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Drug metabolism and cytochrome P-450 (CYPs)

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Abstract

Cytochrome p-450 (CYPs) convert xenobiotics, chemicals, and drugs in the liver into intoxic materials that can be easily eliminated in the body. However, these CYPs sometimes mediate fatal diseases by converting drugs (for instance, paracetamol) into toxic substances that cannot be eliminated or excreted quickly from the body and hence cause hepatocyte damage that decreases the function of the liver. This article review aimed to determine the history, nomenclature, family, and subfamily of CYPs and mainly stress cytochrome P450 roles in drug metabolism. Some toxic byproducts induce autoreactive antibodies by binding to the CYPs, which causes further damage to hepatocytes. The most common causes of liver damage are type II autoimmune hepatitis, drinking alcohol, and free radicals, which cause DNA mutations. Another condition that leads to liver damage is the inability of the liver to detoxify the drug, which leads to further damage to the liver. There are some isoforms of CYPs, such as 3A, 1A, and 2C19, that are severely affected when the liver is no longer able to relieve toxic products, but some isoforms of CYPs are less affected during damage to the liver, which includes 2E1, 2D6, and 2C9. There are parameters for the involvement of CYPs in liver disease, depending on the cause of the damage, which is either drugs or alcohol. Thus, further research must be done to know the exact etiology and management of the diseases related to liver damage through CYPs.

Keywords: Cytochrome P450; Disease; Free radical; Hepatocyte; Liver.

Introduction

Cytochrome p-450 (CYPs) convert xenobiotics, chemicals, and drugs in the liver into intoxic materials that can be easily eliminated in the body[1]. Most of the drugs are lipid-soluble and accumulate in the endoplasmic reticulum of the hepatocyte. If they aren't detoxified, they cause liver damage.[2] Usually, drug metabolism is split into two stages. The first stage depends on CYPs, alcohol dehydrogenases, aldehyde dehydrogenases, monoamine oxidases, and xanthine oxidases. The second stage depends on other enzymes, most notably sucfotransferases (SULTs).[3]

Many researchers focused on phase I drug metabolism, especially CYPs, as they have crucial roles, including detoxification of toxic materials, conversion of lipid-soluble vitamins into water-soluble vitamins (otherwise they induce hepatocyte damage), and oxidation of lipid-soluble drugs into water-soluble drugs to prevent the formation of toxic free radicals such as ROS and RNS. [4]

The most common causes of liver damage are type II autoimmune hepatitis, drinking alcohol, and free radicals, which cause DNA mutations. Another condition that leads to liver damage is the inability of the liver to detoxify the drug, which leads to further damage to the liver. For instance, some toxic byproducts bind with CYPs to produce haptogens that induce auto

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reactive antibodies, which in turn cause severe damage to hepatocytes. Examples of such drugs are tienilic acid and hydralazine.[6] Autoimmune hepatitis is a type of hypersensitivity disease in which the immune complex circulates in the body, attaches to liver cells, and causes damage to them.[7] Furthermore, some diseases, such as hypertriglyceridemia, obesity, and diabetes, induce non-alcoholic steatohepatitis (NASH), in which CYPs are involved.[8]

Thus, the present study aimed to focus on the history, nomenclature, family, and subfamily of CYPs and mainly stress cytochrome P450 roles in drug metabolism.

Cellular composition of the liver

The liver is considered the largest internal organ in humans and is composed of lobes that are further subdivided into lobes. The liver stores sugar in the form of glycogen, and it is the main site for the metabolism of a wide variety of drugs.[9] The large volume of the liver is due to its important role in the body.[10] About 80% of the liver is composed of hepatocytes, and the rest is non-parenchymal cells, which include the satellate cell, kupffer cell, and endothelium.[11] The histology and anatomy of the liver are shown in Figure 1.

The parenchymal cell, or hepatocyte, is the most important for the creation of essential molecules like cholesterol and the degradation of drugs and toxins, while the endothelium acts as a selective barrier for filtering molecules into the liver. The Kuppler cell is a phagocyte that breaks down microbes, and phagocytosis occurs to eliminate the microbe.[12] Inside the liver, especially the endoplasmic reticulum (ER), there are two main groups of enzymes that work in both phases (I and II) of drug metabolism. The key enzymes for phase I metabolism are CYPs, while phase II enzymes aim to make lipid-soluble substances conjugated and converted to water-soluble substances so that they can be easily eliminated in urine or bile.[13]

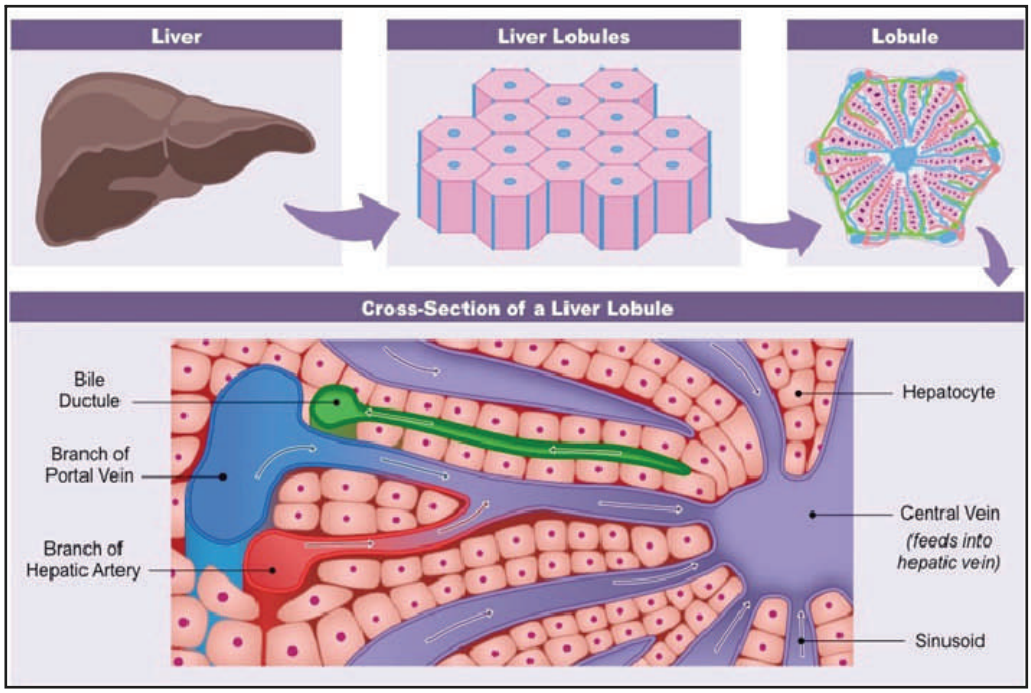

Figure 1 Anatomy and histology of the liver.

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Phases of drug metabolism

There are two phases of drug metabolism: phase I, which depends mainly on CYPs, alcohol dehydrogenases, aldehyde dehydrogenases, monoamine oxidases, and xanthine oxidases, and phase II, which depends on enzymes like UDP-glucuronosyltransferases (UGTs), N-acetyltransferases (NATs), glutathione S transferases (GSTs), and sulfotransferases (SULTs). Figure 2 shows the enzymes of both phases, while Figure 3 shows the role of each phase.

Many articles and investigations in the literature focused on phase I, especially the CYPs, as most of the detoxification occurs by this enzyme in phase I drug metabolisms.[14] However, other enzymes such as xanthine oxidase (XAO), alcohol dehydrogenase, monoamine oxidase, aldehyde dehydrogenase (ALDH), aldehyde oxidase (AO), and flavin monooxygenases (FMO) are also important. [9] Conversely, less focus on phase II drug metabolism is observed among researchers, as there is a rare drug interaction in phase II metabolism. The importance of this phase enzyme appears in non-human mammals like cats, in which sometimes the phase II UGTs are expressed in low quantity and produce serious side effects in which lipid-soluble drugs cannot convert into water-soluble ones, and UGTs, NATs, SULTs, and GSTs are the basic enzymes that are involved in the phase II metabolism of drugs.[3]

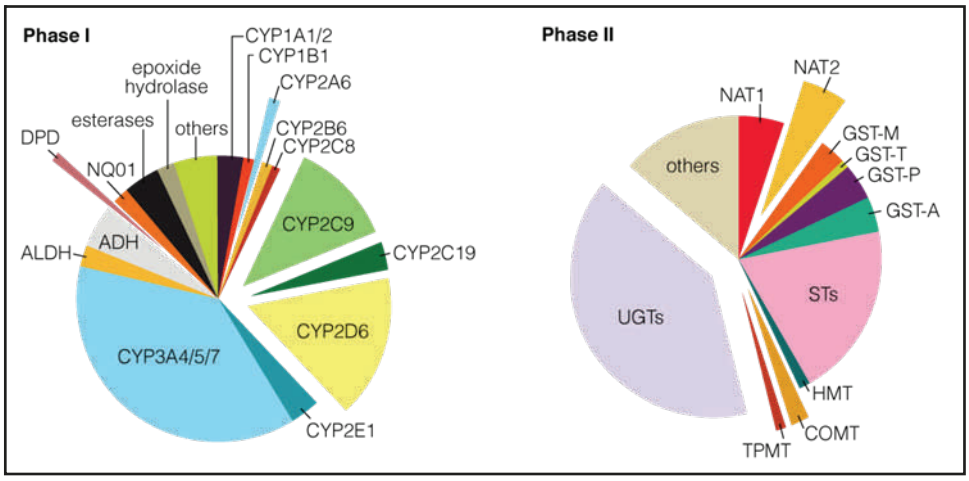

Figure 2 The percentage of enzymes participitate in phase I and II drug metabolism.

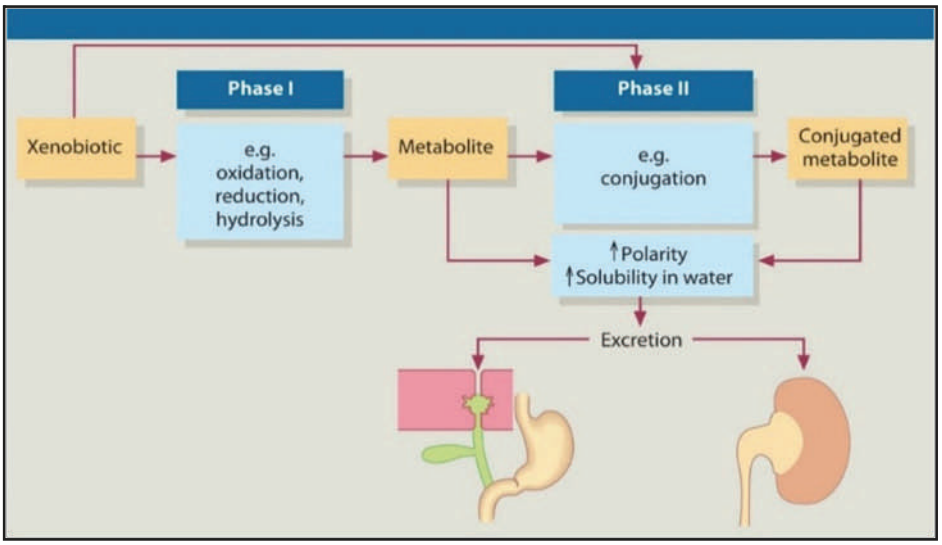

Figure 3 liver biotransformation of xenobiotics.

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Cytochrome P450

This enzyme was discovered for the first time in 1957 by Klingenberg in the microsome of the rat. It belongs to the oxygenase group of enzymes that add oxygen to a substrate. This enzyme is more abundant in plants than animals; in the latter group, the number is nearly 57, but this number is higher in plants because of the diversity of their functions.[16] This enzyme is not just found in eukaryotic-like animals and plants; it is also found in Archaebacter.[17] It was termed CYPs because it was read spectrophotometrically at 450 nm. At this wavelength, CYPs react with CO to form a complex that was read by a spectrophotometer, and the P is derived from the pigment, which for the first time was extracted.[18] The CYPs catalyze the monooxygenase reaction in which the substrate is oxidized and water is formed, and they need the coenzyme NADH, as illustrated in the following chemical reaction.[19]

$$RH + O2 + NAD(P)H + H+ \rightarrow ROH + H2O + NAD(P)+$$

For the purpose of classification, the CYPs are divided into groups: Class I is found in prokaryotes and functions as an antimicrobial, while Class II is found in eukaryotes.[20]

Cytochrome P450 Structure

The synthesis of CYPs resembles that of nitric oxide, while it resembles the peroxidase enzyme in that it has a heme b group as found in myoglobin in muscle and hemoglobin in RBC. Iron constitutes the center of heme b, which is bound to protoporphyrin IX by the sulfur group, as shown in Figure 4, and it is found in eukaryotic microsomes like ER and mitochondria.[18]

Cytochromes P450 Nomenclature

The two researchers, Lipman and Wilbur, set the rule, which displayed that CYPs that are similar in the gene protein family by about 36% were grouped in the same family and those that resemble in the gene protein family by 70% were grouped in a subfamily. This rule was accepted by an international workshop on CYPs, which was held in the USA, Virginia, in 1985, under the name "P450 Genes and Their Regulation.[21] The Roman number was designed for families, but capital letters were utilized for subfamilies and Arabic numbers for genes alone. Later on, this rule was edited, in which CYPs that are similar in gene protein by about 40% were grouped in the same family and those that are similar in gene protein by 55% were grouped in subfamilies, and an Arabic number was used for each family.[22] Recently, there are about eighteen families of CYPs, but only families 1–3, and some of the families 4 are essential for the metabolism of xenobiotics like drugs, pesticides, and chemicals.[23]

Distribution of CYPs in the Human Body

CYPs are found nearly in all regions of the human body but are highly expressed in the liver, which adds oxygen to substrates like endogenous substances like bile, arachidonic acid, and steroid molecules,

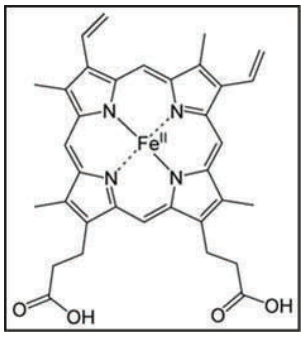

Figure 4 Chemical structure of heme (b).

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or xenobiotics like drugs and pesticides. Lungs and intestines have the second-highest contents of CYPs after the liver.[24] CYPs in the cardiovascular system act as protection for blood vessels and the heart; in the brain, they maintain blood flow; and in the reproductive system, they are involved in the destiny of germ cells.[25, 24] CYPs are found in the microsome, especially in the ER and mitochondria; nearly ten percent of all human CYPs are found in mitochondria. The function of mitochondrial CYPs is the metabolism of endogenous molecules like Vitamin D and steroids, but if they are involved in xenobiotics like drugs and pesticides, they produce diseases that are not normal. Besides the mentioned location, the CYPs are also found in the nucleus.[26]

The Catalytic Cycle of CYPs

Mixed-function oxidase (MFO) enzymes carry electrons from oxygen to the substrate with the help of NADPH oxidoreductase and CYP b5.[18] The CYPs, which are effective in electron transport from NADH to the substrate, also need FAD and FMN as coenzymes, and adrenal CYPs need adrenodoxin reductase and adrenodoxin in addition to NADPH. Pseudomonas putida is the first bacteria in which CYPs are discovered, which is similar to mitochondrial CYPs in action that transfer electrons from NADH via putidaredoxin that contain iron-sulfur to CYPs.[27] Figure 5 shows the summary activity of CYPs.[18]

Inhibition and induction of Cytochromes P450

There are three critical steps in CYPs that are subjected to inhibition by different agents, including competition with the substrate that recovers after the action of inhibitors, irreversibly binding with the heme iron atom of CYPs, and agents like tamoxifen, chloramphenicol, and acetylenes that induce substrate oxidation that irreversibly inactivates the enzyme.[28] Regulation of the expression of CYPs is vulnerable to xenobiotic exposure, which causes the cell to increase the amount of CYP enzymes to promote the removal of the toxicant. Induction is mainly a defensive mechanism that improves the detoxification process.[18]

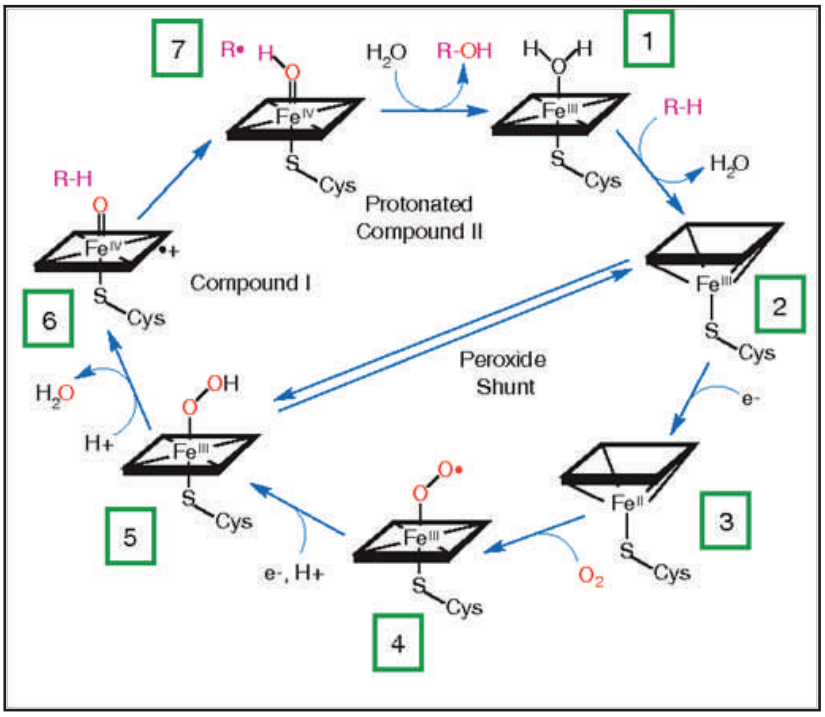

Figure 5 The catalytic cycle of cytochrome P450.

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Human P450s

There is more research on human P450s than on other mammal CYPs due to their link with human diseases, and most of the drugs that are administered to humans are detoxified by CYPs.[29] The number of genes that are related to CYPs is more than fifty-seven, including both structural and regulatory genes. The most important CYPs belong to four families: CYP1, CYP2, CYP3, and CYP4. More drug interactions occur in these four families.[30]

The CYP1 family

This family is highly correlated to the metabolism of polycyclic aromatic hydrocarbons (PAHs) and carcinogenic molecules that humans eat in their lives.[31]

The family of CYP2

The CYP2 family involves a more diverse group of CYP, which occupies half of drug metabolism. The property of the substrate that is metabolized by this family of CYP is medium- or small-molecular-sized molecules, and the most important subfamilies of this group include CYP2C9, CYP2C19, CYP2D6, and CYP2E1.[32]

The CYP3 family

The most important subfamilies of this group are CYP3A4 and CYP3A5, which are involved in drug metabolism in the liver, while others like CYP3A7 and CYP3A43 are present in the fetus and liver, respectively.[33]

The CYP4 family and Orphan Cytochromes P450

There are fifty-seven 'P450' genes in the human genome, of which at least 13 can be considered 'orphans', and the orphan P450s are so-called because their rules, patterns of expression, and functional details are still largely unknown.[34] Information about their mRNA expression and potential substrates is available for some of the orphan P450s, although very limited information about isoforms 3A43, 4A22, 4F22, 20A1, and 27C11 is available.[35]

Hepatic diseases and cytochrome P450

The toxicity of the drug in the liver is due to the main function of the liver, which is the place of detoxification, and if the drug causes damage to the liver, then the body will suffer from toxic by-products of the drug.[36] The type of drug-induced liver injury is shown in Table 1.

There are more than 1000 drugs that lead to drug injuries, which account for 10% of autoimmune hepatitis and 50% of liver failure.[37] of these two groups of hepatic diseases are due to taking drugs; the idiosyncratic drug causes 75% of liver failure and needs liver transplantation; otherwise, it leads to death.[38] The mortality rate of drug-induced liver damage is about 10% around the world, and one of the causes of liver damage is renal failure

Table 1 Types of drug-induced liver injury.

TYPE	ENZYMATIC PROFILE	PROGNOSIS
HEPATOCELLULAR	ALT > 2ULN Serum ALT/Serum Alk. Phos ≥ 5*	More severe prognosis
CHOLESTATIC	Alk Phos ≥ 2ULN Serum ALT/Serum Alk Phos ≤ 2*	More prone to chronic disease
MIXED	ALT > 2 ULN Serum ALT/Serum Alk Phos between 2 and 5*	More prone to chronic disease

*The values in the ratios are expressed as ULN multiples.
ALT = alanine aminotransferase; ULN = upper limit of normal; Alk Phos = alkaline phosphatase.

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because some drugs need kidneys to be eliminated in the body, which means if they don't filtrate in the kidney, they accumulate in the liver and cause liver damage.[39]

Some drugs are still on the market for the treatment of the disease; besides, they cause liver damage because there are no alternatives, but the patients need to screen their blood by evaluating liver enzymes like ALT and AST.[40]

Drug-induced liver injury (DILI) sometimes produces subclinical symptoms leading to death due to liver failure.[41] As mentioned, some drugs are withdrawn from the market due to harmful effects on the liver, and others even withdraw from clinical trials before going to market due to severe damage to the liver. Taking a lot of paracetamol is the most common way that drugs can cause hepatitis. Paracetamol is changed by CYP2E1 into NAPQI (N-acetyl-p-benzoquinone imine) metabolites, which then attach to reduced glutathione (GSH) and form a less harmful product while slowing down the rate of GSH. NAPQI will produce oxidative stress, and free radicals will attach liver cells and cause severe liver damage.[42] Some drugs can jump T-cell activation, which leads to the huge production of antibodies that attach CYP enzymes, leading to drug accumulation and drug toxicity, which means the drug itself is toxic, not its metabolites. For example, if auto-antibodies damage CYP2D6, perhexiline accumulates in the liver, causing severe liver damage and producing alcohol-like-induced liver damage.[43]

Liver transplantation and CYPs

Transplantation can be defined as the transfer of cells, tissue, or organs from one person, who is called the donor, to another person, who is called the recipient.[44] Immunology plays an important role in transplantation rejection, and CYP also plays an important role in transplantation rejection; for example, some CYPs are down-regulated or over-expressed after organ transplantation.[45] CYP2E1 is highly expressed after one month of liver transplantation by evaluation of the metabolic ratio via chlorzoxazone.[46]

CYP3A4 is also up-regulated in liver cells ten days after liver transplantation, and it will return to normal after half a year. The reason for the over-expression of the CYP3A4 is due to taking a high dose of steroids (prednisone) as an immunosuppressant, which is a potent inducer for the CYP3A4.[47]

The expression of CYP2D6 is changed after liver transplantation, which has a main role in the metabolism of anti-depressants and opioids. The polymorphism of CYP2D6 is very important in developing schizophrenia and also has a greater role in the metabolism of other drugs, including beta blockers. While they have no role in the metabolism of cardiovascular drugs and antidepressants.[48]

Conclusion

The present study is a brief review of the history, nomenclature, family, and subfamily of CYPs and mainly focuses on cytochrome P450 roles in drug metabolism. This study concluded the following points: Liver disorders are associated with a decrease in the function of CYP, which can have a direct effect on the metabolism of drugs. The modifications in CYP activity and expression are not only dependent on the severity of the liver disease but also on the etiology of cirrhosis. There is more research on human P450s than on other mammal CYPs. There are more than 1000 drugs that lead to drug injuries, which account for 10% of autoimmune hepatitis and 50% of liver failure. The idiosyncratic drug causes 75% of liver failure and needs liver transplantation. Some drugs are still on the market for the treatment of the disease, and they cause liver damage because there are no alternatives.

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Competing interests

The authors declare that they have no competing interests.

References

1. Kaur G, Gupta S, Singh P, Ali V, Kumar V, Verma MJC, et al. Drug-metabolizing enzymes: role in drug resistance in cancer. Clin Transl Oncol 2020; 10:1667–80. DOI: 10.1007/s12094-020-02325-7.
2. Sahini N, Borlak JJPilr. Recent insights into the molecular pathophysiology of lipid droplet formation in hepatocytes. Prog Lipid Res 2014; 54:86–112. DOI: 10.1016/j.plipres.2014.02.002
3. Jancova P, Anzenbacher P, Anzenbacherova E. Phase II drug metabolizing enzymes. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2010; 154(2):103–16. DOI: 10.5507/bp.2010.017.
4. Wang J, Chen Z, Chen H, Wen YJ. Effect of hydrogen peroxide on Microcystic aeruginosa: Role of cytochromes P450. Total Environ 2018; 626:211–8. DOI: 10.1016/j.scitotenv.2018.01.067.
5. Ramos-TovarE, Muriel PJ. Free radicals, antioxidants, nuclear factor-E2-related factor- 2 and liver damage. J APPL Toxical 2020; 40(1):151–68. DOI: 10.1002/jat.3880.
6. Ma B, Bohnert T, Otipoby KL, Tien E, Arefayene M, Bai J, et al. Discovery of BIIB068: a selective, potent, reversible Bruton's tyrosine kinase inhibitor as an orally efficacious agent for autoimmune diseases. J Med Chem 2020; 63(21):12526–41. DOI: 10.1021/acs.jmedchem.0c00702.
7. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology 2020; 72(2):671–722. DOI: 10.1002/hep.31065.
8. Abdelmegeed MA, Banerjee A, Yoo S-H, Jang S, Gonzalez FJ, Song BJ. Critical role of cytochrome P450 2E1 (CYP2E1) in the development of high fat-induced non-alcoholic steatohepatitis. J Hepatol 2012; 57(4):860–6. DOI: 10.1016/j.jhep.2012.05.019.
9. Almazroo OA, Miah MK, Venkataramanan RJCild. Drug metabolism in the liver. Clin Liver Dis 2017; 21(1):1–20. DOI: 10.1016/j.cld.2016.08.001.
10. Hibi T, Chieh AKW, Chan AC-Y, Bhangui PJIJoS. Current status of liver transplantation in Asia. Int J Surg 2020; 82:4–8. DOI: 10.1016/j.ijsu.2020.05.071.
11. Lauschke VM, Shafagh RZ, Hendriks DF, Ingelman-Sundberg MJ. 3D primary hepatocyte culture systems for analyses of liver diseases, drug metabolism, and toxicity: emerging culture paradigms and applications. Biotech J 2019; 14(7):1800347. DOI: 10.1002/biot.201800347.
12. Deppermann C, Peiseler M, Zindel J, Zbytnuik L, Lee WY, Pasini E, et al. Tacrolimus impairs Kupffer cell capacity to control bacteremia: Why transplant recipients are susceptible to infection. Hepatology 2021; 73(5):1967–84. DOI: 10.1002/hep.31499.
13. Omiecinski CJ, Vanden Heuvel JP, Perdew GH, Peters JM. Xenobiotic metabolism, disposition, and regulation by receptors: from biochemical phenomenon to predictors of major toxicities. Toxicol Sci 2011; 120 Suppl 1:S49–75. DOI: 10.1093/toxsci/kfq338.
14. Wang L, Xu W, Ma L, Zhang S, Zhang K, Ye P, et al. Detoxification of benzo [a] pyrene primarily depends on cytochrome P450, while bioactivation involves additional oxidoreductases including 5-lipoxygenase, cyclooxygenase, and aldo-keto reductase in the liver. J Biochem Molec Toxic 2017; 31(7):e21902. DOI: 10.1002/jbt.21902
15. Guengerich FPJ. A history of the roles of cytochrome P450 enzymes in the toxicity of drugs. Toxical Res J 2020; 1–23. DOI: 10.1007/s43188-020-00056-z.
16. Bathe U, Tissier AJP. Cytochrome P450 enzymes: A driving force of plant diterpene diversity. J Phytochemistry 2019;161:149–62. DOI: 10.1016/j.phytochem.2018.12.003.
17. Kletzin A, Heimerl T, Flechsler J, van Niftrik L, Rachel R, Klingl AJ. Cytochromes c in Archaea: distribution, maturation, cell architecture, and the special case of Ignicoccus hospitalis. Front Microbiol 2015; 6:439. DOI: 10.3389/fmicb.2015.00439.
18. Go R-E, Hwang K-A, Choi K-C. Cytochrome P450 cancers. J Steroid Biochem Mol Biol 2015; 147:24–30. DOI: 10.1016/j.jsbmb.2014.11.003
19. Park H, Park G, Jeon W, Ahn J-O, Yang Y-H, Choi K-YJ. Whole-cell biocatalysis using cytochrome P450 monooxygenases for biotransformation of sustainable bioresources (fatty acids, fatty alkanes, and aromatic amino acids). Bitechnol Advan 2020; 40:107504. DOI: 10.1016/j.biotechadv.2020.107504.
20. Finnigan JD, Young C, Cook DJ, Charnock SJ, Black GW. Cytochromes P450 (P450s): a review of the class system with a focus on prokaryotic P450s. Adv Protein Chem Struct Biol 2020; 122:289–320. DOI: 10.1016/bs.apcsb.2020.06.005.
21. Esteves F, Rueff J, Kranendonk MJ. The central role of cytochrome P450 in xenobiotic metabolism—A brief review on a fascinating enzyme family. J Xenobiot 2021; 11(3):94–114. DOI: 10.3390/jox11030007.
22. Gaedigk A, Ingelman-Sundberg M, Miller NA, Leeder JS, Whirl-Carrillo M, Klein TE, et al. The Pharmacogene Variation (PharmVar) Consortium: incorporation of the human

cytochrome P450 (CYP) allele nomenclature database. Clin Pharmacol Ther 2018; 103(3):399–401. DOI: 10.1002/cpt.910.
23. Waring RHJ. Cytochrome P450: genotype to phenotype. Xenobiotica 2020; 50(1):9–18. DOI: 10.1080/00498254.2019.1648911.
24. Zhang Z, Chen M, Zhang L, Zhao QJBP, Toxicology. The impact of cytochrome 450 and Paraoxonase polymorphisms on clopidogrel resistance and major adverse cardiac events in coronary heart disease patients after percutaneous coronary intervention. BMC Pharmacol Toxicol 2020; 21(1):1. DOI: 10.1186/s40360-019-0378-7.
25. Hatzade KM, Ghatole AM, Gaidhane PK, Gaidhane MK, Gadekar GP. A facile synthesis of some new pyrimidine-2, 4, 6-triones analogs and their O-β-D-glucosides P-glycoprotein and antioxidant, antimicrobial study,blood–brain barrier, cytochrome p450 enzyme activity prediction. Medic Chem Res 2021; 30:163–81. DOI: 10.1007/s00044-020-02649-7
26. Shimada C, Xu R, Al-Alem L, Stasenko M, Spriggs DR, Rueda BR. Galectins and Ovarian Cancer. Cancers J 2020; 12(6):1421. DOI: 10.3390/cancers12061421.
27. Manikandan P, Nagini S. Cytochrome P450 structure, function and clinical significance. Curr Drug Target 2018; 19(1):38–54. DOI: 10.2174/1389450118666170125144557.
28. Lin CY, Huang Z, Wen W, Wu A, Wang C, Niu L. Enhancing Protein Expression in HEK-293 Cells by Lowering Culture Temperature. PLoS One. PLoS One 2015; 10(4):e0123562. DOI: 10.1371/journal.pone.0123562.
29. Yang R, Luo Z, Liu Y, Sun M, Zheng L, Chen Y, et al. Drug interactions with angiotensin receptor blockers: role of human cytochromes P450. Curr Drug Metab 2016; 17(7):681–91. DOI: 10.2174/1389200217666160524143843.
30. Wang C, Becker K, Pfütze S, Kuhnert E, Stadler M, Cox RJ, et al. Investigating the function of cryptic cytochalasan cytochrome P450 monooxygenases using combinatorial biosynthesis. Org Lett 2019; 21(21):8756–60. DOI: 10.1021/acs.orglett.9b03372.
31. G RE, Hwan KA, Choi KC. Cytochrome P450 1 family and cancers. J Biol 2015; 147:24–31. DOI: 10.1016/j.j2sbmb.2015.11.0003.
32. Lim SYM, Loo JSE, Alshagga M, Alshawsh MA, Ong CE, Pan YJTR. In vitro and in silico studies of interactions of cathinone with human recombinant cytochrome P450 CYP (1A2), CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2E1, CYP2J2, and CYP3A5. Toxicol Repor 2022; 9:759–68. DOI: 10.1016/j.toxrep.2022.03.040
33. Guo Y, Lucksiri A, Dickinson GL, Vuppalanchi RK, Hilligoss JK, Hall SD, et al. Quantitative Prediction of CYP3A4- and CYP3A5- Mediated Drug Interactions. Clin Pharmacol Ther 2020; 107(1):246–56. DOI: 10.1002/cpt.1596.
34. Fekry MI, Xiao Y, Berg JZ, Guengerich FP. A Role for the Orphan Human Cytochrome P450 2S1 in Polyunsaturated Fatty Acid ω-1 Hydroxylation Using an Untargeted Metabolomic Approach. Drug Metab Dispos 2019; 47(11):1325–32. DOI: 10.1124/dmd.119.089086.
35. Mo H-Y, Wei Q-Y, Zhong Q-H, Zhao X-Y, Guo D, Han J, et al. Cytochrome P450 27C1 Level Dictates Lung Cancer Tumorigenicity and Sensitivity towards Multiple Anticancer Agents and Its Potential Interplay with the IGF-1R/Akt/p53 Signaling Pathway. Int J Mol 2022; 23(14):7853. DOI: 10.3390/ijms23147853.
36. Shoieb SM, El-Ghiaty MA, Alqahtani MA, El-Kadi AOJP, Mediators OL. Cytochrome P450-derived eicosanoids and inflammation in liver diseases. J Prostaglandins 2020; 147:106400. DOI: 10.1016/j.prostaglandins.2019.106400.
37. Porceddu M, Buron N, Roussel C, Labbe G, Fromenty B, Borgne-Sanchez AJ. Prediction of liver injury induced by chemicals in human with a multiparametric assay on isolated mouse liver mitochondria. Toxical Sci 2012; 129(2):332–45. DOI: 10.1093/toxsci/kfs197.
38. Yokoi T, Oda SJARoP, Toxicology. Models of Idiosyncratic Drug-Induced Liver Injury. Annu Rev Pharmacol Toxicol 2021; 61:247–68. DOI: 10.1146/annurev-pharmtox-030220-015007.
39. Asrani SK, Devarbhavi H, Eaton J, Kamath PSJJoh. Burden of liver diseases in the world. J Heptaol 2019; 70(1):151–71. DOI: 10.1016/j.jhep.2018.09.014.
40. Goorden S, Buffart TE, Bakker A, Buijs MMJNtvg. Liver disorders in adults: ALT and AST. Ned Tijdschr Geneeskd 2013; 157(43):A6443–A. PMID: 24152362
41. Fontana RJ, Hayashi PH, Gu J, Reddy KR, Barnhart H, Watkins PB, et al. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. Gastroen 2014; 147(1):96–108. e4. DOI: 10.1053/j.gastro.2014.03.045.
42. Xie Y, McGill MR, Dorko K, Kumer SC, Schmitt TM, Forster J, et al. Mechanisms of acetaminophen-induced cell death in primary human hepatocytes. Toxicology applied pharmacology. Toxicol Appl Pharmacol 2014; 279(3):266–74. DOI: 10.1016/j.taap.2014.05.010.
43. Jessurun NT, Wijnen PA, Bast A, van Puijenbroek EP, Bekers O, Drent MJ. Tamsulosin Associated with Interstitial Lung Damage in CYP2D6 Variant Alleles Carriers. Int J Mol Sci 2020; 21(8):2770. DOI: 10.3390/ijms21082770.
44. Kargar B, Pishvaee MS, Jahani H, Sheu J-B, Review T. Organ transportation and allocation problem under medical uncertainty: A real case study of liver transplantation. Trans Res 2020; 134:101841. DOI: 10.1016/j.tre.2020.101841

https://doi.org/10.15218/zjms.2024.012

45. Liu J, Ouyang Y, Chen D, Yao B, Lin D, Li Z, et al. Donor and recipient P450 gene polymorphisms influence individual pharmacological effects of tacrolimus in Chinese liver transplantation patients. Int Immunopahrmaco 2018; 57:18–24. DOI: 10.1016/j.intimp.2018.02.005.
46. Harjumäki R, Pridgeon CS, Ingelman-Sundberg MJIJoMS. CYP2E1 in alcoholic and non-alcoholic liver injury. Roles of ROS, reactive intermediates and lipid overload. Int J Mol Sci 2021; 22(15):8221. DOI: 10.3390/ijms22158221.
47. Harskamp RE, Teichert M, Lucassen WA, van Weert HC, Lopes RD. Impact of polypharmacy and P-glycoprotein-and CYP3A4-modulating drugs on safety and efficacy of oral anticoagulation therapy in patients with atrial fibrillation. Cradiovas Drugs Ther 2019; 33(5):615–23. DOI: 10.1007/s10557-019-06907-8.
48. Taylor C, Crosby I, Yip V, Maguire P, Pirmohamed M, Turner RM. A Review of the Important Role of CYP2D6 in Pharmacogenomics. Genes 2020; 11(11):1295. DOI: 10.3390/genes11111295.