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Drug Metabolism Mechanisms And Pharmacokinetics Strategies In Implications For Drug Design: A Comprehensive Review

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The success of drug development is heavily dependent on a comprehensive understanding of drug metabolism mechanisms and pharmacokinetics strategies. The comprehension of drug metabolism mechanisms and pharmacokinetics strategies is crucial for enhancing drug design and enhancing therapeutic outcomes. This review explores the intricate relationship between drug metabolism pathways and pharmacokinetic processes, revealing key mechanisms in drug absorption, distribution, metabolism, and excretion (ADME). The study explores drug metabolism pathways, including phase I and II biotransformation reactions, highlighting the role of cytochrome P450 enzymes and UDP-glucuronosyl transferases. This highlights the significance of genetic polymorphisms and drug-drug interactions in influencing individual drug metabolism variability, emphasizing the need for personalized medicine strategies. This review explores pharmacokinetic strategies in drug design, including prodrug optimization, formulation enhancement, and targeted drug delivery systems, to enhance bioavailability, efficacy, and safety. This comprehensive analysis provides valuable insights for rational drug design and optimization, enabling the creation of novel therapeutics with improved pharmacokinetic properties and clinical efficacy. The study discusses the influence of genetic polymorphisms and drug-drug interactions on individual drug metabolism variations, emphasizing the necessity for personalized therapeutic strategies.

Keywords*:* Drug, metabolism, Pharmacokinetics, UDP-glucuronosyltransferases, Cytochrome P450.

1. Introduction

Pharmaceutical sciences focus on drug metabolism and pharmacokinetics (DMPK), aiming to understand drug candidates' ADME (absorption, distribution, metabolism, excretion) in biological systems. Understanding the physiochemical properties of medications, their effect on ADME, exposure to target organs, and toxicity has advanced significantly during the last ten years. Design principles minimizing drug-drug interaction and attritions are being developed, focusing on membrane transporters' role in drug disposition, safety, efficacy, and their interaction with metabolic processes.

Advancements in bioanalytical and experimental tools were needed to characterize ADME features of novel modalities like oligonucleotides, peptides, and antibody-drug conjugates, which extend beyond conventional medications (Lai et al., 2002).

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Pharmacokinetics has been considered as one of the factors influencing the likelihood that pharmaceutical research will be successful. Drug discovery studies regularly assess a compound's ADME properties to identify "flawed" molecules and develop structure-activity relationships, guiding chemistry synthesis operations. This aims to present a concise synopsis along with a critical assessment of various tactics used in lead optimization procedures; the assessments are bolstered by case studies (Tang et al., 2009). The quantitative study of ADME, or how the body metabolizes a drug while it is acting in the body, is known as pharmacokinetics (PK). PK studies physiological and pathologic conditions, mechanisms, drug-drug interactions, and dose modification for precision medication, focusing on healthy individuals and potential drug-drug interactions. When taken as a whole, these PK factors enable tailored medication dose schedules that improve therapeutic results, Currie (2018). PK research is therefore necessary to determine how a drug relates to its actions and therapeutic advantages, as well as its underlying mechanisms. Data collected is crucial for designing and adjusting dosage regimens in clinical practice, lead identification, and optimization in drug discovery (Yan et al., 2018).

Advancements in computer science, molecular biology, analytical chemistry, and biochemistry have heightened the complexity of PK, necessitating the development of new experimental models and computational modeling tools. This article provides an in-depth analysis of recent advancements in PK research, focusing on the roles of transporters, drug-metabolizing enzymes, nuclear receptors, and ncRNAs in PK regulation. The study will explore the regulatory mechanisms underlying individual differences in pharmacotherapy, and evaluate drug-drug interactions, specifically those involving medications, herbs, therapeutic biologics, and microbiota-mediated interactions. Another section will explore recent advancements in drug-sickness relationships, including the regulation of transporters and metabolizing enzymes, and the modification of PK by various illnesses or physiological conditions.

The other section will explore mathematical modeling trends, non-classical biotransformation pathways, and novel animal models like CRISPR/Cas9-based animal models for DMPK Fig. 1. Research Yuhua et al. (2019) DMPK is a scientific field that studies drug availability, absorption, distribution, biotransformation, and disposal within the body. Fundamental study on drug-metabolizing enzyme mechanisms has advanced various scientific fields, including biochemistry, pharmacology, and genetics of DMEs, transporters, and regulators (Li et al., 2019). The pharmaceutical sciences field's success in developing new therapies is largely due to the translation of new knowledge and technical development in basic DMPK science. Oligonucleotide and modified mRNA therapeutics, due to advanced drug delivery systems and chemistry, have the potential to treat challenging diseases like cancer and cardiovascular diseases. The study emphasizes the need for innovation and regulatory guidance in nonclinical PKPD predictions, despite the three decades of development (Andersson et al., 2018; Wang et al., 2018). The article explores the influence of biotransformation on drug efficacy and safety, highlighting the gut microbiome's role in metabolism and its potential influence on drug design (Shanu-Wilson et al., 2020). Drug metabolism in Table 1. is crucial for drug safety, with reactive metabolites (RMs) being a significant concern. This review investigates the role of these substances in drug discovery and development, safety assessment, drug-drug interaction potential, and the safety of RMs. Factors like dose, correlations, toxicological findings, and metabolite accumulation should be considered for safety assessment. Strategies like avoiding structural alerts and decreasing doses are effective in reducing the risk of idiosyncratic adverse drug reactions (IADRs) (Ju et al., 2020, Praveen, 2024).

CNS diseases cause global mental disability, necessitating effective medications and pharmacotherapy. Understanding inter-species and inter-condition variances is crucial for improving therapeutics and drug development (Bisen et al., 2020). This article explores the role of drug metabolism and pharmacokinetics in determining the efficacy, safety, and therapeutic profile of pharmaceutical compounds. It delves into key mechanisms, factors like genetic polymorphisms, disease states, and drug-drug interactions, and discusses strategies for drug design and development to improve bioavailability, prolong half-life, and mitigate adverse effects. The review also discusses the use of computational modeling and simulation techniques in pharmacokinetic studies.

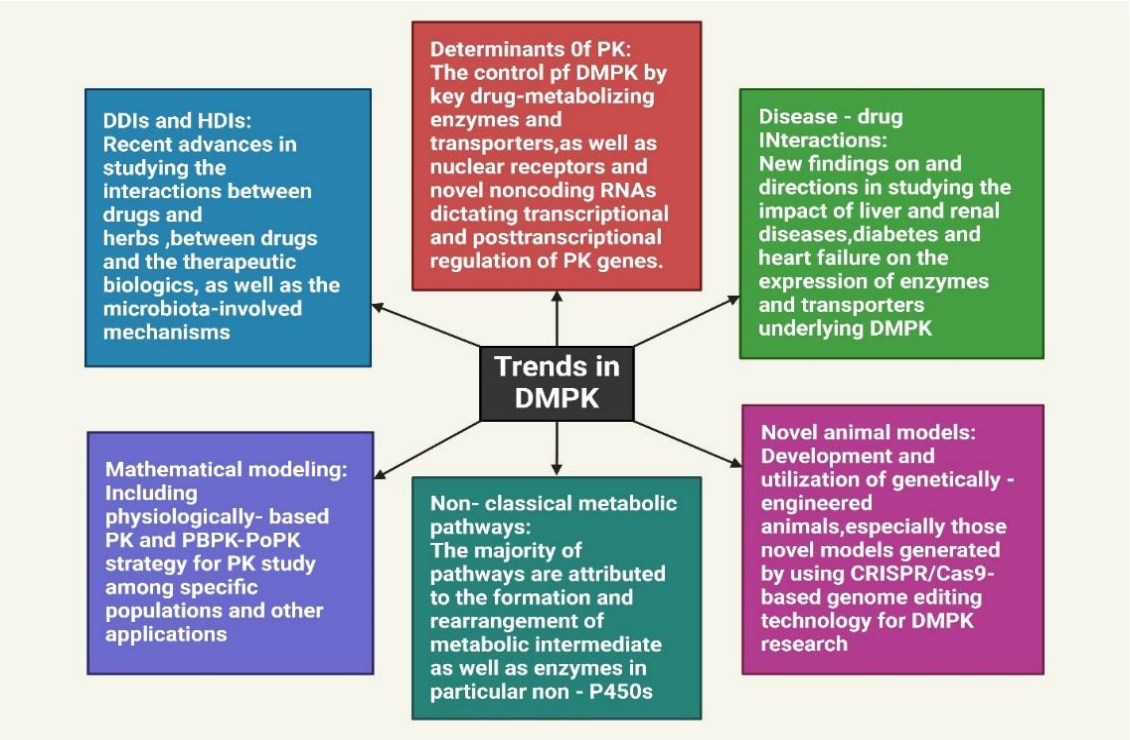

Fig. 1. This depicts an overview of recent research on DMPK properties, focusing on pharmacokinetics, drug-drug interaction, mathematical modeling, and non-classical metabolism, discussing challenges and future directions.

Table 1. Utilizing computer software to predict drug metabolism

Software	*Type*	*Core components*	*Coverage*	*Description*	*Ref.*
QikProp	LB, 2D	Rules	~20 phase I reactions	Quick SMARTS pattern matching tool for phase I reaction SoM prediction	Kirchmair et al. (2020)
P450 SoM Predictor	SB, 3D	Induced-fit docking+ reactivity estimator	CYP2C9, CYP2D6, CYP3A4	Using a quantum chemical model combined with the induced fit docking approach	Li et al. (2011)
Metaprint2D	LB, 2D	Atom mapping. statistical model	Phase I + II	Removing extensive biotransformation databases determines the probability of metabolic transformation for atoms in a given atomic environment. It is also provided as a free-of-charge online service.	Adams et al. (2010)
FAME9	LB, 2D	Random forest	Phase I + II	A collection of random forest models for estimating the metabolism of phases I and II in various animals. trained on natural chemicals, endogenous metabolites, medicines, and drug-like compounds.	Kirchmair et al. (2013)
Meteor Nexus	LB, 2D	Knowledge-based system	Phase I + II	Makes use of a set of knowledge-based biotransformation rules that are established using a specific structural representation language; it also provides a user-accessible knowledge base to help with decision-making; Takes into account estimated logP values for forecasts the most recent version has SMARTCyp.	Marchant et al. (2008)
TIMES	LB, 2D	Knowledge-based system	Phase I + II	Develops metabolic maps by applying a heuristic algorithm and a biotransformation library. Specialized models for rat in vitro (S9), in vivo, and skin metabolism	Mekenyan et al. (2004)
CypScore	LB, 3D	Surface electrostatics+ semi-empirical method	Individual CYP reactions	Six MLR models in total, covering the main CYP reaction types	Hennemann et al. (2009)

2. Novel techniques: Biodistribution and pharmacokinetic aspects

The conventional method of establishing a PK-PD association with both small and large molecules involves determining the drug concentration from the blood compartment and associating it with a response (Butters et al., 2013; Singh et al., 2015). ADME scientists are integrating drug and pharmacodynamic data beyond the blood compartment due to emerging targeted administration technologies, particularly for pharmacological targets outside the vasculature (Shah et al., 2015; Tibbitts et al., 2016). The PK-PD relationship for a new modality often requires understanding the biodistribution and exposure to the active chemical at the therapeutic site of action (Lin, 2009, Shah et al., 2013; Conner et al., 2014; Glassman et al., 2015). The design of new modalities

should consider the molecule's in vivo pharmacokinetic behavior before conducting in vivo research. This will accelerate the time it takes for new modalities to enter clinical trials (Xu et al., 2012; Pearson et al., 2015). This issue introduces a novel in vitro assay that aids in prioritizing compounds for in vivo studies and provides insights into the behavior of new chemical entities like peptide-antibody conjugates (Foti et al., 2019). The capacity to assess medications at the site of action has been improved due to developments in sensitive bioanalytical techniques (Foti et al., 2015; Praveen, 2024). The text emphasizes the importance of determining drug concentration in the appropriate tissue compartment and the consequences of asymmetric drug distribution (Zhang et al., 2019; Daspakan et al., 2018). Combining in vitro and in vivo biodistribution research improves translational understanding of novel modalities, necessitating improvements in existing modeling techniques for precise dosage for efficacy (Li et al., 2019).

3. Determinants of Pharmacokinetics

3.1 Enzymes responsible for breaking down drugs in the regulation of Pharmacokinetics

Enzymes that break down drugs mediate both endogenous and external chemical metabolism. The majority of medications lose most of their pharmacological effects due to metabolic transformation, which produces metabolites that are easily excreted and have a highwater solubility. As a result, metabolizing enzymes are crucial for maintaining medication PK control. Advanced characterization of xenobiotic-metabolizing enzymes is crucial to prevent adverse drug responses during the biotransformation of xenobiotics, involving Phase I and Phase II reactions. The understanding of drug-metabolizing enzymes, including specific isoforms, substrates, inducers, and inhibitors, is improving, with a focus on non-P450 oxidative and conjugative enzymes in Fig. 2. (Gan et al., 2016; Chen, 2018).

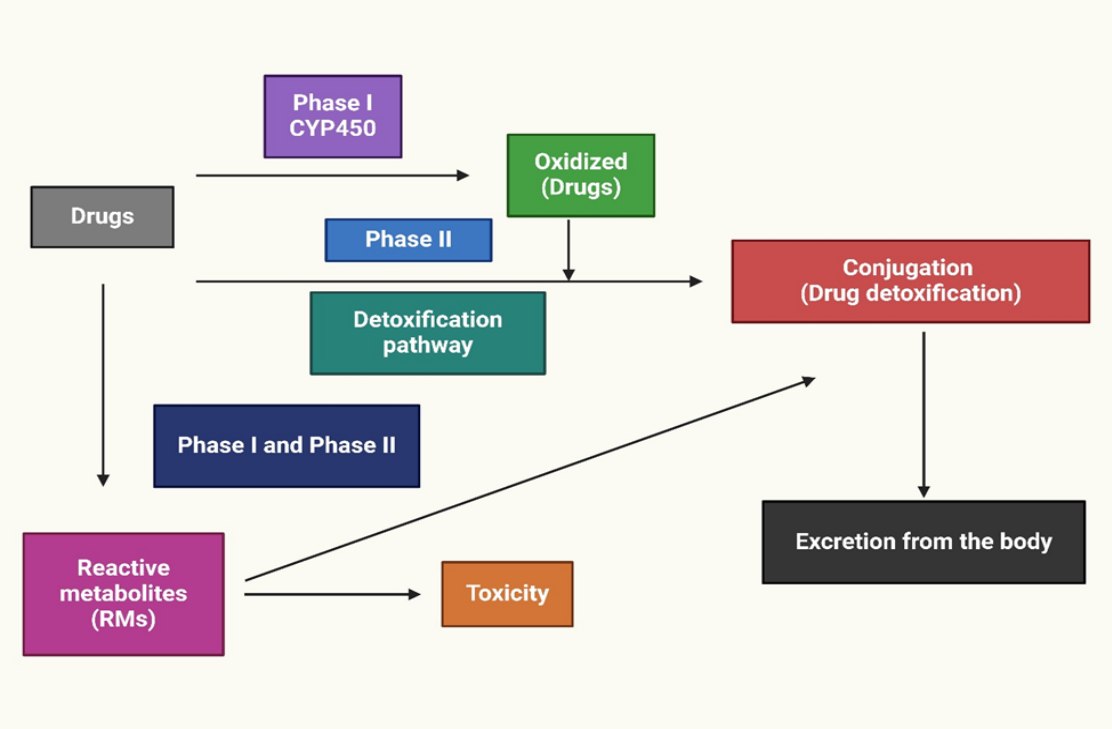

Fig. 2. Overview of drug metabolism routes

3.1.1 Non-P450 oxidative enzymes

Non-P450 enzymes, categorized into oxidative, reductive, conjugative, and hydrolytic categories, significantly influence drug metabolism and medication development. Flavin-containing monooxygenases (FMOs), monoamine oxidases (MAOs), peroxidases, xanthine oxidases (XO), alcohol dehydrogenases (ADHs), and aldehyde dehydrogenases (ALDHs) are examples of non-CYP oxidative enzymes (Marchitti et al., 2008). The regulation of non-P450 oxidative enzymes' content and activity is largely unknown. Recently, natural products and other sources have been shown to include a few specific substrates and inhibitors of non-P450 enzymes. Numerous different xenobiotics are metabolized by FMOs. Two well-known FMO inhibitors are 2-mercaptobenzimidazole and indole-3-carbinol methimazole. Monoamine oxidase (MAOs), enzymes involved in monoamine catabolism, are divided into MAO-A and MAO-B isoforms. New human monoamine oxidase inhibitors like benextramine have been discovered may be promising candidates for the treatment of neurodegenerative illnesses. A new selective hMAO-B inhibitor has been discovered in 3-(3-(dimethylamino) propanoyl)-7-hydroxy-5-methyl-

2H-chromen-2-one hydrochloride, which is expected to be a promising multifunctional Parkinson's disease therapeutic agent (Tao et al., 2019). Aldehydes and heterocycles are oxidized by XO and AO, and carbazeran was employed as a specific probe substrate of AO in hepatocytes Foti et al. (2016). XO inhibitors such as allopurinol and allyl cysteine (SAC) are used to treat hyperuricemia and gout Johnson et al. (2018). POR and P450 isoform content can be controlled by a single-nucleotide polymorphism in the Chinese population of human cytochrome P450 oxidoreductase (POR) (Zhang et al., 2016).

3.1.2 CYPs essential to PK

CYPs have the ability to oxidize foreign compounds, improve drug solubility in water, and facilitate the body's excretion of medications. CYPs, found in the endoplasmic reticulum or mitochondrial inner membrane, are responsible for the majority of medicines' metabolism (Bhattacharyya et al. 2014). 57 human CYP genes are divided into eighteen families, with CYP5 family members primarily metabolizing endogenous substrates, while CYP1 to CYP4 family members oxidize thousands of exogenous and endogenous substrates (Nebert et al. 2006). The CYP1 family, comprising the most known chemical carcinogens like aromatic amines and PAHs, is frequently metabolized to produce active carcinogenic metabolites. 2018 saw the discovery of CYP1B1 in cancer cell mitochondria, where it is thought to convert melatonin to produce the anticancer metabolite N-acetylserotonin (NAS) (Yu et al., 2018). CYP2D6, an additional significant metabolic enzyme, has a role in the metabolism of numerous anti-cancer medications, including gefitinib, tamoxifen, and cyclophosphamide (Ruwali et al., 2016). According to recent studies, CYP2D6 in the brain is capable of converting tyramine and p-tyramine into dopamine (Wang et al. 2014). In recent years, the CYP4 family has drawn more and more attention due to its capacity to produce intriguing metabolites and eliminate endogenous substrates. CYP4F11, alongside CYP4F2, is crucial for vitamin K metabolism and producing 20-HETE from arachidonic acid Yi et al. (2017). An enzyme that demonstrates circadian control is encoded by the mouse counterpart of human CYP2A6, Cyp2a5 Deng et al. (2018). Different endogenous and exogenous substrates are metabolized by the various CYP1–CYP4 subfamilies. Comprehending the fluctuations in mechanism-based enzyme activity is essential to enhancing the therapeutic application of medications. The FDA has included highly selective CYP inducers and inhibitors in Guidance for Industry. Novel compounds and herbal preparations have been identified in recent research as CYP inducers or inhibitors. For instance, PT2385, an intestine HIF-2a inhibitor, upregulates CYP7A1 (Xi et al., 2018). Liver damage may arise from CYP3A4 and CYP3A5 inactivation caused by erlotinib's ketene intermediate Zhao et al. (2018). Herbal products, like catalog, can regulate various enzymes due to their complex components, while *Sophora flavescens* can inhibit certain enzymes (Liu et al., 2019; Yim et al., 2019). The expression of CYPs can also be changed by other regulatory variables. Tumor suppressor p53, for instance, can directly control Cyp2b10, which reduces the hepatotoxicity caused by APAP Chen et al. (2017). When treating illnesses, herbs can be used alone or in combination (Showande et al., 2019). The study reveals that combining ellagic acid from pomegranate peel and guava leaf extract significantly increases the AUC of warfarin by decreasing CYP2C8, 2C9, and 3A4 activity (Alnaqeeb et al., 2019). Chinese and Caucasian populations show significant differences in total CYP concentrations and metabolic capabilities for P450 isoforms, with Chinese liver microsomes showing less than 50% metabolic capacity (Yang et al., 2012). Significant differences have been found in the protein composition, messenger RNA levels, and intrinsic activities of ten P450s. The expression of P450s has been significantly influenced by certain single nucleotide polymorphisms; CYP2C19 activity, for instance, varies over 600 times (Gao et al., 2016). A recent human PK investigation compared Chinese and Caucasian populations' CYP1A2 content, enhancing confidence in pharmacokinetic prediction using theophylline and caffeine (Li et al., 2019). The intestines and kidneys are two other organs with substantial metabolic potential. Several CYPs are expressed in the gut, but CYP2B6 and 3A5 expression in the human kidney has been confirmed conclusively by Kaminsky et al. (2003), Knights et al. (2013). It has been discovered how intestinal and renal enzymes function in the metabolism of herbal products. Combining aminoglycoside antibiotics with herbs or dietary supplements can reduce nephrotoxicity, with *Moringa oleifera* seed oil potentially reducing gentamicin-induced oxidative nephrotoxicity (Edeogo et al., 2020). Yin-Chen-Hao Tang, a hepatoprotective three-herb compound in China and Japan, has been found to have effects on intestinal metabolism (Liu et al., 2019).

3.1.3 Updates on the control of xenobiotic-metabolizing enzymes by nuclear receptors

The family of 48 human nuclear receptors, regulated by ligands, plays a crucial role in controlling target genes related to metabolism and other physiological processes. Certain XMEs, regulated by HNF, LXR, and PPAR, are intriguing in drug metabolism and disposition. PPARa induces the expression of CYP4A in response to various peroxisome proliferators. Human tetrahydropyranyl 1 (THP1) macrophages' production of the fatty acid

metabolizing enzyme CYP4V2 is likewise regulated by PPARg (Yi et al., 2017), Cyp7a1, Cyp27a1, Cyp3a11, and Cyp2e1 transcription is regulated by LXR (Jeong et al., 2015; Graham, 2015). Conventional transcription factors can directly bind to specific DNA sequences, thereby regulating the expression of genes. On the other hand, epigenetic regulation, such as DNA methylation and histone modification, primarily modifies chromatin architecture to regulate UGT or CYP transcription. For instance, in females, the recruitment of histones can suppress the UGT1A gene (Saini et al., 2011; Kalthoff et al., 2013). Several investigations have demonstrated the ability of microRNAs, or miRNAs, to suppress the production of metabolizing enzymes. Recent research on conjugative metabolizing enzymes and non-P450 enzymes is crucial for understanding drug metabolism, treatment prediction, and modification of drug PK.

3.1.4 Additional conjugative enzymes that are essential for PK research.

Conjugative enzymes that mediate phase II reactions include glutathione S-transferases (GSTs) and sulfonyl transferases (SULTs), in addition to UGTs. Drugs or endogenous compounds containing hydroxy or amine group(s) can transfer the water-soluble sulfonate group from 30-phosphoadenosine-50-phosphosulfate with the help of SULTs (Suiko et al. 2017). As of right now, four families of human SULTs—SULT1, SULT2, SULT4, and SULT6—have been identified. The metabolism and detoxification of flavonoids and estrogens are significantly influenced by SULT1E1 (Wang et al. 2017). The primary enzymes responsible for catalyzing the sulfation of hydroxysteroids are SULT2A and SULT2B (Falany et al., 2013). The p53, known as a tumor suppressor, can control SULT expression (Sun et al., 2018). A class of phase II drug-metabolizing enzymes known as GSTs is responsible for catalyzing glutathione's binding to a variety of electrophilic substances. Alpha, zeta, theta, mu, pi, sigma, and omega class cytosolic GST isoenzymes have been identified in humans. Acetaminophen metabolism is significantly influenced by GSTA1 (Li et al., 2017). The endogenous carcinogen 4-hydroxy-2-nonenal is one of the electrophilic and carcinogenic compounds that GSTA4 metabolizes (Yang et al., 2016).

3.1.5 DP-glucuronyltransferases (UGTs) have significance in PK

A class of enzymes called UDP-glucuronyltransferases (UGTs) is attached to the endoplasmic reticulum and is in charge of the glucuronidation process, which is a crucial step in phase II metabolism (Mano et al. 2018). Human UGTs are categorized into four gene groups, UGT1, UGT2, UGT3, and UGT8, and comprise 22 distinct functional enzymes (Mazerka et al. 2016). The UGT1 and UGT2 families are primarily responsible for drug glucuronidation, while the UGT3 and UGT8 families have minimal impact on drug metabolism (Nair et al., 2015). It was discovered recently that UGT1A3 is involved in the glucuronidation of alpinetin (Qi et al. 2019). Metizolam's glucuronidation is facilitated by UGT1A4. Both naturally occurring products and external sources have been reported to contain highly selective substrates and selective inhibitors of UGTs. Resveratrol is used to treat breast cancer and can promote UGT1A8 expression (Zhou et al., 2018). The activity of UGT2B7 can be inhibited by emodin at different dosages (Wu et al., 2018). Linoleic acid and glutaric acid can inhibit the glucuronidation of berberine, a lipid-lowering metabolite, and the actions of UGT isoforms, including UGT1A7, 1A8, and 1A9, (Zhou et al., 2014). The gastrointestinal tract-specific UGTs 1A8 and 1A10 catalyzed the glucuronidation of canalside, an active ingredient of the Veronica species. One important element in controlling the composition and function of UGTs is gene polymorphisms. In smokers who are European and African American, genetic variations in UGT1A and UGT2B can change the levels of nicotine and nitrosamine glucuronidation (Wassenaar et al., 2015). Furthermore, in patients with hematological malignancies, decreased posaconazole plasma concentrations are linked to the UGT1A4 3 genetic variant Suh et al. (2018). In cancer patients, irinotecan-induced neutropenia is linked with UGT1A1 6 polymorphisms (Zhang et al., 2017).

4. Specific drug delivery

A targeted medicine delivery strategy focuses on delivering active ingredients to the site of action to minimize exposure to other body parts (Iqbal et al., 2017; Prabhu et al., 2022). Antibody-drug conjugates (ADCs), in which a cytotoxin is covalently bound to a monoclonal antibody that targets the desired tissue, are commonly used to accomplish targeted drug delivery. This increases the cytotoxin's efficacy and therapeutic index. Both the biodistribution and efficacy of ADCs are impacted by several publications on their ADME characteristics (Bornstein, 2015; Hamblett et al., 2016; Kraynov et al., 2016). Understanding blood stability and delivery rate is crucial for medicines intended to be delivered directly to the site of action since many of these compounds employ linker methods that could be broken down by circulating proteases (Tsuchikama et al., 2019). Two papers define different connections between peptides or antibodies that facilitate efficient warhead delivery (Zhang et al., 2019; Zimmermann et al., 2017). Additionally, these writers highlight factors to take into account while assessing medication stability in vivo or in vitro.

Oligonucleotides have proven successful as treatments due to their directed drug delivery method.

5. Advancements in the prediction of clearance for enzymes other than CYP enzymes

High-quality reagents like human hepatocytes and liver microsomes improve drug clearance accuracy, but literature shows under-prediction in vivo clearance using these methods (Wood et al., 2017). Proteomic approaches for protein quantification have led to major advances in our understanding of the tissue distribution of enzymes. Physiologically based pharmacokinetic (PBPK) modeling uses protein expression data to accurately predict human PK and DDIs. Research on less-studied CYP enzymes is needed to understand their roles in drug metabolism and disposition, such as CYP4 enzymes responsible for ebastine, terfenadine, and fingolimod (Edson et al., 2013). The study will explore enzyme distribution, biochemistry, selective substrates and inhibitors, and clearance extrapolation, focusing on CYPs and non-CYP enzymes in small-molecule pharmaceutical metabolism and drug clearance (Saravanakumar et al., 2019). The small intestine significantly influences pre-systemic drug metabolism, impacting pro-drug activation and drug bioavailability, alongside the liver, which remains the primary focus of drug metabolism research (Xie et al., 2016). Human intestinal mucosa samples, cryopreserved from the ileum, jejunum, and duodenum, are now used for drug metabolism research, despite the lack of readily available GI mucosa reagents for other species (Li et al., 2020, Zhang et al., 2020; Buko, 2017).

5.1 Prediction of clearance for prominent non-CYP drug-metabolizing enzymes

5.1.1 Sulfotransferases (SULTs)

Sulfation is a crucial method for xenobiotic detoxification and removal, where a sulfonate group is transferred from PAPS to a drug molecule by SULTs (Mueller et al., 2018). Except for SULT1A3, which is mostly expressed in the gut, the liver and intestine express these SULT enzymes more than the kidney and lung. SULTs are often low-capacity, high-affinity enzymes as opposed to UGTs. Similar substrates are shared by SULTs and UGTs, and they frequently contribute differently to drug clearance (fm, SULT, vs. fm, UGT). SULTs generally contribute more than UGTs do at low concentrations. Acetaminophen metabolism serves as an example of how UGTs typically contribute more at high concentrations, which is when SULTs are probably saturated (Di, 2014; Praveen and Morales-Bayuelo, 2023). To accurately understand the sulfation pathway's contributions, in vitro investigations using therapeutically relevant drug doses are crucial (Hartmann et al., 1999). Recombinant SULTs and the REF technique can individually determine the contributions of key SULTs to a drug's metabolism.

5.1.2 Carboxylesterases (CESs) and amidases

Catalyzing the hydrolysis of esters, carbamates, and hydroxamic acids, CESs are a significant class of enzymes within the hydrolase family (Di, 2019; Hermant et al., 2017). In humans, the liver expresses both CES1 and CES2, but the intestines only contain CES2. Irinotecan, an ester pro-drug, is hydrolyzed in the gut by CES2 to produce the active metabolite SN-38, which is then circulated throughout the body (Ahmed et al., 1999). For the CESs, significant species differences have been noted. A recent review provided an overview of the variations between species and the distribution of human CES tissue. Numerous nonspecific hydrolase inhibitors, including paraoxon, diisopropyl fluorophosphate, tetraisopropyl pyrophosphoramide, and bis(p-nitrophenyl)phosphate, inhibit both CES1 and CES2. There have been reports of selective inhibitors of CES1 (e.g., digitonin) (Shimizu et al., 2014) and CES2 (e.g., telmisartan and eserine) (Umehara et al., 2016). Nevertheless, additional testing in the HHEP system will be necessary to determine their selectivity against CYPs and UGTs. Using a variety of models, the intestine S9 fraction is useful for predicting the proportion of gut metabolism (Fg) mediated by CESs (Trapa et al., 2017). Because of extra-hepatic contributions, accurate prediction of CES-mediated clearance in humans is still difficult (Rautio et al., 2018). Drug compounds with amide bonds hydrolyze slowly, with amidases, aminoacylases, and fatty acid amide hydrolases generating ammonia and carboxylic acid. Some amides can be digested by liver microsomal carboxylesterases (Cashman et al., 2016).

5.1.3 Flavin-containing monooxygenases (FMOs)

FMOs are microsomal enzymes that oxidize medications that contain soft nucleophiles like phosphorus, selenium, nitrogen, and sulfur. They coexist in the liver with CYPs. Just like CYPs, FMOs need NADPH to function. FMO can be inactivated by heat or inhibited by a chemical inhibitor to differentiate its potential contribution from that of CYPs in liver microsomes without NADPH, (Weber et al., 2013). A recent study utilizing ten FMO substrates demonstrated a strong IVIVE for FMO for both HLM and HHEP, Jones et al. (2017). FMO metabolizes ketoconazole, a CYP3A inhibitor that was often employed in clinical DDI research until it was removed from usage in clinical conditions due to hepatotoxicity. Protein adducts known as hydroxylamine and nitrone are thought to be formed

as a result of the FMO-mediated metabolism of ketoconazole.

5.1.4 Aldehyde oxidase (AO)

AO, a cytosolic molybdoflavoprotein, is responsible for the oxidation of various substances, especially azaheterocyclics Dalvie et al. (2019). AO reduces various functional groups like nitrite, nitro groups, S- and N-oxides, and isothiazoles, requiring flavin adenine dinucleotide, and two 2Fe–2S clusters (Garattini et al., 2012; Coelho et al., 2012). While practically all other animals have several AOX1 orthologs, humans only have one functioning AO gene, AOX, (Garattini et al., 2008). Though expressed everywhere, AO is most abundant in the cytosol of the liver (Zientek et al., 2010; Azad et al., 2024). Therapeutic development should avoid compounds with dominant AO metabolism due to uncertainties in human clearance prediction, species variations, and weak in vitro-in vivo association. The low and variable AO expression in rodents, the lack of AO expression in dogs, and the huge inter-individual differences in AO expression in monkeys, similar to humans, provide challenges to an inter-species correlation method. IVIVE underpredicted in vivo clearance via AO when it used data from S9 fractions or human hepatocytes (Akabane et al., 2012). Typically, human AO-mediated clearance is evaluated using known substrates and drug candidates, with clinical evidence-based drugs like zaleplon-low, zoniporide-medium, and carbazeran-high used as "yardsticks". In clinical trials, drugs with a human PK characteristic that is reasonable can frequently survive when their clearance is slower than that of zaleplon. A decision tree for drug discovery was provided for the AO substrate. A mouse model mimicking human AO activity has not improved enough to quantitatively predict human AO clearance (Uehara et al., 2020).

5.1.5 Glutathione S-transferases (GSTs)

Due to their ability to conjugate the body's produced electrophiles, or reactive metabolites, to the reduced form of glutathione, GSTs are recognized to have significant functions in the detoxification of cells. The development of covalent modifiers with strong inhibition against specific targets, including JAK3, has gained popularity in recent years. A study shows in vitro blood clearance can simulate extrahepatic metabolism by GSTs, scaling up to in vivo human clearance by accounting for hepatic blood flow rate and cardiac output (Leung et al., 2017; Xu et al., 2017).

6. Biotransformation

Nucleases' hydrolysis of the PO or PS backbone produces mononucleotides and truncated or fragmented oligomers, which is the main metabolic fate of oncogenes (ONs). While endonucleases cleave the ON chain centrally, exonucleases remove terminal nucleotides. Exonucleases can further break down ON fragments from their exposed non-modified ends after endonucleases have cleaved them. The introduction of chemically modified nucleotides has addressed several ADME properties, one of which is an increase in metabolic stability relative to the unmodified form. Native ON plasma half-life is seconds to minutes, while modified ONs with higher PPB and nuclease resistance can persist in circulation for weeks or months (Yu et al., 2013, Fitzgerald et al., 2017). Blood and plasma exhibit significant nuclease activity, but chemical stabilization of ONs to exhibit exonuclease activity has proven effective. Excessive metabolic stability is undesirable as ON medication must eventually exit the body, and limited terminal metabolism may still occur, particularly in older PS-only modified ONs. The technique of ON synthesis may result in ON impurities missing one or two nucleotides, although not always from terminal ends (Capasi et al., 2017). Contaminants in medication formulations can confuse metabolites, but chemical modifications for ON metabolic stability result in fewer metabolites and limited PKPD relationship contribution, obstructing protein formation. The detection of mRNA targets is influenced by the concentration, length, sequence, and alignment of the metabolite with the target sequence. This makes it difficult to forecast. The most effective way to investigate these intricate relationships would be to search databases for possible targets that match the metabolite sequence, in addition to doing in vitro studies to determine the likelihood of any off-target effects (Hagedorn et al., 2017) Further research on metabolism rates and products may be necessary if human tissue investigations reveal potential on- or off-target interactions. The ON drug's safety assessment will confirm human metabolites' exposure to animal species, providing insight into potential metabolite contribution to PKPD, as nucleases are commonly described without additional information. It follows that various isoenzyme families exhibit distinct substrate specificities, as suggested by the previous discussion of endo- and exo-nucleases, and that the expression of these enzymes changes to some extent across different organs. Different nuclease activity was seen in serum as opposed to liver microsomes in one instance of the in vitro metabolism of siRNA (Zou et al., 2008). This suggests that nucleases that are membrane-bound and soluble exist and that their substrate specificities may differ. Whole-organ homogenates may be more relevant for in vitro investigations on ON drug metabolism in ON drug candidates compared to tissue fractions (Baek et al., 2010). Small-molecule pharmaceuticals are advised to conduct cross-species

in vitro metabolism assessments before human clinical trials to understand potential drug outcomes in both human and animal species (Guidance, 2005; Guideline, 2009). This is relevant to medications as they can be substrates for various unique metabolizing enzymes, resulting in metabolites that vary across species. The metabolic outcome of an ON drug is likely to be similar across species due to the process of phosphate ester hydrolysis. The quantity of individual metabolites can differ among species due to factors like tissue distribution and enzyme kinetics. As is the case with every medication candidate, in vivo investigations provide the most pertinent data regarding biotransformation. Guidelines for evaluating the safety of metabolites from small-molecule drugs in toxicology research, concentrate on parent and circulating metabolites in blood for determining animal exposure. Metabolite profiles in plasma may not be the best matrix for confirming adequate exposure to ON drugs, as they are rapidly distributed into tissues, resulting in hundreds of exposures (Christensen et al., 2013), or even thousands, of times higher in tissues than plasma (Geary et al., 2015). Tissue samples for metabolite profiling may be made possible by animal research, however, routinely obtaining biopsies from patients or human volunteers might be challenging to convince. However, urine profiling, which may be obtained in clinical and nonclinical investigations without raising ethical issues, could be used in conjunction with the plasma profile of ON medication metabolites. Following PS ON dosage, the parent ON and any metabolites produced by removing one or more nucleotides from the terminal ends are often present in the plasma profiles. The smallest ON fragments that are effectively filtered by the kidneys are frequently preferred in urine profiles, with parent and longer metabolites being less common (Trembley et al., 2009). Because the ON species that are now in use only make up a small portion of the drug-related material, profiling plasma and urine could provide a more thorough picture of the metabolites that are generated in both humans and animals. Conjugated medicines are developed to enhance the absorption of cells and the exposure of active substances to their intended targets. More information about their chemical composition and absorption can be found in the following sections. The three components of a conjugate are the linker, the active ON, and the uptake "enhancer." Certain endogenous substances, such as cholesterol and fatty acids, are lipophilic and can improve membrane permeability. Conversely, other strategies involve receptor-specific uptake, such as GalNAc conjugates that target the ASGPR (Winkler, 2013). The safety of endogenous permeability enhancers from conjugate and their subsequent metabolism should be minimal, requiring minimal metabolic research. The active ON metabolism is further examined about linkers, which are hydrocarbons linked by ester, amide, or disulfide linkages, allowing easy hydrolysis or cleavage. Low-molecular-weight alcohols, carboxylic acids, amines, or thiols are likely eliminated through oxidative metabolism, while linker components like triantennary GalNAc ON conjugates are more intricate (Schmidt et al., 2017). These large linkers (molecular weight up to 1000 Da) undergo continuous biotransformation that can produce several complicated metabolites since they are not immediately broken down into small monomeric components (Shemesh et al., 2016, Praveen et al., 2024). The study confirms that primary metabolites in rats are eliminated in monkey feces after GalNAc injection, but health authorities have not issued guidance on the safety of certain linkers.

7. Drug metabolism and lead optimization

Standard medication candidates have high metabolic stability, numerous clearance pathways, low enzyme inhibition, and low RM formation potential, but fast metabolism leads to high clearance and poor bioavailability. During lead optimization, metabolic studies identify metabolic soft spots for unstable compounds, providing valuable insights into drug's potential metabolic liability through biotransformation. Early-stage drug metabolite data aids in optimizing preclinical safety and efficacy in medicinal chemistry research, often replacing metabolic soft spots with bioisosteres like fluorine atoms (Mascitti et al., 2011, Stepan et al., 2013). Although compound 1 is an agonist of the GPR119 receptor, it has a very high clearance (CL > 300 mL/min/kg) and a high oxidative metabolism in HLM due to its high lipophilicity (log P = 3.9). Pfizer chemists developed an analog that added a stereocenter containing fluorine to lower the CL. The conformational limitation seen in N-β-fluoroethylamide derivatives was leveraged in the design to preserve potency levels while reducing lipophilicity and CL in HLM. Drug biotransformation occasionally produces pharmacologically active metabolites with better PK/PD characteristics than the original molecule. Even active metabolites can be employed as fresh leads for additional structural change in the early phases. Certain drug metabolites have been turned into medicines due to their superior PK/PD characteristics (Fura, 2006). A common example of a prodrug is terfenadine. In the liver, terfenadine is fully converted to active fexofenadine (Ling et al., 1995; Yun et al., 1993). However, fexofenadine, the metabolite of terfenadine, is not cardiotoxic at larger doses (Roy et al., 1996). This biotransformation is only mediated by CYP 3A4, which is inhibited by several strong drugs, including ketoconazole and erythromycin. The FDA published a report in 1990,

Honig et al. (1993). outlining the risk concerns connected to using ketoconazole and terfenadine together.

8. Conclusions

Understanding drug metabolism mechanisms and pharmacokinetics strategies is crucial for optimizing drug design, with enzymatic pathways and genetic factors influencing personalized medicine. This review explores the intricate relationship between drug metabolism mechanisms, pharmacokinetics strategies, and their implications for drug design, emphasizing the importance of understanding enzymatic pathways, genetic polymorphisms, and personalized medicine approaches in drug development. This review provides a detailed analysis of drug metabolism mechanisms, pharmacokinetic strategies, and their significant impact on drug design. Advancements in drug design will benefit from understanding metabolism and pharmacokinetics, integrating omics technologies, and developing innovative strategies for targeted delivery systems and formulation optimization. The intricate interplay between drug metabolism pathways and pharmacokinetic processes is crucial for enhancing drug efficacy, safety, and patient outcomes. The study reveals the crucial roles of key metabolic enzymes like cytochrome P450 and UDP-glucuronosyltransferases in drug metabolism, including phase I and phase II biotransformation reactions. Genetic polymorphisms and drug-drug interactions significantly impact individual variability in drug metabolism, underscoring the necessity for personalized medicine approaches in drug development. Future drug design and development will likely be influenced by a deeper comprehension of drug metabolism and pharmacokinetics. The integration of omics technologies like genomics, proteomics, and metabolomics offers potential for understanding drug responses' complexities and designing personalized therapeutic interventions. The advancement of innovative pharmacokinetic strategies, such as novel drug delivery systems and formulation optimization techniques, is expected to enhance drug bioavailability, efficacy, and safety. Computational modeling and artificial intelligence offer promising opportunities for predictive drug metabolism and pharmacokinetics, enhancing efficiency in drug discovery and optimization processes. Interdisciplinary collaboration between research teams, regulatory agencies, and pharmaceutical industries is crucial for translating scientific advancements into clinically effective therapeutic interventions and enhancing patient care and public health. Computational modeling and artificial intelligence enable predictive drug metabolism, enhancing drug discovery. Collaboration between academia, industry, and regulatory agencies will translate these advancements into clinically meaningful therapeutic interventions.

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