



METABOLIC REWIRING OF THE PENTOSE PHOSPHATE PATHWAY AND ITS IMPACT ON CYP3A-MEDIATED DRUG METABOLISM IN EARLY LIVER PATHOLOGIES

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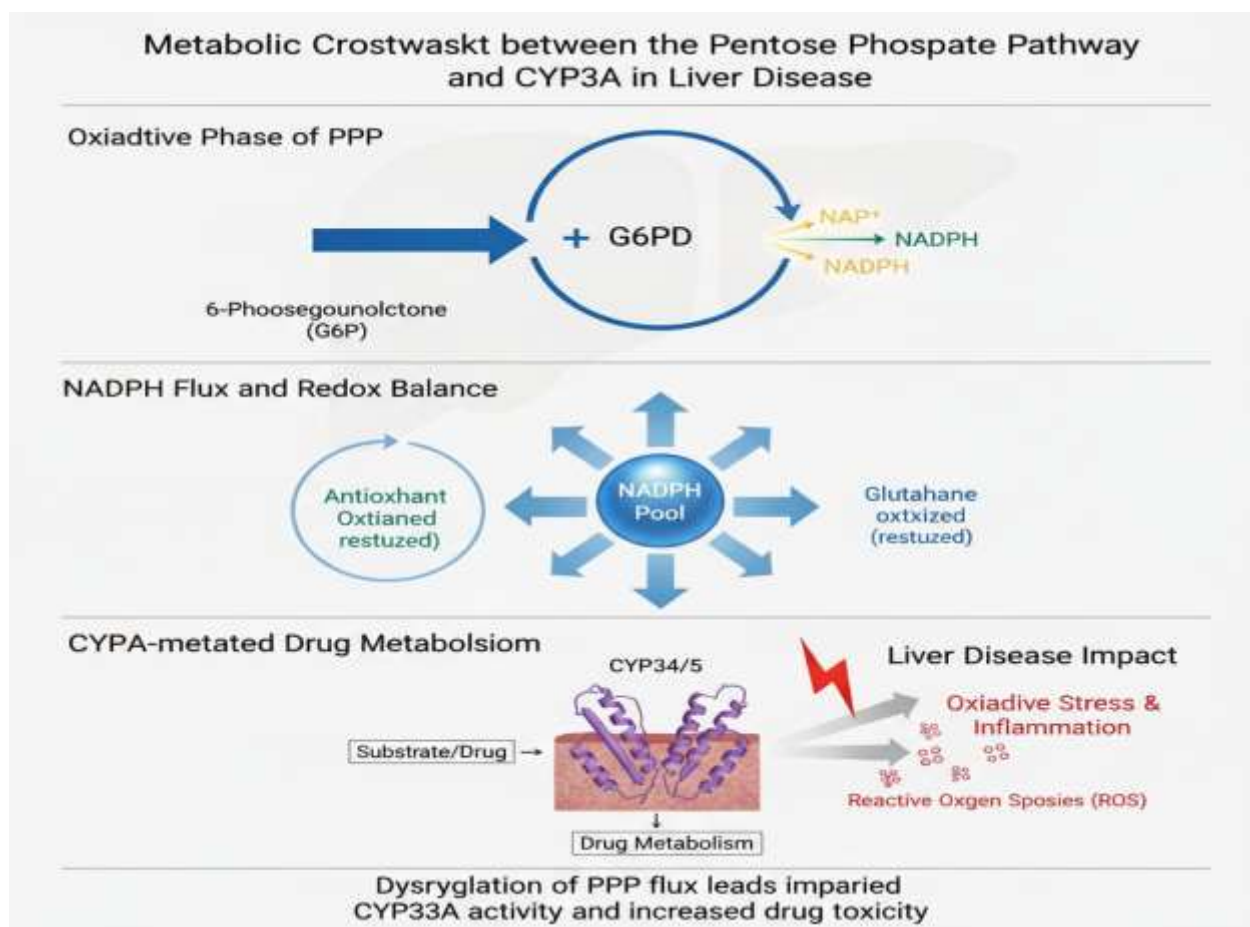
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ABSTRACT

The pentose phosphate pathway (PPP) is an essential cellular metabolic pathway that helps maintain redox homeostasis by producing nicotinamide adenine dinucleotide phosphate (NADPH), thus enabling antioxidant defence, biosynthetic processes, and liver drug metabolism. There is a growing body of evidence showing that PPP rewiring can remarkably affect CYP3A expression and catalytic activity through the changes in NADPH availability, modulation of oxidative stress, and inflammation-related signaling pathways, especially in liver disease. Alterations in PPP flux have been implicated in impaired CYP3A-mediated drug metabolism, which may lead to changes in pharmacokinetics, higher risk of drug-induced toxicity, and potentially therapeutic failure. While PPP, CYP3A crosstalk mechanisms have been elucidated mostly by means of experimental and preclinical studies, clinical implementation is still very limited due to the absence of longitudinal human data and the lack of incorporation of metabolic dynamics into pharmacokinetic models. Innovations such as metabolomics, pharmacometabolomics, and systems pharmacology hold the potential to discover PPP-derived biomarkers capable of evaluating CYP3A activity and interindividual differences in drug response. Additionally, combined metabolic, pharmacokinetic modeling could improve precision dosing approaches and help guide regulatory decisions. Closing the existing gaps in knowledge through translational and multidisciplinary research will be vital for unleashing the full potential of PPP, CYP3A interactions in drug development, therapeutic drug monitoring, and personalized medicine for liver disease.

Keywords: - Pentose phosphate pathway, CYP3A metabolism, NADPH redox balance, Liver disease, Pharmacokinetics, Precision medicine

Graphical Abstract



INTRODUCTION

Xenobiotics include pharmaceutical medications, environmental contaminants, food chemicals, and toxins foreign substances that the body does not normally manufacture. To prevent dangerous buildup and toxicity, xenobiotics need to be processed and removed from the human body as they enter [1]. The body has developed complex mechanisms to deal with these substances, and xenobiotic metabolism is the main process by which they are changed and removed. Maintaining homeostasis, lowering toxicity, and controlling the bioavailability of medications all depend on this mechanism, which mostly occurs in the liver. The two stages of xenobiotic metabolism, known as phase I as well as phase II processes, alter the xenobiotics to increase their water solubility and facilitate their excretion in the form of urine or bile. Drug absorption, distribution, & clearance are all impacted by these metabolic processes, which also have an impact on pharmacokinetics and pharmacodynamics [2]. Comprehending the metabolism of xenobiotics is essential for creating safe and efficient medications and evaluating the possible hazards associated with environmental pollutants. This mechanism is a crucial field for investigation in both toxicology and pharmacology since variations in it can result in variations in medication effectiveness, side effects, along with susceptibility to hazardous responses [3].

Xenobiotic Metabolism Mechanisms

Phase I and phases II of reactions are the two primary stages of xenobiotic metabolism. Every stage of the xenobiotic transformation process contributes differently to the final detoxification or activation of the drug [3].

Phase I reactions: Functional groups (such hydroxyl, amino, as well carboxyl groups) are mostly added in to the xenobiotic molecules during phase I processes. Enzymes known as cytochrome- P450 (CYP450) monooxygenases, a class of enzymes mostly present in the liver but sometimes in other organs including the intestines and lungs, are often responsible for catalyzing these processes. By oxidizing [4], reducing, and hydrolyzing xenobiotics, these enzymes increase their hydrophilicity and facilitate their removal from the body. Genetic polymorphisms, environmental variables,

and the presence of other chemicals that may impact enzyme activity can all cause substantial variation in the activity of the CYP450 enzymes, which are quite varied. There is a chance of cellular damage as well as carcinogenesis when phase I metabolism produces unstable intermediates which are even more hazardous than the parent chemical [3].

Phase II reactions: The xenobiotic or their phase I metabolites are conjugated with endogenous compounds [5], such as glutathione, glucuronic acid, or sulfate, in phase II processes. The xenobiotic's water solubility is greatly increased by this conjugation process, making it easier for the body to eliminate it through bile or urine. Glucuronosyltransferases, sulfotransferases, along with glutathione S-transferases are examples of common phase II enzymes. Phase II metabolism may occasionally neutralize the reactivity of potentially hazardous substances, detoxifying them. Unexpected adverse effects or therapeutic results, however, might result from phase 2 reactions that change certain medications or xenobiotics into more physiologically active forms [6]. For a medicine to be safe and effective in phase II, detoxification and bioactivation must be balanced.

The Role of Enzymes in the Metabolism of Xenobiotics

Cytochrome P450 enzymes (CYP450): The most significant class of enzymes engaged in phase I processes is the cytochrome P450 family. Numerous xenobiotics, such as medications, environmental pollutants, and endogenous substances, are metabolized by CYP450 enzymes. Significant inter-individual changes in metabolism can result from polymorphisms in the genes encoding the CYP450 enzymes, which are widely polymorphic. The rate at which a medication is metabolized can be influenced by these genetic variations, which may have an impact on treatment results and the likelihood of negative drug responses [7].

Glutathione S-transferases (GSTs): The tripeptide glutathione, which is essential for cellular detoxification, is conjugated with xenobiotics by GSTs. This procedure is essential for shielding cells against oxidative stress and aids in the neutralization of reactive intermediates. Many medications, especially those employed in cancer treatment, depend on GSTs for proper metabolism [8].

CYP450 enzyme overview with a focus on CYP3A isoforms

One of the subfamilies of heme-binding monooxygenases is the cytochrome P450 (CYP450) enzymes that play a crucial role in the metabolism of both endogenous and xenobiotic compounds. They are oxidative processes being catalyzed by these enzymes to facilitate drug clearance and detoxification in liver because of their extensive biochemical characterization [9]. Due to its widespread prevalence in the human intestinal and hepatic organs, the CYP3A subfamily has been the most popular of the other CYP families. It is believed that around half of the clinically prescribed medications are processed by CYP3A4, as an individual, hence the reason why it is a major determinant of interindividual differences in drug response [10]. Ligand-controlled nuclear receptors, constitutive androstane receptor (CAR) and pregnane X receptor (PXR) control CYP3A isoforms responses to xenobiotics and endogenous metabolites [11]. The alteration in CYP3A expression and activity has also been repeatedly related to liver disease and influences the metabolism of medications and predisposes an individual to adverse drug reactions [10]. Metabolic rewiring is a concept that has emerged over the past few years as one of the major causes of early liver diseases. Metabolic rewiring is used to refer to changes in cellular metabolic networks that allow hepatocytes to survive oxidative stress, inflammatory cues or dietary overload. Studies of the non-alcoholic fatty liver disease (NAFLD) have revealed that there are metabolic alterations that occur long before the onset of cirrhosis or fibrosis [12]. Early stages of the illness are characterized by reduced mitochondrial oxidative ability, alterations in the process of lipids, and a transition to glycolysis [13]. Such changes are compensatory changes that aim at maintaining redox and energy balance. Nevertheless, oxidative stress and excessive fat accumulation overwhelm defense mechanisms, which eventually results in hepatocellular dysfunction and disease progression in the long-term through metabolic rewiring [14]. One of the most significant pathways in metabolic rewiring is the pentose phosphate pathway (PPP) which is a key source of cellular NADPH. NADPH is also needed in antioxidant defense and catalyzing CYP450 enzymes, that is, the CYP3A isoforms. The PPP flow has been evidenced to increase to maintain the production of NADPH to continue under the state of oxidative stress [15]. CYP3A enzymes need the mediation of NADPH-cytochrome P450 oxidoreductase during substrate metabolism, and this could create a direct relationship between detoxifying capacity and cellular redox condition [16]. Whereas CYP3A-mediated metabolism can be initially upheld by elevated levels of PPP activity at first when liver illness sets in, CYP3A synthesis and activity is likely to be dis-regulated by chronic redox imbalance [17]. This functional dependency makes it highly reasonable to focus on the PPP–CYP3A crosstalk as an important metabolic detoxification interface in early hepatic diseases. The objective of this review is to integrate the latest data on regulation of CYP3A with new data on metabolic rewiring in the early stages of liver pathologies. As discussed in the literature before, early stages of hepatic pathologies

are associated with cytosolic metabolic via and mitochondrial dysfunction in the liver [18]. The metabolism of drugs in liver disease is also complicated by the fact that the CYP450 expression is significantly modulated by the inflammatory and metabolic signaling pathways [19]. This review is an effort to provide a molecular framework which relates redox metabolism to altered clearance of medication through exploring the interaction between the PPP and the CYP3A enzyme. The awareness of this connection could be useful in directing more personalized treatment regimens and improving the forecasting of medication response and toxicity in patients with early liver failure [20].

OVERVIEW OF THE PENTOSE PHOSPHATE PATHWAY

Pentose phosphate pathway (PPP) is an important cytosolic metabolic pathway that works in parallel to glycolysis and is mainly used in the maintenance of redox balance and biosynthetic potential in hepatocytes. Initial biochemical studies identified the central position of the PPP in the metabolism of the liver by diverting glucose-6-phosphate off the glycolysis to the production of reducing equivalents and metabolic intermediates needed by the cell to maintain homeostasis [21]. Due to the high liver metabolic and detoxification need, PPP activity in hepatocytes is also highly regulated and dynamically responds to metabolic perturbations and oxidative stress [22]. Classically, the PPP is divided into two major functional subpoints, the oxidative phase and the non-oxidative phase. The oxidative stage is irreversible and begins with the oxidation of glucose-6-phosphate by glucose-6-phosphate dehydrogenase (G6PD) the rate limiting enzyme of this pathway [23]. The process creates NADPH while it converts glucose-6-phosphate into ribulose-5-phosphate and simultaneously releases carbon dioxide. The scientific study demonstrated that G6PD activity in hepatocytes shows activation during oxidative stress conditions because the body requires NADPH to support its antioxidant and detoxification functions [24]. The non-oxidative step consists of reversible carbon-carbon rearrangement processes which transketolase and transaldolase enzymes perform to transform pentose phosphates into glycolytic compounds such as fructose-6-phosphate and glyceraldehyde-3-phosphate [25]. The energy flexibility of hepatocytes enables them to produce nucleotides while conducting energy metabolism according to changes in their body requirements [26]. The production of NADPH, a very important reducing equivalent in hepatocytes, is also one of the leading physiological roles of the PPP. The NADPH generated in the oxidative phase facilitates the cytochrome P450-mediated xenobiotic metabolism, fatty acid synthesis, and cholesterol biosynthesis, which is directly related to PPP flux to hepatic detoxification and lipid metabolism [27]. NADPH is also involved in the renewal of reduced glutathione and therefore, protects the hepatocytes against reactive oxygen species that are produced during the normal metabolic processes and drug clearance [28]. NADPH homeostasis has been implicated in the occurrence of the excessive oxidative damage and predisposition to liver injury [29]. The other important role of the PPP is that it synthesizes ribose-5-phosphate in the non-oxidative phase which builds the framework on which the nucleotide and nucleic acids are built. This role is especially vital in the context of hepatocyte proliferation and liver regeneration of a damaged liver [25]. Research has also shown that the increased production of ribose-5-phosphate aids in the synthesis of DNA and RNA under early adaptive and pathological conditions of the liver to be able to repair and survive the cells. All these functions highlight the significance of the PPP as a metabolic center bringing together the functions of redox control, antioxidant defense as well as lipid metabolism in the hepatocytes [30].

CYP3A ENZYMES AND HEPATIC DRUG METABOLISM

CYP3A Isoforms (CYP3A4, CYP3A5, CYP3A7)

Table No.:-1 The table shows the main CYP3A isoforms which display different patterns of liver distribution and ability to metabolize substances and their methods of regulation. The study demonstrates how different developmental stages and individual variations affect the drug metabolism processes which involve CYP3A4 and CYP3A5 and CYP3A7.

Isoform	Expression Pattern	Key Substrates	Regulation Factors	References
CYP3A4	Most abundant isoform in adult liver (~30–40% of total CYP content). Highly variable among individuals.	Statins, macrolide antibiotics, benzodiazepines, immunosuppressants.	Regulated by nuclear receptors (PXR, CAR, HNF4 α), diet (grapefruit juice), drugs (rifampicin, ketoconazole).	[31]
CYP3A5	Polymorphic expression; ~10–30% of adults express functional enzyme depending on genotype.	Tacrolimus, vincristine, midazolam.	Genetic variants (CYP3A53, 6, 7 alleles), cytokines, hormonal signals.	[32]
CYP3A7	Predominantly expressed in fetal liver; low levels in adults (CYP3A71C allele may persist).	Endogenous substrates (DHEA-S), some drugs.	Developmentally regulated; controlled by transcription factors (HNF4 α), epigenetic mechanisms.	[33]

Role of CYP3A in Phase I Drug Metabolism

The most common in the adult liver and intestine is CYP3A4 which contributes almost 30–40 percent of all hepatic CYP. It can metabolize structurally diverse compounds that are both promiscuous of substrates because of its large active site and flexible active site [34]. Examples of immunosuppressants, statins, calcium channel blockers, benzodiazepines, macrolide antibiotics, and chemotherapeutics are all examples of substrates. Besides xenobiotics, CYP3A enzymes are also involved in the metabolism of endogenous substrates such as steroid hormones (testosterone, cortisol) and bile acids [35]. The clinical significance of CYP3A enzymes can be explained by the fact that they play the central part in the determination of drug clearance, bioavailability, and therapeutic efficacy. The genetic variation, specifically CYP3A53 allele, determines the expression and activity of the enzyme, resulting in a large interpersonal difference in drug response [36]. Developmental regulation is also a factor where CYP3A7 is prevailing in the fetal liver whereas CYP3A4 is prevailing in the adult. Moreover, such disease conditions as liver disease and inflammation lower the CYP3A expression levels, therefore, modifying the drug metabolism and raising the potential of toxicity. The activity of CYP3A is frequently measured using biomarkers like 4 β -hydroxycholesterol in vivo [37]. The CYP3A enzymes are highly prone to drug-drug interaction (DDIs) that are enforced by either induction or inhibition by the co-administered drugs. Strong inhibitors like ketoconazole and itraconazole (antifungals), clarithromycin and erythromycin (antibiotics), and ritonavir (antiviral) may elevate the level of drugs resulting in toxicity. On the other hand, rifampicin (antibiotic), carbamazepine and phenytoin (antiepileptics) and St. John's wort, which is a herbal product may cause a decrease in the drug levels leading to a therapeutic failure. Such interactions are especially important when using tacrolimus or cyclosporine in polypharmacy and when using chemotherapeutics in cancer patients [38,39].

Redox Requirements for CYP3A Activity

The CYP3A cytochrome P450 enzymes are strictly reliant on NADPH and cytochrome P450 reductase (CPR).

NADPH is the reducing equivalent source, which contributes two sequential electrons during the oxidation of substrates and which are needed to activate oxygen [40]. Nonetheless, NADPH is unable to directly give electrons to CYP3A; rather it is done through CPR which is a flavoprotein involved in the endoplasmic reticulum membrane. FAD and FMN cofactors are embedded in CPR and help to transfer the electrons sequentially to the CYP3A heme iron to convert Fe³⁺ to Fe²⁺ and then binds and activates the oxygen molecules [41]. Catalytic cycle occurs in steps of binding substrate, transfer of electrons, activation of oxygen and development of an extremely active iron-oxo complex that oxidizes or hydroxylates the substrate in other ways [42]. In case CPR expression or activity is impaired, CYP3A is unable to effectively accept electrons, which decreases drug metabolism and promotes the formation of reactive oxygen species by uncoupling reactions [43]. CPR genetic variation in POR gene has been found to modify the CYP3A activity that causes clinically significant changes in pharmacokinetics and drug response [44]. In this way, the redox

needs of CYP3A rely on the presence of NADPH and CPR as its involvement in xenobiotic metabolism and drug detoxification [45]. These differences are depicted in figure 1, where the patterns of developmental expression, substrate specificity, regulatory factors, and redox requirements of CYP3A4, CYP3A5, and CYP3A7 in the liver metabolism are possible.

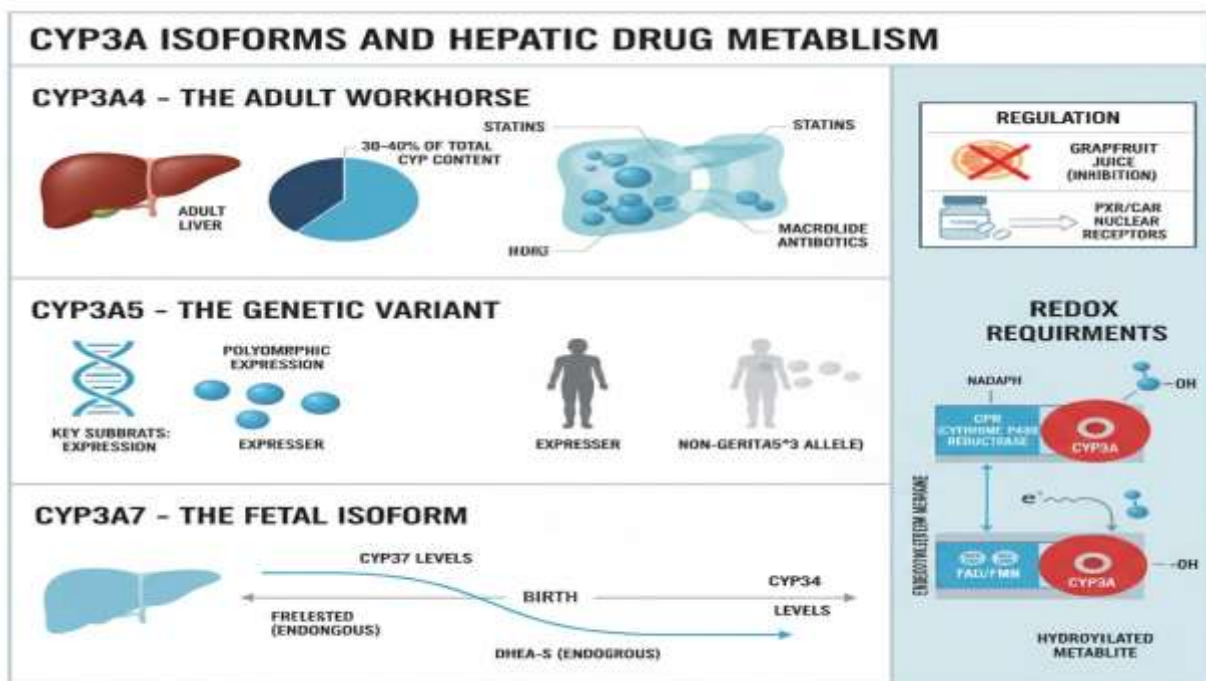


Figure No.: -1. The diagram demonstrates how CYP3A isoforms function in liver drug metabolism. The diagram shows that CYP3A4 serves as the main enzyme which metabolizes 30 to 40 percent of pharmaceuticals. The diagram shows that CYP3A5 functions as a genetic variant while CYP3A7 operates as the fetal isoform which develops into CYP3A4. The study identifies three control elements which include PXR/CAR nuclear receptors and grapefruit juice dietary blockers and the fundamental redox elements that include NADPH and CPR and FAD/FMN which scientists need to conduct their experiments.

METABOLIC REWIRING OF PPP IN EARLY LIVER PATHOLOGIES

Early Liver Pathologies Associated with PPP Alterations

Research shows that early liver pathologies which include non-alcoholic fatty liver disease (NAFLD) and early-stage non-alcoholic steatohepatitis (NASH) and viral hepatitis and drug-induced liver injury (DILI) display increasing connections to metabolic disruptions that affect the pentose phosphate pathway (PPP) because this metabolic change leads to different NADPH levels and redox equilibrium which results in oxidative damage and disease advancement [46]. In NAFLD, hepatocytes use PPP pathways to produce NADPH, which enables them to make fatty acids and protect themselves from oxidative damage, but their high NADPH levels lead to excessive fat production which causes more liver fat accumulation [47]. Early-stage NASH displays disrupted PPP function through its modification of oxidative and non-oxidative pathways which results in decreased antioxidant protection and increased lipid peroxidation and inflammation [48]. The early stages of viral hepatitis show this development because PPP activation happens through viral replication. Host metabolism gets exploited by HBV and HCV to produce ribose-5-phosphate which functions as a building block for nucleotide synthesis. This process enables viral genome replication while it raises oxidative stress levels in hepatocytes [49]. Hepatotoxic drugs cause drug-induced liver injury by damaging PPP enzymes, which leads to decreased NADPH production. This results in reduced glutathione regeneration, which makes hepatocytes more susceptible to oxidative damage from reactive oxygen species [50]. The rewiring of PPP in these conditions shows that this process controls two functions, which are biosynthesis and redox homeostasis. The modulation of this process can function as a biomarker for early liver disease while it serves as a therapeutic target for treatment [51].

Molecular Drivers of PPP Reprogramming

Oxidative stress together with inflammatory signaling pathways and insulin resistance serve as fundamental molecular factors which cause pentose phosphate pathway (PPP) reprogramming to occur in liver disease. The increased production of reactive oxygen species (ROS) in hepatocytes leads to an increase in PPP activity which creates NADPH needed for glutathione regeneration and antioxidant defense. The body uses this compensatory mechanism to protect itself, but its continuous use results in lipogenesis and fibrosis development which affects the course of the illness [52]. Inflammatory signaling through TNF- α and IL-6 cytokines activates PPP flux in liver macrophages (Kupffer cells), which boosts NADPH production needed for ROS and nitric oxide synthesis that helps keep immune cells active while damaging hepatocytes and driving the shift from NAFLD to NASH [53, 54]. Insulin resistance leads to changes in glucose metabolism because it shifts glucose-6-phosphate from glycolysis to PPP, which helps create necessary materials while maintaining redox equilibrium during times of metabolic stress. This metabolic transformation results in increased fatty acid production, which worsens liver fat accumulation while disrupting typical energy processing. The hepatic aldose reductase-driven PPP activity creates a Warburg-like effect which causes insulin resistance and fatty liver development [55, 56].

Key Enzymes Involved in PPP Rewiring

The enzymes glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, and the non-oxidative branch enzymes transketolase and transaldolase drive pentose phosphate pathway (PPP) metabolic changes in liver diseases according to [57]. The rate-limiting enzyme of PPP G6PD controls the first step which produces NADPH through its enzymatic activity because upregulation of this enzyme strengthens both antioxidant protection and fat production in the body. The continuous activation of this enzyme leads to fatty liver disease and liver fibrosis while the absence of G6PD makes people more vulnerable to viral hepatitis and oxidative harm from medications according to [58, 59]. The enzyme 6PGD performs oxidative decarboxylation which transforms 6-phosphogluconate into ribulose-5-phosphate while producing NADPH and when its activity becomes unregulated it damages redox balance and nucleotide production which leads to metabolic distress. The research demonstrates that 6PGD inhibition prevents tumor cells from growing while it affects AMPK/mTOR signaling pathways which connect PPP flux to metabolic changes according to [60, 61]. The non-oxidative branch uses transketolase and transaldolase to convert sugar phosphates into nucleotide and glycolytic intermediate compounds according to [62]. Transketolase generates ribose-5-phosphate for DNA/RNA synthesis through its activity while transaldolase enables the body to use different energy sources according to [63]. The enzymes become unbalanced which leads to the development of hepatocellular carcinoma and genomic instability. Transketolase deficiency leads to changes in nucleotide pools which results in protection against DNA damage but disrupts the metabolic equilibrium of hepatocytes according to [64].

IMPACT OF PPP REWIRING ON CYP3A-MEDIATED DRUG METABOLISM

NADPH Availability and CYP3A Catalytic Efficiency

Rewiring of the pentose phosphate pathway (PPP) significantly affects the drug metabolism catalyzed by CYP3A by directly controlling the cellular NADPH. NADPH is required as a reducing cofactor in cytochrome P450 catalytic pathways, as well as those in CYP3A isoforms. In physiological conditions, the oxidative stage of PPP has a balanced NADPH/NADP⁺ ratio keeping the efficient transfer of electrons between cytochrome P450 reductase and the CYP3A enzymes [65]. Nevertheless, as liver pathologies and metabolic stress emerge in the early stages, the PPP flux does change, causing a substantial change in the intracellular NADPH/ NADP⁺ balance [66]. Such alterations can either transiently increase or permanently impair the CYP3A catalytic activities, depending on the degree and duration of rewiring metabolism. The modulations in the ratio of NADPH and NADP⁺ have a direct effect on the catalytic activities of CYP3A enzymes. In the monooxygenation reaction cycle involved in the catalytic activities of CYP3A enzymes, the catalytic activities require enough NADPH. It has been established that if the amount of NADPH is limited, this limits the rate of oxidation of the substrates and more enters an uncoupling reaction for producing ROS instead of metabolites [67]. However, a high amount of NADPH, because of activated PPP, can lead to constant activity of CYP3A enzymes, culminating into instability and altered expression due to oxidative imbalance and subsequent oxidative stress [68]. In vitro liver disease models have shown that impaired NADPH homeostasis hampers CYP3A turnover, which disrupts the pharmacokinetic pharmacodynamics of drugs and increases interindividual variation in pharmacodynamics [69].

Oxidative Stress and CYP3A Expression

Oxidative stress controls CYP3A expression through two different types of regulatory mechanisms which include transcriptional methods and post-translational methods. Redox-sensitive transcription factors such as Nrf2, PXR, and CAR play central roles: Nrf2 activation under oxidative stress enhances antioxidant gene expression but can repress CYP3A transcription to limit ROS generation [70] while PXR a ligand-activated nuclear receptor modulates CYP3A inducibility and is sensitive to redox changes that alter its cross-talk with other nuclear receptors [71]. Oxidative stress affects CAR activity, which results in changes to both its nuclear translocation and its ability to control CYP3A transcription, which consequently impacts the process of xenobiotic metabolism. The metabolic activity of CYP3A enzymes is controlled through transcriptional methods, while they also undergo post-translational modifications (PTMs) which include phosphorylation, ubiquitination, and nitrosylation, that affect their enzyme stability and energy production capabilities [73]. The process of phosphorylation creates changes in substrate specificity, while ubiquitination directs CYP3A proteins for degradation through the proteasomal system, and nitrosylation prevents catalytic activity during times of oxidative stress [74].

Altered Drug Clearance in Early Liver Disease

Early liver disease changes the drug clearance by affecting the hepatic metabolism as well as decreases the protein binding and changes the distribution of drugs, resulting in slower elimination and wide dispersion of drug clearance across the patients. The unpredictable nature of dosing leads to increased danger of toxic effects. The first three stages of development restrict the hepatic elimination of high-extraction drugs because they block blood circulation together with CYP450 enzyme activity and its respective enzyme functions [75]. Hypoalbuminemia reduces the binding of acidic drugs such as warfarin and phenytoin to proteins and raises the levels of free drugs and toxicity [76]. Ascites increases the distribution of hydrophilic medications including aminoglycosides and this changes half-life and plasma concentrations [77]. Additional effects of portal hypertension and gastrointestinal alterations are observed on drug absorption [78]. The interindividual variability is since CYP450 isoenzymes respond differently in diazepam clearance is slowed down and lorazepam (glucuronidase) is not as affected [79]. Child-Pugh classification of patients with similar diagnoses can exhibit varying pharmacokinetic profiles causing the dose-response relationships to be unpredictable [80]. Portal-systemic shunt bypasses the hepatic metabolism, which elevates systemic drug exposure [81], whereas genetic diversity in hepatic enzyme expression and transporter activity has been found to be the cause of unpredictable drug efficacy and adverse drug reactions [82]. Figure 2 depicts these mechanistic connections, in which the PPP derived NADPH sustains the CYP3A activity in physiological conditions but gets dysregulated during metabolic stress directly causing oxidative stress, transcriptional and post translational regulation of CYP3A, as well as altered drug clearance in early liver disease.

IMPACT THE PPP REWIRING ON CYP3A-MEDHATED DRUG METADOLISM AND CLEARANCE

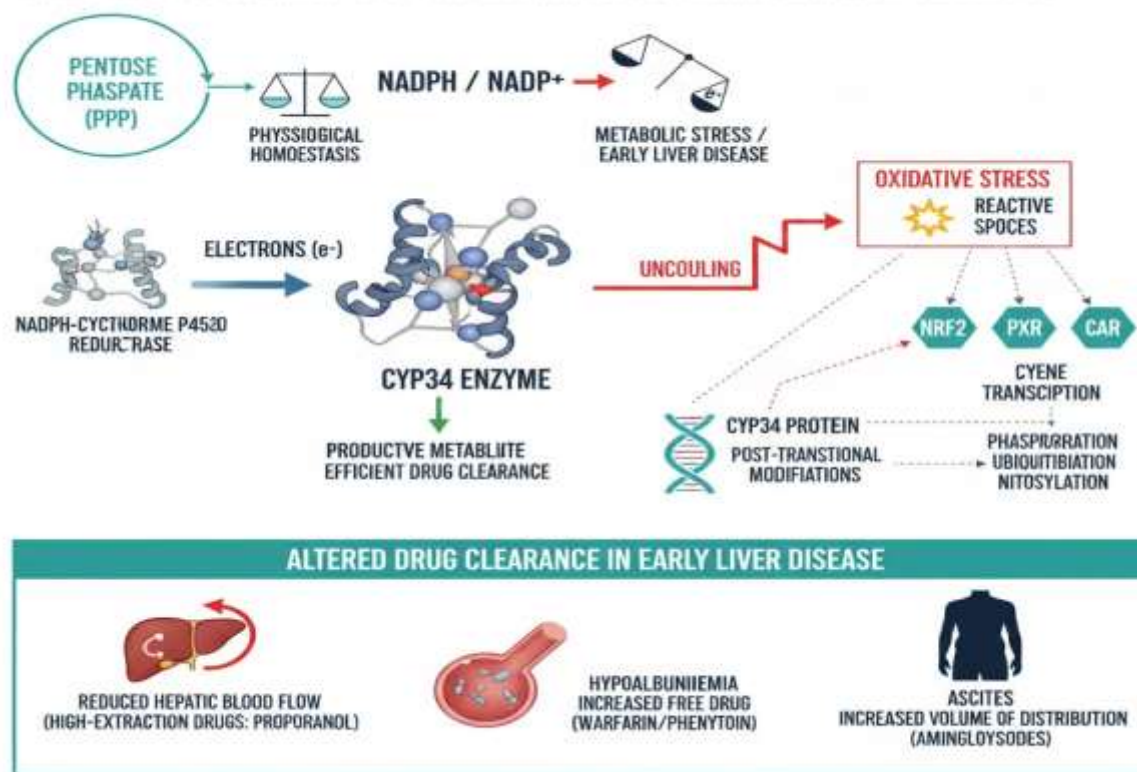


Figure No.: -2. This figure shows the effect of alterations in the pentose phosphate pathway on the metabolism of CYP3A drugs and clearance during the early stages of liver disease. It discusses the role of the balance of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and nicotinamide adenine dinucleotide phosphate (NADP+), the role of metabolic stress, and the roles of different transcription factors such as NRF2, PXR, and CAR in the stabilization of CYP3A enzymes. It also shows the effect of liver physiology, such as blood flow, hypoalbuminemia.

EXPERIMENTAL EVIDENCE LINKING PPP AND CYP3A REGULATION

In Vitro Studies

There is experimental data indicating that the pentose phosphate pathway (PPP) and the regulation of CYP3A are linked. Studies using human hepatocytes, HepG2 and Huh7 cell lines and induced pluripotent stem cell (iPSC) derived hepatocytes, in both in vitro and in vivo animal models have provided supporting evidence to the link between these two metabolic pathways. There are also 3D spheroid hepatocyte cultures which have shown that the activity of the PPP impacts the induction of CYP450s and their metabolism by demonstrating that rifampicin and paclitaxel regulate the activity of CYP3A via PXR/CAR pathways, also in a manner dependent on the activity of the PPP [83-85].

In Vivo and Animal Models

Animal models of NAFLD have shown that high fat diets can induce metabolic stress and impair the pentose phosphate pathway (PPP) thus leading to decreased CYP3A activity without regulation by the PXR [86], while also demonstrating that the induction of liver injury through the use of carbon tetrachloride and other hepatic toxins causes down-regulation of CYP3A expression via oxidative stress mediated disruption of the PPP [87]. Evidence from porcine studies suggests that PPP-CYP3A regulatory mechanisms relevant to human xenobiotic metabolism are evolutionarily conserved [88]. Genetic and dietary induced NAFLD animal models have also illustrated that dysregulation of the PPP contributes to CYP3A suppression which ultimately impacts pharmacokinetics and individual variability in drug response [89].

Emerging Multi-Omics Approaches

Newer multi-omics methods like metabolomics, transcriptomics, and flux analysis are being used more increasingly to analyze liver disease, drug metabolism and regulatory pathways such as PPP-CYP3A interactions. Metabolomics is a procedure that offers detailed profiling of small molecules, which can be used to identify metabolic signatures associated with an impaired clearance of drugs and oxidative stress [90,91]. Transcriptomics enables the high-resolution mapping of the changes of gene expression in CYP enzymes and PPP-related genes, which can display the regulatory networks and interindividual variation [92]. Flux analysis is a method that combines the isotope tracing with computational modeling to measure dynamic metabolic fluxes to relate the activity of PPP to the regulation of CYP3A in normal and diseased conditions [93]. Moreover, trans-omics methods that integrate metabolomics, transcriptomics, and flux analysis in a variety of layers offer a systems level of understanding of drug metabolism and liver pathophysiology connecting the mechanistic knowledge at the molecular and clinical endpoints [94].

CLINICAL AND PHARMACOLOGICAL IMPLICATIONS

Impact on dose optimization and therapeutic drug monitoring

Liver disease is a significant condition that changes drug pharmacokinetics due to a decrease in hepatic blood flow, changes in enzymes and protein binding with unpredictable drug clearance and exposure [95]. The alterations render conventional dosing schedules unreliable, particularly those drugs with small therapeutic indices of immunosuppressants, antimicrobials and antiepileptics [96]. Monitoring of therapeutic drugs (TDM) is needed to personalize the doses by keeping plasma drug levels within the therapeutic range, to enhance efficacy and reduce toxicity [97, 98]. High tech approaches like model-based reliable dosing combine indicators of hepatic functionality, population PK models and real-time drug concentration relies on the concept of patient with a liver issue to help in optimum dose and rational dose modification [99].

Risk of drug toxicity and treatment failure

Liver disease alters the hepatic metabolism, thereby predisposing patients to drug retention, high concentrations of free drugs, and extended half-life, leading to severe adverse drug reactions and hepatotoxicity [100]. On the other hand, other causes of subtherapeutic drug exposure and treatment failure include altered absorption, drug-drug interactions, and enzyme changes, especially in critically ill or transplant patients. It has been demonstrated that a lack of consideration of the hepatic dysfunction leads to inadequate concentrations of the pharmacokinetic targets, higher levels of toxicity, and decreased pharmacological outcomes [101]. Guided dosing and close monitoring of the liver functions is hence of great concern to avert drug toxicity as well as therapeutic failure among patients with liver impairments [102].

Relevance for precision medicine in liver disease

The application of precision medicine approaches for treating patients suffering from liver disease focuses on using individualized pharmacotherapy based on patient-specific variables such as hepatic function severity, genetic polymorphisms of the drug metabolizing enzymes and transporters, comorbidities and concurrent medications [103, 104]. There is considerable variability in CYP enzyme activity, transporter expression and compensatory metabolic pathways leading to differences in drug response among patients who exhibit very similar clinical presentation/disease type. The use of pharmacogenomics, functional liver assessment and pharmacokinetic modeling provide clinicians the ability to more accurately predict drug response and tailor pharmacotherapy [105]. Employing these open-ended approaches to treat liver disease will provide better therapeutic outcomes, decrease adverse drug reactions and constitute a significant advance in providing care to patients with liver disease [106].

THERAPEUTIC AND DIAGNOSTIC PERSPECTIVES

Targeting PPP enzymes to restore redox balance

The therapeutic value of targeting the essential pentose phosphate pathway (PPP) enzymes glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase (6PGD) arises from their crucial function in producing NADPH which maintains intracellular redox balance and supports glutathione-based antioxidant protection [107]. As shown in experimental research, PPP enzyme pharmacological inhibition or modulation of NADPH availability, oxidative stress-induced pathological signalling reduction and cellular survival during disease conditions such as cancer

and metabolic conditions [108,109]. The possibility of redox imbalance and metabolic flux disruption using small-molecule 6PGD inhibitors as well as 6-aminonicotinamide has been demonstrated in preclinical models, which implicates PPP enzymes as potential therapeutic agents to help redress redox balance in disease states of oxidative stress and metabolomics disregard [110].

Biomarkers of PPP rewiring for predicting CYP3A activity

The hepatic PPP (pentose phosphate pathway) has been mechanically associated with changes in the supply of NADPH, the signaling of inflammatory cytokines and the pathways involved in response to stress, which means that components of the PPP are considered potential biomarkers for predicting how CYP3A will metabolize drugs [111]. Inconsistent findings have shown that if sufficient PPP flux is inhibited, this can downregulate CYP3A through mechanisms dependent on $\text{chk2/p53/NF-}\kappa\text{B}$, which affects the clearance of drugs and makes patients more likely to have drug-induced injuries to the liver [111,112]. Improved metabolomics and pharmacometabolomics have also identified endogenous metabolites, ratios of steroid hormones, and signatures related to redox potentials that are connected to CYP3A activity; therefore, by combining these markers with expression profiles of the PPP enzymes, it may be possible to better predict the differences between people in their ability to metabolize drugs and how they will respond to them [113,114].

Implications for drug development and regulatory science

The study of PPP-CYP3A crosstalk reveals its potential impact on both pharmaceutical research and drug approval processes because PPP activity changes result in different effects on drug development through its impact on redox control and liver enzyme activities [115]. The use of PPP biomarkers together with metabolomic information in preclinical research and early clinical trials will enhance the ability to predict how drugs will behave, how they will interact with other drugs, and their potential to cause liver damage especially for drugs that are mainly metabolized through CYP3A [116]. The regulatory frameworks have started to acknowledge systems pharmacology and multi-omics methods which involve PPP activity evaluation as valuable tools for determining appropriate dosages and identifying suitable patients while assessing the potential benefits and risks of treatments that support precision medicine-based drug approval methods [117,118].

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Lack of human longitudinal data

A significant knowledge gap with regard to the pentose phosphate pathway (PPP) rewiring and its effects on CYP3A-mediated drug metabolism is that there are no human studies following the same individuals over long periods that measure the metabolic flux, redox status, and pharmacokinetic changes [47]. Most of the mechanistic evidence that links PPP activity, NADPH homeostasis, and CYP3A regulation comes from in vitro systems or short-term animal studies, which fail to account for the disease progression, adaptive metabolic responses, and interindividual variability that are typical of chronic liver disease and metabolic disorders situations [108]. The lack of long-term human data is one of the factors that hinders a causal explanation, postpones the validation of biomarkers, and limits the use of PPP-related discoveries for clinical decision making in dose adjustment and therapeutic monitoring [104].

Need for integrative metabolic–pharmacokinetic models

Most of the current pharmacokinetic models do not adequately reflect the dynamic metabolic rewiring that occurs, for instance, changes in the PPP, and thus there is a requirement for the development of integrated metabolic-pharmacokinetic modeling strategies that combine redox biology, NADPH availability, and enzyme regulation [119]. The combination of systems pharmacology and physiologically based pharmacokinetic (PBPK) models that consider the PPP-modulated CYP3A activity could have a great impact on the prediction of drug clearance variability, exposure, response relationships, and toxicity risk in patients with metabolic or hepatic dysfunction [120]. These kinds of integrative modeling approaches would make it possible to simulate disease-associated metabolic conditions and the changes in hepatic function over time, thus fostering precision dosing strategies that go beyond the traditional static PK models [121].

Translational challenges and research priorities

Translational application of PPP-focused discoveries is hampered by several issues such as the lack of standardization of biomarkers derived from the PPP, differences between species in the regulation of the pathway, and doubts about the

clinical significance of modulating the PPP to affect CYP3A-dependent drug metabolism [65]. Major points of focus for research include confirming PPP-related metabolic and redox biomarkers in a sufficiently characterized group of patients, combining multi-omics data with clinical pharmacokinetics, and a thorough assessment of the use of pathway-targeted therapies for their drug, drug interaction potential [122]. Resolving these issues will necessitate collaboration amongst basic research, clinical pharmacology, and regulatory science to bring about PPP-informed methods in drug development, safety, assessment, and personalized therapy [117].

CONCLUSION

The pentose phosphate pathway is one of the main metabolic pathways which plays a role in the regulation of liver redox homeostasis as well as drug metabolism through its effect on NADPH supply and the balance of oxidative stress. There is more evidence that changing PPP can have a strong effect on the expression and functioning of CYP3A, thus changing drug clearance, leading to altered therapeutic efficacy and risk of toxicity, especially in the case of liver disease. The experimental research has been able to explain the main mechanistic relations between the PPP flux, redox signaling, and regulation of CYP3A, however, human data are very limited and still integrative metabolic, pharmacokinetic models are missing, which prevent the clinical application of these findings thus far. Metabolomics, systems pharmacology, and precision dosing frameworks development might be used to help biomarker-driven drug response prediction and targeted therapy adjusting personalized treatment at a single cell level. PPP-informed therapeutic drug development, monitoring, and personalizing medicine for hepatic patients can be significantly improved if focusing the research on increasing the level of evidence for clinical use and regulatory acceptance.

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