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THE CURRENT STATUS OF CYP-2D6, 2C9, 2C19 AND 3A4 INDUCED ADVERSE DRUG REACTIONS

Adriana Syuhada Ahmad Najmi, Siti Nor Azizah Ab Halim, Nurul Nadia Feizal and Fazleen Haslinda Mohd Hatta*

Department of Pharmaceutical Pharmacology and Chemistry, Faculty of Pharmacy, Universiti Teknologi MARA Cawangan Selangor, Bandar Puncak Alam Selangor MALAYSIA

*Corresponding Author: fazleen@uitm.edu.my

REVIEW ARTICLE

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Abstract

Adverse Drug Reactions (ADRs) are one of the rising factors of worldwide morbidity and mortality and will remain a critical public health issue with the enhanced complexity in drug therapy. Polymorphism in the genes encoding *CYP2D6, CYP3A4, CYP2C9* and *CYP2C19* enzymes are understood to affect the extent of degradation of various pharmaceutical drug compounds and cause patients more or less likely to respond to personalized therapy or suffer adverse effects. This study reviewed research literature papers published from June 2009 until July 2021, carrying the subjects such as 'drug metabolism enzymes', '*CYP450*s', and 'adverse drug reactions'. The literature search was carried out using PubMed, Science Direct, and Scopus articles, as well as the official reports from the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC). Most East Asian populations are intermediate metabolizers (IM) of *CYP2D6* substrates, due to a predominance of reduced activity allele *CYP2D6*10*. The majority of *CYP3A4* polymorphisms in the East Asian groups are also significantly more frequent. It was demonstrated that South Asian populations also have a higher frequency of *CYP2C9*3* and *CYP2C9*3/*3* alleles than other ethnicities throughout the world. Twenty percent of Asians are poor metabolizers of drugs that depend on *CYP2C19*, which metabolizes phenytoin, phenobarbital, omeprazole, and other drugs. A few of the currently accessible techniques for *CYP450* genotyping tools are inadequate in coverage, neglecting significant variations relevant in Southeast Asian populations. Further research on *CYP450* polymorphisms in specific regions may benefit to improve pharmacotherapy success by delivering personalized medication plan to certain ethnic groups.

INTRODUCTION

The World Health Organization (WHO) describes adverse drug reactions (ADRs) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modifications of physiological function". To define it simply, an adverse drug reaction is any unwanted reaction of a drug beyond its expected therapeutic effects occurring in the period of clinical use. ADRs are among the rising factors of worldwide morbidity and mortality and will remain a critical public health issue with the enhanced complexity in drug therapy, for the treatment of a variety of illnesses especially in an aging population [1].

ADRs have been affecting patients' quality of life and causing an increase in global healthcare costs for the past few years [2]. Recent studies have proven that ADRs are the cause of 3 – 7% of all hospitalizations and 10 – 20% of inpatient facilities [3]. Twenty one percent of admissions in local hospitals in Malaysia were due to ADRs [4]. The causes

of ADRs are often complex and multifactorial. Most of the time, ADRs are possibly to be induced by genetic polymorphism, as 90% of drugs are metabolized by a group of enzymes called the Cytochrome P450 (*CYP450*) in the body. Among them are highly polymorphic genes, such as *CYP3A4, CYP2D6, CYP2C9* and *CYP2C19* [5].

Genetic variation in these enzymes determines how a patient reacts to certain drugs, such as antidepressants, beta blockers, warfarin, statins, and antiepileptics. Altered or undesired response observed in certain patients during clinal medication therapy has been associated with single nucleotide polymorphisms (SNPs) in the *CYP* genes. An established classification system uses a "star allele" as naming for the *CYP* variants, in which the normal allele or wild type is referred to as **1*. An allelic variant is commonly labelled with a * followed by a number other than 1 to distinguish it from other variants. This helps categorizes individuals into different metabolizer status. Four functional types of alleles were identified; normal (wild type), no activity, partial activity, and replicated. These types of alleles combine to produce five recognizable phenotypes: normal metabolizer (NM), intermediate metabolizer (IM), poor metabolizer (PM), rapid metabolizer (RM) and ultra-rapid metabolizer (UM).

Genotyping for *CYP450* polymorphism has been mainly employed to screen for ADRs. The *CYP450* genotyping results are used to predict the enzyme phenotype that ranges from poor metabolism, up to ultra-rapid metabolism. The genotype test can instruct the selection of drugs metabolized by *CYP450* enzymes in drug therapy by physicians. Though there is data of ADRs associated with polymorphisms coding for inefficient *CYP450* mechanism, further prospective clinical trials are still required to decide if genotyping is cost-effective and enhances clinical outcomes by reducing ADRs or recognizing poor responders.

At present, the incidence and pattern of polymorphism induced ADRs have remained as neglected area in southeast Asia. Only 1 in 20 ADRs is recognized and identified as an actual side effect; this contributes to the false belief that the occurrence of adverse responses is significantly lesser than it is [6]. Inefficient reporting of ADRs could also result in the loss of clinical information that might avoid harm to patients and thereby reduce healthcare costs.

Considering the latest advances in pharmacogenomics and the significant number of genes engaged in drug metabolism, the traditional understanding of drug-drug interactions has to be changed to incorporate genetic variation, as it performs a vital role in the occurrence of ADRs [7]. Studies have demonstrated that in *CYP2C9, CYP2C19*, and *CYP2D6* genetic polymorphisms, 15% of the ADRs were the impacts of drug–gene interactions, and 19% were caused by drug–drug–gene interactions [8]. By considering genetic variation, the number of expected clinically important drug interactions can be enhanced up to 51% [8]. Up until now, there has been limited literature on the impact of genetic variation on drug-drug interactions, especially research discussing the effects of *CYP2C9, CYP2C19*, and *CYP2D6* variants in Southeast Asian population [9].

This narrative review addresses the type of polymorphism-induced ADRs, the main drug categories associated with the effects, causes of ADRs, their occurrence as well as consequences of getting ADRs, to decrease the possibility of polymorphism-induced ADR's in Southeast Asia. Knowledge of the most crucial drugs metabolized by *CYP450* enzymes, along with the highly effective inducers and inhibitors, can help lessen the risk of ADRs. This will provide information regarding adverse drug reactions for the clinicians to make decisions based on class of drugs that are associated with these ADRs. Moreover, this may be helpful for researchers and healthcare providers, as well as policy makers, to develop enhanced interventions to lower the risk of ADR's in today's primary care.

We aim to perform a literature search of publications on adverse drug reactions associated with *CYP450* drug interactions, in Southeast Asia specifically and to also look into the implications of *CYP450* drug metabolism on adverse drug reactions. In this narrative review, we will highlight the current and potential ADRs associated with *CYP450* polymorphism and the influence of genetic variation on clinically critical drug interactions specifically for the Southeast Asian population.

MATERIALS AND METHODS

This narrative review focuses on the *CYP450* drug metabolism and how it is linked to adverse drug reactions. We investigated research literature papers published from June 2009 until July 2021 carrying the subjects such as 'drug metabolism enzymes', '*CYP450s*', and 'adverse drug reactions'. The literature search for the preparation of this narrative review was carried out using PubMed, Science Direct, and Scopus articles, as well as the official reports from the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC).

There were no language restrictions on the search. Papers based on animal studies as well as overlapping study papers were excluded. Articles were selected according to their relevance on the topic of this narrative review. The whole body of information was analysed and summarised.

RESULTS AND DISCUSSION

Adverse drug reactions (ADRs) continue to be a common and a critical challenge in healthcare. In 2020, the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) obtained 30,746 reports of ADRs, demonstrating a 7.9% increase from the previous year [10]. Several previous research papers have shown that ADRs are associated with strong genetic predisposition, and the related risk variants involve drug-metabolizing enzymes, such as the *CYP450* enzymes. Majority of ADRs are predictable, dose-dependent

and related to the pharmacodynamic and pharmacokinetic characteristics of drugs. Nevertheless, several are still unpredictable, dose-independent and characterized as idiosyncratic reactions

Pharmacogenetics and pharmacogenomics have emerged in the era of precision medicine, with the goal of optimizing drug therapy for individuals based on their unique genetic traits. Because drug metabolism and dosage differ greatly among different individuals, a person's genetic profile may be significant in determining the most effective drug therapy for them. Several genes have already been identified as part of US FDA guidelines for clinical care [11]. Among these, the *CYP450* genes have been recognized as some of the most significant for the delivery of individualized medical therapy. These discoveries do not only provide understandings of the pathogenesis of ADRs but also result in the advancement of valuable biotechnologies to lessen the occurrence of adverse outcomes. Cytochrome P450 enzymes are crucial for the metabolism of various drugs. Though this class has over 50 enzymes, the four most crucial enzymes being *CYP3A4, CYP2D6, CYP2C9*, and *CYP2C19,* metabolize 90% of drugs. Genetic variability or polymorphism, in these enzymes could affect an individual's reaction to commonly prescribed medication classes, such as beta blockers, antidepressants, warfarin, antiepileptic drugs, and statins.

CYP450 enzymes can be suppressed or stimulated by drugs, producing clinically significant drug-drug interactions which might result in unexpected adverse outcomes or therapeutic failures. Variations in the genes encoding *CYP2D6, CYP3A4, CYP2C9* and *CYP2C19* are understood to affect the extent of degradation of various pharmaceutical drug compounds and cause patients more or less likely to respond to personalized therapy or suffer adverse effects. The potential for adverse reactions is high if a drug has narrow therapeutic index or depends on only one specific enzyme for metabolism. As instance, certain drugs like tramadol or losartan, do not exert their therapeutic effects until they are metabolized to active compounds. These drugs, identified as prodrugs, could trigger an amplified therapeutic or adverse outcome when a *CYP450* inducer is included in the therapy. On the contrary, if a *CYP450* blocker is co-administered with a prodrug, or if a patient is a poor metabolizer of a prodrug, therapeutic failures are expected to happen as there is little to no formation of the active drug.

Majority of drug–drug interactions (DDIs) data including *CYP450* enzymes are the results of either in vitro experiments, pharmacokinetic studies in healthy volunteers or isolated case reports [12]. These research studies do not allow one to understand the actual clinical impact, in terms of adverse drug reactions (ADRs) of the various described DDIs. In vitro studies of *CYP450*-induced interactions, however, can be useful in determining the extent of any interaction and understanding its mechanism. The occurrence of drug–drug interactions in clinical therapy will remain high, posing a challenge to prescribers and drawing clinical pharmacologists' interest.

CYP2D6 Polymorphism and ADRs

CYP2D6 is the most polymorphic drug-metabolizing enzyme in the body. This enzyme represents a minor proportion of all *CYP* enzymes expressed in the liver (1-5%) but metabolizes about 25% of all clinically prescribed medications and its polymorphisms give an important clinical relevance for ADRs [5]. Single nucleotide polymorphisms (SNPs) can cause the enzyme to work rapidly, slowly or not at all, leading to faster or slower *CYP2D6* metabolism than on average (13). 50% of all drugs metabolized by *CYP2D6* are affected by pharmacogenetic variants in the *CYP2D6* gene [13]. Most east Asian populations are intermediate metabolizers (IM) of *CYP2D6* substrates, due to a predominance of reduced activity allele *CYP2D6*10* [13]. In fact, the frequency of the ultra-rapid metabolizer phenotype is low (5%) in most populations, but interestingly, the frequency is quite high in the middle east/north Africa [13].

Currently, over 80 genetic variants of *CYP2D6* have been discovered. *CYP2D6*3, *4, *5* and *6* are the most prevalent variants accountable for the impaired enzyme activity identified in the poor metabolizers [14]. There is a strong correlation between the clearance of a drug by *CYP2D6* and the number of functional copies of *CYP2C6* gene the patient carries. This allows for a reasonable prediction of dosage requirements based on genotype data. If a patient is a poor metabolizer of a certain drug or a *CYP450* enzyme inhibitor is included in the therapy, standard drug doses may result in ADRs due to the increased serum levels of the drug.

CYP2D6 is also a major metabolizer of all tricyclic antidepressants and most SSRI antidepressants [15]. *CYP2D6* is involved in the metabolism of codeine into morphine. A previous study showed that if a patient on codeine therapy is an ultra-rapid metabolizer, they may have accelerated metabolism of anabolize codeine to its active metabolite morphine. That situation could give rise to dangerous or life-threatening toxic adverse outcomes even with administration at normal doses, as morphine glucuronides are responsible for codeine’s analgesic effect [14].

Morphine overdose can cause dangerous adverse effects including respiratory depression. Table 1 shows the codeine guideline as recommended by the Clinical Pharmacogenetic Implementation Consortium (CPIC). If patient is NM (normal metaboliser; normal morphine production), normal doses should be given [7]. On the other hand, if patient is PM (poor metaboliser; greatly reduced morphine production), treatment would lead to failure. For IM patients (reduced morphine production), normal doses are given, but if the response is poor, alternative drug is recommended. Finally, if the patient is UM (ultra-rapid metaboliser; excessive morphine production), codeine is contraindicated.

Table 1. Codeine dosing guideline

Variants	Effects on codeine metabolism	Recommendations
NM (normal metabolizer)	Normal morphine production	Normal doses
PM (poor metabolizer)	Greatly reduced morphine production	Consider alternatives
IM (intermediate metabolizer)	Reduced morphine production	Consider alternatives if no response at normal doses
UM (ultra-rapid metabolizer)	Excessive morphine production	Avoid codeine use

CYP2D6 polymorphisms also greatly affect statin metabolism and drug efficacy. In a previous study, it was revealed that the *CYP2D6* gene polymorphism is also linked to the muscle toxicity due to atorvastatin therapy [17]. In several studies, *CYP2D6* polymorphisms have also been shown to have a significant effect on the cholesterol-lowering drug simvastatin [17]. Among the *CYP2D6* variants, PM show increased reduction of total cholesterol and a higher occurrence of adverse events. This is due to the lowered metabolism of simvastatin and thus, this leads to a higher level of plasma concentration of simvastatin, compared to the wild-type carriers [17]. Thus, low activity variants of *CYP2D6* (PM) lead to lower LDL cholesterol levels. As genetic markers can predict the effects of statin therapy, further study in the field of pharmacogenetics can guide individualized therapy of hypercholesterolemia. This will establish whether pharmacogenetic testing can be employed for cardiovascular disease management.

Paroxetine is a SSRI drug that is also metabolized by *CYP2D6* to inactive metabolites [18]. A study conducted in 2014 indicated that the *CYP2D6*10* allele has a significant impact on the plasma paroxetine concentrations in Asians [19]. Previous data have also shown that the pharmacokinetic parameters of paroxetine were linked to the *CYP2D6* polymorphisms. Thus, therapeutic drug monitoring of paroxetine, particularly in Asian patients with the *CYP2D6*10* genotype, can significantly contribute to lowering the possibility of an overdose. PM have increased concentrations and are more prone to adverse effects. Paroxetine toxicity might lead to serotonin syndrome. These individuals are recommended to change the drug to an alternative drug which is not metabolized by *CYP2D6.*

CYP2D6 is the main enzyme in the metabolism of the prodrug tamoxifen into its active metabolite endoxifen. A study conducted in Morocco demonstrated an association between the *CYP2D6*3* variant with breast cancer risk, regarding tamoxifen [20]. Compared to tamoxifen, endoxifen has over 100-fold higher affinity for the estrogen receptor (ER), and 30-fold to 100-fold greater potency in suppressing estrogen-dependent tumor cell growth. Carriers of the variant in *CYP2D6*3* have been shown to have reduced enzyme activity and lower circulating levels of endoxifen. Currently, a plasma concentration endoxifen of 5.97 ng/mL is maintained to indicate the sufficient efficacy of tamoxifen therapy. Patients with lower *CYP2D6* activity due to genetic variations are less likely to achieve this range. Increasing the dose of tamoxifen in these *CYP2D6*-deficient patients can lead to a greater plasma endoxifen levels without an increase in the incidence of ADRs. In addition to the *CYP2D6* variant, other factors including therapy adherence and drug–drug interactions, such as those caused by the concurrent use of (strong) *CYP2D6* inhibitors, also appear to influence endoxifen levels.

*CYP2D6*2*, *CYP2D6*10* and *CYP2D6*39* allelic variants were also proven to influence the pharmacokinetic profiles of metoprolol [21]. Patients with an inactive *CYP2D6* phenotype have greater clinical consequences of bradycardia with metoprolol than those with an active *CYP2D6* metabolic capacity, according to a prior study [22]. Larger-scale studies are still needed to achieve a better understanding of the metabolic capacity of *CYP2D6*-mediated drugs in mutant population. More prospective data should be obtained to support the implementation of individualized *CYP2D6*-mediated β-blocker therapy. An association study of *CYP2D6* polymorphism with long-term tramadol treatment-induced oxidative damage and hepatotoxicity was conducted in 2018 and the results suggest that tramadol doses should be modified in accordance with patient's *CYP2D6* genotyping assessment to prevent the occurrence of hepatotoxicity [23].

Another study presented a special case of fetal hyperthyroidism in a mother with a previous history of Graves' disease and *CYP2D6* polymorphism. The study revealed that the maternal *CYP2D6* poor metabolizer phenotype inhibits the production of antithyroid drug metabolites, thereby reducing the therapeutic effect of antithyroid treatments [24]. Pregnancy can affect *CYP2D6* pharmacokinetics by increasing *CYP2D6* enzyme metabolism in all but poor metabolizers. Antithyroid medicines should be taken at the lowest possible dose during pregnancy, according to current recommendations. However, when the rare consequences of fetal hyperthyroidism occur, as in the prior example, would signal a problem in therapy. Further studies into the role of *CYP2D6* in the metabolism of antithyroid medicines is required.

The antipsychotic medications risperidone and aripiprazole are also metabolized by *CYP2D6* to their active metabolites, 9OH-risperidone and dehydroaripiprazole. A large patient population was studied to determine the impact of *CYP2D6* genetic variability on risperidone and aripiprazole exposure and therapy [25]. When compared to

normal metabolizers, the *CYP2D6* genotype significantly affected risperidone and aripiprazole metabolism, causing an approximately 1.6-times and 1.4-times increase in risperidone and aripiprazole active fraction exposure in poor and intermediate metabolizers [25]. Physicians lowered poor metabolizers' daily doses of risperidone and aripiprazole by 19% and 15%, respectively. Another recent paper released in 2021 also found that *CYP2D6* activity had a significant impact on the pharmacokinetic characteristics of risperidone [26]. Therefore, *CYP2D6* genotyping may be beneficial for the optimization of individualized risperidone and aripiprazole dosing and therapy.

CYP3A4 Polymorphism and ADRs

Polymorphic *CYP3A4* enzymes could play a key role in explaining variations in medication efficacy and toxicity between people. Enzymatic activity may be eliminated, diminished, changed, or enhanced, because of polymorphisms in the *CYP3A4* gene. According to a study published in 2019, the majority of *CYP3A4* polymorphisms in the European population are uncommon, whereas polymorphisms in African and East Asian groups are significantly more frequent [27]. 856 SNPs (single nucleotide polymorphisms) were discovered in an analysis of a huge database of 141,456 people, with 312 of these being missense polymorphisms [27].

The frequency of polymorphisms varies between different ethnic group, implying that ethnicity-based categorization of *CYP3A4* SNPs is the first step toward precision therapy. A new method for determining the allelic frequency of *CYP3A4* polymorphisms in different ethnic groups has been proposed [27]. This comprehensive approach could identify polymorphisms that are common in specific ethnic groups, and when paired with chemical screening, it can serve as a first step toward personalized therapy. This research may boost awareness of the potential clinical significance of protein altering *CYP3A4* SNPs, as well as provide a few valuable strategies for promoting and implementing precision and individualized medicine.

Statins, such as lovastatin, atorvastatin and simvastatin are mainly metabolized by *CYP3A4*. Previous findings revealed that the polymorphism of *CYP3A4* is related to lipid-lowering efficacy of atorvastatin [16]. *CYP3A4* and *CYP3A5* metabolize atorvastatin to ortho- and parahydroxylated metabolites, which can all reduce HMGCR action. *CYP3A4* also metabolizes simvastatin to its β-hydroxyacid metabolite in the liver. The variant *CYP3A4*19* appears to be common among Hispanics, while the variant *CYP3A4*18* has been reported among ethnic Chinese minorities [28]. In addition, variations have also been discovered in *CYP3A4*IB* and *CYP3A5*3* between Brazilians of African and European descents, between African Americans and Caucasians and between Indian, Malay, Chinese and Caucasians in Singapore. Apart from the *CYP3A4*1B* variant, the number of patients without a *CYP3A4* polymorphism seems to be low among Indo-Pakistanis [28].

A study reported this year on the association of pregnancy-related hormones (PRH) such as estradiol, estriol, estetrol, progesterone, and cortisol, with nifedipine metabolism in human hepatocytes suggest that these hormones increase the metabolism of nifedipine by inducing *CYP3A4* expression in pregnant women [29]. PRH elevated *CYP3A4* protein concentrations to the largest extent among the *CYP* isoforms analyzed, and greatly increased the hepatic metabolism of nifedipine, an antihypertensive medication commonly administered in pregnancy. Hepatocyte-derived exosome *CYP3A4* mRNA levels are positively correlated with hepatocyte *CYP3A4* protein levels and function. Increased nifedipine clearance was detected in pregnant women. The conclusion is that hepatocyte-derived exosomes have the potential to serve as biomarkers of hepatic *CYP3A4* expression and metabolic changes during pregnancy, as well as to provide more precise dose recommendations in obstetric patients.

In a study done on the comparison of contraceptive failures associated with *CYP3A4*-inducing drug-drug interactions by route of hormonal contraceptive in an adverse event reporting system, *CYP3A4* polymorphism was reported to affect levonorgestrel and etonogestrel metabolism and increase the risk for contraceptive failures [30]. When patients on oral and implant contraceptives were exposed to *CYP3A4*-inducing medicines, there were occurrences of unexpected pregnancies. This drug-drug interaction had no effect on intrauterine and vaginal ring devices. These data imply that intrauterine and vaginal ring contraceptive methods, as opposed to oral or implant contraceptive products, may be more appropriate for women concurrently taking *CYP3A4*-inducing drugs. While these findings aren't conclusive, further research should investigate how contraceptive methods and progestin components affect the possibility of drug-drug interaction.

The association between *CYP3A4* variants (*rs4646440, rs35564277*, and *rs4646437*) and COPD susceptibility was studied among the Hainan Han population [31]. The results demonstrated that there is a link between the *CYP3A4* variants and the susceptibility to COPD development. The *rs4646437* polymorphism was linked to a significantly higher susceptibility to COPD in smokers and men while in females and non-smokers, *rs4646440* was shown to be associated with a lower risk of COPD. Another study conducted in the same population also revealed that the variant *CYP3A4*1G* might be linked to poor prognosis, one year after acute ischemic stroke [32]. Additionally, among the Shaanxi Han population in China, it was revealed that the variants *rs4646440* and *rs4646437* were significantly associated with non-small cell lung cancer susceptibility [33]. Thus, these variants may serve as biomarkers in the diagnosis of lung cancer.

Iloperidone, an antipsychotic medication, has been shown to affect CYP3A4 expression in human hepatocytes.

Previous findings showed reduced mRNA level and activity of *CYP3A4* in human hepatocytes on administration of iloperidone, which may lead to unwanted drug interactions [34]. Docetaxel metabolic deactivation mediated by *CYP3A4* could be a key factor of drug pharmacokinetic resistance [35]. This data could be used as a foundation for future in vivo research looking into intratumoural metabolism-based drug resistance.

Polymorphisms in the *CYP3A4 (rs2242480)* and *CYP3A5 (rs776746)* genes have previously been linked to carbamazepine (CBZ) metabolism and resistance in epilepsy [36]. In epilepsy, the G allele of *CYP3A4 rs2242480* was observed to reduce the plasma CBZ levels significantly. On the other hand, the GG genotype, and the GG + GA genotype were shown to cause an increased CBZ plasma levels for the *CYP3A5 rs776746* polymorphism. Because the *CYP3A4 rs2242480* and *CYP3A5 rs776746* polymorphisms are significant in CBZ metabolism and resistance, these findings may help clinicians to optimize the personalized therapy in epileptic patients.

CYP2C9 Polymorphism and ADRs

CYP2C9 is the most extensively expressed variant among the *CYP2C* subfamily and involves in drug metabolism to the greatest degree. It is highly polymorphic, with more than 50 SNPs (single nucleotide polymorphisms) discovered in its noncoding and coding regions [5]. Like other *CYP2C* enzymes, *CYP2C9* can lead to wide interindividual variations in drug metabolism. *CYP2C9* contributes to the metabolism of around 20% of all drugs that are prone to P450-catalyzed biotransformation, including warfarin, phenytoin, acenocoumarol, sildenafil, tolbutamide and some NSAIDs [37].

So far, there have been 60 allelic variations of *CYP2C9* identified [38]. The most prevalent alleles, *CYP2C9*2 (Arg144Cys)* and **3 (Ile359Leu),* have been extensively researched and found to have a significant impact on enzymatic activity in clinical and in vitro tests. As there is diminished interaction with NADPH-CYP-reductase or *CYP2C9* substrate, the *CYP2C9*2* and *CYP2C9*3* allelic variants have been shown to cause in a significant drop in *CYP2C9* enzyme activity. The *CYP2C9*3* variant has been associated with adverse drug response. South Asian populations have a larger frequency of *CYP2C9*3* and *CYP2C9*3/*3* alleles than other ethnicities throughout the world [39]. *CYP2C9*64, *65, *66, *68, *69,* and **70* haplotypes were also discovered to be South Asian-specific [39].

The influence of enzymatic activity of 38 human *CYP2C9* genes, including wild-type *CYP2C9*1* and the 24 *CYP2C9* novel alleles (**36–*60*), were investigated in a recent study. When compared to the wild-type *CYP2C9*1*, sildenafil clearance levels of most *CYPC2C9* allelic variants were found to be lower in the Chinese population [38]. Sildenafil is used in the treatment of erectile dysfunction. It has a great efficacy in vasodilation; patients with *CYP2C9* polymorphism on long-term sildenafil therapy are at a higher possibility of ADRs such as renal toxicity and worsened heart condition. The *CYP2C9*2* and *CYP2C9*8* genotypes resulted in a significantly reduced sildenafil clearance rate. The enzymatic activity of the *CYP2C9*11* genotype on sildenafil was not much different from that of the wild type. This study will aid in the understanding of the many sildenafil dose–response relationships and may help to provide sildenafil treatment that is both effective and safe.

Warfarin is an effective anticoagulant; however, its effectiveness is highly dependent on its large interindividual variability. *CYP2C9* has been associated with this variability, resulting in genotype-guided dosing tables in warfarin labelling. The variants *CYP2C9*2* and *CYP2C9*3* showed diminished clearance of warfarin and hence increased the possibility of bleeding with warfarin treatment [40]. The two polymorphisms (*rs1799853* and *rs1057910*) produce part of the *CYP2C9*2* and *CYP2C9*3* variants [40]. Both alleles are discovered at comparatively high frequencies among white Europeans [41]. Due to large variations in patient ethnicity, navigating the literature to establish how genotype may affect warfarin response in a specific patient may be difficult. Thus, genotyping of patients undertaking therapy with warfarin verified the functional significance of these polymorphisms.

Polymorphisms in the *CYP2C9* gene may also be associated with adverse vascular events following endovascular procedures independent of antiplatelet therapy. An investigation on the impact of *CYP2C9*2* and *CYP2C9*3* loss-of-function polymorphisms on clopidogrel response was conducted and the findings suggest protection against ischemic stroke in carriers of *CYP2C9*2* or **3* polymorphisms undergoing neuro-intervention [42]. *CYP2C9* polymorphism was also shown to impact the metabolism of valproic acid in Chinese patients with epilepsy [43]. These *CYP2C9* loss-of-function polymorphisms have been shown to be less active in the metabolism of valproate than the wild type *CYP2C9*1* [38]. Genetically determined impaired valproic acid metabolism is caused by the *CYP2C9*2* and *CYP2C9*3* allelic variants [43]. Specifically, the mutant allele *CYP2C9*3* may induce liver dysfunction. Therefore, early discovery of *CYP2C9* gene polymorphisms may aid in the prediction or prevention of valproic acid-induced liver damage.

Another study showed that individuals with variants *CYP2C9*2* and *CYP2C9*3* had significantly lower enzymatic activity for phenytoin metabolism, with a reduction of 27–54% of phenytoin metabolism, indicating a higher susceptibility to phenytoin toxicity at standard doses [44]. Patients with severe cutaneous adverse responses in Taiwan, Japan, and Malaysia, particularly *CYP2C9*3* carriers, had delayed clearance of plasma phenytoin, indicating a functional relationship between the related variants and the disease [45]. Sulfonylurea metabolism is also likely to be affected by *CYP2C9*2* and *CYP2C9*3*, as

these *CYP2C9* loss-of-function alleles are known to increase the risk of sulfonylurea-induced hypoglycemia in patients with type 2 diabetes [46, 47]. Findings from another research also showed that the plasma level of sulfonylureas was the highest in the patients with the *CYP2C9*3* allele. In the absence of wild type allele *CYP2C9*1*, a significant increase was observed in retinopathy and nephropathy [48]. Based on these findings, *CYP2C9* genotyping may be valuable in predicting the possibility of hypoglycemia during sulfonylurea therapy for T2DM.

Ibuprofen and diclofenac, two of the most often used painkillers, are affected by genetic variations in the *CYP2C8* and *CYP2C9* enzymes. Hepatotoxicity and gastrointestinal bleeding are the most prominent ADRs caused by the impact of *CYP2C8*3* and *CYP2C9*2*3* variants on ibuprofen and diclofenac pharmacokinetics [49]. Patients at higher risk of these side effects may be identified through *CYP450* genotyping, and their doses could be modified, or they could switch to an alternative NSAID that does not share the same metabolic pathways as ibuprofen or diclofenac.

A study among the Europeans also found that the presence of the *CYP2C9*3* genotype increases the possibility for upper gastrointestinal bleeding (UGIB) associated with NSAIDs [50]. This happens when patients are given doses that are higher than half of the standard dose. Those who took more than 0.5 NSAIDs and had the *CYP2C9*3* allele had a roughly two-fold greater incidence of UGIBs as compared to patients who took the same amount but were not carriers of this genotype. However, the effect of *CYP2C9*2* allele was remarkably comparable to that of the wild type, and no significant variations in the *CYP2C9*-related risk of UGIB were found. Other in vitro and in vivo studies have also found that *CYP2C9*3* has a significant effect on the clearance of most NSAIDs when compared to *CYP2C9*2* [51].

Another study looked into the use of celecoxib to prevent colorectal adenoma and discovered that carriers of *CYP2C9*3*, but not *CYP2C9*2*, were linked to improved protection against adenoma in individuals taking high dosages, though the effect was small overall [52]. The data imply that the higher efficacy of high-dose celecoxib in preventing colorectal adenoma compared to low-dose celecoxib appears to be limited to individuals with slow metabolizer (*CYP2C9*3*) genotypes.

The Clinical Pharmacogenetic Implementation Consortium (CPIC) has released evidence-based recommendations for safe NSAID use based on the *CYP2C9* polymorphism [53]. CPIC offers recommendations for dose adjustments or alternative NSAIDs in individuals with reduced-function or loss-of-function *CYP2C9* allelic variants. The half-life of NSAIDs determines the CPIC recommendations for NSAIDs based on the *CYP2C9* polymorphism. When comparing NSAIDs with longer half-lives, such as meloxicam and piroxicam, to NSAIDs with shorter half-lives, such as celecoxib, ibuprofen, and flurbiprofen, the *CYP2C9* polymorphism has a substantially greater influence on increasing the AUC of NSAIDs. *CYP2C9* testing could be used to identify higher-risk patients who would benefit from lower NSAID doses or NSAIDs that are not processed by the *CYP2C9* enzyme. Pharmacists will play a vital role in adjusting NSAID regimens based on pharmacogenetic test results, as pharmacogenetics becomes more prevalent [53]. Pharmacists are encouraged to implement the latest CPIC guidelines for the most up-to-date recommendation. Table 2 summarizes the adverse drug reactions associated with *CYP2C9* polymorphisms.

Table 2. Adverse drug reactions associated with CYP2C9 polymorphisms

Drug/Classes	Allele	Enzyme activity	ADR	Mechanism
Sildenafil	CYP2C9*2 CYP2C9*8	Decreased	Renal toxicity	Reduced clearance rate.
Warfarin	CYP2C9*2 CYP2C9*3	Decreased	Bleeding	Reduced clearance rate and clotting factors.
Clopidogrel	CYP2C9*2 CYP2C9*3	Decreased	Ischemic stroke	The conversion of clopidogrel into its active metabolite is limited and this affects the platelet coagulation capacity.
Valproic acid	CYP2C9*3	Decreased	Liver dysfunction	Due to mitochondrial toxicity, from the loss of mitochondrial function in patients with the allele *3.
Phenytoin	CYP2C9*3	Decreased	Severe cutaneous reaction	Increased serum phenytoin increases the formation of reactive arene oxide metabolites

Sulfonylureas	CYP2C9*2 CYP2C9*3	Decreased	Hypoglycemia Retinopathy Nephropathy	Epoxyeicosatrienoic acids (EETs) produced by CYP2C9 are known to play an important role in the diabetic retinopathy. Increase in microalbuminuria and decreased GFR are associated with nephropathy.
Ibuprofen Diclofenac	CYP2C9*2*3	Decreased	Hepatotoxicity Gastrointestinal bleeding	Increased levels of reactive metabolites result in higher levels of protein-diclofenac adducts and consequently in hepatotoxicity.
NSAIDS	CYP2C9*3	Decreased	Upper GI bleeding	Inhibition of cyclooxygenase causes decreased mucosal prostaglandin synthesis and results in impaired mucosal defenses.

CYP2C19 Polymorphism Related ADRs

CYP2C19 plays a substantial role in the metabolism of approximately 10% of commonly prescribed drugs such as proton pump inhibitors, antipsychotics, tricyclic antidepressants, warfarin and clopidogrel. 20% of Asians are poor metabolizers of drugs that depend on CYP2C19, which metabolizes phenytoin (Dilantin), phenobarbital, omeprazole (Prilosec), and other drugs [54]. Like many other *CYP450* superfamily members, interindividual variability in response to *CYP2C19* substrate can be explained satisfactorily by factors such as highly polymorphic of *CYP2C19* genes. Currently, at least 34 known variant alleles and numerous subvariants have been identified within the *CYP2C19* gene [55]. Most PMs were identified among Asian and African American population (allele frequencies are 30% and 17% for *CYP2C19*2*; 5% and 0.4% for *CYP2C19*3*, respectively).

A study done among ten Southeast Asian populations found that the overall frequencies of *CYP2C19*1, CYP2C19*2,* and *CYP2C19*3* were 0.39, 0.24, and 0.37, respectively [72]. The most frequent *CYP2C19* genotype found was IM (50.6%), followed by PM (34%) and NM (15.4%). Additionally, variations were observed, with a PM prevalence ranging from 20% in the Malay, 35% in the Indonesians, to nearly 46% in the Bugis and the Thais. In comparison, the prevalence was 23% in the Philippines and 20%, 19%, and 12% in the Chinese, Japanese, and Korean respectively.

The link between genetic variations and clopidogrel resistance has been studied extensively. Clopidogrel is a prodrug that is metabolized into its active metabolite by the enzyme *CYP2C19* for its antiplatelet activity [56]. The polymorphisms of *CYP2C19* involve some variants of loss-of-function or gain-of-function. *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*4* result in loss of function, whereas *CYP2C19*17* imparts gain of function. Those with *CYP2C19* loss-of-function alleles (**2, *3*, and **4*) had higher cardiovascular events compared to patients with the wild-type version of the enzyme [57]. The active derivative was insufficient in *CYP2C19* loss-of-function alleles, and platelet inhibition was reduced.

In a recent study on clopidogrel metabolism among the Bangladeshi population, *CYP2C19*2, CYP2C19*3, CYP2C19*4* variants showed loss of function while *CYP2C19*17* showed gain of function [57]. It was revealed that the *CYP2C19*2* and the *CYP2C19*17* mutant alleles are present at high frequencies in Bangladeshi population. Another study done among the Indian population demonstrated impaired response of clopidogrel to inhibit platelet aggregation with variant genotype of *CYP2C19*2* compared to the wild type [58]. A fast and cost-effective approach to analyze the *CYP2C19* genotypes before prescribing clopidogrel may offer better therapeutic outcomes. In Vietnam, a study revealed that intermediate metabolizers and poor metabolizers for clopidogrel are common in Vietnamese patients with *CYP2C19* polymorphism [59]. A Vietnamese study published in early 2019 discovered that the prevalence of *CYP2C19*17* in the Vietnamese population was significantly lower, but the frequency of *CYP2C19*2* was statistically greater, when compared to Western Asia and several European countries [60]. This study suggests that *CYP2C19* genotype testing for planning the antiplatelet therapy might be beneficial in Vietnam.

Another study on the association between *CYP2C19* polymorphisms and high on-treatment platelet reactivity (HTPR) in clopidogrel-treated ischemic stroke patients with T2DM was conducted among the Chinese population. According to the findings, The *CYP2C19*2* A allele was found to be an associated factor of HTPR events in IS patients with T2DM, but not in patients without T2DM [61]. By using *CYP2C19* genotype testing to guide antiplatelet therapy in clinical practice, the current findings may foretell the situation of HTPR in diverse patient populations, guide

the appropriate use of medicines, and reduce the incidence of adverse drug reactions.

Proton pump inhibitors, which are commonly used to treat peptic ulcers as acid-inhibitory medicines, are mostly metabolized by *CYP2C19*. Thus, *CYP2C19* polymorphisms may be of clinical relevance in the therapy of proton pump inhibitors to treat peptic ulcers. A study on the effect of *CYP2C19*2* polymorphism in Polish peptic ulcer patients found that there is an association between *CYP2C19*2* and H. pylori-infected patients [62]. Nonetheless, further research is still required for a clearer understanding. The effects of rifampicin (inductive) and fluvoxamine (inhibitory) on omeprazole metabolism and *CYP2C19* enzymatic activity in the Japanese population were studied in 2019. The *CYP2C19*1* allele was associated with higher levels of omeprazole metabolism compared to those without the *CYP2C19*1* allele [63]. Rifampicin increased omeprazole metabolism in all subjects, regardless of genotype, implying that rifampicin treatment induced *CYP2C19* enzyme activity in all genotypes. Fluvoxamine, on the other hand, lowered omeprazole metabolism in those with the *CYP2C19*1* allele but had no effect on omeprazole pharmacokinetics in those without this allele. Genotyping for *CYP2C19* polymorphisms has been proposed as a potential guide for individualized proton pump inhibitor therapy.

Sulfonylureas, such as gliclazide, are extensively metabolized in the liver, mostly by *CYP2C9* and *CYP2C19*, to generate several inactive metabolites, including methylhydroxygliclazide and carboxygliclazide. In contrast to other sulphonylureas, gliclazide's pharmacokinetics appears to be largely influenced by *CYP2C19* rather than *CYP2C9*. Individuals with the *CYP2C19*2 (rs4244285)* and **3 (rs4986893)* variants produce a non-functional enzyme, which is linked to lower oral gliclazide clearance [64]. In Asian populations, the allele frequency of *CYP2C19*2* is 40%, while 18% in Caucasian populations. With a mean allele frequency of 7%, the *CYP2C19*3* gene is exclusively found in East Asians [64]. As a result, genetic diversity in *CYP2C19* may play a significant role in treatment efficacy and hypoglycemic risk in Asian diabetic patients. A study published in 2019 found that the *CYP2C19*2* polymorphism is linked to higher total gliclazide concentrations and lower oral clearance in healthy Chinese populations [64]. Given that one-fifth of Asians may be poor metabolizers of *CYP2C19*, further pharmacogenetic research is needed to determine the influence of these polymorphisms on gliclazide therapy response and hypoglycaemic risk.

Escitalopram is a selective serotonin reuptake inhibitor (SSRI) that is largely metabolized by *CYP2C19* and is used to treat depression and anxiety disorders. Polymorphisms in the *CYP2C19* gene are linked to long-term remission of major depressive disorder (MDD) in patients on escitalopram. In 2017, a study in China confirmed the link between *CYP2C19* poor metabolizers and early escitalopram therapy response in panic disorder patients [65]. Moreover, a Brazilian study suggests that *CYP2C19* ultra-rapid metabolizer patients may need higher doses of escitalopram to achieve its efficacy in reducing the depressive symptoms [66]. Understanding that *CYP2C19* polymorphisms can affect escitalopram efficacy and safety, the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline offers SSRI (fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline) dosing recommendations for *CYP2C19* genotypes [67].

While the number of ADR reports received in Malaysia has been growing every year, the National Pharmaceutical Regulatory Agency (NPRA) is also verifying the quality of reports to ensure that comprehensive and accurate information is obtained for better quality assessment which will be beneficial for drug safety monitoring. WHO also reported that the NPRA has seen a slight increase in ADR reporting quality from 63% in 2014, to 72% in the year 2015.

Among the reports received, Ministry of Health (MOH) pharmacists were the highest reporters, followed by MOH doctors. There was a reduction in the number of reports obtained from private sector doctors, which is a reason for concern as unreported ADRs will delay or prevent the recognition of drug safety issues. Currently, the NPRA offers ADR reporting forms for healthcare professionals (blue form), as well as a reporting form for medicine complaints by patients. The consumer complaints form can be applied for all types of medicinal product complaints, such as side effects, efficacy concerns, or reporting unregistered products. In the attempt to make the form convenient for consumers, the information gathered tends to lack a lot of crucial details necessary for an efficient ADR reporting. Hence, an ADR reporting form exclusively for consumers; the Consumer Side Effect Reporting Form (ConSERF) was established.

Some of the *CYP450* genes are highly polymorphic with various alleles and the prediction of phenotypes by identifying polymorphisms of *CYP450* genes that are crucial for drug metabolism can be achieved by genotyping [68]. *CYP450* genotyping may be valuable to detect patients at high risk for ADRs or drug toxicity with standard doses of medication therapy. Furthermore, previous studies suggest that genotyping for *CYP2C19* for clopidogrel should include the variants *CYP2C19*2* and **3* polymorphisms in Chinese, *CYP2C19*2* and **17* polymorphisms in Indians, and *CYP2C19*2, *3,* and **17* polymorphisms in Malays [69].

Available techniques for *CYP450* genotyping consist of restriction fragment length polymorphism analysis, allele-specific PCR or Sanger sequencing. A few of the currently accessible commercial tools are inadequate in coverage, neglecting significant variations relevant in Asian populations [68]. Currently there are 6 different *CYP450* genotyping tests approved by the FDA. The most used is the AmpliChip CYP450 GeneChip, which is an oligonucleotide microarray hybridisation method for genotyping *CYP2D6* and *CYP2C19* [70]. It has been widely used in the western countries and some parts of Asia like China and Japan.

However, the use is still lacking in Southeast Asian countries.

Tools to Evaluate ADRs

While the MADRAC database is a great tool to promote pharmacovigilance, and provide evidence for new, rare, or unknown reaction towards medication, there is no part of the database that allows or label any link of genetic markers to these adverse reactions. The database would probably be a great source of reference for pharmacogenetics and pharmacogenomics studies should some genetic markers information are added in the future.

It has not been proven if genotyping is cost-effective for every drug and that it enhances clinical outcomes by reducing ADRs or recognizing poor responders. To provide a guide on the assessment of drug interaction causation in a specific patient, the Drug Interaction Probability Scale (DIPS) method can be applied [71]. DIPS aims to aid physicians in the evaluation of ADR-induced drug interactions. It consists of a series of questions associated with the potential drug interactions to estimate a probability score. An accurate evaluation using the DIPS method involves knowledge of the pharmacologic characteristics of both drugs involved in the interaction and the basic mechanisms of the interaction.

Additionally, the Naranjo Algorithm, or Adverse Drug Reaction Probability Scale can be employed to assess the presence of a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to obtain probability scores [73]. Another interesting method available to evaluate drug induced liver injury (DILI), that could lead to a change in CYP450 enzymes secretion and function is RUCAM (Roussel Uclaf Causality Assessment Method) or its previous synonym CIOMS (Council for International Organizations of Medical Sciences). This diagnostic algorithm is very specific for hepatic injury caused by drugs and herbs [74]. Among the top 10 ranking drugs implicated in causing DILI according to the RUCAM criteria and algoritm were amoxicillin-clavulanate, flucloxacilllin, atorvastatin, disulfiram, diclofenac, simvastatin, carbamazepine, ibuprofen, erythromycin, and anabolic steroids [75]. Out of these 10 drugs, flucloxacillin was observe to induce CYP3A4 [76] while atorvastatin and simvastatin are metabolised by CYP3A4 and therefore are metabolically dependent on the polymorphism of the enzyme [77].

CONCLUSION

Although genotyping tests can verify if a patient possesses a specific enzyme polymorphism, it has not been concluded if regular application of these tests will enhance clinical results. Extensive knowledge on how drugs impact the polymorphic variants of *CYP* enzymes can help personalize drug therapy, leading to optimization of the proper choice of drugs and doses for individuals based on genetic information gathered. Thus, understanding of the highly crucial drugs metabolized by *CYP450* enzymes, along with the most effective inducers and inhibitors, can help lessen the risk of ADRs caused by *CYP450* polymorphism. Further research on *CYP450* polymorphisms in specific regions may also benefit to improve pharmacotherapy success by delivering personalized medication plan to certain ethnic groups.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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