP2C8, CYP2C9, and CYP2C19).

The possibility of DDIs in the human body can be predicted by the ratio of the steady-state peak concentration in the plasma (C_{max}) of the perpetrator exposed to the active center of the DME to the K_i (I/K_i). The K_i value can be measured through in vitro studies or calculated based on the IC_{50} and substrate concentration using the Cheng-Prusoff equation, or roughly estimated using $IC_{50}/2$. The FDA has suggested the following approach for determining the possibility of a DDI. Based on the I/K_i ratio, the potential of the drugs to cause clinically relevant interactions was classified as likely (I/K_i >1), possible (I/K_i ranging from 0.1 to 1.0) or remote (I/K_i <0.1).[16] Table 2 lists typical examples of CYP2C8-mediated DDIs prediction based on this version of the guideline (eg, teriflunomide, efavirenz, trimethoprim).[17–19]

However, some drugs, despite showing strong inhibition of CYP2C8 in vitro studies, have not been shown to interact significantly with CYP2C8 substrates in humans. For example, montelukast exhibits strong inhibition of CYP2C8 in human liver microsomes (HLMs) with K_i values ranging from 0.0092 to 0.15 μmol/L, depending dramatically on microsomal protein concentrations.[26] Based on the I/K_i values, DDIs between montelukast and CYP2C8 substrates are

Table 2 Typical Examples of Predicting CYP2C8-Mediated DDIs

Substrates	Prediction Results and Clinical Scenario
Teriflunomide	Teriflunomide could inhibit the activity of CYP2C8 in HLMs (K_i =0.10–0.15 μmol/L).[3] The $f_{u,mic}$ is 0.796,[20] and thus the $K_{i,u}$ is calculated as 0.13–0.19 μmol/L. The mean steady-state free teriflunomide serum concentration is 0.38 μmol/L.[21] The R1 is calculated as 3.00–3.92 according to FDA Guideline (2020),[15] more than the cut-off criterion of 1.02. The CYP2C8-mediated interactions have been described in the package insert of teriflunomide,[22] ie, repeated doses of teriflunomide can increase the average C_{max} and *AUC* of repaglinide by 1.7 times and 2.4 times, respectively.
Efavirenz	The K_i of efavirenz is 6.05 μmol/L (recombinant CYP2C8 cell lines), and the C_{max} of efavirenz is 12.6 μmol/L,[3] so the I/K_i ratio is 2.08. Based on FDA Guideline (2006),[16] efavirenz is likely to trigger the DDIs with CYP2C8 substrates, consistent with the findings in healthy volunteers that concurrent administration of efavirenz increased the *AUC* of amodiaquine by 1.8-fold.[17]

(*Continued*)

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Table 2 (Continued).

Substrates	Prediction Results and Clinical Scenario
Trimethoprim	Trimethoprim has an inhibitory effect on CYP2C8 in HLMs (K_i=9.2 μmol/L). The I/K_i value is 0.43 based on the C_{max} of trimethoprim (4 μmol/L).[3] The potential of DDIs is judged as possible according to FDA Guideline (2006).[16] Based on the the $f_{u,mic}$ (0.832) and f_u (0.509),[20] the $K_{i,u}$ and $I_{max,u}$ are calculated as 11.06 μmol/L and 2.04 μmol/L, respectively. According to FDA Guideline (2020),[15] the R1 is calculated as 1.09, more than the cut-off criterion of 1.02.[15] There is a potential of DDIs between trimethoprim and CYP2C8 substrates, which has been confirmed in humans, ie, continuous administration of sulfamethoxazole/trimethoprim increased the *AUC* of amodiaquine by 1.6-fold and that of loperamide by 1.9 times.[18,19]
Montelukast	Based on the f_u (0.01), $I_{max,u}$ (0.0089 μmol/L), $f_{u,mic}$ (0.01),[23] the $K_{i,u}$, $I_{max,u}/K_{i,u}$, and R_1 are calculated as 0.92~15 μmol/L, <0.01, and <1.01, respectively, indicating that montelukast unlikely acts as a CYP2C8 inhibitor to trigger clinical DDIs according to FDA Guideline (2020).[15] Indeed, no clinically significant CYP2C8-mediated interactions have been reported.
Clofazimine	Clofazimine reversibly inhibited CYP2C8 in pooled HLMs ($K_{i,u}$ =0.00372 μM). The $I_{max,u}$ is 0.00189 μmol/L calculated from f_u (0.001) and C_{max} (1.89 μmol/L). The R_1 is calculated as 1.51 according to FDA Guideline (2020).[15] Taking into account the f_m and F_g of the interacting substrate, a net-effect mechanistic static model indicated that the AUCR of repaglinide in the presence of clofazimine was 1.34, and the predicted AUCR by PBPK modeling was 1.60. Clofazimine is judged as a weak CYP2C8 inhibitor in humans (AUCR, ≥1.25-fold to <2-fold),[24] dramatically different from the predicted DDI magnitude using I_{max} value (AUCR=509).
Deferasirox	Deferasirox is a moderate in vitro CYP2C8 inhibitor (IC_{50}=100 μmol/L). The $f_{u,mic}$ is 0.443,[20] and the $K_{i,u}$ is 112.9 μmol/L. Based on the f_u (0.4–1.8%) and C_{max} (120 μmol/L), the $I_{max,u}$ is 0.48–3.89 μmol/L. The R_1 value may reach 1.034, greater than the cut-off criterion of 1.02. According to FDA Guideline (2020),[15] deferasirox may inhibit elimination of CYP2C8 substrates. This has been confirmed in clinical studies, ie, the C_{max} and *AUC* of repaglinide both increased by 2.3 times in the presence of deferasirox.[25]

Notes: R_1=1+ ($I_{max,u}/K_{i,u}$), where $I_{max,u}$ refers to the maximal free plasma steady-state concentration of the perpetrator, while $K_{i,u}$ is the unbound inhibition constant measured in vitro.

Abbreviations: *AUC*, area under the concentration–time curve; AUCR, the ratio of *AUC* of a sensitive probe substrate in the case of combined use or non-combined use of a drug under investigation; C_{max}, peak plasma concentration; f_m, the fraction of hepatic clearance of the substrate mediated by the given CYP enzyme; F_g, the fraction available escaping intestinal metabolism; $f_{u,mic}$, unbound fraction in the microsomal system; f_u, unbound fraction in plasma; HLMs, human liver microsomes; K_i, inhibitory constant; I/K_i, the ratio of the steady-state; C_{max} of the perpetrator exposed to the active center of the drug-metabolizing enzyme to the K_i; PBPK, physiologically based pharmacokinetic.

predicted to be likely, but in vivo interaction studies showed that coadministered montelukast had not significant influences on the *AUC* of sensitive CYP2C8 substrates (pioglitazone, rosiglitazone, and repaglinide).[27–29] The absence of interaction in the human body may be due to the high plasma protein-binding characteristic of montelukast.

Correction of the free fraction of a perpetrator in in vitro drug-metabolizing system and plasma is known to be critical for the measurement of kinetic constants and the reliability of subsequent DDI predictions. The updated FDA guidance adopts a different prediction method and cutoff criteria.[15] Based on the basic type of reversible inhibition, the calculation formula of, the R-value is as follows:

$$R_1 = 1 + \left(I_{max,u}/K_{i,u}\right)$$

$$R_{1,gut} = 1 + \left(I_{gut}/K_{i,u}\right)$$

where $I_{max,u}$ refers to the maximal free plasma steady-state concentration of the perpetrator, while $K_{i,u}$ is the unbound inhibition constant measured in vitro, and I_{gut} is the concentration of the perpetrator in the intestinal lumen and is estimated as the dose divided by 250mL. Nonspecific binding can be determined through the techniques such as ultrafiltration and equilibrium dialysis. In addition, in silico approaches can also be used to address this aspect.

If it is a kinetic modeling of time-dependent enzyme inhibition, the formula for calculating the R-value is as follows:

$$R_2 = \left(k_{obs} + k_{deg}\right)/k_{deg}$$

$$k_{obs} = \left(k_{inact} \times 50 \times I_{max,u}\right)/K_{I,u} + 50 \times I_{max,u})$$

where k_{obs} and k_{deg} refer to the observed inactivation rate constant and apparent first-order degradation rate constant of the given DME, respectively, while k_{inact} and $K_{I,u}$ are the maximal rate of inactivation and unbound concentration of inhibitor when the inactivation rate reaches half of the maximum value, respectively.

If $R_1 \geq 1.02$, $R_2 \geq 1.25$, or $R_{1,gut} \geq 11$ (gut; only for CYP3A4/5), the sponsor is recommended to conduct further investigation into the potential of DDI by applying mechanistic modeling or conducting a clinical study. The sponsor should use the sensitive probe substrate for clinical DDI studies if the ratio of *AUC* (AUCR) of a sensitive probe substrate in the case of combined use or non-combined use of a drug under investigation is predicted to be 1.25 or greater based on mechanistic static and dynamic physiologically based pharmacokinetic (PBPK) modeling.[15] According to the updated guideline,[15] typical examples of CYP2C8-mediated DDIs prediction are shown in Table 2.[20–25]

Factors Influencing the Interaction Magnitude

Table 3 summarizes the factors influencing the magnitude of CYP2C8-mediated interactions. These factors need to be considered clinically in the identification and management of drug interactions.

Genetic Polymorphism

CYP2C8 Genotype

The first example is the pioglitazone-gemfibrozil DDI. Pioglitazone is mainly metabolized by CYP2C8.[30] Patients with

Table 3 Factors Influencing the CYP2C8-Mediated Interaction Magnitude

Factors	Drug Combination
Genetic polymorphism	
CYP2C8 genotype	• Pioglitazone+gemfibrozil • Pioglitazone+clopidogrel • Paclitaxel+raloxifene • Paclitaxel+losartan
SLCO1B1 polymorphism	• Gemfibrozil+repaglinide
*UGT2B17*2*	• Clopidogrel acyl-β-D-glucuronide+CYP2C8 substrates
PXR polymorphism	• Repagnilide+flucloxacillin
Hepatic and renal impairment	• Daprodustat+gemfibrozil • Co-trimoxazole+repaglinide
Properties of CYP2C8 perpetrators	
Dose	• Repaglinide+gemfibrozil
Treatment course	• Ginkgo leaf tablet+rosiglitazone
Systemic concentrations	• Candesartan+repaglinide • Deferasirox+repaglinide
Inhibitory potency of CYP2C8 inhibitors	• Gemfibrozil+enzalutamide • Clopidogrel+enzalutamide
Time after discontinuation of perpetrator use	• Repaglinide+gemfibrozil • Repaglinide+rifampicin
The inhibitory abilities of drug metabolites on CYP2C8	• Sorafenib *N*-oxide+CYP2C8 substrates • Terifunomide+CYP2C8 substrates • Glucuronides of gemfibrozil and clopidogrel+CYP2C8 substrates • Deleobuvir-acyl glucuronide+CYP2C8 substrates

(*Continued*)

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Table 3 (Continued).

Factors	Drug Combination
Properties of object drugs	
Whether the active metabolite of object drug is a CYP2C8 substrate	• Gemfibrozil+selexipag • Clopidogrel+selexipag
Therapeutic index	• Gemfibrozil+desloratadine • Clopidogrel+desloratadine
Stereoselectivity	• Gemfibrozil+ibuprofen • Gemfibrozil+tucatinib
Different DDI risk of drugs from similar therapeutic classes	• Clopidogrel vs other antiplatelet agents (eg, low-dose aspirin, ticagrelor, or prasugrel) +montelukast, paclitaxel • Montelukast vs zafirlukast+CYP2C8 inhibitors (eg, gemfibrozil) • Repaglinide vs nateglinide and mitiglinide +CYP2C8 inhibitors (eg, gemfibrozil, clopidogrel) • Gemfibrozil vs other fibrates+CYP2C8 substrates (eg, repaglinide, cerivastatin) • Fluvoxamine vs other antidepressants+CYP2C8 substrates (eg, rosiglitazone) • Enzalutamide vs apalutamide+CYP2C8 inhibitors or inducers • SGLT2 inhibitors vs oral antidiabetic drugs (rosiglitazone, pioglitazone, repaglinide) +rifampicin
Whether DDIs with CYP2C8 substrates involve multiple mechanisms	• Repaglinide+nilotinib+febuxostat • Gemfibrozil+imatinib • Itraconazole+gemfibrozil+loperamide

Abbreviations: CYP, cytochrome P450; DDIs, drug–drug interactions; PXR, Pregnane X receptor; SGLT2, sodium-glucose cotransporter-2; SLCO1B1, solute carrier organic anion transporter family member 1B1; UGT, UDP-glucuronosyltransferase.

the *CYP2C8*3* allele had a lower *AUC* of pioglitazone and a higher metabolite formation rate than individuals with the *CYP2C8*1/*1* genotype (wild type).[31] Gemfibrozil, a lipid-lowering drug for treatment of hypertriglyceridemia, is a strong CYP2C8 inhibitor in the body. Aquilante et al observed that the *CYP2C8*3* variant was not only accompanied by a lower pioglitazone *AUC* in the body, but also significantly affected the magnitude of pioglitazone-gemfibrozil DDI in healthy Caucasian volunteers.[32] Subjects received a single dose of pioglitazone 15 mg or a combination regimen (gemfibrozil 600 mg twice daily for four consecutive days plus 15 mg pioglitazone once on the morning of day 3). Gemfibrozil significantly increased the average $AUC_{(0,\text{infinity})}$ of pioglitazone by 4.3 times ($P<0.001$), and the magnitude of the interaction varied widely among individuals (range, 1.8–12.1 times). The magnitude of change in pioglitazone *AUC* after gemfibrozil treatment was remarkedly associated with the *CYP2C8* genotypes. The *AUC* of pioglitazone increased by 5.2 times in carriers of the genotype *CYP2C8*3*, but only 3.3 times in *CYP2C8*1* homozygous carriers.

The second example is the pioglitazone-clopidogrel DDI. Itkonen et al explored the influence of clopidogrel on the disposition of pioglitazone and its active metabolite hydroxypioglitazone.[10] During the clopidogrel period, the *AUC* ratio of hydroxypioglitazone to pioglitazone (HTP), an indicator reflecting the metabolic activity of pioglitazone via CYP2C8, was only 49% of the corresponding indicator in the placebo period ($P<0.001$). Compared with the individuals not carrying *CYP2C8*3*, carriers of *CYP2C8*1/*3* had the highest *AUC* ratio of HTP in the placebo period ($P<0.001$), however they experienced a greater reduction in the *AUC* ratio of HTP in the presence of clopidogrel ($P<0.05$). Interestingly, the presence of clopidogrel abolished the difference in the *AUC* ratio of HTP among patients with different *CYP2C8* genotypes.

The third example is the paclitaxel-raloxifene DDI. Raloxifene is a selective estrogen receptor modulator used to prevent and treat postmenopausal osteoporosis. It is also indicated to reduce the risk of developing invasive breast cancer (IBC) in women with postmenopausal osteoporosis or those with a high risk of IBC. Therefore, raloxifene may be used in combination with paclitaxel in the treatment of breast cancer. There was a moderate risk of DDI between raloxifene and paclitaxel in human

body when extrapolating data from recombinant yeast cells expressing wild-type *CYP2C8* (*CYP2C8.1*). The IC_{50} and $[I]/K_i$ values indicated that the risk of DDI between paclitaxel and raloxifene reduced in R139K, a mutation carried by *CYP2C8.3* (IC_{50}, 10.12±1.09 μmol/L versus 2.43±1.03 μmol/L, $P<0.01$; $[I]/K_i$, 0.33 versus 0.07).[33]

The fourth example is paclitaxel-losartan DDI. Mukai et al investigated the DDI between losartan and paclitaxel in HLMs from healthy donor livers genotyped for *CYP2C8*3* polymorphism.[34] When the concentration of losartan was 50 μmol/L, the paclitaxel metabolism in HL60 (*CYP2C8*1* homozygote) and HL54 (*CYP2C8*3* heterozygote) was inhibited by 29% and 57%, respectively ($P<0.01$). The IC_{50} values in HL60 and HL54 were 161 and 73 μmol/L, respectively, indicating that *CYP2C8*3* allele carriers were more prone to the DDI between losartan and paclitaxel.

The significance of CYP2C8 genetic polymorphism on the interaction is summarized as follows: *CYP2C8*3* is common throughout Europe and the Americas (6.9–19.8%). Among these populations, *CYP2C8*3* allele frequency in Caucasians is 11.3%. However, prevalence of *CYP2C8*3* allele is obviously much lower in Africans (Zanzibar, 2.1%; Ghana, 0%; Eritreans, 4.6%), Asians (2.2%), and different Asian ethnic groups (North Indian, 3.9%; Jordanian-Arabs, 8.2%; Circassians, 0%; Japan, 0%; Han, Uighur, Hui, and Mongolian Chinese populations were 0%, 2.9%, 1.6%, and 1.6%, respectively).[35–41] In the DDIs mediated by CYP2C19 or CYP2D6, the influence of CYP inhibitors on the pharmacokinetics of substrates can be ignored in poor metabolizers. Clinical data indicate that the *CYP2C8*3* allele is related to the accelerated biotransformation of CYP2C8 substrates. Compared with non-carriers, individuals carrying *CYP2C8*3* allele are more prone to the CYP2C8-mediated inhibitory interactions such as pioglitazone-gemfibrozil, pioglitazone-clopidogrel, paclitaxel-raloxifene, and paclitaxel-losartan. It seems necessary to know *CYP2C8* genotypes to prescribe the dosage of CYP2C8 substrates and facilitate the clinical management of relevant DDIs.

SLCO1B1 Polymorphism

The gemfibrozil-repaglinide DDI is a good example. CYP2C8 and CYP3A4 can metabolize repaglinide into several inactive metabolites.[42] Moreover, active uptake of repaglinide from portal vein to liver by organic anion transporting polypeptide 1B1 (OATP1B1) is an essential step prior to repaglinide biotransformation in the liver. Among individuals carrying the *SLCO1B1 c.521CC* genotype, repaglinide *AUC* was 107% and 188% higher, respectively, than the corresponding values in subjects with the *SLCO1B1 c.521TC* or *c.521TT* genotype ($P<0.0001$).[43]

Kalliokoski et al investigated whether the magnitude of DDI between gemfibrozil and repaglinide depended on *SLCO1B1* polymorphism.[44] To reduce repaglinide pharmacokinetic variations among individuals caused by the genetic polymorphism of *CYP2C8*, a randomized crossover study only recruited *SLCO1B1*-genotyped healthy subjects without the *CYP2C8*3* variant. The average increase in the repaglinide *AUC* due to the combined use of gemfibrozil was 1.56-and 1.54-fold greater in individuals carrying the *c.521CC* genotype than in those carrying the *c.521TC* and *c.521TT* genotypes, respectively (both *P* values <0.01). Gemfibrozil prolonged the elimination half-life ($t_{1/2}$) of repaglinide in the *c.521 CC* group longer than in the *c.521TT* group ($P<0.05$). In the presence of gemfibrozil, individuals with the *c.521CC* genotype had 19% lower minimum blood sugar levels after oral administration of reaglinide compared with those with the *c.521TT* genotype ($P<0.01$).

The magnitude of DDI between gemfibrozil and repaglinide was greatest in individuals with the *c.521CC* genotype, indicating that *SLCO1B1* polymorphism is an important factor affecting the degree of interaction. Compared with the placebo group, there was no difference in the effect of the *SLCO1B1* variant *c.521C* on the pharmacokinetics of repaglinide in the gemfibrozil combination group, suggesting that OATP1B1 inhibition is less involved in the mechanism of this DDI. The changes in plasma exposure to drug metabolites of repaglinide indicate that the DDI between gemfibrozil and repaglinide is mainly achieved by CYP2C8 inhibition.

UDP-Glucuronosyltransferase (UGT) Polymorphisms

Clopidogrel is mainly hydrolyzed by carboxyesterase 1 to its carboxylic acid metabolite and then converted to acyl glucuronide by UGT isoenzymes (UGT2B7, 2B4 and 2B17), resulting in CYP2C8 inactivation in a time-dependent manner.[45] Kahma et al evaluated the influences of polymorphisms in the *UGT* gene on the disposition of clopidogrel in healthy participants.[46] In individuals with *UGT2B17* gene deletion, the formation of clopidogrel glucuronide conjugate was disrupted, and *UGT2B17*2* deletion allele reduced the plasma $AUC_{(0–4h)}$ ratio of glucuronide to carboxylic acid by 10.1% per copy ($P<0.05$). Moreover, *UGT2B17*2* was significantly associated with the $t_{1/2}$ and $AUC_{(0–4h)}$ of clopidogrel acyl glucuronide.

Deletion of the *UGT2B17* gene is more prevalent in Asian subjects than in Caucasian subjects, with an estimated incidence of 66.7% in Asians compared to 9.3% in Caucasians.[47] Furthermore, this gene deletion is associated with reduced glucuronidation activity. The degree of the DDI is closely related to the drug concentration of the perpetrator at the interaction site. In general, the higher the concentration of the perpetrator, the greater the degree of impact on the object drug. The findings of Kahma et al may have important implications for a deeper understanding of the inter-individual variation in DDIs due to CYP2C8 inhibition by clopidogrel acyl glucuronide. A reduced degree of DDI can be expected in patients with *UGT2B17* deletions who receive clopidogrel and CYP2C8 substrates.

Pregnane X Receptor (PXR) Polymorphism

Repagnilide-flucloxacillin DDI is an example. Du et al investigated the effects of 500 mg flucloxacillin versus placebo twice a day for six days on the pharmacokinetics and pharmacodynamics of a single 4-mg dose of repaglinide.[48] Coadministration of flucloxacillin significantly increased the metabolism of repaglinide by inducing the transcriptional expression of CYP3A4 and CYP2C8 through PXR activation, and this effect varied among different genotypes. The individuals carrying absolutely homozygous mutations (−*298G/G* and *11193C/C*) were less sensitive to the impact of flucloxacillin compared to the homozygous wide-type carriers (−*298A/A* and *11193T/T*) (percent increase in oral clearance: 33% vs 88%, $P<0.01$).

Homozygous mutations of *c.298A>G* and c.*11193T>C* can reduce the activity of PXR, decrease the expression of CYP3A4 and CYP2C8, thereby weakening the clearance of repaglinide. As the most common genotypes are wild-type (nonmutated) or heterozygous variants, caution should be exercised when these two drugs are coadministered. Therefore, it is necessary to increase the dose of repaglinide in combination with flucloxacillin.

Hepatic and Renal Impairment

Daprodustat is an oral drug for treating anemia in adult patients with chronic kidney disease who are undergoing dialysis. Daprodustat is mainly metabolized via CYP2C8, and it is also a substrate of OATP1B. An approximately 18-fold increase in daprodustat *AUC* after gemfibrozil treatment is due to strong inhibition of CTP2C8 and moderate suppression of OATP1B. Bi et al utilized a PBPK model to simulate the impact of 600 mg gemfibrozil twice a day on the pharmacokinetics of daprodustat in patients with hepatic insufficiency (Child-Pugh classes A, B, and C), which is an example of analyzing the drug-drug-disease interactions.[49] Results showed a 17-fold increase in daprodustat *AUC* due to gemfibrozil comedication in a mildly impaired population, which was generally consistent with the results observed in healthy participants. However, the effect of increasing *AUC* was reduced to 13 times in Class B patients and only 4.5-fold in Class C patients.

Trimethoprim, a component of co-trimoxazole, is a CYP2C8 inhibitor.[50] Roustit et al presented an adverse event of clinically significant hypoglycemia caused by coadministration of co-trimoxazole by inhibiting the metabolism of repaglinide via CYP2C8.[51] The elderly patient with type 2 diabetes who had no history of hypoglycemia received repaglinide treatment at a dose of 1 mg three times a day. This patient with impaired renal function, whose estimated glomerular filtration rate was 35 mL/min, developed symptomatic hypoglycemia five days after starting co-trimoxazole treatment for urinary infection. Repaglinide and co-trimoxazole were discontinued, and glucose was intravenously given to restore blood glucose levels to normal. Five days later, repaglinide was resumed, but co-trimoxazole was no longer be used. After that, no subsequent episodes of hypoglycemia occurred again. An objective causality assessment indicated a probable interaction between co-trimoxazole and repaglinide. A study showed that TMP increased the $AUC_{(0,\ \text{infinity})}$ of repaglinide by 61% and the C_{max} by 41% (both P values <0.01), but the hypoglycemic effect was not affected.[52] The DDI-related hypoglycaemia in the above case may be partly due to the accumulation of serum TMP resulting from impaired renal function, which in turn leads to increased inhibition of drug metabolism. Clinicians should pay attention to special monitoring when prescribing co-trimoxazole and repaglinide to diabetic patients with renal insufficiency.

Properties of CYP2C8 Perpetrators

Dose

Repaglinide was used as a probe drug to study the effect of gemfibrozil dose on human CYP2C8 activity.[53] Ten healthy subjects were given a single 0.25 mg dose of repaglinide 1 h after the administration of placebo or gemfibrozil in various doses. Compared with placebo, a single dose of gemfibrozil (30, 100, 300, and 900 mg) raised the *AUC* of repaglinide by 1.8-, 4.5-, 6.7, and 8.3 times, respectively, while increasing C_{max} by 1.4-, 1.7-, 2.1, and 2.4 times, respectively (all

P <0.05). This was equivalent to about 50% inhibitory effect of a single 30 mg dose of gemfibrozil on CYP2C8 activity, while a dose of 900 mg produced 95% inhibitory effect. The mechanism of DDI between gemfibrozil and repaglinide is mechanism-based inactivation of CYP2C8 by gemfibrozil acyl glucuronide in a concentration-dependent manner, with a small contribution from the competitive inhibitory effect of high-dose gemfibrozil on OATP1B1.

Gemfibrozil is used to lower triglycerides and is commonly used in adults at a dosage of 600 mg twice a day, and such use will have a significant inhibitory effect on CYP2C8, so special attention needs to be paid to safety when combined with CYP2C8 substrates.

Treatment Course

Herbal formulas of Ginkgo leaf are often comedicated with rosiglitazone for diabetes. Xing et al studied the effects of Ginkgo leaf tablets (GLTs) on the pharmacokinetics of rosiglitazone.[54] The pharmacokinetics of rosiglitazone 10 mg/kg was investigated in rats, following a single and multiple-dose administration of vehicle, 100 mg/kg (low dose) or 200 mg/kg (high dose) GLTs. After a single dose of GLTs, the mean $t_{1/2}$ of rosiglitazone prolonged from 2.14 h (vehicle) to 2.79 h (low dose) and 3.26 h (high dose). Multiple-dose GLTs treatment significantly decreased $AUC_{(0\text{-}t)}$ by 39.4% (low dose) and 52.3% (high dose), while shortening $t_{1/2}$ by 27.6% (low dose) and 38.9% (high dose). When amodiaquine was used as probe substrate of CYP2C8, the IC_{50} of three ginkgo flavonoids (quercetin, kaempferol and isorhamnetin) against CYP2C8 ranged from 7.67 to 11.90 μmol/L. Multiple doses of GLTs resulted in a 44% (low dose) and 88% (high dose) increase in CYP2C8 activity, respectively. A single dose of GLTs weakened the biotransformation of rosiglitazone in rats through CYP2C8 inhibition, but multiple administrations of GLTs might accelerate the biotransformation of rosiglitazone through CYP2C8 induction, indicating that dose adjustments may be required when rosiglitazone is comedicated with GLTs in clinical practice. Further studies are necessary to investigate whether multiple doses of Ginkgo leaf extract formulas show a statistically significant impact on CYP2C8 in humans.

Systemic Concentrations

Katsube et al demonstrated that candesartan and its acy- and *N*-glucuronides could inhibit paclitaxel metabolism via CYP2C8. The inhibitory effect of candesartan acyl glucuronide was the strongest (IC_{50}=18.9 μmol/L), while the IC_{50} values of candesartan and candesartan *N*-glucuronide were 150 μmol/L and 166 μmol/L, respectively.[55] A randomized crossover study further studied the influence of repeated administration of candesartan on the pharmacokinetics and glucose-lowering effect of a single dose of repaglinide.[56] Compared with placebo, candesartan had no statistically significant effects on the repaglinide *AUC* and blood sugar levels. The unbound systemic drug concentrations of candesartan acyl glucuronide were much lower than the in vitro K_i for CYP2C8 (0.0004 μmol/L vs 7.12μmol/L). In addition, no evidence of reduced paclitaxel clearance was identified in the four cancer patients who received concurrent therapy of candesartan and paclitaxel. Because of the low systemic concentrations, comedicated candesartan seems unlikely to have clinically meaningful inhibition of CYP2C8-mediated drug metabolism.

Time After Discontinuing the Perpetrator

The first example is the repaglinide-gemfibrozil DDI. A study investigated the profile of restoring CYP2C8 activity after discontinuation of gemfibrozil administration, and estimated the in *vivo* turnover of CYP2C8.[57] Healthy subjects ingested repaglinide 0.25 mg alone or at various time points after 3 days of pretreatment with gemfibrozil at the dosage of 600 mg twice daily. At 1, 24, 48 and 96 hours after the last administration of gemfibrozil, the *AUC* of repaglinide was 7.6-, 2.9-, 1.4 and 1.0 times that when repaglinide is used alone (P<0.001). Thus, strong CYP2C8 inhibition persisted even after the plasma levels of gemfibrozil and its glucuronide had fallen below 1% of their respective maximum values 24 hours after drug withdrawal. Additionally, the metabolite-to-parent *AUC* ratio showed that significant metabolic inhibition of repaglinide by gemfibrozil persisted for 48 hours (P<0.05). The activity of CYP2C8 gradually recovered from days 1 to 4 after gemfibrozil discontinuation, indicating that the turnover of CYP2C8 was 4 days in the human body.

The second example is the repaglinide-rifampicin DDI. Bidstrup et al evaluated the impact of repeated administration of 600 mg rifampicin once a day for 1 week on repaglinide biotransformation.[58] Participants were randomly assigned to receive 4 mg repaglinide on the last day of rifampicin administration (group 1) or 24 h after the last rifampicin dose (group 2). In

Group 1, the median *AUC* of repaglinide decreased by almost 50%, although the C_{max} was not significantly altered. While in Group 2, the median *AUC* and C_{max} of repaglinide decreased by 80% and 78.6%, respectively. When rifampicin was used concurrently with repaglinide, it played two roles, one was to induce CYP3A4 and CYP2C8, and the other was to inhibit OATP1B1 and OATP1B3-mediated drug uptake. Furthermore, the OATP inhibition of rifampicin may partially offset its metabolic induction. After rifampicin was discontinued, the inhibition of OATP1B1 and OATP1B3 by rifampicin quickly disappeared, although the induction effects on CYP3A4 and CYP2C8 persisted, which resulted in a greater decrease in the plasma levels of repaglinide. Therefore, the combination of rifampicin and repaglinide may reduce the effect of repaglinide in lowering blood sugar in clinical practice, especially when rifampicin therapy is stopped.

The Inhibitory Potency of CYP2C8 Inhibitors

Enzalutamide can be used to treat advanced prostate cancer. It is not only a potent inducer of various CYP isoenzymes but also a substrate of CYP2C8. Enzalutamide is primarily converted to its active metabolite *N*-desmethylenzalutamide by CYP2C8. A study evaluated the influence of gemfibrozil 600 mg twice a day on the disposition of enzalutamide and *N*-desmethylenzalutamide following a single oral dose of enzalutamide 160 mg.[59] The comedicated gemfibrozil raised the *AUC* of both enzalutamide and *N*-desmethylenzalutamide by 2.2-fold, and thus the dose of enzalutamide should preferably be reduced to 80 mg/day if concurrent therapy with a potent inhibitor of CYP2C8 is clinically necessary.

Verhulst et al presented a case of an 82-year-old patient with advanced prostate cancer who concomitantly used enzalutamide and clopidogrel.[60] Comparing the trough concentrations of the active moiety (enzalutamide plus its *N*-desmethyl metabolite) with and without clopidogrel, it was found that concurrent treatment of clopidogrel did not excert significant effect on total concentrations of active moiety and treatment tolerance. Coadministration of enzalutamide with a moderate CYP2C8 inhibitor may be safe and generally does not require dose reduction.

The Inhibitory Abilities of Drug Metabolites on CYP2C8

There are two examples of phase-I metabolites that have inhibitory effects on CYP2C8. Sorafenib is metabolized through CYP3A4 to generate its *N*-oxide (active metabolite). Sorafenib was a strong inhibitor of CYP2C8, as demonstrated by in vitro inhibition assays using amodiaquine *N*-deethylation as a probe for CYP2C8 activity in HLMs (IC_{50}=0.7 μmol/L).[61] The estimated R1 value of sorafenib is 1.0031 based on the C_{max} (21.5 μmol/L), unbound fraction in plasma (0.01), K_i (0.35 μmol/L), and $f_{u,mic}$ (0.005), indicating that sorafenib itself is less likely to elicit CYP2C8-mediated DDIs in vivo. Nair et al compared the ability of sorafenib and its *N*-oxide in inhibiting 6α-hydroxylation of paclitaxel via CYP2C8.[62] Its *N*-oxide metabolite had a 3.7-fold lower IC_{50} compared with sorafenib. Molecular docking studies have shown that sorafenib *N*-oxide could interact more efficiently with core amino acid residues in the binding and catalytic sites of CYP2C8 than sorafenib. This evidence indicates that sorafenib *N*-oxide may impair the elimination of coadministered CYP2C8 substrates and trigger adverse drug events, especially in patients with extensive formation of sorafenib *N*-oxide. The C_{max} of sorafenib *N*-oxide in one patient reached 8.5 μmol/L, comparable to the K_i value (12±2 μmol/L) derived from the CYP2C8 inhibition study. Sorafenib may cause pharmacokinetic DDIs in patients with high serum *N*-oxide concentrations. The CYP3A4 activity and sorafenib *N*-oxide formation are related to many factors (eg, genetic polymorphisms, exposure to CYP3A4 perpetrators, sex, and liver disease). Therefore, it is necessary to conduct therapeutic drug monitoring of sorafenib *N*-oxide during sorafenib treatment in order to decide whether to adjust the dose of CYP2C8 substrate or switch to alternative drugs.

Leflunomide, a well-known immunomodulatory prodrug, is almost completely and quickly metabolized in the gastrointestinal tract into active metabolite terifunomide, a CYP2C8 inhibitor in vivo. Patients taking teriflunomide may have a higher plasma exposure of CYP2C8 substrates (eg, paclitaxel, pioglitazone, repaglinide, rosiglitazone).[22] The blood concentrations of terifunomide after leflunomide administration are equivalent to those observed during terifunomide administration; therefore, it is also possible that leflunomide could trigger clinically relevant CYP2C8 inhibitory interactions. Therefore, it is necessary to strengthen pharmacotherapeutic monitoring among these patients and the dose of combined CYP2C8 substrates may need to be adjusted.

There are several interesting examples of phase-II metabolites with inhibitory effects on CYP2C8. Several conjugated metabolites, including acyl-, *O-, N-*, and carbamoyl glucuronides, are substrates of CYP2C8 or have time-dependent inhibitory effects on CYP2C8.[63] The glucuronides of gemfibrozil and clopidogrel, rather than the parent drugs, are

perpetrators of interactions with CYP2C8 and could trigger significant clinical DDIs (eg, with cerivastatin and repaglinide). In HLMs, the inhibitory effect of gemfibrozil glucuronide on the generation of montelukast metabolite M6 is 35 times stronger than that of gemfibrozil (IC_{50}, 3 μmol/L vs 107 μmol/L).[64]

Deleobuvir is an oral inhibitor of hepatitis C virus polymerase. Systemic exposure to deleobuvir-acyl glucuronide was 43% of the parent drug following a single dose of deleobuvir 800 mg in healthy subjects. Sane et al observed that deleobuvir-acyl glucuronide exhibited more potent CYP2C8 inactivation than deleobuvir (K_i, 0.022 μmol/L vs 0.13 μmol/L). This is another example of acyl glucuronide metabolite with a strong inhibitory effect on CYP2C8. A comparison of the k_{inact}/K_I ratios indicates that deleobuvir-acyl glucuronide demonstrates a more effective inactivation than gemfibrozil and clopidogrel (1.00 vs, 0.0105, 0.0047 $\mu moL^{-1}\ min^{-1}$).[65]

Properties of Object Drugs

Whether the Active Metabolite of Object Drug Is a CYP2C8 Substrate

Selexipag is a prostacyclin receptor agonist indicated for managing pulmonary arterial hypertension. CYP2C8 plays a major role in the biotransformation of selexipag and its active metabolite ACT-333679. Gemfibrozil increased the $AUC_{(0\text{-infinity})}$ of ACT-333679 by 11 times although it had less effects on selexipag.[66] According to prescribing information, combination of gemfibrozil and selexipag is contraindicated.

As for clopidogrel, a single loading-dose administration (300 mg once daily) and multiple administrations (75 mg once daily) could increase the plasma concentrations of ACT-333679 by 1.9 times and 2.7 times, respectively.[67] Katayama et al observed that coadministered clopidogrel did not affect the C_{max} and plasma exposure of selexipag; however, the plasma exposure of ACT-333679 was significantly increased by about 1.9-fold, but the C_{max} was not changed.[68] Using pharmacokinetic simulations, Axelsen et al found the plasma exposure levels of ACT-333679 were comparable, regardless of which of the three administration regimens was taken, namely, selexipag 400 μg twice a day, selexipag 400 μg once a day plus 75 mg of clopidogrel once a day, and selexipag 200 μg twice a day plus 75 mg of clopidogrel once a day.[67] When selexipag is combined with clopidogrel, the plasma levels of ACT-333679 will remain within the therapeutic window by decreasing the administration frequency of selexipag to once a day or by a 50% reduction in the dose of selexipag.

Therapeutic Index

Desloratadine is a less-sedating histamine H1 antagonist, and 3-hydroxydesloratadine is a major metabolite with pharmacological properties similar to those of the parent drug. The formation of 3-hydroxydesloratadine is catalyzed by CYP2C8 but glucuronidation of desloratadine by UGT2B10 is required first.[69] A study in healthy volunteers showed that gemfibrozil at the dose of 600 mg twice a day for 5 days had a stronger effect on desloratadine pharmacokinetics than clopidogrel at a loading dose of 300 mg followed by 75 mg once daily for the next two days.[70] Meanwhile, clopidogrel and gemfibrozil could reduce the $AUC_{(0\text{–}71h)}$ of 3-hydroxyloratadine to 52% and 6%, respectively (all $P<0.001$). This equates to approximately doubling the total plasma exposure of desloratadine and 3-hydroxydesloratadine by clopidogrel, whereas gemfibrozil treatment resulted in a three-fold increase. Because desloratadine has a wide therapeutic index, such DDI will not cause dangerous consequences.

Stereoselectivity

A study confirmed the stereoselective impact of gemfibrozil on the disposition of ibuprofen enantiomers in healthy volunteers.[71] Gemfibrozil inhibited the metabolism of *R*-ibuprofen more than *S*-ibuprofen, which significantly increased the mean *AUC* ratio of *R*-ibuprofen to *S*-ibuprofen from 0.79 to 0.99 ($P<0.001$). The metabolism of *R*-ibuprofen is primarily mediated by CYP2C8, which may explain the stereoselective DDIs between gemfibrozil and ibuprofen. Because *S*-ibuprofen is the only enantiomer with pharmacological activity, the increased concentrations of *R*-ibuprofen caused by gemfibrozil do not seem to have clinical significance.

Tucatinib, a targeted therapy used to treat metastatic HER2-positive breast cancer, is metabolized primarily via CYP2C8, and CYP2C8 can stereoselectively catalyze *gem*-dimethyl hydroxylation to generate M1, the predominant circulating metabolite of tucatinib. The ratio of the *R*-enantiomer to the *S*-enantiomer of M1 is about 3 to 5.[72] Compared

with tucatinib treatment alone, concomitant use of gemfibrozil raised the $AUC_{(0\text{-infinity})}$ of tucatinib 3 times ($P<0.05$), while reducing the metabolic ratio of M1 to tucatinib in terms of $AUC_{(0\text{-infinity})}$ by 71% ($P<0.05$).[73] It is worthy to investigate whether CYP2C8 inhibitor can stereoselectively inhibit the formation of M1.

Different DDI Risk of Drugs from Similar Therapeutic Classes

Antiplatelet Agents

A clinical trial studied the influences of two commonly prescribed P2Y12 inhibitors on the disposition of montelukast in healthy subjects.[74] Compared with placebo, coadministered clopidogrel (300 mg on the first day and 75 mg on the next day) doubled the *AUC* of montelukast while decreasing the *AUC* ratio of 1,2-diol (M6) to montelukast by 55% (both $P<0.001$); however, the presence of prasugrel (60 mg on the first day and 10 mg on the next day) did not elicit a clinically relevant influence on the disposition of montelukast. Evidence show that clopidogrel is a moderately potent CYP2C8 inhibitor whereas prasugrel does not demonstrate clinically meaningful CYP2C8 inhibition. Physicians should be aware of the difference in the interaction risk between clopidogrel and prasugrel, and make the right drug choice when patients need to receive both CYP2C8 substrate and antiplatelet therapy simultaneously. In vitro evaluations showed little or no inhibition of CYP2C8 by ticagrelor and ticagrelor-*O*-glucuronide.[75,76] Ticagrelor may also be an alternative to clopidogrel when combining antiplatelet agents with CYP2C8 substrates.

Paclitaxel is primarily metabolized via CYP2C8 which can be strongly suppressed by clopidogrel acyl glucuronide. Utilizing databases and prescription registration system, Agergaard et al identified forty-eight patients receiving clopidogrel in combination with paclitaxel.[77] Compared with the matched control group that received paclitaxel and low-dose aspirin simultaneously, the combined use of clopidogrel and paclitaxel was associated with an increased overall risk of peripheral neuropathy (crude hazard ratio=1.7), and the hazard ratio even increased to 2.3 in patients receiving a high-dose paclitaxel regimen. When concomitant administration of paclitaxel and clopidogrel is required, drug monitoring should be strengthened or other alternative antiplatelet agents (eg, low-dose aspirin, ticagrelor, or prasugrel) can be considered.

Leukotriene Receptor Antagonist

Coadministration of gemfibrozil could markedly elevate the plasma levels of montelukast in humans due to potent CYP2C8 inactivation by gemfibrozil glucuronide.[64] However, no such effect was observed in a study on the DDI between gemfibrozil and zafirlukast. Healthy subjects received 600 mg of gemfibrozil or placebo twice daily for five consecutive days, and on the third day, they were orally administered a single dose of 20 mg zafirlukast.[78] The main pharmacokinetic parameters of zafirukast did not alter between the two phases, indicating that zafirlukast is not prone to CYP2C8-mediated DDIs, and it may be a better choice for montelukast when patients are concomitantly taking CYP2C8 inhibitors.

Glinides

Nateglinide is an antidiabetic agent metabolized mainly via CYP2C9 and CYP3A4.[79] The combination of gemfibrozil and itraconazole had only a limited impact on the pharmacokinetics of nateglinide,[80] which contrasted sharply with the phenomenon that the *AUC* of repaglinide increased by 8 times after the combination use of gemfibrozil.[63] A retrospective cohort study examined the effect of coadministered clopidogrel on the blood sugar and the risk of hypoglycemia after initiating treatment with repaglinide or miglinide.[81] Patients receiving clopidogrel 75 mg daily were given repaglinide at a daily dose of 1.5 mg or miglinide at a daily dose of 30 mg. The extent of reduction in the minimum plasma sugar levels after glinide initiation was more obvious in the repaglinide/clopidogrel group than in the miglinide/clopidogrel group or the repaglinide/no clopidogrel group ($P<0.05$). The occurrence rate of hypoglycemia was 40% in the repaglinide/clopidogrel group, but 6.7% in the miglinide/clopidogrel group and zero in the repaglinide group.

To avoid the risk of hypoglycemia, miglinide and nateglinide may be alternatives to repaglinide when patients need to combine glinides with CYP2C8 inhibitors.

Fibrates

An in vitro study showed different influences of gemfibrozil, bezafibrate and fenofibrate on the CYP2C8 activity in HLMs.[82] The K_i values of three fibrates against CYP2C8-mediated paclitaxel 6α-hydroxylation were 9.7 μmol/L

(bezafibrate), 30.4 μmol/L (gemfibrozil) and 92.6 μmol/L (fenofibrate). The IC_{50} values of bezafibrate, gemfibrozil, and fenofibrate were 37.7 μmol/L, 111 μmol/L and 164 μmol/L, respectively. However, in vivo studies showed that bezafibrate and fenofibrate did not elicit pharmacokinetic DDIs with repaglinide,[83] whereas gemfibrozil could trigger a marked interaction. The underlying mechanism is related to the fact that the inhibitory effect of gemfibrozil glucuronide has a greater inhibitory effect on CYP2C8 than gemfibrozil.[63] For bezafibrate, the $I_{max,u}/K_i$ is estimated as 0.20, but the $I_{max,u}/K_{i,u}$ is unknown because the $f_{u,mic}$ of bezafibrate was not reported. For fenofibrate, the $f_{u,mic}$ value is 0.008,[20] and the $I_{max,u}/K_{i,u}$ is estimated to be 0.000021. Therefore, fenofibrate is unlikely to elicit CYP2C8-mediated DDIs in vivo based on the predicted R1 value according to the cutoff criteria (R1≥0.02) of the updated FDA guidelines.[15]

It is sometimes necessary to prescribe statins with fibrates because the combination regimen can simultaneously lower triglyceride and low-density lipoprotein cholesterol, while increasing high-density lipoprotein cholesterol. However, the risk of DDIs should be considered. By strong inhibition of CYP2C8, gemfibrozil coadministration could increase the plasma exposure to cerivastatin and its lactone form by 5.6 times and 4.4 times, respectively. This is the main reason for the increased myotoxicity caused by such concurrent therapy.[84] However, the interactions of gemfibrozil with other statins are mediated by the inhibition of transporters such as OATP, and the effect against CYP2C8 appears to be limited or absent. Gemfibrozil could increase plasma exposure to several statins, whereas fenofibrate did not show similar effects, indicating that fenofibrate is a better fibrate to comedicate with statins.[85]

Antidepressants

Fluvoxamine is commonly prescribed to depressive patients. Repeated administration of 50 mg fluvoxamine once daily for three days elicited a moderate increase in the plasma exposure to rosiglitazone in healthy volunteers (P<0.01).[86] Derived from in vitro studies and clinical data, desvenlafaxine and venlafaxine showed no or low inhibitory effect on the activities of CYP isoenzymes (CYP1A2, 2A6, 2C8, 2C9, 2C19, and 3A).[87] Sertraline and citalopram exhibit weak inhibitory effects on CYP2D6 activity at commonly doses and do not trigger clinically significant inhibition of any other isoenzymes.[88] Therefore, fluvoxamine should not be selected when CYP2C8 substrates are used in combination with antidepressants.

Androgen Receptor Signaling Inhibitors

Apalutamide and enzalutamide are androgen receptor signaling inhibitors used to treat non-metastatic advanced prostate cancer. Enzalutamide is metabolized primarily by CYP2C8. When the strong CYP2C8 inhibitor gemfibrozil is combined with enzalutamide, it causes significant DDI.[59] Apalutamide is metabolized mainly by CYP2C8 and CYP3A4, and the metabolic contributions of the two isozymes are altered due to automatic induction of repeated administration, that is, the contribution of CYP2C8 decreased from 58% to 40% and that of CYP3A4 increased from 13% to 37%. Van den Bergh et al applied a PBPK modeling and simulated the DDIs between apalutamide and the perpetrators (ie, ketoconazole, gemfibrozil, or rifampicin) following a single dose or repeated doses of apalutamide.[89] None of these strong perpetrators of CYP3A4 and CYP2C8 would be expected to cause meaningful changes in the disposition of apalutamide. This finding supports the existing label recommendation that dose adjustment is not required if apalutamide is combined with a known perpetrator of CYP2C8 or CYP3A4. Therefore, apalutamide may be preferable to enzalutamide in the presence of CYP2C8 inhibitors.

Oral Antidiabetic Drugs When Comedicated with Rifampicin

Rifampin administration of 600 mg once a day for 6 days significantly decreased the mean AUC and C_{max} of rosiglitazone by 65% and 32.6%, respectively, while shortening the $t_{1/2}$ by 2.4 h, and increasing the apparent oral clearance by 3 times (both P <0.001).[90] Similarly, rifampicin reduced the mean plasma exposure of pioglitazone by half.[91] The underlying mechanism is that rifampicin can induce CYP2C8 expression and thus affect the in vivo disposition of rosiglitazone and pioglitazone. Rifampicin reduced the repaglinide AUC by 57–80% by inducing CYP2C8 and CYP3A4,[92] while reducing the average nateglinide AUC by 22% through CYP2C9 and CYP3A4 induction (all P<0.001).[93] Rifampicin could also induce CYP2C9-mediated biotransformation and subsequently reduce the plasma levels of sulfonylurea drugs.[94]

To avoid lower efficacy, treatment failure, or increased toxicity, clinicians should be aware of these DDIs when rifampicin is newly introduced or withdrawn from the existing treatment regimens. With respect to SGLT2 inhibitors,

rifampicin did not have a clinically significant effect on the hypoglycemic efficacy of dapagliflozin and ertugliflozin, although UGT induction by rifampicin reduced the *AUC* of dapagliflozin and ertugliflozin by 22% and 39%, respectively.[95,96] However, the coadministration of rifampicin decreased the *AUC* of canagliflozin by 51%, and such DDI may require appropriate blood glucose monitoring.[97]

Taken together, from the perspective of pharmacokinetic interactions, the SGLT2 inhibitors dapagliflozin and ertugliflozin may be alternatives to repaglinide, nateglinide, sulfonylurea drugs, and glitazones in the presence of rifampicin.

Whether DDIs with CYP2C8 Substrates Involve Multiple Mechanisms

Repaglinide-Nilotinib-Febuxostat

A case of severe hypoglycemia demonstrated the DDIs among nilotinib, febuxostat and repaglinide in a type 2 diabetic patient.[98] The possibility of a clinical DDI mediated by CYP2C8 is judged as likely, based on the K_i (20 μmol/L) of febuxostat against CYP2C8 in HLMs, and the calculated I/K_i ratio of 0.47.[99] In addition, the delayed elimination of repaglinide may also be due to DDIs between repaglinide and nilotinib. Nilotinib is an OATP1B1 inhibitor that can reduce the uptake of repaglinide in the liver mediated by this transporter,[100] Meanwhile, nilotinib is a potent in vitro inhibitor of CYP3A4 (K_i = 0.448 μmol/L) and CYP2C8 (K_i = 0.236 μmol/L).[3,61] The $I_{max,u}/K_i$ values were 0.19 (CYP3A4) and 0.36 (CYP2C8), respectively, indicating that nilotinib may impair repaglinide metabolism in the human body. Three different types of interaction mechanisms (eg, impaired drug metabolism mediated by CYP2C8 and CYP3A4, and reduced hepatic uptake mediated by OATP1B1) work together to increase the DDI magnitude, thereby significantly raising the blood concentration of repaglinide and ultimately leading to the occurrence of hypoglycemic adverse events.

Gemfibrozil-Imatinib

Both CYP2C8 and CYP3A4 participate imatinib *N*-demethylation in HLMs.[101] A randomized crossover study investigated the effect of 600 mg of gemfibrozil twice a day for six days on the pharmacokinetics of imatinib and its *N*-desmethyl metabolite.[102] In the presence of gemfibrozil, the C_{max} of imatinib reduced by 35%, and the C_{max} and $AUC_{(0\text{-infinity})}$ of *N*-desmethylimatinib decreased by 56% and 48%, respectively (all *P* values<0.001), whereas the $AUC_{(0\text{-infinity})}$ of imatinib remained unaffected. In vitro studies showed that OATP1A2 and OATP2B1 participated imatinib pharmacokinetics,[103] and gemfibrozil could significantly inhibit OATP2B1 in vitro.[104] Therefore, the unexpectedly impaired absorption of imatinib by gemfibrozil in humans (ie, reduced C_{max}) is probably due to inhibiting transporters responsible for imatinib uptake (eg, OATP2B1), while CYP2C8 inhibition by gemfibrozil impaired the formation of *N*-desmethylimatinib (ie, both C_{max} and *AUC* of this metabolite are reduced).[102]

Itraconazole-Gemfibrozil-Loperamide

The metabolism of loperamide is mainly mediated by CYP2C8 and CYP3A4. A study assessed whether the pharmacokinetics of loperamide in healthy volunteers were affected by itraconazole (a dual inhibitor of CYP3A4 and P-glycoprotein) and/or gemfibrozil (an inhibitor of CYP2C8).[105] The changes in the C_{max} and *AUC* of loperamide were as follows: 2.9- and 3.8-fold with itraconazole, 1.6- and 2.2-fold with gemfibrozil, 4.2- and 12.6-fold with itraconazole plus gemfibrozil, respectively; the $t_{1/2}$ of loperamide prolonged by 6.8, 4.8, and 25 hours in the itraconazole, gemfibrozil, and itraconazole plus gemfibrozil groups, respectively. When loperamide is combined with itraconazole and gemfibrozil, the metabolism of loperamide via CYP2C8 and CYP3A4 is impaired, and the efflux effect of P-gp was reduced. The synergistic effect of the three mechanisms eventually leads to an increase in the *AUC* of loperamide. Compared with inhibition of a single DME, simultaneous inhibition of two or more DMEs and/or transporters often leads to a stronger degree of DDIs.

The Potential of Botanical Supplements to Trigger CYP2C8-Mediated DDIs

Daphne Genkwa Extracts

Daphne genkwa is a traditional herb with various pharmacological actions (eg, anti-HIV, anti-cancer, anti-inflammatory, antibacterial, antiviral, antioxidation, and immunomodulation). Hou et al determined the influences of total flavonoid extracts (TFE) from *Daphne genkwa* and their respective monomers on the activity of CYP2C8 in recombinant

transgenic cell lines and rat models.[106] Using rosiglitazone as CYP2C8 probe substrate, the IC_{50} values were as follows: 7.27 (apigenin), 11.9 (luteolin), 28.1 (hydroxy-genkwanin), 127 (genkwanin), and 13.4 μg/mL (TFE), respectively. In vivo study showed a pronounced difference in the absorption and disposition of rosiglitazone between control and TFE groups. The TFE treatment significantly decreased the C_{max} and $AUC_{(0\text{-infinity})}$ of rosiglitazone by 66.6% and 32.2%, respectively, and significantly prolonged the time to reach the C_{max}, $t_{1/2}$ and mean residence time by 287%, 96.9%, and 110%, respectively. These data indicate an inhibitory capacity of TFE on the absorption of rosiglitazone and the metabolic capacity of CYP2C8. The four monomers did not strongly inhibit in vitro activity of CYP2C8 whereas the TFE significantly inhibited CYP2C8 activity in in vitro incubation studies and in vivo pharmacokinetic studies. This might be related to two possible reasons (ie, the TFE may contain other flavonoids with significant inhibition against CYP2C8 activity, or the combined four monomers may exhibit a synergistic effect). More care should be taken regarding possible interactions between herbs and drugs when concomitantly receiving *Daphne genkwa* and CYP2C8 substrates.

Myricetin Supplements

Myricetin is a flavonoid found in a variety of foods and herbs, and is usually used as a powder extract. It helps protect against certain diseases (eg, cancer, diabetes mellitus, cardiovascular disease and cognitive decline). Bhatt et al explored the inhibitory potential of myricetin on CYP2C8 using a combination of in silico modeling, in vitro incubation, and in vivo pharmacokinetic studies.[107] In HLMs using amodiaquine as a probe substrate, myricetin was confirmed as a mixed CYP2C8 inhibitor (K_i =1.7 μmol/L). A molecular docking analysis revealed that myricetin elicited a potent interaction with the active site residues in CYP2C8. Additionally, myricetin inhibited *N*-deethylation of amodiaquine via CYP2C8 and thus increased the plasma exposure to amodiaquine by 1.6 times in rats. It is essential to further examine the ability of myricetin supplementation to trigger CYP2C8-mediated DDIs in humans.

Hedera Helix Extract

Hedera helix extract is used for treating respiratory complaints (eg, bronchitis, whooping cough, acute upper respiratory tract infections),[108] and this herb may be used concurrently with conventional drugs. Rehman et al evaluated the possibilities of *Hedera helix* extract to elicit pharmacokinetic interactions using a cocktail approach in pooled HLMs and transgenic cell lines expressing CYP isozymes.[109] *Hedera helix* extract exhibited significant concentration-dependent inhibitory effects on CYP2C8, using paclitaxel as a probe substrate. The IC_{50} values in HLMs and recombinant CYP2C8 systems were 0.13 and 0.08 mg/mL, respectively. In addition, *Hedera helix* extract showed time-dependent inhibition of CYP2C8. Caution may be required when consuming herbs or food supplements containing *Hedera helix* extract, and further human studies are needed to determine whether this herb interferes with CYP2C8 and triggers clinically relevant DDIs.

Green Tea Extract

Misaka et al assessed the influences of green tea extract (GTE) and epigallocatechin gallate (EGCG) on the activities of five CYP isozymes in HLMs. CYP2C8 was the most sensitive to GTE inhibition (IC_{50}=4.5 μg/mL). In addition, EGCG elicited competitive inhibitions against CYP2C8 (K_i=6.8 μmol/L).[110] To date, no clinical studies have been reported regarding the interaction between EGCG and substrates of CYP2C8. More human studies are needed to confirm clinical significance. Based on the plasma protein binding (99.8%) and C_{max} (7.4 μmol/L) of EGCG following intake of green tea with high-content catechins,[111,112] the $I_{max,u}/K_i$ of EGCG is estimated as 0.0022 for CYP2C8 in the human body. These data indicated that GTE could not elicit clinically significant DDIs mediated by CYP2C8.

Honokiol

Honokiol is a pleiotropic compound isolated from Magnolia species and has various pharmacological actions (eg, antioxidative, anti-inflammatory, antithrombotic, anti-cancer, neuroprotective effects). Cho et al investigated the effect of honokiol following 48-hour exposure on the induction of DMEs in human hepatocytes.[113] Honokiol could weakly induce CYP2B6 but did not significantly affect the mRNA levels of other CYP enzymes (CYP1A2, 3A4, 2C8, 2C9, 2C19), UGT isoforms (UGT1A1, 1A4, 1A9, 2B7), and sulfotransferase 2A1, indicating that honokiol at the usual dose may not trigger DDIs with the substrates of the tested DMEs via enzyme induction. However, researchers from the same team examined the in vitro metabolic inhibition assay of honokiol in HLMs.[114] Honokiol could potently inhibit the

activities of CYP1A2, CYP2C8, CYP2C9, CYP2C19, and UGT1A9. As there have been no attempts to predict the interaction potential of honokiol by the extrapolation from in vitro data to clinical situations in accordance with the latest guidance on DDI study, it is worth conducting the necessary clinical interaction studies related to CYP1A2, CYP2C8, CYP2C9, CYP2C19, and UGT1A9.

Gaps in Current Knowledge

There are several gaps in current knowledge regarding CYP2C8-related interactions. Firstly, there is insufficient predictability and sometimes ambiguous clinical relevance. There are still uncertainties in in vitro to in vivo extrapolation in predicting the actual degree of DDI in the clinical setting according to the latest guidance on DDI studies. The $f_{u,mic}$ and $K_{i,u}$ values of some drugs are still unknown, and the relevant parameters (K_i, IC_{50}, K_m) determined by in vitro experiments vary significantly. Other reasons include inaccurate estimation of drug concentration in the liver, first-pass effect in the intestine, protein binding rate, contribution of metabolic pathways, participation of transporters (eg, OATP, P-gp) and the role of drug metabolites in DDIs. Additionally, the thresholds for clinical significance of some DDIs are unclear. For CYP2C8-mediated DDI, the threshold for changes in *AUC* required to cause clinically significant adverse reactions (eg, aggravated neurotoxicity of paclitaxel) or loss of efficacy (eg, failure of antimalarial drugs) has not been fully established or widely agreed upon. Also, numerous factors significantly affect CYP2C8 activity, causing the same DDI to show great differences among different patients, making it difficult to accurately predict individual risks.

Secondly, many CYP2C8 substrates (eg, paclitaxel, repaglinide, rosiglitazone) are also metabolized by other CYP enzymes (eg, CYP3A4) or non-CYP pathways (eg, UGT). When these parallel pathways exist, the degree of clinical DDI caused by inhibiting or inducing CYP2C8 is often underestimated or overestimated, as other pathways may play a compensatory role. It is challenging to accurately quantify the relative contribution of CYP2C8 to the clearance of specific drugs ($f_{mCYP2C8}$) in vivo.

Thirdly, the identification and characterization of perpetrators are still incomplete. Some marketed drugs or common herbs/supplements may have inhibitory or inducing effects on CYP2C8, but have not been fully studied or identified. Conventional in vitro screening may have false negatives or false positives. Compared with inhibitors, clear clinical inducers of CYP2C8 are relatively rare. For known inhibitors/inducers, the clinical classification of their inhibition/induction intensity (strong, moderate, weak) is sometimes not precise enough.

Fourthly, some data on special populations are still lacking. CYP2C8 activity may change in liver diseases (such as liver cirrhosis) or severe kidney diseases. The risk and extent of CYP2C8-mediated DDI in these populations may differ from those in healthy individuals or those with mild impairment, but the relevant research data is limited. Inflammation (eg, infection, autoimmune diseases) may down-regulate the expression of CYP enzymes. There has not been sufficient research to show whether CYP2C8-mediated DDI patterns are altered under inflammatory conditions.

Priorities for Future Research

The research directions that can be pursued in the future are as follows. First is to improve DDI prediction model. Utilize PBPK models to integrate in vitro data, physiological parameters, and patient factors (genotype, pathological status) to more accurately predict the DDI risk of specific populations. Developing and applying more reliable methods (such as specific inhibitor cocktail tests, radiolabeling tracers, and advanced bioanalytical techniques) to precisely determine the $f_{mCYP2C8}$ in the human body is crucial for predicting DDI involving multi-enzyme metabolic substrates. Based on large-scale clinical studies or meta-analyses of drug efficacy and safety endpoints, it is necessary to establish thresholds for clinically significant changes in *AUC* and C_{max} brought by CYP2C8-mediated DDIs.

Secondly, it is necessary to conduct in-depth research on the mechanism of known inhibitors (especially time-dependent inhibitors), including metabolite formation, enzyme deactivation, recovery time, etc. Systematic screening and characterization are also needed. A more systematic and standardized in vitro and in vivo (including clinical) assessment is necessary to be conducted on the CYP2C8 inhibition/induction potential of the marketed drug libraries and commonly used herbs/supplements. It is also interesting to explore how the synergistic effect of hepatic uptake (eg, OATP1B1) or efflux transporters with CYP2C8 affects the pharmacokinetics of the object drugs and the DDI pattern (eg, gemfibrozil inhibits both OATP1B1 and CYP2C8).

Thirdly, it is necessary to design rigorous clinical DDI studies targeting important CYP2C8 substrates with narrow therapeutic windows (eg, paclitaxel and certain hypoglycemic drugs) and suspected moderate to strong inhibitors/inducers to clarify their clinical impact. Studies are necessary to be conducted, focusing on CYP2C8 activity and DDI risk in patients with liver and kidney dysfunction, pregnant women, children, and the elderly. Genotype-oriented DDI studies are necessary to evaluate the differences in pharmacokinetic and pharmacodynamic responses of patients with different *CYP2C8* genotypes when encountering inhibitors/inducers and provide a basis for precise medication. Utilizing real-world data (eg large electronic medical record databases and pharmacovigilance data), potential CYP2C8-mediated DDI signals that have not been discovered in clinical trials should be mined and verified.

Fourthly, develop and apply clinical decision support tools. Optimize DDI databases and early warning systems. Based on continuously updated research evidence, it is important to improve the information on CYP2C8-mediated DDI in drug databases (eg, Lexicomp, Micromedex), especially the accuracy of inhibition/induction strength, clinical significance, and management recommendations. Integrating the patient's *CYP2C8* genotype information into the electronic prescription system, and combining it with the information of contraindicated drugs will provide more personalized DDI risk warnings and management suggestions.

Lastly, explore alternative strategies and clinical pharmaceutical care. Develop new drugs that are less likely to cause DDI. In the early stage of new drug development, reduce the reliance on CYP2C8 metabolism through drug design, or select molecules that are insensitive to CYP2C8 inhibition/induction. Develop refined dose adjustment plans. For inevitable DDI combinations, based on more precise predictive models and clinical research evidence, it is wise to develop individualized dose adjustment plans for different risk populations (eg, different genotypes, liver and kidney function status). Educate patients (especially those who have been using CYP2C8-sensitive drugs for a long time) about the risks of DDI and avoid self-use of over-the-counter drugs or supplements that may interact.

Conclusion

CYP2C8 is an important DME and metabolizes weakly acidic compounds with relatively large molecular weights (eg, cerivastatin, paclitaxel and pioglitazone). However, CYP2C8 is underrecognized compared to the major CYP enzymes such as CYP3A4 and CYP2D6. Especially, CYP2C8-related DDIs are still insufficiently recognized in the real world of older adults with polypharmacy (eg, clopidogrel-pioglitazone). This review identified 5 CYP2C8 inducers, 53 strong/moderate CYP2C8 inhibitors, and 32 major/intermediate CYP2C8 substrates. Also, it provided the first comprehensive summary of the factors influencing the magnitude of CYP2C8-mediated DDIs. These factors include genetic polymorphisms (eg, *CYP2C8, SLCO1B1, UGT*, and *PXR*), hepatic and renal function, properties of CYP2C8 perpetrators (dose, treatment course, systemic concentrations, time after discontinuation, inhibitory potency, inhibitory abilities of metabolites on CYP2C8), properties of object drugs (whether the active metabolite of object drug is a CYP2C8 substrate, therapeutic index, stereoselectivity), differences in DDI risk for drugs from similar therapeutic classes, and whether multiple interaction mechanisms are involved. Additionally, the potential of botanical supplements to trigger CYP2C8-mediated DDIs is also worthy of attention.

The knowledge about the progress of CYP2C8-related interactions will enhance the awareness of safe medication use among clinical professionals. Interventions to manage polypharmacy in older adults should involve team work to monitor DDIs mediated by DMEs and transporters (including CYP2C8), adjust doses, select alternatives, and strengthen pharmacotherapeutic monitoring. Only in this way can the occurrence of adverse drug interactions be avoided or reduced, and the rationality of patients' medication be guaranteed. Moreover, if we recognize the gaps in current knowledge and priorities for future research, more progress in this regard will emerge.

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