



International Journal of Preclinical & Pharmaceutical Research

Journal homepage: www.preclinicaljournal.com

THE ROLE OF CYTOCHROME P450 ENZYMES IN DRUG METABOLISM, TOXICITY, AND PERSONALIZED MEDICINE

Sai Madhuri P^{1*}, Madhuri D¹, Sree Lakshmi K¹, Sravani B¹, Dr. Lavanya A^{2*}

¹Pharm. D, V Year Student, Department of Pharmacy Practice, KLR Pharmacy College, Paloncha, Telangana, India.

²Assistant Professor, Department of Pharmacy Practice, KLR Pharmacy College, Paloncha, Telangana, India.

ABSTRACT

Cytochrome P450 (CYP450) enzymes play a crucial role in the metabolism of drugs and endogenous compounds, influencing drug efficacy, toxicity, and interactions. These enzymes, found primarily in the liver, catalyze oxidative reactions, converting substrates into more water-soluble metabolites for easier excretion. CYP450 isoenzymes such as CYP3A4, CYP2D6, and CYP2C9 are involved in the metabolism of a wide range of medications, with genetic polymorphisms affecting enzyme activity and individual drug responses. Variations in CYP450 activity can lead to altered drug metabolism, necessitating personalized treatment strategies to optimize drug dosing and minimize adverse effects. Environmental factors, drug-drug interactions, and disease states also influence CYP450 function, further complicating drug therapy. Advances in pharmacogenomics and personalized medicine allow for more precise dosing based on genetic variations in CYP450 enzymes, improving treatment outcomes and reducing drug toxicity. Future research aims to enhance CYP450-related drug safety through AI-driven models, pharmacometabolomics, and global population-specific studies.

Key Words: CYP450 Enzymes, Drug Metabolism, Toxicity Control, Pharmacogenomics, Bioengineering.

INTRODUCTION

Drug metabolism can be defined as the biochemical action of the body in transforming the pharmaceuticals to be excreted in a easier manner. This is normally done in two stages, Phase I, during which the drug is altered by enzymes (typically through oxidation, reduction, or hydrolysis), and Phase II, during which conjugating agents are included to increase the water-solubility of the compound [1–6]. Knowledge of drug metabolism is fundamental in the determination of drug absorption, distribution, metabolism, and excretion systems into and out of the body, which contributes to the effectiveness, safety, and toxicity in using drugs.

Cytochrome P450 (CYP450) enzymes play important roles in drug metabolism, absorption, and addiction. <[human]>1.2.2 Significance of the Cytochrome P450 (CYP450) Enzymes Cytochrome P450 (CYP450) enzymes are significant in drug metabolism, absorption, and addiction.

Corresponding Author

Sai Madhuri P

Email: madhursai115@gmail.com

The enzymes known as the cytochrome P450 (CYP450) are important in the metabolism of most drugs. A group of enzymes that are mostly found in the liver catalyzes these oxidative metabolites, and they oxidize a large variety of endogenous and exogenous substances, including the majority of therapeutic drugs [7–11]. CYP450 enzyme activity may lead to considerable changes in the pharmacokinetics of drugs (absorption, distribution, elimination) and, in turn, their therapeutic efficacy and safety. Drug responses in individuals can be altered because of variations in CYP450 enzyme activity amongst individuals or disparities in the activity of enzymes when there is an interaction of other drugs.

History Research History of CYP450

The knowledge and definition of CYP450 enzymes have been discovered within decades. Originally discovered in the 1950s as the major participants of the metabolism of several drugs, the CYP450 family has since been discovered to be a large number of isoenzymes, each being a participant in the metabolism of a specific substance[9,12–15]. Studies on

these enzymes have greatly progressed especially with the discovery of genetic polymorphism in an enzyme activity that has played a role in the field of personalized medicine. The research on CYP450 enzymes has guided in clarifying the complicated relationship between drugs and the metabolic processes resulting in effective and harmless pharmacotherapy.

Cytochrome P450 Enzymes Structure and Function. Molecular Structure of CYP450 Proteins

Cytochrome P450 enzymes are a huge group of heme-binding proteins with an extensive structural dispersion wherein they are capable of catalyzing a broad range of reactions[9,16,17]. These are membrane-bound enzymes, which are normally found in the endoplasmic reticulum of liver cells, but are also found in other tissues. CYP450 enzymes are made up of a globular protein that comprises of a single polypeptide chain. In an active site, the site that holds the substrate and catalyses is in a hydrophobic pocket and therefore, makes the hydrophobic substrates to be efficiently processed.

Heme Center and Active Site

Heme cofactor is the main characteristic of the CYP450 enzyme as it consists of an iron atom on the center. This is an iron that is necessary in the catalytic activity of the enzyme and is involved in the binding and activation of molecular oxygen[18,19]. CYP450 enzymes have their active site close to the heme center and it is at this position that the enzyme and substrate interact. Different CYP450 enzymes have the ability to metabolise a wide variety of substrates, such as drugs, hormones and other endogenous molecules, because the structure of the active site can be very different in each individual enzyme.

Substrate Binding Domain

CYP450 enzymes have a substrate binding domain that is adapted to bind a particular chemical structure of the substrate and this enables the enzyme to recognize and bind various molecules. This space consists of elastic loops and helices that fit the shapes and sizes of substrates[19,20]. The exact order of arrangement of the amino acids in this field dictates the substrate specificity of the enzyme and this is crucial in which the enzyme can process different compounds. This area also plays a role in dictating the manner in which the enzyme stabilizes the transition state in the catalysis process to provide the enzyme with an efficient metabolism.

Genetic Basis of CYP450 Enzymes CYP Gene Families and Subfamilies

CYP450 family is divided into the gene families and subfamilies according to homologous

sequences. These gene families are numbered and each family comprises of similar genes that encode enzymes with high level of sequence identity (typically 40 percent or more). In each family, sub families (designated by letters) exist and within a subfamily, individual genes are generally named by addition of numbers[9,21]. CYP1A2 is an example of a member of CYP1 family and subfamily A. The variousness of the CYP450 genes provides an opportunity to metabolize a broad range of substances, such as drugs, environmental toxins, and endogenous substances.

Tissue Distribution

CYP450 enzymes are distributed and expressed in many tissues where liver is the main site of enzyme expression. Yet these enzymes can be found in other tissues such as the intestine, lungs, kidney, and the brain where they contribute to both endogenous and exogenous compound metabolism[8,9,22,23]. Some variation may occur in the expression of individual CYP450 enzymes, depending on the type of tissue, the level of development and exposure to certain conditions including drugs or environmental chemicals. This tissue-specific expression is part of the complicated drug metabolism and the various functions of CYP450 enzymes in the body.

Catalytic Cycle of CYP450

Oxygen Activation and Formation of Product

The heme iron activates molecular oxygen as the last step of the catalytic cycle. After oxygen is bound to the heme, it is activated through electron transfer, and this leads to the generation of a reactive oxygen species[24,25]. This form of oxygen species subsequently reacts with the substrate resulting in the product. It is generally a more hydrophilic metabolite, which is expelled more easily out of the body. The efficiency of the entire cycle depends upon the structure of the enzyme, the type of substrate and the conditions which are available in the cell.

Drug Metabolism CYP450 Isoenzymes. CYP3A Family

The CYP3A family is one of the greatest and most significant families of cytochrome P450 enzymes that play a part in the metabolism of drugs. There is a large range of pharmaceuticals that is metabolized by CYP3A enzymes such as anticancer agents, immunosuppressants, and antivirals. CYP3A family comprises two large isoenzymes CYP3A4 and CYP3A5, which play an important role in drug metabolism in liver and intestines. Such isoenzymes have a significant overlap in the substrates that they act on yet may be more or less expressed by genetic factors, environmental factors, and drug interactions[13,14,26,27].

CYP3A4 and CYP3A5 Substrates

The most predominant CYP enzyme in the liver is CYP3A4, which forms the central position in the metabolism of most of the drugs used in clinical practice. Although CYP3A5 is not so abundant it is very relevant in some population because of genetic polymorphisms that influence its expression. CYP3A4 has a very large number of substrates that include statins, benzodiazepines, opioids, and calcium blockers. CYP3A5, in its turn, is of particular relevance to such drugs like tacrolimus and cyclosporine, in particular, to patients possessing certain genetic types that precondition the excessively high expression of this isoenzyme. Drug-drug interactions may also involve these enzymes because they may either increase or decrease the metabolism of other drugs which results in different therapeutic effects or toxicity [28].

CYP2D6

One of the most polymorphic enzymes is CYP2D6 which metabolizes a large proportion of the number of drugs prescribed in clinical practice. It has a role in the metabolism of most antidepressants, antipsychotics, beta-blockers, and opioids. The activity of the enzyme has a big interindividual variability subject to many genetic variation, drugs and environmental effects. These genetic variations may lead to various metabolizer phenotypes (i.e. poor metabolizer, intermediate metabolizer, extensive metabolizer, or ultra-rapid metabolizer), the effect of drug, and the potential of adverse effects [29, 30].

Genetic Polymorphisms

It is known that CYP2D6 has genetic polymorphisms which cause high variability in the metabolism of different people. Those polymorphisms consist of deletions, duplications, and point mutations in the gene of CYP2D6 that cause various phenotypes of metabolizers [29,31,32]. The poor metabolizers possess lower or no enzyme activity thus resulting in elevated concentration of drugs and increased likelihood of side effects. The ultra-rapid metabolizers possess more than one copy of the CYP2D6 gene which leads to enhanced faster metabolism of drugs and may lead to less therapeutic effects. In the middle and far between these extremes are the intermediate and extensive metabolizers. Individual dosing on the basis of CYP2D6 genotyping is vital to drug therapy optimization in people with some polymorphisms.

CYP1A2

CYP1A2 is engaged in the processes of the metabolism of various substances, such as caffeine, theophylline, and some antipsychotic medications. It is mainly found in the liver and it is also important in the degradation of aromatic hydrocarbons and other

environmental toxins. CYP1A2 is affected by genetic and environmental influences including smoking and diet. An example of this is the effect of cigarette smoke that causes CYP1A2 that may increase the metabolism rate of drugs such as caffeine. Some foods, on the contrary, could inhibit this enzyme: cruciferous vegetables. The differences in CYP1A2 activity have the potential to affect the efficacy and toxicity of drugs and knowledge of the variation can be used to achieve personalized therapy. [33, 34]

CYP2E1

Another protein enzyme is CYP2E1 which is important in the metabolism of small molecules especially alcohol, acetaminophen, and other volatile substances. It is mainly expressed in the liver and is a part of the oxidative metabolism of both endogenous and exogenous substances. The chronic alcohol intake and smoking are leading to the increased activity of the CYP2E1, which may change the metabolism of various drugs including acetaminophen, exposing the person to the risk of intoxication [35, 36]. Genetic differences in CYP2E1 variability, which is dependent on genetic factors and environmental exposures, potentially affect the metabolic clearance of a number of drugs and toxins. CYP2E1 activity is especially necessary to be monitored in patients at risk of liver damage or in those who are using the medications which are broken down by this enzyme.

Oxidation Reactions

One of the major reactions in the Phase I metabolism is oxidation, in which CYP450 enzymes add oxygen atoms to molecules. These reactions result in the generation of more water-soluble metabolites and they are easier to excrete in form of urine or bile. The two primary categories of oxidation reactions performed by the CYP450 enzymes are aromatic hydroxylation, aliphatic hydroxylation as well as N-, O-, and S-dealkylation processes among which the substrate is modified in various forms. [37–39]

Aromatic Hydroxylation

A typical example of oxidation reaction catalyzed by CYP450 enzymes is aromatic hydroxylation, in which a hydroxyl group (-OH) is appended onto an aromatic ring of a substrate. This response enhances the solubility of the compound making it easier to get it out of the body. Most drugs and environmental chemicals are metabolized by aromatic hydroxylation [40–43]. An example is that hydroxylation of substances such as benzene, and other polycyclic aromatic hydrocarbons (PAHs) is an essential detoxification process. Also aromatic hydroxylation is important in the metabolism of some drugs like acetaminophen with the subsequent production of

metabolites which may be metabolized further and excreted.

Aliphatic Hydroxylation

In the aliphatic hydroxylation, CYP450 enzymes hydroxylate a non-aromatic carbon chain (aliphatic chain) of a substrate. This mechanism normally happens on the terminal carbon atoms of straight or branched chains and it leads to the synthesis of more polar metabolites, which can again be conjugated during Phase II metabolism. The Aliphatic hydroxylation plays a crucial role in the metabolism of many drugs, such as some of the anti-inflammatory drugs, anesthetics, and steroids. This response is commonly an important stage in enhancing the solubility of lipophilic compounds in water, which helps in their elimination by the body [44–49].

Epoxidation and Reactive Species

Epoxidation is a metabolically essential reaction with the help of the CYP450 enzymes, in which an epoxide group (a three-membered oxygen-containing ring) is added to a substrate. The reaction plays a role in the activation of a number of prodrugs, which transform them into their active metabolites [50]. Nevertheless, the presence of epoxide intermediates may be also dangerous, because such reactive intermediates may be covalently bound to cellular macromolecules, which may cause possible toxicity and undesired action of the drug [51–53]. As an example, the epoxidation of aromatic hydrocarbons, e.g., benzene or styrene, can result in the production of highly reactive metabolites that are able to cause damage to DNA, proteins, and lipids, which can cause mutagenesis and carcinogenesis.

Influencing Factors with CYP450 Activity.

Enzymes Cytochrome P450 enzymes (CYP450) are very important in drug metabolism, although their activity may be affected by various factors. All these aspects may cause differentiation in the way a person handles medications, which plays a crucial role in the interpretation of the therapeutic effectiveness and adverse drug reactions [54, 55]. Genetic polymorphism, environmental factors (smoking, diet, etc.), drug-drug interactions, and individual patient factors (age, gender, and disease state, etc.) are the major factors that can affect the activity of CYP450. These factors are important in the that they help in personalizing drug therapy and maximizing the treatment results.

Genetic Polymorphisms

CYP450 enzymes have genetic polymorphisms resulting in an interindividual difference in drug metabolism. Such differences could have an influence on the ability of an individual to metabolize a drug, which determines the effectiveness of a drug, as well as its

toxicity [8, 56, 57]. The variation in the genes that code CYP enzymes may lead to a variation in metabolic phenotype, such as poor, intermediate, extensive, and ultra-rapid metabolizers. The efficacy of the CYP450 enzymes in metabolizing drugs is represented in these classifications. As an example, poor metabolizers experience fewer or no capacity to metabolize particular drugs, which may result in an accumulation and toxicity of drugs. Ultra-rapid metabolizers on the other hand can be rather fast in metabolizing drugs which lowers the therapeutic effect. Discovering variations in genes can be used to determine drug dosing and enhance treatment.

Metabolizer Phenotypes

Personalized medicine is dependent on the classification of the individuals by comparing their metabolic activity status (cypr450). Poor metabolizers are genetically varied such that enzyme activity is severely decreased and this may cause the buildup of drugs in the body which may cause adverse side effects. Intermediate metabolizers are average, and extensive metabolizers are normal in the enzyme activity that should occur in the general population. On the other hand, ultra-rapid metabolizers have a genetic variation that results in an enzyme activity that is too high resulting in the fact that the drugs are being broken down too fast leading to a suboptimal therapeutic effect. The recognition of these metabolic phenotypes may assist in drug therapy with minimizing chances of adverse effects and maximizing drug effectiveness. [13,58,59].

Strategies to Control CYP450 Toxicity

The toxicity caused by CYP450 is one of the major problems in drug discovery and clinical practice, especially since the enzymes CYP450 are the primary participants in the metabolism of many drug agents. In order to deal with this, novel approaches are being considered in order to control and alleviate CYP450-related toxicity. Such new strategies are either to control the activity of CYP450 or to improve the detoxification of toxic metabolites in the body. By these developments, the negative impact of drugs can be minimized, the patient outcomes may be enhanced, and safer treatment regimes may be developed.

Bioengineered CYP Variants

The manipulation of CYP450 enzymes is a developing field that aims at developing modified forms of these enzymes in order to enhance the process of drug metabolism as well as reduction of toxicity. Researchers are striving to make CYP450 variants that can metabolize drugs more effectively or selectively, and hence lead to a reduction in the toxicity of the intermediates formed. The other area of bioengineering may be to make these enzymes less prone to inhibition or induction by outside influences so that drug metabolism

becomes more predictable. Researchers seek to come up with more effective and safe drugs with reduced side effects by altering the structure or functionality of the enzyme. These bioengineered versions may be important in personalized medicine, whereby the affected individual may have a treatment tailored to his or her unique metabolic profile.

Nanotechnology Based Detoxification Plans.

Detoxification techniques based on nanotechnology are a novel approach to the treatment of CYP450-poisoning. To counteract toxic metabolites formed by CYP450 enzymes, nanomaterials, which include nanoparticles and nanocarriers, are being designed to attack them. The nanomaterials may be modified to specifically target the harmful compounds, and therefore, avoid interaction with cellular formations and their toxicity. Also, nanoparticles can be employed to introduce drugs that will improve the actions of detoxifying enzymes or prevent the production of toxic compounds. These approaches can potentially provide a more effective and focused method of drug toxicity management, used in acute and chronic health. This is because the capacity to administer therapeutics at the

toxicity locations will reduce the systemic side effect and optimize the overall therapeutic outcome.

CRISPR Based Regulation of CYP Expression.

CRISPR mediated CYP450 expression is a state of the art in the management of CYP450-mediated toxicity. Using the CRISPR-Cas9 gene-editing mechanism, a researcher can specifically regulate the expression of particular CYP450 enzymes at the genetic level. This can be used to upregulate or down regulate enzymes implicated in the process of toxic substance or drug metabolism. As an example, CRISPR may be applied to silence the expression of some CYP-like enzymes that produce toxins (or turn on the expression of enzymes that detoxify toxins). The genetic modulation has the prospect of a more individualized approach to drug toxicity management, particularly in the case of patients who might have genetic differences which cause abnormal CYP450 activity. Moreover, CRISPR technology may be utilized to fix genetic mutations that result in the diseases caused by abnormal CYP450 activity and provide the long-term solutions to the patients with CYP-related disorders.

Table 1: CYP450 Isoenzymes and Substrates

CYP450	Major Substrates
CYP3A4	Dexamethasone, Midazolam, Simvastatin, Tacrolimus
CYP2D6	Codeine, Tamoxifen, Metoprolol, Venlafaxine
CYP2C9	Warfarin, Phenytoin, Losartan
CYP2C19	Omeprazole,
CYP1A2	Caffeine, Theophylline, Clozapine
CYP2E1	Acetaminophen, Ethanol, Aniline
CYP2B6	Efavirenz

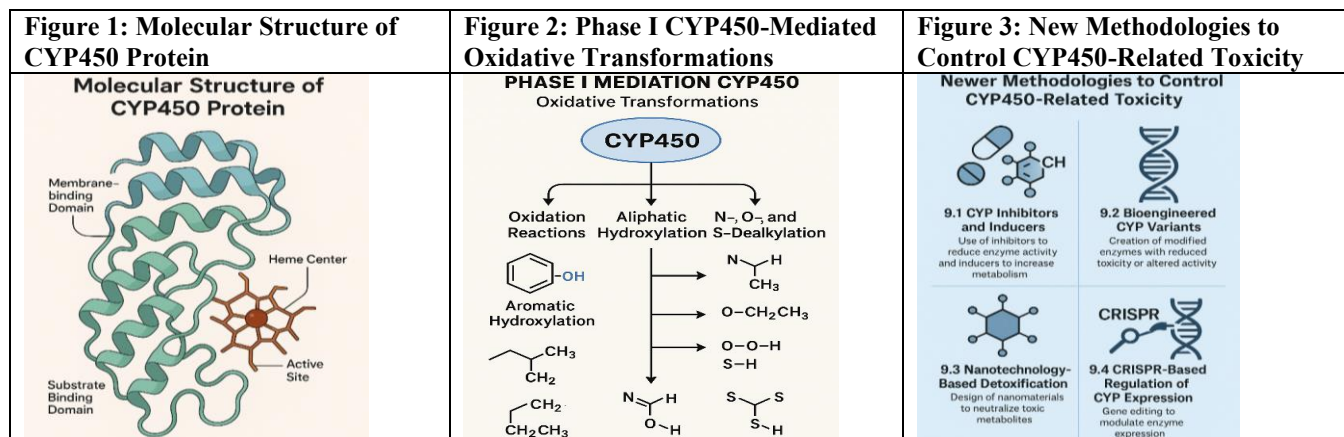
Table 2: Factors Influencing CYP450 Activity

Factor	Influence on CYP450 Activity
Genetic Polymorphisms	Variations in CYP450 genes lead to different metabolizer phenotypes (e.g., poor, intermediate, extensive, ultra-rapid)
Environmental Inducers	Smoking, high-fat diets, and other environmental factors may increase CYP450 activity
Drug-Drug Interactions	Certain drugs can inhibit or induce CYP450 enzymes, affecting drug metabolism and therapeutic outcomes
Age	CYP450 activity can change with age, often lower in neonates and elderly populations
Gender	Gender differences can influence CYP450 enzyme activity and expression levels
Disease States	Liver diseases, such as cirrhosis, can impair CYP450 function, affecting drug metabolism

Table 3: CYP450 Enzyme Inhibition and Induction.

CYP450 Enzyme	Inhibitors	Inducers
CYP3A4	Ketoconazole, Grapefruit juice, Erythromycin	Rifampin, Carbamazepine, St. John's
CYP2D6	Quinidine, Fluoxetine, Paroxetine	Rifampin, Dexamethasone
CYP2C9	Fluconazole, Amiodarone, Sulfamethoxazole	Rifampin, Phenobarbital
CYP2C19	Omeprazole,	Rifampin, Carbamazepine
CYP1A2	Fluvoxamine, Cimetidine, Ciprofloxacin	Smoking, Cruciferous vegetables

CYP2E1	Disulfiram, Cimetidine	Ethanol, Isoniazid
CYP2B6	Ticlopidine	Rifampin, Phenobarbital



Future Directions

Drug metabolism and toxicity management is a rapidly developing field, and new technologies and methods are emerging, which can tie up to improve our knowledge and capacity to predict, prevent, and control CYP450-mediated drug interactions and toxicities. These developments revolve around the use of advanced technologies (artificial intelligence (AI), pharmacometabolomics, and personalized medicine strategies) to deliver a more accurate and personalized treatment plan. These innovations have been central in streamlining drug development procedures in the coming years to enhance patient safety and reduce adverse drug reactions.

AI-based predictive cyP-Interaction models.

Artificial intelligence (AI) will significantly transform drug metabolism, leaving the creation of complex predictive models of CYP450 interactions. These AI-based systems have the capability of analyzing large volumes of clinical and molecular data in order to detect patterns, predict drug-drug interactions, and anticipate specific responses of patients to different drugs. Combining information on genomic studies, pharmacokinetics, and clinical trial results, AI models may provide a more precise perspective on how the specified drug will be metabolized by CYP450 enzymes, predicting the likelihood of any toxicity or failure of the treatment even before it takes place. This proactive ability would greatly enhance the safety profile of the drugs, decrease clinical development failures, and make the drug development process more efficient, which will eventually result in an improved treatment outcome among patients.

Toxicity Prediction Pharmacometabolomics.

Pharmacometabolomics, the examination of the metabolites in relation to the drug administration, is becoming a potent method of drug toxicity prediction. Pharmacometabolomics can provide information on the biochemical alterations caused by CYP450 enzymes through the analysis of the metabolic profiles of people subjected to drugs prior to and after drug exposure. This technology enables the determination of biomarkers that can be linked with drug toxicity to have a better insight into the metabolism pathway involved. The integration of the pharmacometabolomics data with the genomic data can help researchers to determine those people who are at increased risk of adverse drug reactions due to their metabolic profiles. Such a strategy may result in fewer personalized and safer drug regimens, where the doses and combinations of the drugs are adjusted according to the metabolic capacity of an individual.

CYP Data Incorporation into Digital Twins.

A novel solution to customizing drug therapy is the addition of the CYP450 information to the digital twin technological implementation. Digital twins are simulated models of specific patients, which are developed after integrating genetic, clinical, and environmental information. With the incorporation of CYP450 detailed data into these models, one is able to predict the way the body of the patient will react to various drugs in account to the enzyme profile of the patient. It provides the possibility to test drug interaction in silico and predict possible toxicities and drug dosage optimization prior to clinical use. Different treatment regimens could be simulated using digital twins, thus providing clinicians with real-time decision support so that patients could be treated in a manner that offers the most effective and safe treatment options depending on their metabolic peculiarities.

CONCLUSION

Cytochrome P450 (CYP450) enzymes play a critical role in drug metabolism, influencing therapeutic efficacy, toxicity, and drug–drug interactions. Genetic polymorphisms and variability in CYP enzyme activity significantly affect individual responses to medications, highlighting the importance of pharmacogenomics in personalized medicine. Understanding the functions of major isoenzymes such as CYP3A4, CYP2D6, CYP2C9,

and CYP2E1 enables clinicians to optimize drug selection and dosing strategies. Despite significant progress, challenges remain in interpreting complex genetic variations and their clinical implications. Future research integrating pharmacogenomics, pharmacometabolomics, and AI-based predictive tools may further improve precision in drug therapy. Continued investigation into CYP450 variability across populations will also enhance drug safety and therapeutic outcomes worldwide.

REFERENCES

1. Wheeler NE. Responsible AI in biotechnology: balancing discovery, innovation and biosecurity risks. *Front Bioeng Biotechnol.* 13, 2025.
2. Haga SB. Artificial intelligence, medications, pharmacogenomics, and ethics. *Pharmacogenomics.* 25, 2024, 611–622.
3. Taherdoost H, Ghofrani A. AI's role in revolutionizing personalized medicine by reshaping pharmacogenomics and drug therapy. *Intell Pharm.* 2, 2024, 643–650.
4. Afrose N, Chakraborty R, Bhowmick M, Bhowmick P, Hazra A. AI-driven drug discovery and development. In: *AI-Driven Drug Discovery and Development*. IGI Global, 2024, 259–277.
5. Trevor GR, Lim YJ, Urquhart BL. Pharmacometabolomics in drug disposition, toxicity, and precision medicine. *Drug Metab Dispos.* 52, 2024, 1187–1195.
6. Ryan DK, Balston A, Scourfield A, Maclean RH, Shah AD, Ross J. Artificial intelligence and machine learning for clinical pharmacology. *Br J Clin Pharmacol.* 90, 2023, 629–639.
7. Kandel SE, Tooker BC, Lampe JN. Drug metabolism of ciprofloxacin, ivacaftor, and raloxifene by *Pseudomonas aeruginosa* cytochrome P450 CYP107S1. *J Biol Chem.* 300, 2024, 107594.
8. Abdelmonem BH, Abdelaal NM, Anwer EKE, Rashwan AA, Hussein MA, Ahmed YF, et al. Decoding the role of CYP450 enzymes in metabolism and disease: a comprehensive review. *Biomedicines.* 12, 2024, 1467.
9. Wang X, Rao J, Zhao J, Tan Z, Yang X, Xun T. Inflammatory signaling on cytochrome P450-mediated drug metabolism in hepatocytes. *Front Pharmacol.* 13, 2022.
10. Zuo HL, Huang HY, Lin YCD, Cai XX, Kong XJ, Luo DL, et al. Enzyme activity of natural products on cytochrome P450. *Molecules.* 27, 2022, 515.
11. Guo J, Zhu X, Wang X, Badawy S, Ihsan A, Liu Z, et al. Metabolism and mechanism of human cytochrome P450 enzyme 1A2. *Curr Drug Metab.* 22, 2021, 40–49.
12. Guengerich FP. Roles of individual human cytochrome P450 enzymes in drug metabolism. *Pharmacol Rev.* 76, 2024, 1104–1132.
13. Iacopetta D, Catalano A, Ceramella J, Scumaci D, Pellegrino M, Scali E, et al. Impact of cytochrome P450 enzymes on the phase I metabolism of drugs. *Appl Sci.* 13, 2023, 6045.
14. Zhao M, Ma J, Li M, Zhang Y, Jiang B, Zhao X, et al. Cytochrome P450 enzymes and drug metabolism in humans. *Int J Mol Sci.* 22, 2021, 12808.
15. Hakkola J, Pelkonen O, Turpeinen M, Hukkanen J. Inhibition and induction of CYP enzymes in humans: an update. *Arch Toxicol.* 94, 2020, 3671–3722.
16. Sellner M, Fischer A, Don CG, Smieško M. Conformational landscape of cytochrome P450 reductase interactions. *Int J Mol Sci.* 22, 2021, 1023.
17. Mukherjee G, Wade RC, Nandekar PP. An electron transfer competent structural ensemble of membrane-bound cytochrome P450 1A1 and cytochrome P450 oxidoreductase. *Commun Biol.* 4, 2021.
18. Han SB, Teuffel J, Mukherjee G, Wade RC. Multiresolution molecular dynamics simulations reveal the interplay between conformational variability and functional interactions in membrane-bound cytochrome P450 2B4. *Protein Sci.* 33, 2024.
19. Padayachee T, Lamb DC, Nelson DR, Syed K. Structure–function analysis of the biotechnologically important cytochrome P450 107 enzyme family. *Biomolecules.* 13, 2023, 1733.
20. Pan Y, Xu K, Li Y, Wu R, Liu M, Li G, et al. Unnatural activities and mechanistic insights of cytochrome P450 PikC gained from site-specific mutagenesis by non-canonical amino acids. *Nat Commun.* 14, 2023.
21. Pankov KV, Wilson JY, Goldstone JV, Nelson DR, McArthur AG, Gold DA. The cytochrome P450 superfamily in cnidarians. *Sci Rep.* 11, 2021.
22. Rai M, Tisato V, Gemmati D, Singh AV, Khan IA, Kanase A, et al. Perspective on quantitative structure–toxicity relationship models to predict hepatic biotransformation of xenobiotics. *Livers.* 3, 2023, 448–462.

23. Bromek E, Daniel WA. Regulation of liver cytochrome P450 expression and activity by the brain serotonergic system in experimental models. *Expert Opin Drug Metab Toxicol.* 17, 2021, 413–424.
24. Runda ME, Schmidt S, Miao H, De Kok NAW. Developing hybrid systems to address oxygen uncoupling in multi-component Rieske oxygenases. *J Biotechnol.* 389, 2024, 22–29.
25. Jiang Q, Wang S, Zhang C, Sheng Z, Zhang H, Feng R, et al. Active oxygen species mediate the iron-promoting electrocatalysis of oxygen evolution reaction on metal oxyhydroxides. *Nat Commun.* 14, 2023.
26. Jin J, Zhong XB. Epigenetic mechanisms contribute to intraindividual variations of drug metabolism mediated by cytochrome P450 enzymes. *Drug Metab Dispos.* 51, 2023, 672–684.
27. White CM. Inflammation suppresses patients' ability to metabolize cytochrome P450 substrate drugs. *Ann Pharmacother.* 56, 2021, 809–819.
28. Saiz-Rodríguez M, Mejía G, Koller D, Román M, Almenara S, Ochoa D, et al. Effect of CYP3A4 and CYP3A5 polymorphisms on pharmacokinetic parameters of CYP3A substrates. *Biomedicines.* 8, 2020, 94.
29. Forster J, Duis J, Butler MG. Pharmacogenetic testing of cytochrome P450 drug-metabolizing enzymes in patients with Prader-Willi syndrome. *Genes.* 12, 2021, 152.
30. Fischer A, Don CG, Smieško M. Molecular dynamics simulations reveal structural differences among allelic variants of cytochrome P450 2D6. *J Chem Inf Model.* 58, 2018, 1962–1975.
31. Shen C, Jiang X, Yang H, Wang L, Zheng L, Shao W, et al. Physiologically based pharmacokinetic modeling to unravel drug-gene interactions of venlafaxine. *Pharm Res.* 41, 2024, 731–749.
32. Elfaki I, Mir R, Almutairi FM, Duhier FMA. Cytochrome P450 polymorphisms and roles in cancer, diabetes and atherosclerosis. *Asian Pac J Cancer Prev.* 19, 2018, 2057–2070.
33. Begriche K, Penhoat C, Bernabeu-Gentey P, Massart J, Fromenty B. Acetaminophen-induced hepatotoxicity in obesity and nonalcoholic fatty liver disease. *Livers.* 3, 2023, 33–53.
34. Ioannides C, Konsue N. A principal mechanism for cancer chemopreventive activity of phenethylisothiocyanate. *Drug Metab Rev.* 47, 2015, 356–373.
35. Zhang M, Rottschäfer V, De Lange ECM. Impact of CYP and UGT enzymes on brain target-site drug exposure. *Drug Metab Rev.* 56, 2024, 1–30.
36. Kumar S, Singla B, Singh AK, Thomas-Gooch SM, Zhi K, Singh UP. Hepatic and extrahepatic cytochrome P450 2E1 in alcohol and acetaminophen interactions. *Cells.* 11, 2022, 2620.
37. Zhang Y, Zhang G, Wang T, Chen Y, Wang J, Li P, et al. Understanding cytochrome P450 enzyme substrate inhibition. *ChemBioChem.* 25, 2024.
38. Song Y, Liu G, Li W, Cao Z, Chen Y, Lu C, et al. Drug-metabolizing cytochrome P450 enzymes influence treatment outcomes. *Clin Pharmacokinet.* 60, 2021, 585–601.
39. Sen A, Stark H. Role of cytochrome P450 polymorphisms in development of ulcerative colitis. *World J Gastroenterol.* 25, 2019, 2846–2862.
40. Lopes J, Marques-Da-Silva D, Samhan-Arias AK, Lagoa R, Videira PA. Cardiolipin membranes promote cytochrome c transformation of polycyclic aromatic hydrocarbons. *Molecules.* 29, 2024, 1129.
41. Smith JN, Gaither KA, Pande P. Competitive metabolism of polycyclic aromatic hydrocarbons assessed using PBPK modeling. *Int J Environ Res Public Health.* 19, 2022, 8266.
42. Stoddard EG, Smith JN, Martin J, Gibbins T, Shukla AK, Nag S, et al. Environmental mixtures of polycyclic aromatic hydrocarbons induce hepatic CYP enzymes in mice. *Chem Res Toxicol.* 34, 2021, 2145–2156.
43. Goedtke L, Hammer HS, Sprenger H, Hessel-Pras S, Zanger UM, Hofmann U, et al. Polycyclic aromatic hydrocarbons activate xenobiotic metabolism in human liver cells. *Int J Mol Sci.* 22, 2020, 372.
44. Liu Y, Yang C, Zhang J, Ihsan A, Ares I, Martínez M, et al. Adverse events of carboxylic acid NSAIDs and their metabolic consequences. *Expert Opin Drug Metab Toxicol.* 20, 2024, 765–785.
45. Balmanno A, Ravuri HG, Falconer JR, Mills PC. Strategies to improve transdermal delivery of poorly soluble NSAIDs. *Pharmaceutics.* 16, 2024, 675.
46. Sohail R, Habib A, Abdin ZU, Chaudhry WR, Akbar A, Haider Z, et al. Effects of NSAIDs on the gastrointestinal tract. *Cureus.* 15, 2023.
47. Alrouji M, Saad HM, Al-Gareeb AI, Batiha GE, Al-Kuraishy HM. Potential effects of NSAIDs in Parkinson's disease. *Inflammopharmacology.* 31, 2023, 673–688.
48. Garg U, Azim Y. Pharmaceutical cocrystals in NSAIDs: challenges and opportunities. *RSC Med Chem.* 12, 2021, 705–721.
49. Volkova T, Surov A, Terekhova I. Metal–organic frameworks based on β -cyclodextrin for selective entrapment of NSAIDs. *J Mater Sci.* 55, 2020, 13193–13205.
50. Zehetner P, Höferl M, Buchbauer G. Essential oil components and cytochrome P450 enzymes. *Flavour Fragr J.* 34, 2019, 223–240.

51. Foti RS. Cytochrome P450 and other drug-metabolizing enzymes as therapeutic targets. *Drug Metab Dispos.* 51, 2023, 936–949.
52. Havrylyuk D, Glazer EC, Heidary DK, Hachey AC, Fenton A. Ru(II) photocages enable precise control over enzyme activity with red light. *Nat Commun.* 13, 2022.
53. Bart AG, Scott EE. Structures of human cytochrome P450 1A1 with bergamottin and erlotinib. *J Biol Chem.* 293, 2018, 19201–19210.
54. Zhang Y, Wang Z, Wang Y, Jin W, Zhang Z, Jin L, et al. CYP3A4 and CYP3A5 roles in clinical drug metabolism and genetic polymorphisms. *PeerJ.* 12, 2024.
55. Langmia IM, Masimirembwa C, Stingl JC, Just KS, Brockmüller J, Yamoune S. CYP2B6 functional variability in drug metabolism. *Front Genet.* 12, 2021.
56. Mangó K, Fekete F, Kiss ÁF, Erdős R, Monostory K. CYP2B6 allelic variants and non-genetic factors influencing enzyme function. *Sci Rep.* 12, 2022.
57. Kumondai M, Saito S, Hiratsuka M, Rico EMG, Ueda A, Abe A, et al. Functional characterization of CYP3A4 variants. *Drug Metab Dispos.* 49, 2020, 212–220.
58. Lee J, Beers JL, Geffert RM, Jackson KD. Review of CYP-mediated drug interactions. *Biomolecules.* 14, 2024, 99.
59. Manikandan P, Nagini S. Cytochrome P450 structure, function and clinical significance. *Curr Drug Targets.* 19, 2018.
60. Teo YL, Ho HK, Chan A. Metabolism-related pharmacokinetic drug interactions with tyrosine kinase inhibitors. *Br J Clin Pharmacol.* 79, 2015, 241–253.