BIOCHEMISTRY OF DRUG METABOLISM: A REVIEW

OGIDI, O. I.[1*] – OMABEMITUALE, I. F.[1]

[1] *Faculty of Basic Medical Sciences, Bayelsa Medical University Yenagoa, Bayelsa State, Nigeria.*

**Corresponding author*
e-mail: ogidiodangowei[at]gmail.com

(Received 28th March 2025; revised 28th June 2025; accepted 18th July 2025)

Abstract. Drug metabolism is a crucial process in the fields of pharmacology and biochemistry. It involves the conversion of medicinal chemicals in the body to aid in their removal. The liver is the primary site of drug metabolism, where enzymes incorporate reactive or polar groups into drug molecules. Drug-metabolizing enzymes (DMEs) play a vital role in the breakdown of foreign substances in the body. They facilitate the transformation of prodrugs into their active state, hence enhancing their pharmacological efficacy. Drug-metabolizing enzymes (DMEs) are classified according to their specific mechanisms of drug metabolism, which may involve oxidative, reductive, and/or conjugative enzymes. These enzymes possess bio-activation routes and particular mechanisms of action to carry out their functions. The drug metabolism process involves the classification of metabolic reactions into either phase I or phase II reactions. In this review, a comprehensive explanation of xenobiotic metabolism, including how drugs function. The important biochemical characteristics and catalytic processes are detailed, along with a vast assortment of hydrolases and their nomenclature. The disciplines of medicine, toxicology, and environmental science are illustrated through several instances. The investigated mechanisms involve the hydrolysis of a range of unstable rings, such as carboxylic esters, amides, peptides, lactones, and esters generated by inorganic acids. The review provides an explanation of the enzymology and procedure involved in hydrating epoxides.
Keywords: *drug metabolism, enzyme, biochemistry, pharmacology, xenobiotics*

Introduction

Drug metabolism is the enzymatic process that seeks to transform or alter a medication into a form that is either more potent or less potent. After being digested and absorbed into cells, both nutrients and medications undergo a series of chemical reactions that produce new, chemically unique substances. These compounds are referred to as metabolites. The process of chemical transformations involved in the body's processing of drugs is commonly known as drug metabolism (Testa and Kraemer, 2008). Drug metabolism takes place within the body as a biological process. The liver is the primary site of drug metabolism, where enzymes incorporate reactive or polar groups into drug molecules. The metabolic reactions are categorised as either phase I or phase II reactions. Metabolism has the ability to either render the medicine inactive or enhance its activity. Some medications can be given in an inactive state and subsequently go through metabolism to create the active component (Testa and Kraemer, 2008). On the other hand, other medications in their active form may undergo metabolism to generate a molecule that can be eliminated from the body. Drug metabolism was serendipitously discovered in the 1920s when researchers investigating alcohol metabolism saw the excretion of small amounts of vivid blue chemicals from the body following the use of quinine, an anti-malarial medicine. Subsequent investigation revealed that quinine is metabolised into a substance called quinoline, which then undergoes additional metabolism to generate a molecule commonly referred

to as indigo blue. This chemical exhibits a vivid blue hue and is eliminated from the body through urine. Drug metabolism has been recognised as a vital process for the removal of medicines from the body (Testa and Kraemer, 2008).

The pace of metabolism plays a crucial role in defining the half-life of a drug as some metabolites of medication metabolism can have detrimental effects on the body. The half-life of a medicine refers to the duration required for half of its original plasma concentration or total body concentration to decrease. For instance, medications with a shorter half-life necessitate more frequent administration compared to those with a longer half-life. This can have ramifications for patient adherence to medication regimens as they may be required to remember to take medication multiple times during the day. Furthermore, understanding the half-life of drugs can be advantageous in the fields of toxicology and drug enforcement. This knowledge can be applied, for instance, in the surveillance of individuals who are under the effect of drugs (Testa and Kraemer, 2008). This review highlights the significance of biochemistry in drug metabolism, specifically focusing on new molecular methodologies and approaches. It is important for non-scientific readers to understand and appreciate its extensive clinical and medical application. Additionally, drug metabolism might result in the creation of reactive intermediates or metabolites that have the potential to induce toxicity or negative consequences. Comprehending the biochemistry of drug metabolism is essential for foreseeing and reducing these hazards by creating safer and more efficient medications (Testa and Kraemer, 2008). Examining the complex biochemical processes of drug metabolism offers useful insights into drug development, personalised medicine, drug-drug interactions, and pharmacogenomics. Through the clarification of the processes involved in drug metabolism, scientists can improve medication treatments, improve patient results, and progress the discipline of pharmacology. Therefore, this review focuses on the biochemistry of drug metabolism.

Drug metabolism pathways

Metabolic reactions such as oxidation, reduction, hydrolysis, hydration, condensation, and isomerization are frequently observed in drug metabolism. The ultimate objective is to enhance the body's ability to expel the medication, irrespective of the specific mechanism involved. Metabolic enzymes are found in various tissues, however they are often more abundant in the liver. Patients exhibit variability in drug metabolism rates. Certain people exhibit quick drug metabolism, resulting in insufficient blood and tissue concentrations to provide therapeutic effectiveness. Conversely, some patients experience sluggish metabolism, leading to hazardous consequences even with normal doses. Several factors can influence an individual's medication metabolism rates, including heredity, co-occurring diseases (such as chronic liver difficulties or severe heart failure), and drug interactions (particularly those that activate or inhibit metabolism). The metabolism of many drugs involves two distinct stages (*Figure 1*). Phase I reaction encompass the creation or alteration of new functional groups and the breakdown of chemical bonds, including hydrolysis, oxidation, and reduction. These reactions are very natural. Phase II reaction involve the conjugation of an endogenous compound, such as glycine, glucuronic acid, or sulphate. The artificial nature of these reactions is what sets them apart. The kidneys and liver can more efficiently eliminate metabolites that are produced synthetically compared to those generated through non-synthetic processes due to the higher polarity of these substances. The numerical designations of the phases do not indicate a sequential

sequence, but rather serve as a means of functionally categorising medications, as certain compounds may only undergo phase I or phase II responses (Farrukh et al., 2024). Drug elimination from the body takes place once they have undergone a process of enzymatic reactions, known as drug metabolism pathways, which transform them into metabolites. These paths can be divided into two main stages: The body eliminates drugs and foreign compounds through two main processes called Phase I and Phase II metabolism (Farrukh et al., 2024). In order to aid their elimination from the body, these processes undergo a sequence of chemical events that convert the chemicals into molecules that are more easily dissolved in water.

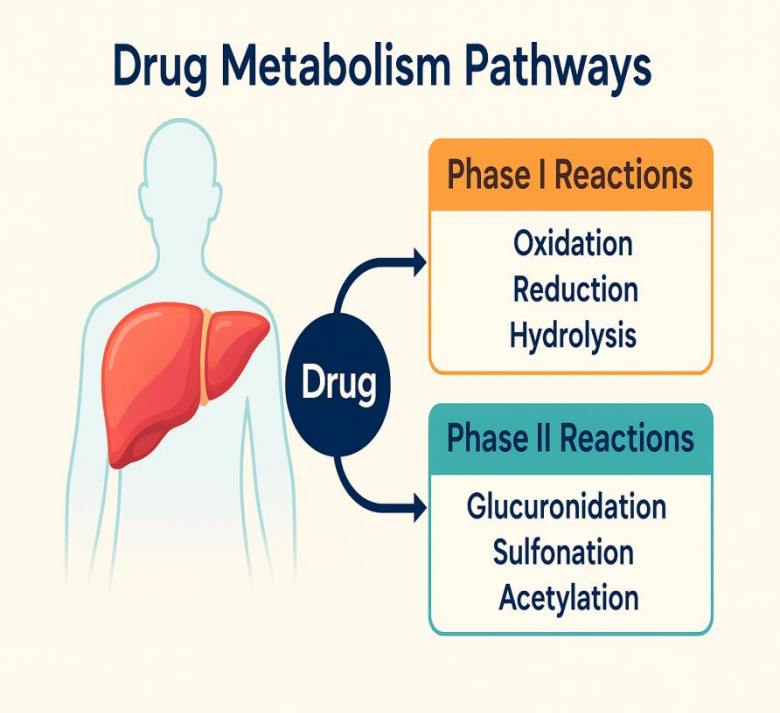

Figure 1. *Drug metabolism pathways.*

Phase 1 reactions

In the phase 1, many enzymes bind polar and reactive groups to their substrates. The cytochrome P-450-dependent mixed-function oxidase system facilitates the process of hydroxylation, which is a common type of modification. Enzyme complexes catalyse the incorporation of oxygen atoms into non-activated hydrocarbons, resulting in the addition of hydroxyl groups or the removal of alkyl groups from substrates. The reaction below depicts the reaction mechanism of the P-450 oxidases, which involves the reduction of oxygen that is bound to cytochromes, resulting in the formation of a highly reactive oxyferryl species.

$$O_2 + NADPH + H^+ + RH \rightarrow NADP^+ + H_2O + ROH \qquad \text{Eq. (1)}$$

Phase I reactions, often known as non-synthetic reactions, encompass several processes such as oxygen or hydrogen addition or removal, oxidation, reduction, hydrolysis, cyclization, and decyclization (*Figure 2*). Mixed function oxidases are hepatic enzymes that catalyse these specific processes. These oxidative processes

typically necessitate the presence of oxygen, NADPH, and cytochrome P450 monooxygenase (also known as CYP). Phenothiazines, paracetamol, and steroids, along with other therapeutic medicines, use this metabolic route. Eliminating the metabolites of phase I reactions becomes effortless after they acquire a high degree of polarity. During a subsequent reaction, a naturally occurring substrate reacts with the newly added functional group to produce a highly polar conjugate. This phenomenon persists despite the fact that numerous phase I products exhibit a prolonged process of elimination.

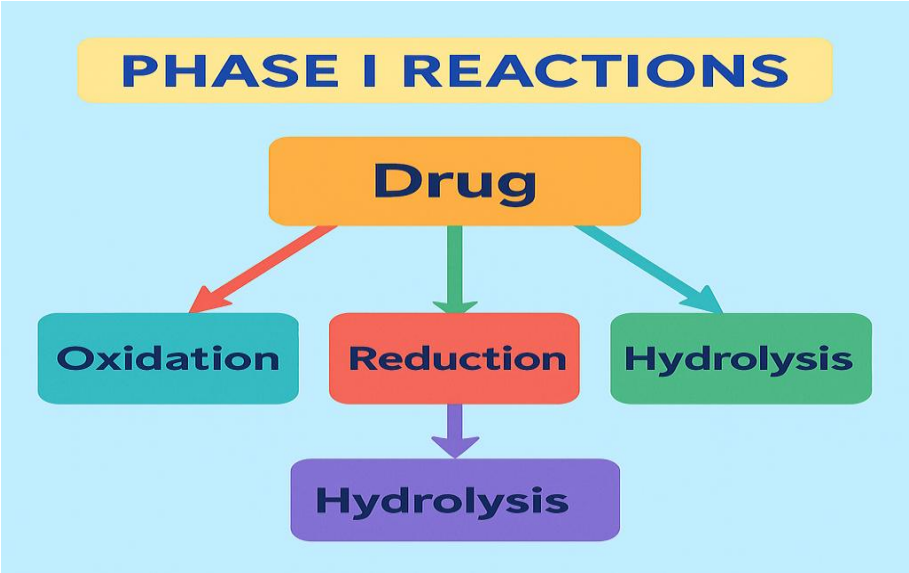

Figure 2. *Phase I reactions.*

Oxidation

During phase I reactions, oxidation often entails the incorporation of an oxygen atom or the elimination of hydrogen atoms from a substrate molecule. Cytochrome P450 enzymes catalyse this activity. Oxidation is the primary metabolic process. The whole oxidation process in phase I reactions can be expressed as (Eq. (2):

$$Substrate + NADPH + H^+ + O_2 \rightarrow Oxidized\ product + NADP^+ + H_2O \quad \text{Eq. (2)}$$

In this process, the substrate is oxidised by integrating an oxygen atom from molecular oxygen (O_2) with the assistance of NADPH as a co-factor. The resultant oxidised product frequently exhibits increased polarity and reactivity compared to the initial substrate, hence promoting more metabolism or excretion of the molecule. Oxidation can introduce or alter functional groups, such as alcohols, aldehydes, ketones, and carboxylic acids, which can impact the pharmacological and toxicological aspects of a medicine. For example, the process of oxidation can enhance the polarity, water solubility, or clearance of a medicine, so facilitating its elimination from the body. Nevertheless, oxidation can also result in the creation of metabolites or extremely reactive intermediates that have the potential to harm DNA, proteins, or lipids, hence causing cellular malfunction or tissue damage. Hence, maintaining a delicate equilibrium between the activation and deactivation of drugs by oxidation is of utmost

importance for ensuring their effectiveness and safety. The rate and selectivity of oxidation can be affected by several factors, including the nature and position of the oxidizable functional groups, the specific isoform of the cytochrome P450 enzyme involved, and the presence of other drugs or endogenous compounds that compete for the same enzyme or modify its activity.

Reduction

During phase I reactions, the process of reduction occurs when a substrate molecule gains electrons. Enzymes, such as cytochrome P450 reductase, facilitate this process. The general reaction for reduction in phase I reactions can be expressed as (Eq. (3):

$$Substrate + NADP^+ + 2^{e-} + 2H^+ \rightarrow NADPH + H^+ \quad \text{Eq. (3)}$$

During this reaction, the substrate is reduced by acquiring electrons (2^{e-}) and protons ($2H^+$) from NADPH, leading to the creation of a reduced product. The diminished product may have modified characteristics in comparison to the initial substrate, rendering it more vulnerable to phase II conjugation processes or elimination from the organism. During reduction processes, a chemical may engage in fruitless cycling, when it acquires a free-radical electron and quickly releases it to oxygen, resulting in the formation of a superoxide anion. Reduction is a significant form of Phase I process in drug metabolism, wherein enzymes extract electrons from the drug molecule. This procedure has the ability to modify or remove functional groups such as nitro, carbonyl, or double bonds, which can cause changes in the chemical or biological activity of the medicine. Reduction can diminish the toxicity, reactivity, or selectivity of a medicine, either reducing its harmfulness or enhancing its effectiveness. Nevertheless, reduction can also produce reactive intermediates or metabolites that have the potential to induce harmful effects or disrupt other metabolic pathways. Hence, maintaining a delicate equilibrium between medication activation and deactivation through decrease is imperative for ensuring optimal drug effectiveness and safety. Comprehending the processes and outcomes of decreased drug metabolism is crucial for the development of drugs, improvement of their effectiveness, and evaluation of potential risks.

Hydrolysis

During phase I metabolism, hydrolysis events occur, which entail the breaking of chemical bonds in a substrate molecule by adding water (H_2O). Enzymes, such as esterases, amidases, and epoxide hydrolases, usually catalyse these processes. This procedure has the capability to cleave or alter ester, amide, peptide, or glycosidic bonds, resulting in potential impacts on the stability, solubility, or bioavailability of the medicine. Hydrolysis has the ability to transform pro pharmaceuticals into active versions, or convert inactive medicines into metabolites that can undergo further processing through Phase II processes. Nevertheless, hydrolysis has the potential to produce harmful or highly reactive substances, such as acyl or alkylating agents that have the ability to harm cellular structures or initiate immunological reactions. Hence, maintaining a delicate equilibrium between medication activation and inactivation through hydrolysis is of utmost importance for ensuring optimal pharmacological effectiveness and safety (Farrukh et al., 2024). Several factors can affect the rate and selectivity of hydrolysis, including the nature and location of the hydrolyzable group,

the pH and temperature of the surrounding environment, and the presence of other enzymes or co-factors that can either promote or hinder the activity. Comprehending the function and control of hydrolysis in drug metabolism is crucial for the processes of drug discovery, formulation, and toxicity. The hydrolysis reaction in phase I reactions can be represented by the following Eq. (4)

$$Subtrate + H_2O \rightarrow Hydrolyzed\ Products \quad \text{Eq. (4)}$$

Hydrolysis is the process in which the addition of a water molecule to a substrate leads to the breakdown of bonds and the creation of hydrolyzed products. During this process, certain functional groups such as esters and amides can be transformed into acids or alcohols. This transformation enhances the polarity of the substrate and aids in its elimination from the body.

Phase II reactions

Phase II reactions refer to a collection of metabolic reactions where a substrate molecule is combined with a polar moiety to enhance its water solubility and aid in its elimination from the body. Typically, these reactions occur after Phase I events, which entail the addition of a functional group to the substrate molecule. Phase II metabolism encompasses enzymatic activities that transform the medication or phase I metabolites into molecules that possess sufficient solubility to be eliminated by urine. These reactions include the attachment of a molecule (drug or metabolite) to an ionizable group. The process of combining two terms by changing the sign between them is known as conjugation, and the resulting term is referred to as a conjugate. Metabolites that are produced during phase II are improbable to possess pharmacological activity. Phase II reactions play a crucial role in the process of detoxifying and eliminating substances from the body (Farrukh et al., 2024). Below is an illustration of a phase II reaction Eq. (5):

$$Drug + Conjugating\ Enzyme\ (UDP - glucuronyl\ transferase) + Co - substrate\ (UDP - glucuronic\ acid) = Drug\ conjugate + Co - substrate \quad \text{Eq. (5)}$$

Common Phase II processes encompass glucuronidation, sulfation, methylation, acetylation, and glutathione conjugation (*Figure 3*). These processes are facilitated by certain enzymes and lead to the production of conjugated metabolites that can be more readily excreted from the body. Phase II reactions are essential for removing and eliminating different xenobiotics and endogenous chemicals from the body, contributing significantly to detoxification.

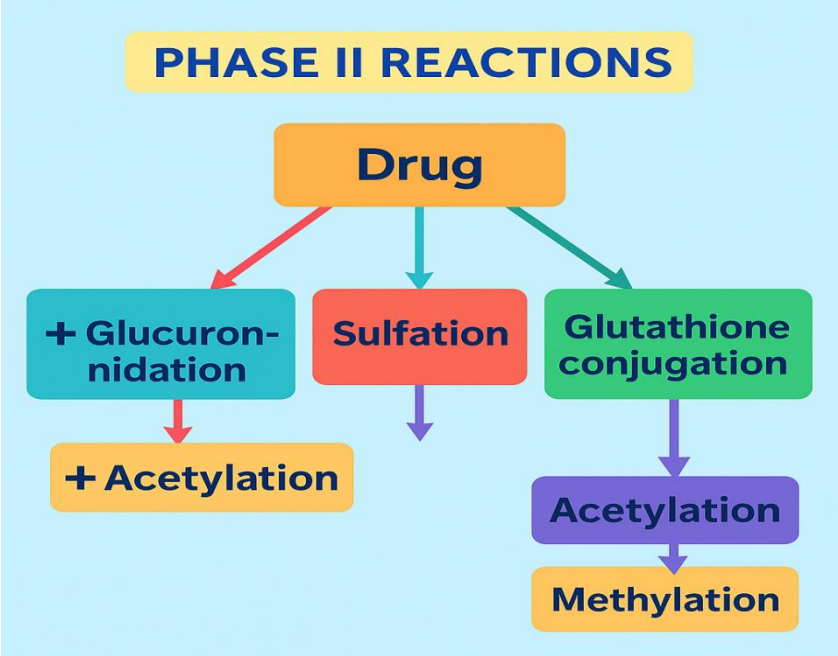

Figure 3. *Phase II reaction.*

Glucuronidation

Glucuronidation frequently plays a role in the metabolism of several compounds, including medications, pollutants, bilirubin, and hormones such as androgens, oestrogens, mineralocorticoids, and glucocorticoids. It also metabolises bile acids, retinoids, and fatty acid derivatives. King et al. (2000) states that glycosidic links are the cause of these connections. Glucuronidation is a metabolic process that utilises different UDP-glucuronosyltransferase enzymes to transfer the glucuronic acid portion of uridine diphosphate glucuronic acid to a specific substance. UDP-glucuronic acid, a product of liver metabolism, serves as an intermediary in the process. It consists of glucuronic acid connected to uridine diphosphate via a glycosidic bond. The process of converting 4-aminobiphenyl to glucuronidation takes place when the UGT1A4 or UGT1A9 enzymes, found in the livers of humans, rats, and mice, facilitate the reaction (Al-Zoughool and Talaska, 2006). The glucuronidation reaction can be represented as (Eq. (6):

$$Substrate\ (X) + UDP - glucuronic\ acid \rightarrow Glucuronide\ conjugate + UDP \quad \text{Eq. (6)}$$

In this reaction, the substrate molecule (X) undergoes conjugation with glucuronic acid in the presence of UDP-glucuronic acid as the co-substrate. The resultant Glucuronide conjugate exhibits higher water solubility compared to the initial substrate, facilitating its effortless elimination by urine or bile. The products of glucuronidation are referred to as glucuronides (or glucuronosides) and generally exhibit higher water solubility compared to the substances that do not include glucuronic acid and were initially formed. Glucuronidation is a process utilised by the human body to enhance the water solubility of a wide range of chemicals. This enables their effective excretion from the body via faeces or urine, facilitated by bile produced by the liver. Hormones are glucuronidated to facilitate their distribution throughout the body. Pharmacologists have demonstrated that the utilisation of glucuronic acid can enhance the delivery of

certain categories of medications. Glutaronidation can reduce the toxicity of some chemicals. The enzyme UDP-glucuronyltransferase has been discovered in various important organs such as the intestines, kidneys, brain, adrenal gland, spleen, and thymus. However, the liver is the main place where glucuronidation occurs (Ohno and Nakajin, 2009). Glucuronidation is an essential process for removing and getting rid of various natural substances (such as bilirubin and steroid hormones) and foreign substances (such as medications and environmental pollutants) from the body. The liver has a crucial function in the overall metabolism and elimination of many chemicals in the body (Farrukh et al., 2024).

Sulfation

The process of introducing a SO3 group to a chemical molecule is referred to as sulfation. Typically, interactions involving sulphur trioxide (SO3) would be one among several sulfations. In practical applications, sulfations are typically achieved indirectly. Irrespective of the specific method employed, the addition of a sulfate-like group to a substrate consistently results in a substantial alteration (Farrukh et al., 2024). Sulfation is the method employed to eliminate "sulphur" from fossil fuel burning. The reason is to reduce the emissions of pollutants generated by the combustion of petrol. Sulphur dioxide is a resultant of the combustion of fuels that contain sulphur. Sulphur dioxide that naturally exists in the environment can chemically react with oxygen to form sulfuric acid, which is a caustic material. Utilising calcium oxide or calcium carbonate in combustion is a prevalent method for mitigating the issue. According to Anthony and Granatstein (2001), these chemicals have the ability to form calcium sulfite by either direct or indirect interactions with sulphur dioxide or a small quantity of oxygen. Sulfation is a Phase II metabolic reaction where a substrate molecule is combined with a sulphate group to enhance its solubility in water and aid in its removal from the body. The enzyme sulfotransferase catalyses this reaction (Anthony and Granatstein, 2001). The general reaction for sulfation can be represented as (Eq. (7):

$$Substrate\ (X) + 3' - phosphoadenosine - 5' - phosphosulfate\ (PAPS) \rightarrow Sulfate\ conjugate + Adenosine - 3', 5' - diphosphate\ (ADP) \quad \text{Eq. (7)}$$

In this chemical reaction, the substrate molecule (X) undergoes conjugation with a sulphate group in the presence of PAPS, which acts as the sulphate donor. The resultant sulphate conjugate exhibits higher water solubility compared to the initial substrate, facilitating its effortless elimination from the body. Sulfation is a crucial process for the breakdown and removal of different natural substances (such as hormones and neurotransmitters) and foreign substances (such as medicines and environmental toxins) from the body. Sulfation, like other Phase II processes, is crucial in the process of detoxification and the general metabolism of chemicals in the body (Anthony and Granatstein, 2001).

Methylation

Methyl transfer is a crucial process in the breakdown of both foreign substances and naturally occurring molecules in the body. Methylation is a process that many medicines, neurotransmitters, hormones, proteins, lipids, polysaccharides, and nucleic

acids experience. It plays a crucial role in controlling gene transcription (Sider, 2024). Methylation is a Phase II metabolic activity in which a methyl group (-CH_3) is added to a substrate molecule. This process usually occurs by using S-adenosyl methionine (SAM) as the source of the methyl group. The enzyme methyltransferase catalyses this process. The general reaction for methylation can be represented as (Eq. (8):

$$Substrate\ (X) + S - Adenosyl\ methionine\ (SAM) \rightarrow Methylated\ product + S - Adenosyl\ homocysteine\ (SAH) \quad \text{Eq. (8)}$$

During this process, the substrate molecule (X) is methylated through the transfer of a methyl group from SAM, resulting in the formation of a methylated product. The introduction of a methyl group can modify the characteristics of the substrate molecule, hence impacting its activity, stability, or metabolism. Methylation has a role in the breakdown of many substances produced within the body (such as catecholamines and histamine) as well as foreign substances (such medications and poisons). It has a pivotal function in controlling gene expression, neurotransmitter activity, and detoxification activities in the body. In contrast to many other conjugative reactions, methylation typically does not significantly modify the solubility of substrates. Instead, it leads to the formation of either inert or active molecules. Methylation processes generally participate in the metabolism of small endogenous substances, such as neurotransmitters. However, they also contribute to the metabolism of larger molecules, such as nucleic acids, and are engaged in the bio-transformation of specific medications. Methylation is a crucial Phase II reaction that plays a significant role in the overall metabolism and disposal of many substances in the body.

Acetylation

Acetylation is a Phase II metabolic reaction where an acetyl group ($^{-}COCH_3$) is added to a substrate molecule. The enzyme N-acetyltransferase catalyses this reaction. In terms of the amount and diversity of substrates, acetylations are less extensive compared to sulfonations and glucuronidation. However, they still hold importance from a toxicological standpoint. Substances that are acetylated in intact animals include drugs and other foreign molecules. These substances can be either aromatic amines or hydrazines. When acetylated, they are transformed into aromatic amides and aromatic hydrazides (Ali et al., 2018). Acetylation reactions involve the transfer of an acetyl group, with the donor often being acetyl coenzyme A, and the recipient being a main amino group (Ali et al., 2018). The acetylation process involves the introduction of an acetyl group (CH_3CO^{-}) into a molecule. The representation of this can be expressed as follows (Eq. (9):

$$OH + CH_3COCl \rightarrow R - O - COCH_3 + HCl \quad \text{Eq. (9)}$$

The equation represents the acetylation of molecule R, where R is the molecule being acetylated and OH indicates a hydroxyl group (-OH) present on that molecule. An ester bond (R-O-$COCH_3$) is formed by adding the acetyl group to the hydroxyl group. This reaction is commonly conducted in the presence of a base, which serves to neutralise the HCl that is generated as a secondary product.

Glutathione conjugation

Glutathione is a peptide molecule composed of amino acids that is present in several tissues throughout the body, with particularly high levels in the liver. It has a crucial function in safeguarding hepatocytes, erythrocytes, and other cells from detrimental toxins (Bock and Köhle, 2005). Glutathione consists of three amino acids: L-cysteine, L-glutamine, and glycine. Glutathione conjugation is a vital component of the phase II reaction in the process of metabolism. Glutathione is involved in numerous enzymatic and non-enzymatic processes. For instance, the enzyme glutathione-S-transferase catalyses processes that include glutathione. Glutathione conjugation plays a vital role in the body's detoxification process. The glutathione-S-transferase enzymes facilitate the conjugation of glutathione with aromatic compounds and halides (compounds containing halogens such as chlorine). The liver synthesises these glutathione conjugates, which are then eliminated intact through the bile. Upon reaching the kidneys, these molecules undergo conversion into mercapturic acid, which is highly soluble in water, and are subsequently eliminated through urine. Glutathione conjugation helps remove xenobiotic compounds from the body. These compounds are toxic substances that are not naturally produced by the body. If there is a deficiency in glutathione-S-transferases, it can lead to hepatotoxicity (toxin damage to the liver) and an increased risk of harmful mutations in the body's cells. Glutathione conjugation is implicated in the following processes: (1) It eliminates organic and inorganic xenobiotic substances by detoxification; (2) It eliminates carcinogens (substances that cause cancer), arsenic, and mycotoxins produced by moulds (or fungus), etc.; (3) It is the primary method for removing industrial pollutants from the body; (4) Produces water-soluble mercaptan by-products that are easily eliminated by the kidneys; (5) It helps in the elimination of toxins produced by fungal molds; (6) Facilitates elimination of heavy metals like mercury and lead from the body. Glutathione conjugation is a crucial process for the detoxification and removal of many endogenous substances and xenobiotics, such as medications and environmental pollutants. Glutathione functions as a vital antioxidant and has a pivotal part in cellular defence mechanisms against oxidative stress and harmful chemicals (Bock and Köhle, 2005).

Factors affecting drug metabolism

Drug metabolism can be influenced by several factors as shown in Table 1 and some factors are discussed in *Table 1*.

Table 1. *Factors affecting drug metabolism.*

Factor Category	Specific Factors	Clinical Implications
Genetic	- Enzyme polymorphisms (e.g., CYP2D6, CYP2C19, NAT2, TPMT)- Pharmacogenomic profiles	Determines metabolic phenotype (poor, intermediate, extensive, ultra-rapid). Affects efficacy/toxicity; guides personalized dosing.
Physiological	- Age (neonates: immature enzymes; elderly: reduced hepatic blood flow)- Sex-related hormonal differences- Pregnancy increases volume of distribution and hepatic enzyme activity	Requires age- and sex-adjusted dosing. Pregnant women may need altered dosing schedules.
Pathological	- Liver disease (e.g., hepatitis, cirrhosis)- Renal impairment- Heart failure (reduced hepatic perfusion)- Inflammatory diseases (e.g., infections, cancer)	Impairs drug clearance and metabolism; may lead to accumulation, reduced efficacy, or toxicity.
Environmental	- Smoking (induces CYP1A2)- Chronic alcohol use (induces enzymes)- Acute alcohol use (inhibits enzymes)- Occupational or environmental toxins	Alters enzyme expression and metabolic rates; can affect long-term drug responses.

Dietary	- Grapefruit juice (CYP3A4 inhibitor)- High-protein diets (increase metabolism)- Starvation or malnutrition (depresses enzyme activity)- Cruciferous vegetables (induce phase II enzymes)	Nutrition significantly impacts metabolic enzyme levels and function.
Drug Interactions	- Enzyme inducers: rifampin, carbamazepine, phenobarbital- Enzyme inhibitors: ketoconazole, erythromycin, ritonavir	Leads to unpredictable drug levels; inducers lower efficacy, inhibitors raise toxicity risk.
Microbiome	- Gut bacteria can activate, inactivate, or modify drugs (e.g., reduction of digoxin)- Influences enterohepatic recycling	The microbiome modulates both local and systemic drug metabolism.
Hormonal Status	- Thyroid hormone levels (hypothyroidism slows, hyperthyroidism speeds metabolism)- Estrogen/testosterone	Hormonal imbalances can alter the activity of drug-metabolizing enzymes.
Route of Administration	- Oral (subject to first-pass effect)- Sublingual, rectal, IV (bypass first-pass metabolism)	Route selection influences bioavailability and required dosing.
Plasma Protein Binding	- Albumin levels- Alpha-1-acid glycoprotein levels	Affects free drug concentration available for metabolism; changes impact drug effect and clearance.
Stress and Circadian Rhythms	- Acute or chronic stress- Diurnal enzyme activity fluctuations	Stress hormones and circadian variation affect liver enzyme levels and drug breakdown rates.
Ethnicity and Population Variability	- Ethnic differences in allele frequency (e.g., slower acetylators in Middle Eastern and Asian populations)	Important for population-specific prescribing and clinical trial interpretation.
Exercise	- Chronic exercise can increase hepatic blood flow and enzyme activity	May accelerate drug clearance and reduce duration of drug action.

Genetic variations

Variations in individuals' genetic composition influence the metabolic processes of drugs within the body as well as the effects of drugs on the body. Pharmacogenetics refers to the examination of genetic variations in medication responsiveness. Prior to initiating therapy, it is possible to quantify the activity of an enzyme responsible for metabolising medicines in certain instances. Prior to prescribing, this should be taken into consideration. Due to their genetic composition, certain individuals exhibit a slow metabolism when it comes to medication processing. Consequently, a drug can build up in the body, leading to toxicity. Some individuals have so rapid medication metabolism that even after taking a typical dose, the drug concentration in their bloodstream never reaches a level sufficient for the medicine to have a therapeutic effect. Approximately 50% of individuals in the United States exhibit reduced activity of N-acetyltransferase, a hepatic enzyme responsible for the metabolism of specific medications. Individuals with this characteristic are commonly referred to as sluggish acetylators. Drugs, like isoniazid, which is employed for tuberculosis treatment, have a tendency to accumulate in higher concentrations in the bloodstream and have a longer duration of action in individuals with slow acetylation metabolism compared to those with quick acetylation metabolism (Cashman and Zhang, 2006). Approximately 10% of males and a smaller percentage of females with African or Black American heritage exhibit a deficit in glucose-6-phosphate dehydrogenase (G6PD), an enzyme that safeguards red blood cells against specific harmful substances. Individuals with G6PD deficiency may get hemolytic anaemia when exposed to certain medicines, such as chloroquine and primaquine, which are commonly prescribed for malaria treatment (Cashman and Zhang, 2006). Approximately 1 in 20,000 individuals possess a genetic abnormality that causes their muscles to be excessively responsive to specific inhaled anaesthetics, such as halothane, isoflurane, and sevoflurane. Administering one of these anaesthetics, typically succinylcholine, along with a muscle relaxant can lead to the potentially fatal condition known as malignant hyperthermia. It induces a severe hyperthermia. Cashman and Zhang (2006) states that the body experiences muscle stiffness, increased heart rate, and a decrease in blood pressure.

Age

Old age is characterised by significant alterations in the way medications affect the body, resulting from age-related changes in both the way drugs are absorbed, distributed, metabolised, and eliminated, as well as how they exert their effects on the body. The pharmacological changes mentioned are a result of the same biological mechanisms that underlie other ageing changes. These mechanisms include altered gene expression, oxidative damage, and mitochondrial failure (Liston et al., 2001). Therefore, it is important to take into account that alterations in drug metabolism due to ageing are a common phenotypic trait associated with the ageing process. Typically, advancing age is linked to higher levels of pharmaceuticals in the blood and changes in how the body processes them. This can lead to decreased effectiveness and a greater likelihood of experiencing negative side effects for various prescriptions. It is important to acknowledge that drug metabolism is just one component of the body's reaction to any potentially harmful and disease-causing foreign substance. Consequently, the impact of age-related alterations in medication metabolism and clearance extends to a wider range of implications for susceptibility to diseases. The liver is the main organ responsible for drug metabolism in the body. Changes in liver function that occur with age might affect the way drugs are processed in the body. Hepatic drug-metabolizing enzyme activity may be reduced in newborns and early children compared to adults, resulting in delayed drug clearance and the possibility of drug buildup. Age-related alterations in liver volume, blood flow, and enzyme activity might impact drug metabolism in older persons, potentially resulting in changes in drug clearance and heightened vulnerability to drug-induced toxicity.

Gender

The physiological differences between males and females have an impact on the pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics (actions on the body) of drugs, hence influencing their efficacy. Pharmacokinetics in women are influenced by several features, such as their smaller physical size, reduced rate of glomerular filtration, decreased activity of intestinal enzymes, and lower gastrointestinal motility. According to Liston et al. (2001), women may need to wait a longer period of time after eating before taking drugs that are most effective when taken on an empty stomach. This is because women's stomachs take longer to empty compared to men. Medication dosages may be influenced by various physiological variables. Due to the slower renal clearance in women, certain drugs that are excreted through the kidneys, including digoxin, may necessitate a modification in dosage. Women's physiology exhibits distinct pharmacodynamic modifications, such as heightened sensitivity and enhanced effectiveness of opioids, conventional antipsychotics, selective serotonin reuptake inhibitors, and beta blockers. In addition, women have a 50 to 75 percent higher likelihood than men of experiencing an unfavourable drug reaction. Cashman and Zhang (2006) suggests that in order to address the greater death rate of women from digoxin compared to men, it is recommended to provide lower dosages and target lower serum concentration levels for women. The pharmacokinetics of drugs can be affected by various factors, such as body composition, plasma volume, plasma protein binding capacity, body mass index (BMI), and plasma volume. Men have greater weight, body mass index (BMI), and internal

organ size compared to women. When estimating loading or bolus dosages, it is important to take into account these variations. Administering smaller doses to women is advised in order to reduce the probability of undesired side effects. Medications such as digoxin, heparin, lidocaine (Xylocaine), thrombolytics, aminoglycosides, chemotherapeutics, and class I and III antiarrhythmics necessitate the determination of loading doses (Liston et al., 2001).

Women possess bigger adipose tissue compared to men, leading to potentially higher drug distribution capacities, contingent upon the hydrophilic or hydrophobic characteristics of the drug. Women have a longer duration of effect for lipophilic medicines, such as benzodiazepines and neuromuscular blockers, due to their higher quantities of adipose tissue compared to men. Moreover, it has been found that women exhibit a 30 percent higher sensitivity to neuromuscular blockers compared to men. As a result, women necessitate 22 percent smaller doses of these blockers (Retti and Jones, 2005). Women should be started on lower dosages of benzodiazepines. Alcohol and fluoroquinolone antibiotics are hydrophilic substances that exhibit a tendency to distribute in lower concentrations in women. Consequently, the impacts are more apparent because of higher initial concentrations in the plasma (Retti and Jones, 2005). The initiation of metabolic pathways involves the oxidation, reduction, or hydroxylation of substances catalysed by cytochrome P450 enzymes. While most drugs undergo phase I hepatic metabolism in the liver, warfarin (Coumadin) is an exception since its dosage requirements vary between genders. Research indicates that females should consume a weekly dosage of warfarin that is 2.5 to 4.5 mg lower than that of males. Phase II metabolism involves processes such as glucuronidation, sulfation, acetylation, or methylation. These processes result in the production of polar conjugates of the original drugs or phase I metabolites. These polar conjugates are then removed from the body through the kidneys. Certain drugs, such as acetaminophen, caffeine, digoxin, doxorubicin (Adriamycin), fluorouracil, levodopa, mercaptopurine, and propranolol (Inderal), are metabolised more rapidly in men, leading to faster clearance from the body.

Drug-drug interactions

Drug-drug interactions (DDIs) happen when a medication changes the way another medication is absorbed, transported, distributed, metabolised, or excreted. DDIs can lead to either an increase or a decrease in medication concentrations, which can have a substantial impact on the effectiveness and safety of the treatment in patients. Enzyme-mediated drug-drug interactions (DDIs) are the main focus of concern, whereas transporter-mediated DDIs are less comprehended but nonetheless significant (Cashman and Zhang, 2006). The study of drug interactions include both pharmacodynamics and pharmacokinetics. A pharmacodynamic interaction refers to the situation when one medication alters the response of tissues to another treatment, either by imitating its effect or by completely inhibiting it. While these effects may occur within the cell, they often manifest at the receptor level. Pharmacokinetic interactions often occur when one medication affects the absorption, distribution, protein binding, metabolism, or elimination of another medication. The availability of drugs at receptor sites might vary in terms of both quantity and duration. Pharmacokinetic interactions modify the extent and duration, but not the nature, of the effect. Adverse drug reactions are frequently anticipated through understanding of the specific medications or identified by observing drug levels or clinical symptoms (Teh and Bertilsson, 2012).

Disease states

The efficacy of a drug relies on the synchronised actions of many organs that absorb it, distribute it throughout the body, metabolise it, and then eliminate it at varying speeds. An anomalous condition affecting any of these organs can exert a distinct influence on the drug's effects, potentially causing secondary effects on other organs as well. Several studies examining the impact of heart, intestines, liver, and kidney diseases have demonstrated that these organ dysfunctions can alter the rate and extent of absorption, distribution, and protein binding to plasma, plasma degradation time, and liver and plasma clearance (Bock and Köhle, 2005). Furthermore, it has been clinically observed that different medicines may have varying pharmacokinetic effects on a certain disease (Ohno and Nakajin, 2009). Currently, it is not always feasible to anticipate the impact of a specific disease on the efficacy of treatment or to establish a connection between altered kinetics and traditional organ function tests. Monitoring the plasma drug level of each individual patient is highly recommended in certain illness situations, particularly for medications with a low therapeutic index. Additional meticulously controlled pharmacokinetic investigations are necessary to clarify the underlying mechanisms that cause the observed alterations in kinetic constants. Enhanced comprehension of the characteristics of these systems may ultimately contribute to the formulation and advancement of novel pharmaceuticals and the more efficient utilisation of current ones (Ohno and Nakajin, 2009).

Clinical implications of drug metabolism

Drug metabolism is a vital factor in determining the pharmacokinetics, effectiveness, and safety of drugs in clinical settings. Healthcare personnel must have a thorough understanding of drug metabolism's clinical consequences in order to optimise medication therapy, personalise treatment plans, and reduce the likelihood of adverse drug responses. Pharmacokinetics, drug interactions, and drug toxicity are important clinical implications of drug metabolism (*Table 2* and *Figure 4*).

Table 2. *Aspects of drug metabolism and their clinical implications*.

Aspect	Clinic implication
Enzyme Polymorphisms	Genetic variants (e.g., CYP2D6, CYP2C19) cause inter-individual variability in drug metabolism, influencing efficacy and toxicity. Genotyping may guide therapy choices.
Drug-Drug Interactions	Competing drugs may inhibit or induce metabolic enzymes, affecting blood drug levels. Requires vigilance when prescribing multiple medications.
Prodrug Activation	Prodrugs require metabolic conversion to active forms (e.g., clopidogrel, codeine). Metabolic defects can lead to reduced or exaggerated effects.
First-Pass Effect	Drugs heavily metabolized during first liver passage (e.g., morphine) have reduced systemic availability, influencing route and formulation choices.
Liver and Kidney Function	Hepatic or renal impairment alters metabolism and clearance. Close monitoring and dose adjustments are vital to prevent adverse events.
Age and Disease	Age-related changes (e.g., in neonates or elderly) and diseases (e.g., cirrhosis) affect enzyme activity. Individualized dosing is often required.
Environmental and Lifestyle Factors	Smoking, alcohol use, and diet can induce or inhibit enzymes, altering drug levels. Lifestyle assessment is key for accurate dosing.
Autoinduction	Some drugs accelerate their own metabolism over time (e.g., phenytoin), leading to reduced plasma levels and therapeutic effects.
Metabolite Activity	Active or toxic metabolites (e.g., acetaminophen's hepatotoxic metabolite) require monitoring, especially with prolonged use or overdose.
Therapeutic Drug Monitoring (TDM)	Used for drugs with narrow therapeutic windows (e.g., vancomycin, cyclosporine) to adjust doses based on plasma concentrations.
Enzyme Saturation (Non-linear Kinetics)	At high doses, metabolism may become saturated (e.g., phenytoin), leading to disproportionate increases in drug levels and toxicity.
Phase I vs Phase II Reactions	Phase I (e.g., oxidation, reduction) often activates drugs or introduces polar groups. Phase II (e.g., glucuronidation, sulfation) aids in solubility and excretion.

Enterohepatic Recirculation	Some drugs (e.g., oral contraceptives) undergo reabsorption after biliary excretion, prolonging half-life and potential interactions.
Pharmacogenomics in Cancer Therapy	Drug metabolism impacts chemotherapy outcomes. Variants in TPMT, UGT1A1, or DPD can predict toxicity in drugs like 6-mercaptopurine or irinotecan.
Induction Time Course	Enzyme induction (e.g., by rifampin) doesn't occur instantly—it may take days to weeks, necessitating gradual dosing adjustments.
Impact on Drug Formulation	Knowledge of metabolism can guide sustained-release designs or the need for non-oral routes in drugs with extensive first-pass effects.

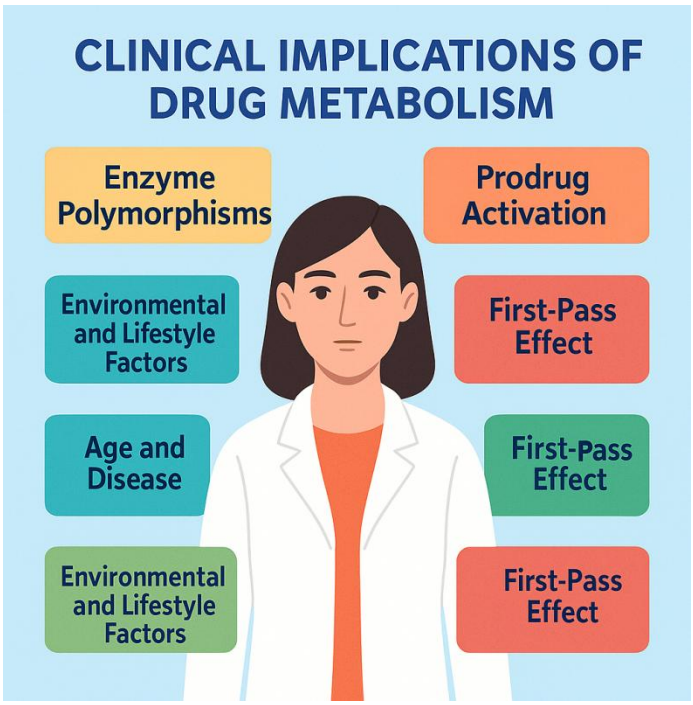

Figure 4. *Clinical implications of drug metabolism.*

Pharmacokinetics

Pharmacokinetics, also referred to as PK, is a branch of pharmacology that aims to comprehend the body's response to a drug following its administration (Teh and Bertilsson, 2012). The chemicals in question encompass chemical xenobiotics, which encompass substances like as medications, insecticides, food additives, cosmetics, and related compounds. The objective is to investigate chemical metabolism and elucidate the process by which a chemical substance traverses the body, starting from its introduction until its elimination (Teh and Bertilsson, 2012). Mathematical models are essential in pharmacokinetics, as they primarily study the time-dependent correlation between the concentration of drug in the blood and the time of delivery. The subject of pharmacokinetics explores how live organisms might influence the actions and effects of medicines. Pharmacokinetics refers to the scientific investigation of the process by which medications are absorbed into the bloodstream, distributed throughout the body, and ultimately excreted. "Drugs" refer to any chemical or therapeutic substance that, upon ingestion, induces an alteration in the body's physiological reaction. Absorption, distribution, metabolism, and excretion are the four primary stages involved in the processing of medicine within the human body. Occasionally, the complete process is shortened to ADME (Teh and Bertilsson, 2012). Absorption refers to the process by which a drug enters the body and moves from the place of delivery into the bloodstream. It is the initial stage of pharmacokinetics. Distribution is the second step in the process of pharmacokinetics. The phrase refers to the mechanism via which

medications are distributed throughout the entire body. During the third phase of pharmacokinetics, referred to as metabolism, a pharmacological compound undergoes decomposition. Excretion is the final step of pharmacokinetics, referring to the process of eliminating waste products from the body (Teh and Bertilsson, 2012).

The next stage in pharmacokinetics is the process of distributing the drug throughout the body. The term "distribution" refers to the systematic flow of a drug through the tissues and bloodstream of the organism. Once a drug is absorbed or directly administered into the body, it will move from the blood vessels to the tissues. In the tissues, the drug will interact with certain receptors, resulting in the desired effect of the medicine (Rettie and Jones, 2005). Drugs are specifically engineered to primarily induce a singular effect by exhibiting a higher affinity for a certain receptor location, hence reliably causing or inhibiting a single action. Nevertheless, the medicine may produce side effects and unfavourable effects by binding to places other than the intended target tissue, resulting in undesired actions. The side effects might vary in severity from bearable to intolerable, perhaps leading to the cessation of the prescription. For instance, someone who suffers from muscle soreness in their leg, they may opt to consume the pain-relieving medication ibuprofen (Advil) in order to enjoy some relief. It is important to note that stomach discomfort may potentially arise as a negative consequence (Rettie and Jones, 2005). The distribution of a medicine throughout the body is influenced by various physiological processes, including blood circulation, alterations in tissue composition, plasma protein binding, the blood-brain barrier, and the placental barrier. Once a drug has been absorbed into the bloodstream and distributed throughout the body, it undergoes metabolism before it can be eliminated. Drugs undergo metabolic alterations by many physiological systems to enhance their removal efficiency. Metabolism represents the third stage in the drug processing pipeline. The term "first-pass impact" refers to the process by which the intestines and liver metabolise and render inactive drugs that are taken orally or absorbed via the skin. Regardless of the method of drug administration, whether it is through ingestion, injection, inhalation, skin absorption, or endogenous production, the liver will metabolise it. Biotransformation refers to the process of a chemical change occurring within a living organism. The liver is responsible for carrying out biotransformations, which are facilitated by enzymes (Rettie and Jones, 2005).

Excretion is the final stage in the process of a drug's interaction within the body. The kidney typically handles the task of digesting any residual parent drugs or metabolites in the bloodstream after the absorption, distribution, and metabolism of pharmacological chemicals. Some of these molecules are reabsorbed into the bloodstream, while the rest are eliminated through urine. The liver secretes bile to eliminate waste materials and metabolic byproducts. The lungs can provide as an alternative pathway for excretion. It is common practice to eliminate opioids and alcohol from the body through the lungs. The kidneys and liver are the organs responsible for excretion. Additional pathways to take into account include perspiration, emotional secretion, reproductive fluids (such as semen), and lactation, all of which can potentially contain medications and their byproducts/metabolites. This situation can present a hazardous risk, such as when a baby is exposed to breast milk that contains drugs or substances derived from medications consumed by the mother. Hence, it is imperative for nurses to consult a drug reference and communicate with a healthcare expert if they have any concerns prior to administering drugs to a breastfeeding mother (Rettie and Jones, 2005).

Drug interactions

Drug interactions arise when many medications interact, causing changes in their effects on the body. These interactions can lead to alterations in the pharmacokinetics (absorption, distribution, metabolism, and excretion) or pharmacodynamics (effects on the body) of the medications involved. Drug interactions can have many therapeutic ramifications, such as (Wang et al., 2009): (1) Potentiation or Inhibition of Effects: Drug interactions can result in potentiation, which is the enhancement of one drug's effects by another, or inhibition, which is the reduction of one drug's effects by another. Combining a sedative with alcohol might cause an intensified depression of the central nervous system, which can result in excessive drowsiness or respiratory depression. On the other hand, the use of a medicine that stimulates liver enzymes might speed up the breakdown of another drug, leading to a decrease in its effectiveness. (2) Adverse responses: The occurrence of adverse responses or side effects can be heightened by drug interactions. For example, the combination of two medicines that both induce gastrointestinal irritation may worsen stomach discomfort or ulcers. Likewise, the interplay between medications and specific meals or supplements can result in undesirable consequences or diminished effectiveness of the medication. (3) Altered Drug Metabolism: Drug interactions can impact the process by which drugs are broken down and processed by the body, resulting in modifications to the quantities of drugs present in the body. The suppression or stimulation of drug-metabolizing enzymes, such as cytochrome P450 enzymes in the liver, can affect the rate at which medications are eliminated from the body, which may lead to either harmful effects or less than ideal therapeutic results. (4) Drug Accumulation: Certain drug interactions might hinder the process of eliminating drugs, resulting in their buildup in the body. This can happen in people who have reduced kidney or liver function, as well as in those who are taking many medications that are in competition for the same pathways of elimination. The buildup of drugs can heighten the likelihood of experiencing harmful consequences and toxicity. (5) Therapeutic Failure: Drug interactions can lead to therapeutic failure, whereby the intended effects of a drug are not attained as a result of interactions with other medications. For instance, the combination of a medicine that necessitates activation by a particular enzyme with another drug that hinders the activity of that enzyme can diminish the effectiveness of the former treatment (Wang et al., 2009).

Drug toxicity

Toxicity pertains to the degree of toxicity or harm that a material can cause. Pharmacologically, drug toxicity refers to the excessive accumulation of a prescription drug in an individual's bloodstream, resulting in adverse effects (Dasgupta, 2018). Drug toxicity is described as the occurrence of various harmful effects resulting from the use of drugs, whether they are taken at recommended or excessive levels (Silakari and Singh, 2021). Excessive consumption of medication can lead to drug toxicity, resulting in elevated levels of the drug in an individual's bloodstream (Dasgupta, 2018). This can occur if the dosage is excessive or if an excessive amount of medication is used. Adverse drug responses can lead to toxic effects of drugs. Under these circumstances, the standard therapeutic dosage of the medication can lead to inadvertent, detrimental, and undesirable adverse reactions (Dasgupta, 2018). Occasionally, there is a minimal difference between a dose that is beneficial and a one that is harmful. The dosage that is considered therapeutic for one individual may be hazardous for another one.

Furthermore, medications with a prolonged half-life can accumulate in an individual's bloodstream and progressively elevate, leading to drug toxicity (Schulz et al., 2012). The toxicity of a prescription drug is assessed based on three factors: its chemical composition, the body's ability to absorb it, and the body's capacity to detoxify and expel it.

Conclusion

Drug metabolism is an intricate process. This is due to the fact that medications undergo both metabolic processes within the body and are also metabolised by the body itself. Drugs undergo metabolism in multiple organs of the body, resulting in the formation of distinct metabolites. The liver is the primary site for these metabolic activities, which are facilitated by enzymes. The primary objective of drug metabolism is to modify the chemical composition of the drug in order to facilitate its efficient elimination from the body. Drug metabolism is an essential process that has a critical impact on how drugs are absorbed, distributed, and eliminated in the body. The intricacy of drug metabolism arises from the sophisticated interaction between medications and multiple enzymes and pathways in various organs, with the liver serving as a central location for drug metabolism. The primary objective of drug metabolism is to enhance the conversion of medicines into metabolites that can be readily eliminated from the body. Comprehending the processes involved in drug metabolism is crucial for healthcare practitioners in order to achieve the most effective drug dosage, reduce the likelihood of negative side effects, and customise treatment plans according to the specific requirements of each patient. Health care practitioners can improve patient care and boost therapeutic results by acknowledging the significance of drug metabolism in pharmacological efficacy and safety.

Acknowledgement

This research is self-funded.

Conflict of interest

The authors confirm that there is no conflict of interest involve with any parties in this research study.

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