

XENOBIOTICS INDUCED LIVER TOXICITY

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ABSTRACT

Technological advancement and industrialization have significantly increased human exposure to xenobiotics, a diverse group of foreign chemical substances with potential toxic effects. Xenobiotics include pharmaceuticals, pesticides, personal care products, industrial chemicals, and environmental pollutants. The liver, as the primary organ responsible for biotransformation, plays a central role in the detoxification and activation of these compounds. However, metabolic processes may generate reactive intermediates that contribute to hepatocellular injury. This review provides a comprehensive overview of xenobiotic classification, mechanisms of hepatic biotransformation, and the molecular pathways underlying xenobiotic-induced hepatotoxicity. Special emphasis is placed on oxidative stress, reactive metabolite formation, and immune-mediated mechanisms. Clinical manifestations, diagnostic approaches, and current management strategies are also discussed. Understanding these processes is essential for early detection, prevention, and improved therapeutic outcomes in patients with xenobiotic-induced liver injury..

Keywords: xenobiotics, chemicals, hepatotoxicity, biotransformation, clinical management

INTRODUCTION

Technological progress, industrialization, and urbanization have direct and negative impacts on the environment by introducing substances that have short- and long-term effects on the ecosystem. Chemicals enter the environment through industries, wastewater, sewage plants, agriculture, and livestock consumption [1]. Technological progress introduces pollutants either as single or mixture of substances. They are released deliberately or accidentally and rarely remain in the same form or at the location of release. All substances cannot degrade naturally or have long degradation period and require secondary technological treatment that is not always effective for complete removal of all contaminants. Chemicals released into the environment are susceptible to chemical degradation, a process often stimulated by ultraviolet

light. Many chemicals are susceptible to fungal or bacterial degradation and are rapidly detoxified to products that can enter the carbon, nitrogen, and oxygen cycles. Halogenated organic compounds are metabolized to greater or lesser extent and persist in soil and water. When chemicals are taken up by plants and aquatic organisms, they easily enter biological food chains and move to higher trophic levels or persist in processed crops as food contaminants. Lipid-soluble toxicants are readily taken up by organisms following exposure in air, water, or soil. Unless rapidly metabolized, they persist in the tissues long enough to be transferred to the next trophic level [2].

The term xenobiotics comes from the Greek *xenos* (foreign) and *bios* (life). It defines chemicals

that do not necessarily occur naturally in the environment or whose naturally occurring concentrations are significantly different from those caused by anthropogenic activity. They can be endobiotic, substances produced within an organism or exobiotic, foreign substances introduced from the external environment. Exobiotics are anthropogenic (human-made) or natural xenobiotics. Xenobiotics can have complex structures (small molecular size, ionizability, lipo or water solubility, polarity, and volatility) that make their degradation difficult, so they accumulate in the living organisms [3]. Often, they are not completely metabolized but converted into secondary metabolites that are more toxic [4].

Exposure of humans and other organisms may result from ingestion, occupational or environmental exposure or accidental poisoning. The toxicity of a particular compound may vary with the port of entry into the body, whether through the alimentary canal, the lungs, or the skin [5]. Manifestations by which environmental factors alter biological processes in humans are often present as lung irritation, neurological disorders, triggered autoimmune diseases, and the development of cancer [5-8]. In our lifetime we might be exposed to 1-3 million compounds that may accumulate in human tissues [9, 10].

Exposure to toxic substances does not necessarily translate into a toxicological response. The human body has several defense mechanisms and membrane barriers that prevent absorption and distribution of toxicants. The skin, as the largest organ in the human body, is effective physical barrier contrary to the respiratory and gastrointestinal tract (GIT), which offers less resistance to toxicant absorption. The major difference in the absorption depends on the membrane thickness, physical distance between the external environment (skin surface, air in the lung, intestinal lumen) and the blood capillaries. The absorption in the GIT occurs mostly in the intestine by the process of passive diffusion strongly dependent on the ionization and the lipid solubility of substances. Toxicants with smaller particle size and aqueous solutions are vastly absorbed [8]. Lipid-soluble toxicants and drugs are presented as emulsions through the action of detergent-like bile acids. Very strong bases and acids are not readily absorbed in the GIT. Compounds such as bacterial endotoxins, large particles of azo dyes, and carcinogens are absorbed by endocytosis [11-13].

Intestinal microbiome can significantly impact xenobiotic biotransformation. Microbio-

ta can determine its bioavailability by altering its pharmacokinetic characteristics, but reciprocally xenobiotics also influence the viability and metabolism of the microbiota. Increased xenobiotic metabolism also occurs through re-entering the gut via enterohepatic circulation [13]. If the toxicant survives these microbial and chemical reactions, it is absorbed and carried by the hepatic portal vein to the liver [10]. Lipophilic xenobiotics are converted to more hydrophilic forms by biotransformation which makes their excretion more efficient. The enzymes for xenobiotic metabolism are located in the subcellular structures such as the endoplasmic reticulum (ER), cytosol, lysosomes, mitochondria, plasma membrane, and the blood with the liver being the main organ of xenobiotic biotransformation in the human organism [14].

Chemicals from the site of origin to the site of elimination are transported via the circulatory system. This is more the case for water-soluble than for lipid-soluble substances. Lipid-soluble xenobiotics utilize transporting proteins to facilitate mobilization and transport via the blood. At the elimination site xenobiotics diffuse from the transport protein to the membranes of the excretory organ, or the transport protein binds to surface receptors where it undergoes processes of endocytosis and intracellular processing [15]. After the release, xenobiotics are eliminated generally through the three major routes of elimination: liver, kidneys, and lungs. Minor routes for elimination from the body include the skin, sweat, lactation and the hair [16].

XENOBIOTICS – PHARMACEUTICALS AND CHEMICALS

Xenobiotics are a diverse group of chemicals that can be divided into several groups: pesticides (insecticides, bactericides, herbicides, fungicides), pharmaceutical compounds (multiple-class pharmaceuticals, essential medicines, antibiotics, endocrine disruptors, psychiatric drugs, NSAID), personal care products (fragrances, fire retardants, sunscreen components, antiseptics, plasticizers), illicit drugs (hallucinogenic compounds, stimulating compounds, inhibitor compounds), other industrial products (organic and inorganic waste, e-waste and heavy metals) and nuclear waste [1].

Xenobiotics are known to have hepatotoxic potential and include industrial chemicals (N-nitrosodimethylamine, hydrazine and carbon disulfide), inorganic elements from environmental exposure (heavy metals) and drugs (acetaminophen, vitamins, dietary supplements and alternative medicine substances). Hepatotoxins can also be introduced through food (hepatotoxic mushrooms and fruits), through food processing (polycyclic aromatic hydrocarbons) or as beverage (alcohol) [14].

Herbal and dietary supplements (HDs) are commonly used substances for health improvement or health maintenance. HDs include vitamins, minerals, herbs, amino acids, enzymes, organ tissues and metabolites. In the US, multi-vitamin-mineral products are the most frequently reported type of supplement taken, followed by ω -3 or fish oil supplements [17]. During the COVID-19 pandemic the interest in HDs with potential immune-enhancing effects dramatically increased [18].

As products, they lack uniform regulation criteria. In the United States herbal products are classified as dietary supplements or botanicals and are regulated as food products. Manufacturers are not required to conduct preclinical safety or efficacy testing prior to marketing [19]. The European Union regulation is more precise. An herb may be considered a medicinal product or a dietary supplement depending on the medical claims of a therapeutic indication. The European Directive 2004/24/EC provides the guidelines for the use of herbal medicines [20]. Accordingly, an herbal product is considered a medicinal product when presented as having properties treating or preventing disease in human beings or when it has a pharmacological, immunological or metabolic action. If the herbal products are marketed as food supplements, Directive 2002/46/EC on food supplements and Regulation (EC) No 1924/2006 on nutrition and health claims made on foods of the European Food Safety Authority (EFSA) apply [21].

Causality assessment of HDs has many limitations. The general population considers them safe and usually forgets to disclose consumption of these products to their health care provider. The intake of products may be irregular, but, more importantly, compounds may vary or are not precisely defined in the product label. Parallel to their increasing popularity, published reports of hepatotoxicity are increasing. Typical

liver damage is of a hepatocellular pattern accompanied with very high transaminase levels as clinical presentation. Liver injury caused by dietary supplements is an important cause of acute liver failure in transplantation centers [22].

Herbs related to liver injury include: Aloe Vera (*Aloe barbadensis*), Arrowroot juice (*Maranta arundinacea*), Black Cohosh (*Actaea racemosa*), Cascara (*Cascara sagrada*), Celandine (*Chelidonium majus* L.), Chaparral (*Larrea divaricata*), Comfrey (*Symphytum officinale*), Fo-ti (*Polygonum multiflorum*), Gotu kolu (*Centella asiatica*), green tea extract (*Camellia sinensis*), Groundsel (*Senecio vulgaris*), Hathisunda (*Heliotropium*) and others [23]. Reported cases of dietary supplements-induced liver injury include: linoleic acid, usnic acid and vitamin A. Multi-ingredient products such as Herbalife products, Hydroxycut, LipoKinetix and Oxy ELITE Pro taken for weight loss and muscle building are also connected to liver injury [22].

Anabolic androgenic steroids used for muscle building usually without medical supervision are frequently mentioned as a cause for liver injury. Reports of illicit anabolic steroids include use of stanozolol, methyltestosterone, oxandrolone, fluoxymesterone and danazol. Liver injury is manifested as focal nodular hyperplasia, non-alcoholic fatty liver disease, cholestasis hepatitis, hepatocellular adenoma or carcinoma.

Hepatotoxicity is associated with a distinct phenotype, increase of the total bilirubin and low values of transaminases and alkaline phosphatase. These patients also suffer from hypertension, cardiomyopathy, left ventricular hypertrophy, dyslipidemia, coagulation disruption, temporary hypogonadism and neuropsychiatric disturbances [24].

Drugs of abuse affect the higher nervous functions. Regular intake produces physical dependence sometimes with fatal overdoses. This group includes depressants of CNS (ethanol, methaqualone and secobarbital), stimulants (cocaine, methamphetamine), opioids (heroin) and hallucinogens (lysergic acid diethylamide- LSD, phencyclidine-PCP, and tetrahydrocannabinol) [25]. Drugs of abuse are illegally synthesized and contaminated with unknown compounds. Chronic abuse ultimately leads to liver damage, acute fatty infiltration, cholestatic jaundice, granulomas, hepatitis and liver cirrhosis. The mechanisms of drug-induced hepatotoxicity are dependent on the reactive metabolite formation,

modification of the covalent bonding between the cellular components, generation of ROS, activation of signal transduction pathways and cellular mitochondrial damage [26].

Ethanol: Alcohol-related liver diseases are complex. Changes usually begin as fatty liver, progressing to alcoholic hepatitis and culminating in alcoholic cirrhosis. Alcohol metabolism by alcohol dehydrogenase increases the production of NADH. This shift in the metabolic balance leads to the formation of glycerol phosphate which combines with fatty acids to generate triglycerides that accumulate in the liver leading to

“fatty liver disease”. Interleukins attack the hepatocyte causing swelling known as the “alcoholic hepatitis”. The ongoing liver injury leads to irreversible liver damage or liver cirrhosis. Alcoholic hepatitis is characterized with jaundice, fever, hepatomegaly, splenomegaly and portal hypertension with ascites, pedal edema, encephalopathy and distended superficial abdominal veins [27].

Pesticides are generally regulated substances. Before being registered and introduced to the markets, rigorous tests are performed to determine their influence on humans and the environment. Primary classes in use include fumigants, fungicides, herbicides, and insecticides. When properly applied they possess little risk to human health [28]. Organophosphorus pesticides (OPs) can be highly toxic. Human exposure is mostly through environmental or occupational exposure. Suicidal poisonings are also registered in rural areas. Their toxic effect is mostly on the nervous system through the inhibition of acetylcholinesterase. Liver damage is marked with changes of hepatic markers (AST, ALT, direct and indirect bilirubin). Key disturbance mechanisms in liver metabolism and metabolic mitochondrial pathways are caused by oxidative damage [29].

Heavy metals are inorganic chemicals widely spread in nature. Increased human exposure is usually occupational: mining, emissions of metal-related by-products of industrial processes or during disposal. Physiological amounts can be taken through the food chain or through drinking water. In the recent years especially in large cities the polluted air is also common source of exposure. Heavy metals are not biodegradable and may be deposited in the liver. Liver injury caused by exposure to heavy metals in experimental animals is characterized with

hepatocellular necrosis and abnormal liver tests. The mechanism responsible for the liver damage is the overproduction of reactive oxygen species due to oxidative stress and covalent binding of radicals to macromolecular proteins or lipids in the membranes of subcellular organelles [30].

Drugs are important and common cause of liver injury. In the US drugs account for 50% of the cases of acute liver failure i.e., 39% due to acetaminophen. Namely, acetaminophen is a widely used analgesic. When used in therapeutic doses it is considered safe. Overdoses, accidental or deliberate, however, may cause fatal acute centrilobular hepatic necrosis. Acetaminophen is conjugated with either sulfate or glucuronic acid to water-soluble, readily excreted metabolites. A small proportion is metabolized by cytochrome P450 to a reactive electrophilic intermediate quinonimine. When therapeutic doses of acetaminophen are ingested, quinonimine is efficiently deactivated by conjugation with glutathione. When higher doses are ingested the sulfate and glucuronide cofactors become depleted, resulting in more of the acetaminophen being metabolized to the reactive intermediate. As long as glutathione (GSH) is available, most of the reactive intermediate can be detoxified. When the concentration of GSH in the liver also becomes depleted, however, covalent binding to the sulfhydryl (-SH) groups of various cellular proteins increases, resulting in hepatic necrosis. The severity of liver damage after acetaminophen overdose is greater in chronic alcoholics and patients taking drugs that induce the levels of the P450 isozymes responsible for the activation of acetaminophen [31]. Moreover, worldwide, amoxicillin-clavulanate is mostly responsible for drug-induced liver injury (DILI). Amoxicillin-clavulanate is a combination antibiotic used to treat gram-positive bacterial infections. It has been associated with delayed liver injury following exposure. The pathogenesis of amoxicillin-clavulanate-related DILI appears to result from an immune-mediated injury to the interlobular bile ducts. Both amoxicillin and clavulanate form unique antigens that trigger a T-lymphocyte mediated immune response. In early stages, this injury is histologically characterized by periportal inflammatory cell accumulation, swelling and vacuolation of biliary epithelial cytoplasm, increased mitotic figures, lymphocytic infiltration, and hepatocellular and canalicular accumulation of the bile. In later stages, the injury is characterized by loss of interlobular ducts, irregular proliferations of

bile ducts, and fibrosis. This immune-mediated pathogenesis is associated with certain HLA polymorphisms. Clinical laboratory findings typically include increased serum enzymes and bilirubinemia; however, serum enzyme elevations are minor in many cases [32].

In the creation of the LiverTox[®] database the drugs were arbitrarily divided into four different categories of likelihood for causing liver injury based on reports in the published literature. Drugs in categories A (more likely to have at least one fatal case of liver injury and reported cases of positive rechallenge) include drugs for: gout prophylaxis (allopurinol), arrhythmia (amiodarone), antihypertensive (methyldopa, hydralazine), antimicrobial agents (amoxicillin-clavulanate, nitrofurantoin, minocycline, didanosine, efavirenz, erythromycin, nevirapine, flucloxacillin), antituberculostatics (isoniazid), antifungal treatment (ketoconazole), antiepileptic (carbamazepine), multiple sclerosis (interferon beta), anabolic steroids for body building, lipid lowering agent (atorvastatin), immunosuppressive agents (azathioprine/6-mercaptopurine, infliximab, methotrexate, gold salts), contraceptives, malignancy (busulfan), psychosis (chlorpromazine), muscle relaxant (dantrolene), NSAID (diclofenac, nimesulide, ibuprofen), antineoplastic (floxuridine, flutamide), anaesthetic (halothane) and other [33].

Drug induced liver injury is a common reason for the withdrawal of marketed drugs. FDA has recommended withdrawal for bromfenac and troglitazone due to severe liver injury and has issued warnings for several other drugs: pemoline, felbamate, zileuton, tolcapone, trovafloxacin, benoxaprofen, telithromycin etc. FDA has also added boxed warning for propylthiouracil informing of risk for severe liver injury and acute liver failure and limiting use [34].

Literature review uncovered new reports of previously unrecognized hepatotoxins as causes of DILI: immune modulators (glatiramer acetate), novel gene therapy (onasemnogene abeparvovec), novel NSAID (pelubiprofen), GLP-1 analog (liraglutide), tyrosine kinase inhibitors and others. A number of drugs used to treat COVID-19 have been suspected to cause DILI (lopinavir/ritonavir, remdesivir, tocilizumab) but causality has been difficult to establish. It still remains unclear if the virus itself is a true risk DILI factor [35]. Below, several chemicals

xenobiotics responsible for toxic effect on the human health are mentioned.

Vinyl chloride: Vinyl chloride is an industrial chemical used in the manufacture of polyvinyl chloride (PVC). PVC is commonly used material for production of plastic piping, floor coverings, consumer goods and electrical applications. The main route for human exposure is occupational inhalation. Exposure to vinyl chloride causes non-cancerous changes in the liver (fatty liver, steatohepatitis, peliosis hepatitis, and fibrosis). Highly reactive metabolites (2-chloroethylene oxide and 2-chloroacetaldehyde) induce the mitochondrial damage, alter the hepatocyte metabolic functions, and increase the production of ROS. The increased oxidative stress and fatty liver promote the formation of cytotoxic lipid peroxidation products. Combined cellular responses activate pro-inflammatory signals and promote remodeling of the extracellular matrix and fibrosis. Epidemiological and experimental animal studies provide sufficient evidence that exposure to vinyl chloride causes liver cancer (hepatocellular carcinoma, angiosarcoma). Carcinogenic mechanism involves binding of the reactive metabolites to DNA and promutagenic action that leads to mutations in proto-oncogenes and tumour-suppressor genes [36].

Carbon Tetrachloride: Carbon tetrachloride (CCl_4) is a chemical compound formerly used in fire extinguishers, cleaning agents and in refrigerants. Human exposure is generally through inhalation. Exposure to CCl_4 affects several organs (liver, kidneys and CNS). Short-term inhalation causes headache, weakness, lethargy, nausea, and vomiting. Acute exposures to higher levels or chronic exposure produces liver and kidney damage. The generation of free radical during the hepatic metabolism of CCl_4 by cytochrome P-450 leads to lipid peroxidation, covalent bonding of radicals with the structural proteins, nuclear and mitochondrial DNA leading to DNA aberration. Studies in animals have shown that ingestion of CCl_4 increases the risk of liver cancer. US Environmental Protection Agency (EPA) has classified CCl_4 as a Group B2, probable human carcinogen [37].

Bromobenzene: Bromobenzene is a toxic industrial solvent known to produce centrilobular hepatic necrosis through the formation of reactive epoxides. Free radicals (bromobenzene 2,3-epoxide and bromobenzene 3,4-epoxide) are produced by P450 oxidations. 3,4-epoxide

covalently binds to cellular proteins leading to cell injury. If 3,4-epoxide is not over produced it can be detoxified through: rearrangement to the 4-bromophenol, hydration to the 3,4-dihydrodiol catalyzed by epoxide hydrolase, or conjugation with glutathione. Pretreatment of animals with inhibitors of cytochrome P450 is known to decrease tissue necrosis by slowing down the rate of formation of the reactive metabolite, whereas pretreatment of animals with certain P450 inducers (e.g., phenobarbital) can increase the toxicity of bromobenzene [38].

BIOTRANSFORMATION AND MECHANISMS OF LIVER INJURY

The liver is the principal site of metabolism for orally ingested drugs, alcohol, and other xenobiotics after their absorption from GIT. These substances are distributed through the hepatic portal vein or may be concentrated during the enterohepatic circulation. The main location of the xenobiotic metabolizing enzymes, primarily the cytochrome P450-dependent monooxygenase system (CYPs) is the centrilobular region of the liver. CYPs in the liver are abundant in the microsomal fraction. Besides their main role in the bile acid biosynthesis and metabolism of foreign compounds, CYPs are also involved in the homeostasis of steroid hormones, metabolism of vitamins, unsaturated fatty acids as well as cholesterol biosynthesis. In the process of biotransformation, CYPs are involved in the metabolic activation of the environmental chemicals to reactive carcinogenic products. 15 isoforms of 18 human CYP families, mostly 1, 2 and 3 are accountable for 70–80% of the metabolism of drugs, environmental chemicals and carcinogens. CYP1A2, CYP2C9, CYP2D6 and CYP3A4/5 are mostly responsible for CYP-mediated metabolism of clinically marketed drugs [10].

Besides CYPs, several other families of enzymes are involved in the metabolism of xenobiotics in the liver: flavin-containing monooxygenases (FMOs), alcohol and aldehyde dehydrogenases, amine oxidases, cyclooxygenases, reductases and hydrolases as well as conjugating enzymes [39]. Metabolism occurs in various reactions, categorized as phase I (modification), phase II (conjugation), and phase III (additional modification and excretion). The net result

of these coordinated functions is an efficient removal of xenobiotics and their metabolites from the body [40].

Phase I modifications alter the chemical structure of the lipophilic drug through oxidation, reduction, hydrolysis, cyclization/decyclization, and either by removing hydrogen or adding oxygen. These processes create a metabolite with increased polarity compared to the parent molecule. Oxidation typically results in metabolites that still retain some of their pharmacological activity. The cytochrome P450 system catalyzes most of the phase I reactions.

Phase II reactions usually, but not always, occur sequentially. In phase II modifications, a drug molecule couples with another molecule in a conjugation reaction. Conjugation usually renders the compound pharmacologically inert and water-soluble, allowing easy excretion in the urine (or, less often, in the bile). The enzymes responsible for phase II metabolism belong to five enzyme families: UDP-glucuronosyltransferases, glutathione S - S-transferases, sulfotransferases, N - acetyltransferases, and methyltransferases [41]. Conjugation mechanisms include methylation, acetylation, sulphation, glucuronidation, and glycine or glutathione conjugation. Most conjugation enzymes are located in the cytosol, whereas the family of UDP-glucuronosyltransferases is found in the ER. Besides the liver, these processes can occur in other locations, such as the kidneys, lungs, intestines, and other organ systems.

Phase III metabolism may also follow phase II. During phase III, conjugates and metabolites are excreted from the cells. Transport proteins located on the canalicular membrane are responsible for the chemical transport. Transport proteins are members of a multi-gene superfamily known as the ATP-binding cassette transporters. The *P*-glycoprotein (ABC B) subfamily is responsible for the elimination of many structurally diverse compounds. The multidrug-resistance associated protein (ABC C) subfamily recognizes anionic chemicals. Transporters can be found in both the canalicular (apical) and sinusoidal membranes of hepatocytes. Biotransformation enables active transport across the canalicular membrane into the bile. The bile duct transfers chemicals to the gall bladder that fur-

ther excretes the bile into the intestines for fecal elimination [42].

Conversion of xenobiotics to more stable hydrophilic forms enables excretion, however, biotransformation of certain xenobiotics can lead to the production of highly reactive unstable chemical species that can interact with functional biomolecules. These reactive metabolites include epoxides, quinones, free radicals, reactive oxygen species, and unstable conjugates. Depending on their half-life of a reaction or the possibility of being transported, intermediates can be divided into ultra-short-lived, short or longer-lived metabolites [14]. Ultra-short-lived or "suicide" metabolites primarily bind to the parent enzyme substrates and form enzyme-bound intermediates that react with the active site of the enzyme. Many xenobiotics fall into the second group of short-lived metabolites. They remain in the cell or migrate to the nearby cells and cause localized tissue damage at the site of their activation. Longer-lived metabolites in contrast can be transported to cells and tissues distant from the site of activation in their original form or as conjugates, which then release the reactive intermediate under the specific conditions in the target tissue [43].

Once reactive metabolites are formed, different cell mechanisms enable their rapid removal or inactivation. Toxicity depends primarily on the balance between the rate of metabolite formation and the rate of removal. When balance is disrupted, reactions are triggered. These reactions can lead to alteration of the structure and function of cellular macromolecules leading to deregulation of the cell signaling pathways, dysfunction of target organelles and eventual cell death [44]. Depending on the nature of the reactive variety of reactions, this can occur: reactive metabolites may covalently bind to nucleophilic sites on cellular macromolecules (proteins, polypeptides, RNA, and DNA) and initiate events like mutagenesis, carcinogenesis, and cellular necrosis. Radicals produced during the oxidation, may induce lipid peroxidation and subsequent destruction of lipid membranes leading to cellular necrosis.

Reduced glutathione has an important role in preventing the trapping of metabolites and preventing the binding to hepatic proteins and enzymes. Although conjugation reactions occasionally result in bioactivation of a compound, the acetyl-, glutathione-, glucuronyl-, or sulfo-

transferases usually result in the formation of a nontoxic, water-soluble metabolite that is easily excreted [45].

CLINICAL PERSPECTIVES ON XENOBIOTICS-INDUCED HEPATOTOXICITY

Xenobiotics-induced hepatotoxicity (XIH) is acute or chronic liver impairment secondary to drugs or herbal drugs, which makes it very difficult to distinguish from other liver conditions. Acute hepatic impairment is more often seen and can be presented as acute hepatitis, cholestasis or mixed pattern [46].

The characteristics of XIH can vary from asymptomatic, with elevated alanine aminotransferase (ALT) concentrations to jaundice, encephalopathy and acute liver failure [47].

When cholestasis predominates, the bile secretory components are affected, either at the canalicular membrane or beyond. The associated jaundice and pruritus may be severe, and a permanent loss of bile ducts may happen [48].

The lists of drugs that can cause acute and chronic hepatic failure are presented in Table 1 [49, 50]. XIH may be classified as intrinsic or spontaneous (idiosyncratic) and their characteristics are shown in Table 2 [47, 51, 52]. Unpredictable liver injury (idiosyncratic) can happen as a result of two possible mechanisms: Idiosyncratic reactions and Immune-mediated reactions (allergic reactions) that are shown in Table 3 [48,51]. Unpredictable (idiosyncratic) XIH usually occurs as mild, asymptomatic with transient ALT abnormalities, which may occur 10 to 20 times more often than overt disease [46].

The transient state of these reactions suggests a type of adaptation. Patients that show failure to adapt to injury can progress to clinically overt disease. This is all in line with the rationale of AST monitoring.

If hepatocyte injury predominates, aminotransferase levels may be at least five times higher than normal. Threshold abnormality is considered as ALT level greater than three times the upper limit of normal. XIH is usually seen as a moderate to severe injury to hepatocytes with a clinical picture as a viral hepatitis, with a rapid onset of malaise and jaundice. Elevations of alkaline phosphatase and bilirubin levels predomi-

nate in cholestatic syndromes. Acute liver failure may develop after a week or more of disease, especially if the patient has continued the drug after the onset of symptoms [53].

A summary of the type of idiosyncratic drug reactions and their effect on cells is presented in Table 4 [48].

DIAGNOSIS OF XENOBIOTIC-INDUCED LIVER INJURY

There should be caution for drug reaction when the patient presents liver injury. The practitioner should include taking anamnesis for drug

Table 1. *Drugs-induced hepatic failure*

	Drug-induced acute hepatitis		Drug-induced acute cholestasis or mixed pattern			
	Chronic hepatitis	Chronic cholestasis	Granulomatous hepatitis	Nonalcoholic Steato-hepatitis	Fibrosis	
Acute hepatic failure	Acetaminophen Dihydralazine Dantrolene Fluoxetine Isoniazid Ketokonazole Minocycline Nefazodone Paroxetine Pyrazinamide Sertraline Terbinafine Tienilic acid Troglitazone Valproic acid					
Chronic hepatic failure	Dantrolene Methyldopa Minocycline Nitrofurantoin	Flucloxacillin Tetracycline Trimethoprim-sulfamethoxazole	Allopurinol Diltiazem Quinidine Penicillamine Procainide	Amiodarone Tamoxifen	Methotrexate Vitamin A	

Table 2. *Characteristics of intrinsic and idiosyncratic xenobiotics-induced hepatotoxicity*

	Intrinsic	Idiosyncratic
Predictable	Yes	No
Common	Less	More
Dose-dependent	Yes (ex. acetaminophen, aspirin, cocaine)	No
Predominant pattern of injury	Zonal hepatocellular necrosis	Diffuse necrosis and cholestasis
Inflammatory infiltrates	Rare	Common
Systemic signs of hypersensitivity	Rare	Common
Latency period	Short	Variable
Reproducible in animal models	Yes	No

Table 3. *Mechanisms of unpredictable liver injury (idiosyncratic)*

Unpredictable liver injury	Immune-mediated reactions	Idiosyncratic reactions
Immunoallergenic features	Yes	No
Clinical patterns	Fever, rash, eosinophilia, Lymphadenopathy, severe hepatocyte injury	Damage to hepatocytes throughout the hepatic lobule, various degrees of necrosis and apoptosis
latency	Intermediate (1 to 6 weeks). Rapid recognition of toxic effects and immediate discontinuation of the offending drug for limiting hepatic and cutaneous damage.	Delayed (days or weeks after the initial exposure, up to 1 year), may continue even after the offending drug is withdrawn.
rechallenge	positive	

Table 4. *Idiosyncratic Drug Reactions, cells that are affected and examples of drugs*

Idiosyncratic drug reaction	Cells effect	Drugs
Hepatocellular	Direct effect or production by enzyme–drug adduct leads to cell dysfunction, membrane dysfunction, cytotoxic T-cell response	Isoniazid, trazodone, diclofenac, nefazodone, venlafaxine, lovastatin
Cholestasis	Injury to canalicular membrane and transporters	Chlorpromazine, estrogen, erythromycin and its derivatives
Immunoallergic	Enzyme–drug adducts on cell surface induce IgE response	Halothane, phenytoin, sulfamethoxazole
Granulomatous	Macrophages, lymphocytes infiltrate hepatic lobule	Diltiazem, sulfa drugs, quinidine
Microvesicular fat	Altered mitochondrial respiration, b-oxidation - lactic acidosis and triglyceride accumulation	Didanosine, tetracycline, acetylsalicylic acid, valproic acid
Steatohepatitis	Multifactorial	Amiodarone, tamoxifen
Autoimmune	Cytotoxic lymphocyte response directed at hepatocyte membrane components	Nitrofurantoin, methyl dopa, lovastatin, minocycline
Fibrosis	Activation of stellate cells	Methotrexate, excess vitamin A
Vascular collapse	Causes ischemic or hypoxic injury	Nicotinic acid, cocaine, methylenedioxymethamphetamine
Oncogenesis	Encourages tumor formation	Oral contraceptives, androgens Amoxicillin–clavulanate, carbamazepine, herbs, cyclosporine, methimazole, troglitazone
Mixed	Cytoplasmic and canalicular injury, direct damage to bile ducts	

Table 5. *Biomarkers used to assess the degree of liver injury [61,62]*

Type of hepatic injury	Biomarkers	Characteristics
Cytotoxic	Serum aspartate aminotransferase	Low specificity for liver injury
	Serum alanine aminotransferase	High specificity for acute hepatocellular injury
	Serum albumin	Reliable marker of chronic hepatocellular injury
	Prothrombin time	Reliable marker of acute or chronic hepatocellular injury; specificity poor
Cytotoxic or cholestatic	Serum alkaline phosphatase	Highest increases occur with cholestatic injuries
	Serum-glutamyl transferase	Correlates with alkaline phosphatase (can exclude bone disease)
	Serum bilirubin	High increase(at least 50% of the direct fraction) indicates liver injury
	Serum bile acids	Higher sensitivity and specificity for liver injury than serum bilirubin
Cholestatic	Serum 5-nucleotidase Urinary bilirubin	Highly specific for cholestasis Higher sensitivity than serum bilirubin; specificity for cholestasis

history of any drug used in the previous period (prescription, over-the counter medication, herbal or alternative medications) [54,55].

Other reasons for liver injury, such as viral hepatitis, hypotension, and biliary tract or liver disease related to alcohol abuse, must be excluded by taking a thorough medical history, ultrasonography, and serologic tests. Assessment of causality can be difficult because many agents are used simultaneously. There are no specific tests available to detect XIH [56-59].

When taking the anamnesis, important data that should be carefully documented and screened such as the time of the onset, (whether the onset of the symptoms was between 5 and 90 days after the initial exposure); what happened after the patient stopped taking the suspected drug (improvement); are there any risk factors (alcohol use, pregnancy, or old age); the concomitant use of any other drugs; comorbidities (e.g., viral hepatitis); were there any previous toxic effects of the suspected drug; and the response to rechallenge, if done before.

Many drug-induced liver injuries are much more severe with re-exposure, so rechallenge with the suspected agent is generally not recommended. If there should be rechallenge, it should be done with caution, but only if the diagnosis of DIH is highly questionable [60].

Most of these drug reactions are idiosyncratic and the individual or total dose used for the indication given is important. The therapy for XIH is the immediate withdrawal of the suspected drug.

Hepatic biomarkers are important instruments as a signal for hepatic injury, its severity, type, prognosis and causative factor, along with drug-specific biomarkers which are elevated in particular drug toxicity (Table 5) [47].

FUTURE DIRECTIONS AND CONCLUSION

Taking into account that most of the xenobiotic-induced liver injuries are reversible, it is

very important, the evolution of the injury to be recognized as soon as possible and the offending drug to be withdrawn [63].

Unfortunately, many injuries of this type are presented with nonspecific symptoms that resemble others diseases. Usually, when classic signs of hepatic injury such as jaundice or coagulopathy are registered, the condition is often severe and the risk of mortality is increased [64].

Prescription of any drug known to potentially cause liver injury should involve an extra measure of caution and vigilance [63].

Regular monitoring of hepatic aminotransferase enzymes may be proper in some cases, especially during the initial period of the administration of the drug. Before giving the medication, the patient's medical history should be carefully reviewed to identify potential risk factors for injury, including concomitant medications. Patients should be educated, so many liver injuries are detected in early stages when symptoms are still mild and severe injuries might be preventable because the offending drug will be withdrawn on time [63].

Once XIH is registered, usually frequently, treatment options are limited. Prevention strategies are crucial. In addition to the laboratory monitoring, patients need to be educated about the symptoms of liver disease, such as jaundice, dark urine, pruritus, abdominal pain, fever and fatigue.

Future research should focus on integrating molecular biomarkers, omics technologies, and individualized risk assessment to improve prediction, prevention, and management of xenobiotic-induced liver injury.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

- Štefanac T, Grgas D, Landeka Dragičević T. Xenobiotics-Division and Methods of Detection: A Review. *J Xenobiot*. 2021;11(4):130-141. DOI: 10.3390/jox11040009.
- Hodgson E. Introduction to Toxicology. A Textbook of Modern Toxicology. 3rd ed. John Wiley & Sons, Ltd; 2004.p. 75-110. DOI: <https://onlinelibrary.wiley.com/doi/10.1002/0471646776.ch6>
- de Oliveira M, Frihling BEF, Velasques J, Filho FJCM, Cavalheri PS, Migliolo L. Pharmaceuticals residues and xenobiotics contaminants: Occurrence, analytical techniques and sustainable alternatives for wastewater treatment. *Sci. Total Environ*. 2020; 705:135568. DOI: 10.1016/j.scitotenv.2019.135568.
- Attia SM. Deleterious effects of reactive metabolites. *Oxid Med Cell Longev*. 2010; 3(4):238-253. DOI:10.4161/oxim.3.4.13246
- Stapleton PA, Abukabda AB, Hardy SL, Nurkiewicz TR. Xenobiotic pulmonary exposure and systemic cardiovascular response via neurological links. *Am J Physiol Heart Circ Physiol*. 2015 ;309(10):H1609-H1620. DOI:10.1152/ajpheart.00546.2015
- Vojdani A. A Potential Link between Environmental Triggers and Autoimmunity. *Autoimmune Dis*. 2014; 2014:437231. DOI:10.1155/2014/437231
- Virolainen SJ, VonHandorf A, Viel KCMF, Weirauch MT, Kottyan LC. Gene-environment interactions and their impact on human health. *Genes Immun*. 2023; 24(1):1-11. DOI:10.1038/s41435-022-00192-6
- Xuan L, Ju Z, Skonieczna M, Zhou PK, Huang R. Nanoparticles-induced potential toxicity on human health: Applications, toxicity mechanisms, and evaluation models. *MedComm (2020)*. 2023; 4(4):e327. DOI:10.1002/mco2.327
- Idle JR, Gonzalez FJ. Metabolomics. *Cell Metab*. 2007; 6(5):348-351. DOI:10.1016/j.cmet.2007.10.005
- Esteves F, Rueff J, Kranendonk M. 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
- Feng J, Cerniglia CE, Chen H. Toxicological significance of azo dye metabolism by human intestinal microbiota. *Front Biosci (Elite Ed)*. 2012; 4(2):568-586. DOI:10.2741/e400
- Long J, Zhang CJ, Zhu N, et al. Lipid metabolism and carcinogenesis, cancer development. *Am J Cancer Res*. 2018; 8(5):778-791.
- Baynes R, Hodgson E. Absorption and Distribution of Toxicants. A Textbook of Modern Toxicology. 3rd ed. John Wiley & Sons, Ltd; 2004.p. 75-110. DOI: <https://onlinelibrary.wiley.com/doi/10.1002/0471646776.ch6>
- Gu X, Manautou JE. Molecular mechanisms underlying chemical liver injury. *Expert Rev Mol Med*. 2012; 14:e4. Published 2012 Feb 3. DOI: 10.1017/S1462399411002110
- Klaassen CD, Aleksunes LM. Xenobiotic, bile acid, and cholesterol transporters: function and regulation. *Pharmacol Rev*. 2010; 62(1):1-96. DOI:10.1124/pr.109.002014

16. Genuis SJ. Elimination of persistent toxicants from the human body. *Hum Exp Toxicol*. 2011; 30(1):3-18. DOI: 10.1177/0960327110368417
17. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. *JAMA Intern Med*. 2013; 173(5):355-361. DOI:10.1001/jamainternmed.2013.2299
18. Günelan E, Cebioglu İK, Çonak Ö. The Popularity of the Biologically-Based Therapies During Coronavirus Pandemic Among the Google Users in the USA, UK, Germany, Italy and France. *Complement Ther Med*. 2021;58:102682. DOI:10.1016/j.ctim.2021.102682
19. van Breemen RB. Development of Safe and Effective Botanical Dietary Supplements. *J Med Chem*. 2015; 58(21):8360-8372. DOI:10.1021/acs.jmedchem.5b00417
20. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use [Internet]. 2004. Available from: <http://data.europa.eu/eli/dir/2004/24/oj> [Accessed: 2024-08-05]
21. Consolidated text: Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods [Internet]. 2014. Available from <http://data.europa.eu/eli/reg/2006/1924/2014-12-13> [Accessed: 2024-08-06]
22. García-Cortés M, Robles-Díaz M, Ortega-Alonso A, Medina-Caliz I, Andrade RJ. Hepatotoxicity by Dietary Supplements: A Tabular Listing and Clinical Characteristics. *Int J Mol Sci*. 2016;17(4):537. DOI:10.3390/ijms17040537
23. Brown AC. Liver toxicity related to herbs and dietary supplements: Online table of case reports. Part 2 of 5 series. *Food Chem Toxicol*. 2017;107(Pt A):472-501. DOI:10.1016/j.fct.2016.07.001
24. Petrovic A, Vukadin S, Sikora R, et al. Anabolic androgenic steroid-induced liver injury: An update. *World J Gastroenterol*. 2022;28(26):3071-3080. DOI:10.3748/wjg.v28.i26.3071
25. Ciucă Anghel DM, Nițescu GV, Tiron AT, Guțu CM, Baconi DL. Understanding the Mechanisms of Action and Effects of Drugs of Abuse. *Molecules*. 2023;28(13):4969. DOI:10.3390/molecules28134969
26. Roy DN, Goswami R. Drugs of abuse and addiction: A slippery slope toward liver injury. *Chem Biol Interact*. 2016;255:92-105. DOI:10.1016/j.cbi.2015.09.018
27. Patel R, Mueller M. Alcoholic Liver Disease. [Internet]. StatPearls Publishing 2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK546632/> [Accessed: 2024-08-26]
28. Kalyabina VP, Esimbekova EN, Kopylova KV, Kratasyuk VA. Pesticides: formulants, distribution pathways and effects on human health - a review. *Toxicol Rep*. 2021;8:1179-1192. DOI:10.1016/j.toxrep.2021.06.004
29. Karami-Mohajeri S, Ahmadi-pour A, Rahimi HR, Abdollahi M. Adverse effects of organophosphorus pesticides on the liver: a brief summary of four decades of research. *Arh Hig Rada Toksikol*. 2017;68(4):261-275. DOI:10.1515/aiht-2017-68-2989
30. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. *Exp Suppl*. 2012;101:133-164. DOI:10.1007/978-3-7643-8340-4_6
31. Lee WM. Acetaminophen-related acute liver failure in the United States. *Hepatol Res*. 2008;38 Suppl 1:S3-S8. DOI:10.1111/j.1872-034X.2008.00419.x
32. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases [Internet]. 2012. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK547852/> [Accessed: 2024-08-26]
33. Björnsson ES. Hepatotoxicity by Drugs: The Most Common Implicated Agents. *Int J Mol Sci*. 2016;17(2):224. DOI:10.3390/ijms17020224
34. Mehta N, Ozick LA, Gbadehan E. Drug-Induced Hepatotoxicity. [Internet]. 2022. Available from <http://emedicine.medscape.com/article/169814-overview#showall> [Accessed on: 2024-08-15]
35. Clinton JW, Kiparizoska S, Aggarwal S, Woo S, Davis W, Lewis JH. Drug-Induced Liver Injury: Highlights and Controversies in the Recent Literature. *Drug Saf*. 2021;44(11):1125-1149. DOI:10.1007/s40264-021-01109-4
36. Rusyn I, Arzuaga X, Cattley RC, et al. Key Characteristics of Human Hepatotoxicants as a Basis for Identification and Characterization of the Causes of Liver Toxicity. *Hepatology*. 2021;74(6):3486-3496. DOI:10.1002/hep.31999
37. CARBON TETRACHLORIDE TOXICITY [Internet]. 2018. Available from: https://www.atsdr.cdc.gov/csem/carbon-tetrachloride/toxicological_effects.html [Accessed: 2024-08-12]
38. Lau SS, Zannoni VG. Bromobenzene epoxidation leading to binding on macromolecular protein sites. *J Pharmacol Exp Ther*. 1981;219(2):563-572.
39. Rendić SP, Crouch RD, Guengerich FP. Roles of selected non-P450 human oxidoreductase enzymes in protective and toxic effects of chemicals: review and compilation of reactions. *Arch Toxicol*. 2022; 96(8):2145-2246. DOI:10.1007/s00204-022-03304-3
40. ul Amin Mohsin N, Farrukh M, Shahzadi S, Irfan M. Drug Metabolism: Phase I and Phase II

- Metabolic Pathways [Internet]. Pharmaceutical Science. IntechOpen; 2024. Available from: <http://dx.doi.org/10.5772/intechopen.112854> [Accessed: 2024-08-26]
41. [41] Susa ST, Hussain A, Preuss CV. Drug Metabolism. [Internet]. StatPearls Publishing. 2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK442023/> [Accessed: 2024-08-26]
 42. Choi YH, Yu AM. ABC transporters in multi-drug resistance and pharmacokinetics, and strategies for drug development. *Curr Pharm Des.* 2014;20(5):793-807. DOI:10.2174/138161282005140214165212
 43. Zhao M, Ma J, Li M, et al. Cytochrome P450 Enzymes and Drug Metabolism in Humans. *Int J Mol Sci.* 2021;22(23):12808. Published 2021 Nov 26. DOI:10.3390/ijms222312808
 44. Attia SM. Deleterious effects of reactive metabolites. *Oxid Med Cell Longev.* 2010;3(4):238-253. DOI:10.4161/oxim.3.4.13246
 45. Potęga A. Glutathione-Mediated Conjugation of Anticancer Drugs: An Overview of Reaction Mechanisms and Biological Significance for Drug Detoxification and Bioactivation. *Molecules.* 2022;27(16):5252. DOI:10.3390/molecules27165252
 46. Gunawan, B., & Kaplowitz, N. (2004). Clinical Perspectives on Xenobiotic-Induced Hepatotoxicity. *Drug Metabolism Reviews*, 36(2), 301–312. <https://doi.org/10.1081/DMR-120034148>.
 47. Allison, R., Guraka, A., Shawa, I. T., Tripathi, G., Moritz, W., & Kermanizadeh, A. (2023). Drug induced liver injury – a 2023 update. *Journal of Toxicology and Environmental Health, Part B*, 26(8), 442–467. <https://doi.org/10.1080/10937404.2023.2261848>.
 48. Lee WM. Drug-induced hepatotoxicity. *N Engl J Med.* 2003 Jul 31;349(5):474-85. doi: 10.1056/NEJMr021844. PMID: 12890847.
 49. Kaplowitz N. Drug-induced liver injury. *Clin Infect Dis.* 2004;38(Suppl 2):S44–S48. doi: 10.1086/381446.
 50. Liu Z, Que S, Xu J, Peng T. Alanine aminotransferase-old biomarker and new concept: a review. *Int J Med Sci.* 2014;11(9):925.
 51. Zimmerman HJ, Maddrey WC. Toxic and drug-induced hepatitis. In: Schiff L, Schiff ER, eds. *Diseases of the liver*, 7th ed. Philadelphia: JB Lippincott, 1993:707±83.
 52. Katarey, D., and S. Verma. 2016. Drug-induced liver injury. *Clin. Med (Northfield Il)* 16:104–09. doi:10.7861/clinmedicine.16-6-s104.
 53. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002;137: 947-54.
 54. Chitturi S, Farrell GC. Herbal hepatotoxicity: an expanding but poorly defined problem. *J Gastroenterol Hepatol* 2000;10:1093-9. Stedman C. Herbal hepatotoxicity. *Semin Liver Dis* 2002;22:195-206.
 55. Favreau JT, Ryu ML, Braunstein G, et al. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. *Ann Intern Med* 2002;136:590-5.
 56. Danan G, Benichou C. Causality assessment of adverse reactions to drugs. I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993;46:1323-30.
 57. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs. II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol* 1993;46:1331-6.
 58. Lucena MI, Camargo R, Andrade RJ, Perez-Sanchez CJ, Sanchez De La Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity. *Hepatology* 2001;33:123-30.
 59. Kaplowitz N. Causality assessment versus guilt-by-association in drug hepatotoxicity. *Hepatology* 2001;33:308-10.
 60. Marc G Sturgill, George H Lambert, Xenobiotic-induced hepatotoxicity: mechanisms of liver injury and methods of monitoring hepatic function, *Clinical Chemistry*, Volume 43, Issue 8, 1 August 1997, Pages 1512–1526, <https://doi.org/10.1093/clinchem/43.8.1512>.
 61. Friedman LS, Martin P, Munoz SJ. Liver function tests and the objective evaluation of the patient with liver disease. In: Zakim D, Boyer TD, eds. *Hepatology: a textbook of liver disease*, 3rd ed. Philadelphia: WB Saunders, 1996:791±833.
 62. Francis P, Navarro VJ. Drug-Induced Hepatotoxicity. 2022 Nov 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 32491467.
 63. Lee WM. Drug-induced hepatotoxicity. *N Engl J Med* 1995;333: 1118±27.
 64. Lee WM. Acute liver failure. *N Engl J Med* 1993;329:1862±72.
 65. Le Daré B, Ferron PJ, Gicquel T. Il était une fois l'hépatotoxicité... [Once upon a time the hepatotoxicity...]. *Med Sci (Paris)*. 2021 Mar;37(3):235-241. French. doi: 10.1051/medsci/2021009. Epub 2021 Mar 19. PMID: 33739270.
 66. Thakur S, Kumar V, Das R, Sharma V, Mehta DK. Biomarkers of Hepatic Toxicity: An Overview. *Curr Ther Res Clin Exp.* 2024 Apr 26;100:100737. doi: 10.1016/j.curtheres.2024.100737. PMID: 38860148; PMCID: PMC11163176.

Резиме**ТОКСИЧНОСТ НА ЦРНИОТ ДРОБ ИНДУЦИРАНА ОД КСЕНОБИОТИЦИ**

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Технолошкиот развој и индустријализацијата значително ја зголемија изложеноста на човекот на ксенобиотици, разновидна група хемиски супстанции со потенцијално токсични ефекти врз здравјето. Ксенобиотиците опфаќаат фармацевтски производи, пестициди, производи за лична нега, индустриски хемикалии и други еколошки загадувачи. Црниот дроб, како главен орган за биотрансформација, има клучна улога во нивната детоксикација, но истовремено, и во нивната метаболичка активација. Во текот на овие процеси може да се создадат реактивни метаболити, кои предизвикуваат оштетување на хепатоцитите преку механизми како оксидативен стрес, липидна пероксидација и имунолошки медијирани реакции.

Овој ревијален труд дава сеопфатен преглед на класификацијата на ксенобиотиците, механизмите на хепаталната биотрансформација и молекуларните патишта вклучени во ксенобиотички индуцираната хепатотоксичност. Посебен акцент е ставен на улогата на реактивните кислородни видови, митохондријалната дисфункција и нарушувањето на антиоксидативниот баланс. Дополнително, се разгледуваат клиничките манифестации, дијагностичките пристапи и современите стратегии за менаџмент на овие состојби.

Подоброто разбирање на овие механизми е од суштинско значење за раната детекција, превенцијата и унапредувањето на терапевтските пристапи кај пациентите со ксенобиотички индуцирано оштетување на црниот дроб.

Клучни зборови: ксенобиотици, хемиски супстанции, хепатотоксичност, биотрансформација, клинички менаџмент