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# Characterization of Differential Tissue Abundance of Major Non-CYP Enzymes in Human

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## ABSTRACT

Non-cytochrome P450 (non-CYP) drug-metabolizing enzymes (DMEs)—including aldehyde oxidase (AO), carboxylesterases (CES1 and CES2), multiple UDP-glucuronosyltransferases (UGTs), and sulfotransferases (SULTs)—play a crucial role in the metabolism of nearly 30% of clinically approved drugs. However, comprehensive data comparing their abundance across human tissues remains limited. In this study, the protein levels of eighteen non-CYP DMEs were measured across five human tissues: liver, kidney, small intestine, heart, and lung. Aldehyde oxidase was highest in liver, with modest levels in kidney, and undetectable in intestine, heart, and lung. CES1 was most abundant in liver, while CES2 was enriched in the small intestine. UGT1A4, UGT2B4, and UGT2B15 were liver-specific; UGT1A10 was intestine-specific; UGT1A1 and UGT1A3 were present in both liver and intestine; UGT1A9 was detected in liver and kidney; and UGT2B17 levels were significantly higher in intestine compared to liver. All five SULT isoforms were found in liver and intestine, with SULT1A1 and SULT1A3 also present in lung. Moreover, kidney expression showed considerable variability. Notable interindividual variability (>15-fold) was observed for UGT2B17, intestinal CES2, hepatic SULT1A1, UGT1A9, UGT2B7, and renal CES1. These data are valuable for integrating non-CYP metabolism into physiologically based pharmacokinetic (PBPK) modeling to predict tissue-specific drug metabolism and toxicity

**Keywords:** non-CYP DME, UGT, SULT, aldehyde oxidase, carboxylesterase, absolute quantification, CES, LC-MS/MS proteomic

## 1. INTRODUCTION

Non-cytochrome P450 (non-CYP) enzymes, such as carboxylesterases (CES), monoamine oxidases (MAOS). aldehyde oxidases (AOXs), and UDP-glucuronosyltransferases (UGTs). play critical roles in the metabolism of endogenous compounds and xenobiotics. Unlike the well-characterized CYP enzymes predominantly found in the liver, non-CYP enzymes exhibit a broader and more variable tissue distribution, influencing both local and systemic drug metabolism. For example. CES enzymes are abundant in the liver and intestine, while MADs are primarily located in the brain and gastrointestinal tract. Understanding the differential tissue abundance of these enzymes is crucial for accurate prediction of drug disposition, efficacy. and toxicity. Advances in quantitative proteomics and transcriptomic profiling have enabled more precise mapping of enzyme levels across human tissues, shedding light on the physiological and pharmacological significance of non-CYP enzymes (Achour et al., 2017). These insights are vital for refining in vitro-in vivo extrapolation (IVIVE) models and for developing tissue-targeted drug delivery strategies**.**

While cytochrome P450 (CYP) enzymes have been extensively studied due to their central role in drug metabolism, non-CYP enzymes also significantly contribute to the biotransformation of a wide range of endogenous and exogenous compounds. Major non-Cyp enzyme families-including carboxylesterases (CES), aldehyde oxidase (AO), monoamine oxidases (MAOS), flavin-containing monooxygenases (FMOs), and conjugative enzymes such as UDP-glucuronosyltransferases (UGTS) and sulfotransferases (SULTS)-exhibit distinct patterns of tissue-specific expression. These enzymes are differentially expressed across human organs, including the liver, kidney. intestine,

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lung, and brain, and their distribution can critically influence the pharmacokinetics. efficacy, and toxicity of drugs.
For example, CEST is predominantly expressed in the liver, whereas CES2 shows higher abundance in the intestine. impacting first-pass metabolism of ester-containing drugs. MAOs, localized mainly in the brain and gastrointestinal tract, play a key role in the metabolism of neurotransmitters and psychoactive drugs. UGTs and SULTs are broadly distributed, with UGT1A isoforms showing hepatic dominance, and UGT2B isoforms present in both liver and extrahepatic tissues. The expression levels and tissue specificity of these enzymes are influenced by genetic.

developmental, and environmental factors, making their characterization essential for accurate in vitro-in vivo extrapolation (IVIVE) and physiologically based pharmacokinetic (PBPK) modeling.

Recent advances in quantitative proteomics, transcriptomics, and single-cell sequencing technologies have enabled a more comprehensive mapping of non-CYP enzymes across human tissues. These approaches not only enhance our understanding of enzyme function and drug metabolism but also inform drug design. dosing strategies. and predictions of interindividual variability.

Research over the past three decades has greatly advanced our understanding of cytochrome P450 (CYP) metabolism, and has enabled the design and synthesis of new chemical entities (NCEs) which are less susceptible to CYP-mediated oxidation. The widespread use of metabolism studies in drug discovery using human-derived in vitro models (e.g., microsomes and hepatocytes) has led to a significant reduction in pharmacokinetics (PK) related drug attrition

The prediction of non-CYP metabolism is challenging because of the limited quantitative data pertaining to tissue abundance of non-CYP DMEs, including their interindividual variability and the lack of in vitro models and specific probe substrates and inhibitors.

## 2. EXPERIMENTAL SECTION

### 2.1 Tissue Sample Preparation

Human tissue samples, including liver. kidney. small intestine, lung, and heart. were obtained from commercial biorepositories le.g.. XenoTech. Sekisuil. Pooled tissue S9 fractions or homogenates from multiple donors ($n \geq 3$ per tissue) were used to minimize donor-specific variability. The tissues were handled following standard biosafety and ethical protocols.

### 2.2 Protein Extraction and Digestion

Total proteins were extracted from S9 fractions using a standardized protocol. The samples were denatured, reduced with dithiothreitol (DTT), alkylated with iodoacetamide (IAA), and digested overnight with sequencing-grade trypsin at 37 °C. Digested peptides were desalted and dried for quantitative proteomics.

### 2.3 Surrogate Peptide Selection and Internal Standards

For each target non-CYP enzyme-including aldehyde oxidase (AO), carboxylesterases (CEST and CES21, UDP-glucuronosyltransferases (UGTs). and sulfotransferases (SULTS)-unique proteotypic surrogate peptides were selected. Stable isotope-labeled internal standard peptides were synthesized and spiked into each sample at known concentrations for absolute quantification.

### 2.4 LC-MS/MS Quantification

Targeted quantitative proteomics was performed using a triple quadrupole mass spectrometer coupled with nano-or micro-flow liquid chromatography. Peptides were separated on a C18 column using a gradient of acetonitrile in 0.1% formic acid. Multiple reaction monitoring (MRM) transitions were optimized for each peptide. Quantitation was performed using calibration curves generated from standard peptides and normalized against internal standards.

### 2.5 Proteomic Quantification

Quantification of protein abundance was performed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with stable isotope-labeled peptide standards. This approach allows for

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the absolute quantification of target enzymes across tissues. with high specificity and sensitivity. UGT isoforms le.g.. UGT1A1, UGT1A6. UGT2B7, UGT2B15. UGT2B17). CES isoforms (CEST, CES2), AOX1. and various SULT isoforms were quantified.

## 2.6 Tissue Distribution Patterns

UGTS: UGT1A1 and UGT2B7 are predominantly expressed in the liver. whereas UGT1A10 and UGT2B17 show higher expression in the intestine. UGT2B17 exhibited particularly high interindividual variability and up to 4.4-fold higher expression in the intestine compared to the liver [1.2].

CES: CEST is liver-enriched, while CES2 is more abundant in the intestine. contributing to tissue-specific hydrolysis of esterified drugs [1.3].

AOX1: Primarily localized in the liver. AOX1 shows significantly lower expression in other tissues [1].

SULTS: SULTIA1 and SULT2A1 show tissue-specific expression, with SULT2A1 more abundant in the liver and adrenal tissues, while SULTI isoforms are more evenly distributed [1,4].

## 2.7 Integration with Transcriptomics

In some studies, mRNA expression profiles were also evaluated using RNA-Seq to complement proteomic data. However, due to discrepancies between mRNA and protein levels, proteomic quantification is considered more reliable for assessing functional abundance [5].

## 2.8 Data Analysis and Enzyme Quantification

*Protein* abundance was calculated using Skyline or similar software platforms. Enzyme levels were expressed in picomoles per milligram of S9 protein. Inter-tissue and inter-individual variability was assessed. Notably, high expression of AO and CEST was found in liver. CES2 and UGT1A10 in intestine. and SULT isoforms across both liver and intestine. UGT2B17 showed substantial interindividual variability (>15-fold ).

3. **Result** The study by Basitetal. (2020) used absolute quantification via LC-MS/MS to measure the protein abundance of 18 major non-CYP drug-metabolizing enzymes across five human tissues: liver. kidney, small intestine, heart, and lung. The main insights include:

## 3.1 Aldehyde Oxidase (AO):

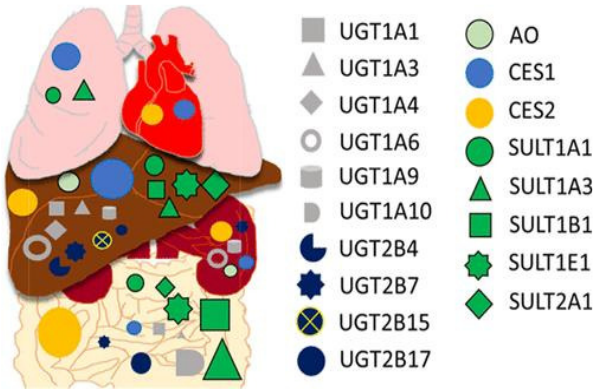
Highest levels in liver, moderate in kidney, and absent in intestine, heart, and lung.

The protein abundance (pmol/mg S9 protein) of AO was 7.8-fold higher in the liver than in the kidney, but it was not detected in the intestine, heart, and lungs

AO expression is largely restricted to the liver. with negligible levels in other tissues.

This enzyme is absent in fetal liver and shows age-dependent expression.

It plays a crucial role in the metabolism of aza-heterocyclic drugs




AO shows high expression in the adult human liver, with minimal levels detected in extrahepatic tissues. It is largely absent in fetal liver, suggesting developmental regulation. Interindividual variability in hepatic AD expression is also significant. impacting drug clearance predictions for AO substrates

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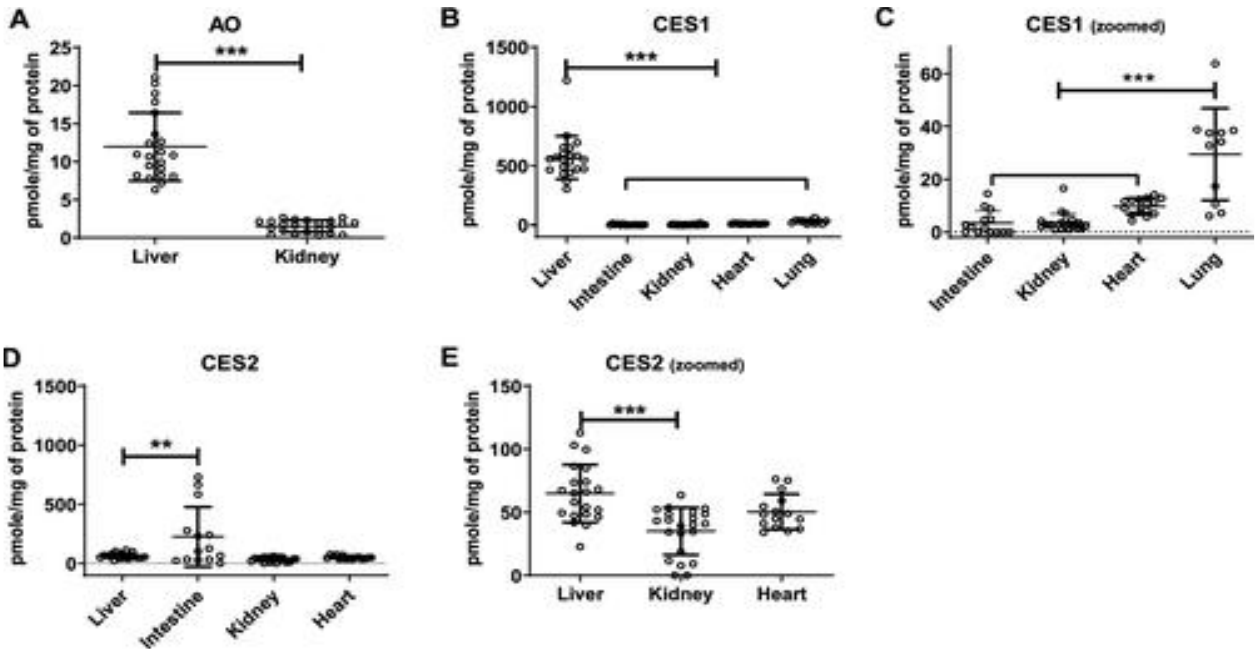


**Figure 2: Differential tissue abundance of AO (A), CES1 (B-C), and CES2 (D-E) in S9 fractions of liver (n = 21) intestine (n = 14) , kidney (n = 22) heart (n = 17) and lung (n = 11)** AO was not detected in the intestine, heart, and lung. CES2 was not detected in the lung. Each dot represents the individual samples and the data are represented as the mean plus/minus S .D **P < 0.01; ** P < 0.0001

### 3.2 Carboxylesterases (CESS):

CEST is predominant in the liver, while CES2 is enriched in the small intestine, with both expressed across all tissues studied.

CES1 abundance was 162-, 159-, 58-, and 19-fold higher in the liver when compared with the intestine, kidney, heart, and lung

CES2 is highly abundant in the small intestine, supporting its role in intestinal first-pass metabolism.

Minimal expression of CES enzymes is found in the kidney and lung.

Quantitative proteomic data reveal that CEST is predominantly expressed in the liver, with significantly lower levels in other tissues such as lung and kidney. In contrast, CES2 is highly abundant in the small intestine, aligning with its known role in intestinal first-pass metabolism. The liver-to-intestine expression ratio is notably inverse between CEST and CES2. demonstrating a clear differential tissue distribution.

### 3.3 UDP-Glucuronosyltransferases (UGTS):

Liver-specific: UGT1A4. UGT2B4. UGT2B15.

Intestine-specific: UGT1A10.

Mixed tissue expression:

UGTIA1 and UGT1A3 (liver and intestine). UGT1A9 (liver and kidney).

Notably high intestinal abundance:

UGT2B17 (higher in intestine than liver).

UGTs show broad expression. with UGTIA and UGT2B families highly expressed in the liver. followed by kidney and intestine. UGT1A10 is mainly present in the small intestine, contributing to presystemic glucuronidation. Expression profiles indicate that both hepatic and extrahepatic tissues play significant roles in phase II metabolism.

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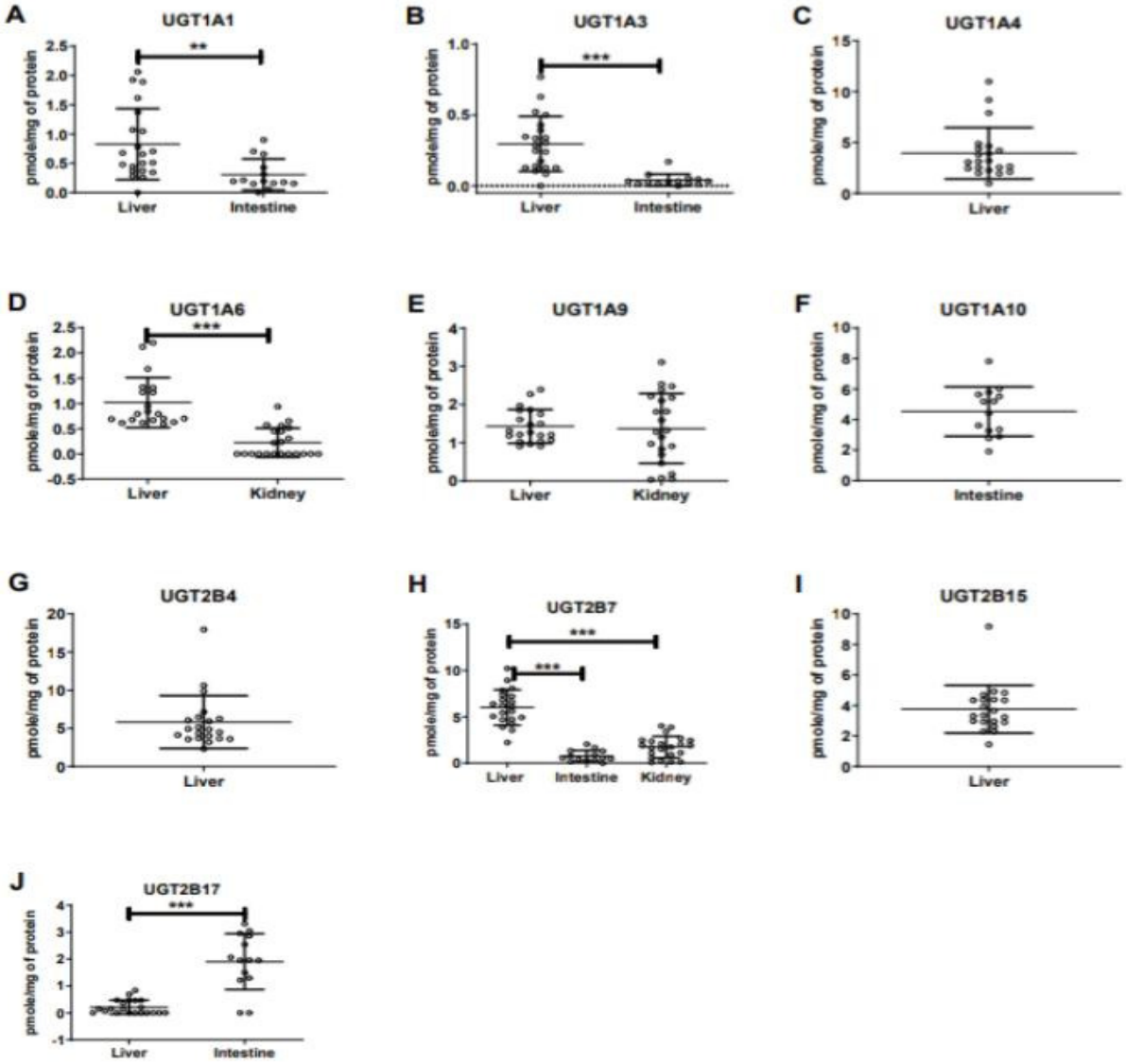


**Figure 3: Differential tissue abundance of UGTs (pmol/mg of S9 protein) in S9 fractions of liver (n = 21) , intestine (n = 14) , and kidney ( (n = 22)** A-F represent the tissue abundance of UGT1As whereas G-J represent the differential tissue abundance of UGT2Bs. None of the studied UGTs were detected in the lung and heart. Each dot represents the individual samples and the data are represented as the mean plus/minus S .D. ** p < 0.01 leftrightarrow* p < 0.0001 .

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### 3.4 Monoamine Oxidases (MAO-A and MAO-B)

Both MAO-A and MAO-B are expressed in the liver, brain, and intestine, though their distribution varies:
MAO-A: Higher in gut and placenta
MAO-B: Predominant in brain and platelets
These enzymes are vital for the oxidative deamination of neurotransmitters and dietary amines.
Both MAO-A and MAO-B are highly expressed in the brain and liver, with MAO-A being more prominent in the gut and placenta, while MAO-B is enriched in the brain and platelets. These enzymes are critical for the metabolism of neurotransmitters and other amines. and their distribution reflects their physiological roles

### 3.5 Flavin-Containing Monooxygenases (FMOS)

FM03 is the major isoform in the adult liver, involved in the oxidation of soft nucleophiles like sulfur- and nitrogen-containing compounds.
FM01 is expressed in the fetal liver and adult kidney.
The transition from FM01 (fetal) to FM03 (adult) reflects ontogenic regulation.
FM01 is primarily expressed in the kidney and fetal liver, whereas FM03 dominates in the adult liver. FM05 is also detected in the liver but at lower levels. The age-dependent switch from FM01 to FM03 in the liver is a notable finding influencing drug metabolism across life stages.

## 4. Discussion

The metabolism of xenobiotics and endogenous compounds in humans is not solely dependent on cytochrome P450 (CYP) enzymes. A variety of non-CYP enzymes also play essential roles in drug metabolism, biotransformation. and detoxification processes. These enzymes include carboxylesterases (CES), aldehyde oxidase (AO), monoamine oxidases (MAOs), flavin-containing monooxygenases (FMOs), and UDP-glucuronosyltransferases (UGTs). among others. The tissue-specific abundance and distribution of these enzymes affect drug disposition, efficacy, and toxicity.
The characterization of non-cytochrome P450 (non-CYP) drug-metabolizing enzymes across different human tissues has gained significant attention in recent years due to their substantial role in both phase I and phase II metabolism. Unlike CYP enzymes, which are predominantly hepatic, non-CYP enzymes exhibit diverse and tissue-specific expression patterns. influencing drug absorption. distribution, metabolism, and excretion (ADME) in a more complex manner.
CEST is predominantly expressed in the liver, whereas CES2 is more abundant in the intestine, reflecting their respective roles in hepatic and intestinal drug metabolism. CES enzymes are involved in hydrolysis of ester and amide bonds. making them critical in the activation or deactivation of esterified drugs.
The characterization of non-CYP (non-cytochrome P450) enzymes across various human tissues has become increasingly important due to their critical role in drug metabolism. particularly for drugs not extensively metabolized by CYPs. These enzymes. including carboxylesterases (CES) aldehyde oxidase (AO), monoamine oxidases (MAOs), flavin-containing monooxygenases (FMOs), and UDP-glucuronosyltransferases (UGTs). show distinct and often tissue-specific expression patterns, influencing local and systemic drug metabolism.
Recent quantitative proteomic analyses have provided a clearer map of where key non-CYP drug-metabolizing enzymes (DMEs) are expressed in human tissues-and the variability of that expression across individuals and organs.

1. Comprehensive Liver Extrahepatic Profiling
A landmark study employed LC-MS/MS proteomics to quantify 18 non-CYP DMEs lincluding AD, CEST/2, ten UGTs. and five SULTS) across human liver. kidney, intestine, heart, and lung. Key findings include:

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Aldehyde oxidase (AO): Highest expression in liver, moderate in kidney, with no detectable levels in intestine, heart, or lung.
Carboxylesterases: CEST is predominant in liver, while CES2 is enriched in the small intestine.
SULTS: All were found in both liver and intestine: SULT1A1 and SULT1A3 were additionally present in lung.
Interindividual variability: Over 15-fold variability was observed for UGT2817. intestinal CES2. hepatic SULT1A1. UGT1A9, UGT287, and renal CEST. These insights are directly relevant for physiologically-based pharmacokinetic IPBPK modeling and predicting organ-specific drug metabolism and toxicity.

2. Species Comparisons: Human vs. Animal Models
Cross -species comparisons highlight significant differences, emphasizing the importance of human-specific data
AO is abundant in humans and primates. but poorly expressed in rodents and absent in dogs.
CEST is highest in human liver, whereas CES2 shows greater hepatic expression in monkeys, unlike human intestine-enriched CES2.

## 5. Conclusion

The differential tissue abundance of major non-cytochrome P450 (non-CYP) enzymes such as carboxylesterases (CES), aldehyde oxidase (AO), monoamine oxidases (MAOs), flavin-containing monooxygenases (FMOs), and UDP-glucuronosyltransferases (UGTs)-plays a crucial role in the metabolism. disposition, and pharmacokinetics of many therapeutic agents. Unlike the CYP enzymes, which are primarily liver-based, non-CYP enzymes show diverse expression across various human tissues, including the intestine, kidney, brain, and lung, influencing first-pass metabolism, organ-specific drug clearance, and potential toxicities.
The characterization of the tissue-specific abundance of major non-cytochrome P450 (non-CYP) enzymes has provided crucial insights into human drug metabolism beyond hepatic CYP-mediated pathways. Enzymes such as carboxylesterases (CEST and CES2), aldehyde oxidase (AO), monoamine oxidases (MAO-A and MAO-B), flavin-containing monooxygenases (FMOs), and UDP-glucuronosyltransferases (UGTS) demonstrate distinct expression profiles across various human tissues, influencing both local and systemic drug disposition.

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