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REVIEW

DRUG-INDUCED LIVER TOXICITY

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Abstract. *The liver performs many vital functions such as regulating homeostasis, bile production, storage of vitamins, and more. Another important function of the liver is to neutralize toxic substances entering the body. Substances entering the human body can be eliminated unchanged, retained unchanged, or undergo chemical transformation. Drugs are one of the most important and common causes of hepatotoxicity. It can manifest in various forms, ranging from elevated serum levels of transaminases to acute liver failure. The mechanisms of drug-induced liver damage may include the formation of a toxic metabolite (paracetamol), induction of oxidative stress, mitochondrial damage, suppression of key transcription factors and enzymes (methotrexate), suppression of beta-oxidation (valproate), impaired bile secretion and others. In some cases, hepatotoxicity is an idiosyncratic type and the exact mechanism of damage is unclear. Due to the importance of the problem, knowledge about the metabolism, potential adverse drug reactions, and the correct dosage regimen is essential.*

Key words: *drug-related disturbances, hepatotoxicity, mechanism, metabolism*

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INTRODUCTION

The liver is the largest and most important organ in the body involved in the metabolism of food, drugs and other xenobiotics [1]. Its proper functioning is essential for maintaining stable conditions in the body. Many drug-induced liver reactions can lead to hepatotoxicity. It can present in a variety of forms of acute and chronic liver damage, ranging from elevated serum levels of transaminases to acute liver failure [2]. For this reason, it is important to know well the drug metabolism, potential adverse drug reactions (ADRs) and the correct dosage regimen. In this review, we discuss some of the drugs with expressed and proven hepatotoxicity, the type of damage they cause, and the mechanism of its occurrence.

LIVER – ANATOMICAL AND PHYSIOLOGICAL FEATURES

The liver performs many vital functions such as regulating the body‘s homeostasis, producing bile, storing

vitamins, minerals, proteins and fats. Another important function of the liver is to neutralize toxic substances entering the body [1]. The liver of an adult has a multicellular structure consisting of large lobes subdivided into liver fragments containing portal triads lined with specialized blood vessels [3]. The liver lobe is composed of parenchymal cells - mainly hepatocytes, which compose about two-thirds of the total cell population in the liver, and non-parenchymal cells. Nonparenchymal cells include cholangiocytes, hepatic sinusoidal endothelial cells, hepatic stellate cells, Kupffer cells, bile cells, and intrahepatic lymphocyte immune cells [4, 5]. The liver fragments have a hexagonal shape, the tops represent the area of the portal triad. Each triad contains branches of the hepatic artery, portal vein and bile duct. Oxygen-rich blood from the hepatic artery mixes with nutrient-rich blood from the portal circulation. When mixed, this blood is balanced and flows through the lobule through the sinusoidal network before draining to the branches of the central vein. This blood contacts the hepatocytes through the sinusoids and ensures their blood supply, also - the hepatocytes carry out the metabolic changes of the substances absorbed in the gastrointestinal tract. This organization leads to the formation of a number of substances, including oxygen, hormones, nutrients and waste products. This gradient formation and the subsequent organization of metabolic processes are called the „metabolic zone“ [6].

METABOLISM OF XENOBIOTICS

Metabolism of xenobiotics takes place largely in the liver, which accounts for the organ's susceptibility to metabolism-dependent drug-induced injury. Drug-induced liver injuries are widespread and account for approximately one-half of the cases of acute liver failure and all forms of acute and chronic liver disease [7]. Xenobiotics include all the substances an organism is exposed to and which are not part of its metabolism. If not metabolized and eliminated, most xenobiotics accumulate and have toxic effects on the body [8]. The main organ engaged in these processes is the liver [9]. The fate of the substances entering the human body is different. They can be eliminated unchanged, retained unchanged, or undergo chemical transformation. Most often, they undergo enzymatic metabolism and prepare for their removal from the body. The biotransformation of xenobiotics is divided into two phases – reactions of phase I and reactions of phase II. Phase I reactions aim to make compounds more hydrophilic and prepare them for phase II conjugation reactions, after which they can be excreted more easily (Figure 1) [8]. A large number of enzymes are involved in biotransformation reactions. Most of them are found in many tissues as various isoforms. The greatest importance have those localized in the liver, as it performs the main detoxifying function [10]. The biotransformation of a substance most often requires several enzymes acting together. Usually, the first reaction in phase I is oxidative [8]. Several enzyme systems are involved in this phase, but the most important is that of cytochrome (CYP) P450. CYP catalyzes various functionalization reactions such as N-and O-dealkylation, aliphatic and aromatic hydroxylation, S-oxidation, and deamination [11].

Cytochrome P450 has many isoforms and all act by a similar mechanism. Each monooxygenation reaction involves the reduction of one molecular oxygen atom to water and the incorporation of the other oxygen atom into the substrate. The required electrons are transferred from NADPH by NADPH-cytochrome P450 oxidoreductase or in some cases from NADH by cytochrome b5 [8] (Figure 2).

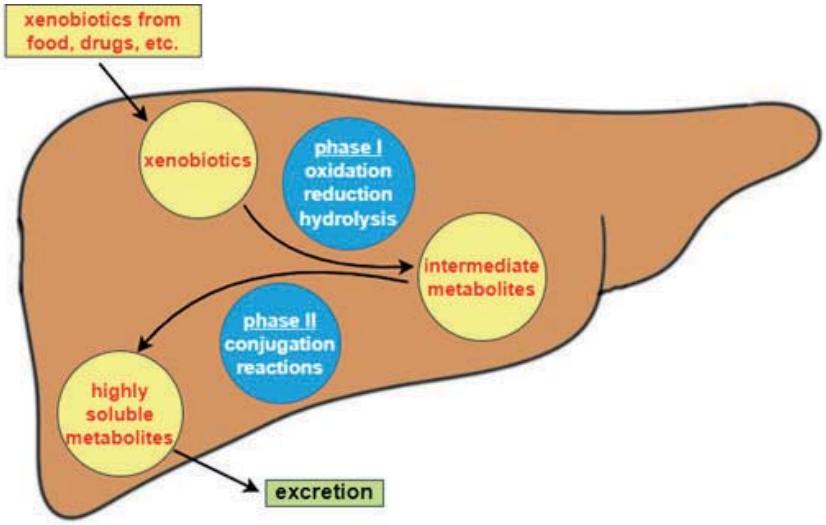

Fig. 1. Metabolism of xenobiotics

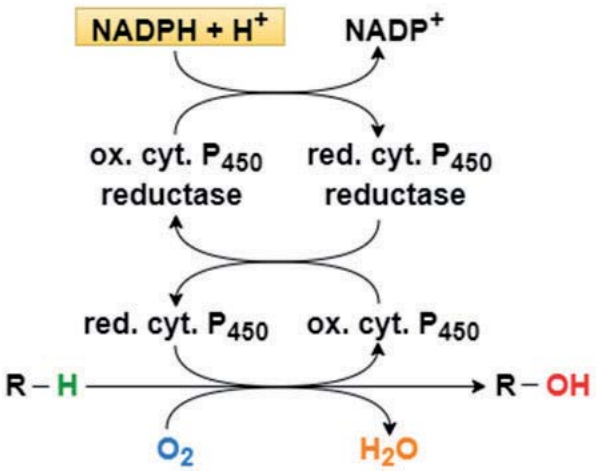

Fig. 2. Hydroxylation of substrates mechanism

Other major phase I enzymes are epoxide hydrolases, prostaglandin synthetase, glucose-6-phosphate dehydrogenase, alcohol and aldehyde dehydrogenase, amino oxidases, hydrolases, and others [8]. Xenobiotic metabolism continues during phase II, which consists of conjugation reactions. They include glucuronidation, sulfation, methylation, amino acid conjugation, and more [12]. Conjugation enzymes are usually transferase enzymes. The products are often more hydrophilic than the initial compounds and are much easier to excrete. Phase II enzymes include glucuronyl transferases, sulfotransferases (STs), N-acetyltransferases, glutathione S-transferases (GSTs), and various methyltransferases such as catechol O-methyl transferase [11].

DRUG-INDUCED LIVER INJURY

Paracetamol-induced hepatotoxicity

Paracetamol (acetaminophen) is the most widely and commonly used antipyretic and analgesic in the world. It is an over-the-counter product and is available as a stand-alone product or in combination with other medicinal substances [13]. It can be used in combination with other non-opioid and opioid analgesics and NSAIDs for the symptomatic treatment of various kinds of pain [14]. Serious and dangerous side effects can occur when taking a single or multiple high dose of paracetamol exceeding the toxic dose (4 g per day) even though the Food and Drug Administration (FDA) advises doses below 3.25 g/day for chronic use [15]. This usually results in acute liver failure (ALF), liver necrosis, renal tubular necrosis, and hypoglycemic coma [16]. There are also some risk factors that contribute to an increased risk of hepatotoxicity even when administered in therapeutic doses. These include alcohol abuse, pre-existing liver damage, malnutrition, and concomitant use of other hepatotoxic drugs [13]. For more than 30 years, a series of experimental and clinical investigations suggested that paracetamol could be more hepatotoxic in obesity and related metabolic diseases [17]. Paracetamol is absorbed in the intestine and transported to the liver, where it undergoes glucuronidation by the enzymes UDP-glucuronosyl transferases or sulfation by sulfotransferases, and the metabolites are excreted in the urine (Figure 3). A small part of ingested paracetamol is metabolised by cytochrome P450 isoforms (CYP2E1, CYP2A6) in the reactive metabolite N-acetyl-para-benzoquinone imine (NAPQI). In case of overdose, the first two pathways are saturated and significantly larger amounts of the toxic metabolite (NAPQI) are formed [18]. Low doses NAPQI are rapidly metabolised from glutathione to mercaptate and cysteine complexes, which are eliminated from the body. When high doses of paracetamol enter the liver glutathione in the body is rapidly depleted, leading to the accumulation of toxic doses of NAPQI [19].

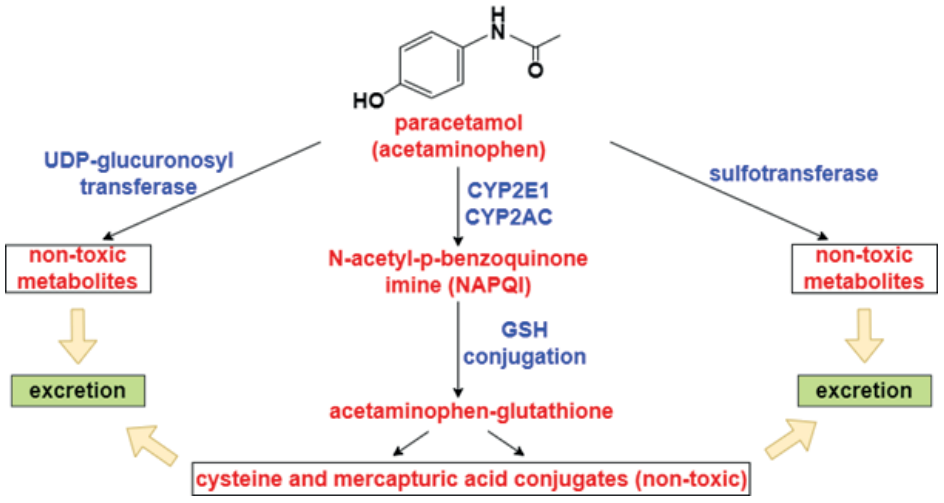

Fig. 3. Metabolism of paracetamol

NAPQI has the ability to bind to the sulfhydryl groups of cysteine residues of mitochondrial proteins. This leads to suppression of mitochondrial respiration, induction of oxidative stress and depletion of ATP stores in hepatocytes [18]. Another mechanism of cell damage is the formation of the free radical peroxynitrite, which is responsible for DNA fragmentation and inhibition of ATP synthesis [20]. NAPQI-induced mitochondrial dysfunction disrupts homeostasis, alters cell membrane permeability, and causes hepatocyte necrosis, leading to severe and often life-threatening conditions (Figure 4).

NSAIDs-induced hepatotoxicity

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs in the world. They are used mainly to treat various inflammatory diseases or to relieve acute or chronic pain [21]. The pharmacological effects of NSAIDs are due to COX blockade and subsequent reduction in PGs synthesis, leading to a reduction in inflammation, pain, and fever [22]. COX-1 is expressed in most tissue types, and prostanoids produced by this isoform typically provide functions such as cytoprotection of the gastric mucosa, regulation of renal blood flow, and platelet aggregation [23]. COX-2 expression is severely limited under normal conditions but is greatly increased at sites of inflammation in response to cytokines such as interferon, TNF, IL-1, hormones, growth factors, and hypoxia [24]. NSAIDs are classified according to their molecular structure: propionic acid derivatives, acetic acid derivatives, salicylates, enol acid derivatives (oxicams), and selective COX-2 inhibitors [25]. There are two main clinical models of hepatotoxicity due to NSAIDs. The first is acute hepatitis with jaundice, fever, nausea, severe transaminases increase, and sometimes eosinophilia. The second model has serological (ANF-positive) and histological (periportal inflammation with plasma and lymphocytic infiltration and fibrosis) characteristics of chronic hepatitis [26]. Diclofenac was discovered to be the most common causative NSAID in the United States (63%) and Iceland (100%), while nimesulide more frequently caused drug-induced liver injury in Latin America (38%) and Italy (39%). Ibuprofen was the NSAID responsible for most cases in Spain (29%) and India (25%). However, these results need to be reconsidered due to lack of sales/prescription data [27].

Propionic acid derivatives

This class includes the two most hepatotoxic compounds ibuprofen and naproxen. They mainly cause acute hepatocellular or cholestatic hepatitis [28]. Delayed-onset cholestasis is much rarer. The mechanism of toxicity is predominantly metabolic-idiosyncratic. NSAIDs in this class are also responsible for microvesicular steatosis due to the inhibitory effect of the carboxyl radical on mitochondria. Cross-hepatotoxicity has been reported between naproxen and fenoprofen [26].

Acetic acid derivatives

Diclofenac and sulindac belong to this class of NSAIDs. They can cause acute hepatocellular or cholestatic hepatitis. The mechanism of toxicity is mostly idiosyncratic. Prolonged use of diclofenac leads to liver damage. Studies in diclofenac-treated rats showed a significant increase ($p < 0.5$) in serum levels of glutamic-oxaloacetic transaminase (GOT), glutamate pyruvate transaminase (GPT), alkaline phosphatase (ALP), and uric acid compared to control group. Other effects include protein alteration, oxidative stress, idiosyncratic drug response, and mitochondrial damage caused by reactive oxygen species (ROS) [29].

Salicylic acid derivatives

One of the most widely used analgesic and antipyretic drug in the world is acetylsalicylic acid. It acts as an irreversible inhibitor of COX 1. Its level of toxicity is dose-dependent. While most cases are asymptomatic, cases of severe hepatitis occur at doses between 1800 and 3200 mg per day. Reye's syndrome is a specific form of acetylsalicylic acid

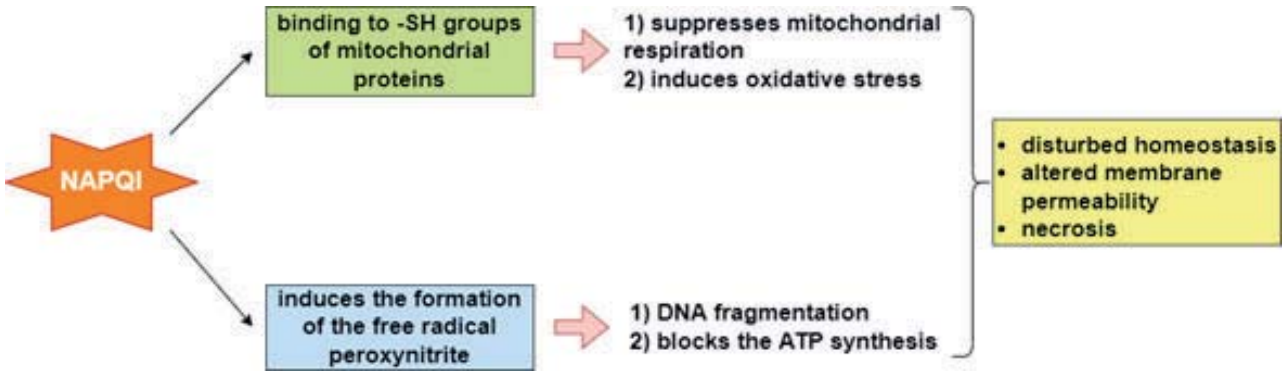

Fig. 4. Effects of NAPQI

toxicity in children taking acetylsalicylic acid during a viral infection (chickenpox, influenza). It can lead to severe hepatitis with severe microvesicular steatosis [21]. Other signs of the syndrome are leukocytosis, hypoglycemia, slightly elevated serum protein, elevated liver enzymes, and abnormal prothrombin time [30].

Enolic acid derivatives

Piroxicam – one of the enolic acids derivatives, is used in various painful and inflammatory conditions associated with rheumatoid arthritis, ankylosing spondylitis and musculoskeletal disorders. Since piroxicam is metabolized in the liver, there is a possibility of liver injury. The toxicity developed after piroxicam use is mediated through oxidative stress, which leads to lipid peroxidation and production of free radicals [31]. Significant increases in serum GOT, GPT and ALP were observed in piroxicam-treated mice. Liver preparations from rats reveal dilatation of central veins and sinusoids. There are also many hyperplasic hepatocytes with central pale nuclei and vacuolated cytoplasm. Some central veins are surrounded by cellular infiltration, and hepatocytes show early signs of apoptosis with fragmented nuclei and unclear cell boundaries [32].

Selective COX-2 inhibitors

Coxibs are selective cyclooxygenase 2 (COX-2) inhibitors, which have gained worldwide popularity due to their improved tolerance and safety in the gastrointestinal profile compared to non-selective NSAIDs [33]. The incidence of coxib-induced hepatotoxicity has not been defined. Cases of acute hepatitis or cholestatic hepatitis have been reported with celecoxib and rofecoxib [34]. A study showed an increased risk of hospitalization due to celecoxib-induced acute hepatitis. However, most findings show a lower risk of liver damage compared to other NSAIDs [35].

Antibiotics-induced hepatotoxicity

Antibiotic-induced hepatotoxicity is rare compared to other adverse reactions such as gastrointestinal disorders and allergic reactions, but due to their widespread use, they are an interesting object of study. Damage caused by antimicrobials can manifest itself in various forms of acute and chronic liver damage such as hepatocellular necrosis, hepatitis, cholestasis, steatosis and granulomatous diseases. In most cases, they are classified as idiosyncratic, making it difficult to assess the mechanisms of damage. Various factors must be taken into account, such as genetic variations in the activity of drug metabolism, repeated drug use, and others [36].

Beta-lactam antibiotics

Hepatotoxicity caused by beta-lactams is relatively rare. Amoxicillin is one of the most widely prescribed antibiotics for bacterial infections, including those of the lungs, skin, and soft tissues. Clavulanic acid helps treat bacteria by inhibiting beta-lactamase, the enzyme responsible for penicillin resistance. The most common side effects due to the use of amoxicillin-clavulanic acid are diarrhea, nausea, rash, and vomiting. It is also linked to severe adverse effects, including neutropenia, hemolytic anemia, hepatitis, and Stevens-Johnson syndrome. Drug-induced liver damage is a profound but uncommon side effect of this combination [37]. It is more associated with clavulanic acid or the combination with amoxicillin, as amoxicillin alone is less commonly associated with liver damage [38]. Toxicity occurs in different periods after administration from a few days to 6 weeks [36]. The damage is of cholestatic type, but the mechanism is not fully understood. Some HLA haplotypes are thought to be associated with its occurrence, especially in patients with immunoallergy [39].

Macrolides

Erythromycin is the most common macrolide that could be hepatotoxic. The pattern of damage is cholestatic, and symptoms appear 3-4 weeks after the initial course of treatment. Hepatotoxicity is usually reversible. The mechanism of damage is immune-mediated. Erythromycin is not usually associated with severe fatal liver damage [36]. Clarithromycin also causes cholestatic hepatotoxicity. At high doses in elderly patients it can even lead to death due to acute liver failure [40].

Fluoroquinolones

Ciprofloxacin, levofloxacin, ofloxacin and norfloxacin have been shown to cause hepatotoxicity. Patterns of hepatocellular and cholestatic hepatitis and even acute liver failure have been observed, but the incidence of these damages is very low [41]. In most cases, fluoroquinolones cause a slight increase in transaminases levels with minimal symptoms [36].

Tetracyclines

Tetracyclines have well-known hepatotoxicity and cause microvesicular steatosis. They accumulate in the mitochondria in hepatocytes and disrupt the oxidation of fatty acids, leading to the accumulation of lipids in the liver [36]. Minocycline can cause hepatitis associated with hypersensitivity reactions. Tetracycline and doxycycline cause chronic cholestasis in very rare cases [38].

Sulfonamides

Some sulfonamides, such as sulfamethoxazole, trimethoprim-sulfamethoxazole, and sulfasalazine, can cause hepatotoxicity, which occurs several days after initiation of treatment [36]. The most common pattern of damage is cholestatic, but there are also cases of granulomas. Sulfadoxine pyrimethamine, which is used to treat malaria, has been associated with fatal liver necrosis and granuloma formation. The mechanism of liver damage induced by sulfonamides is immunoallergic [42].

Valproate-induced hepatotoxicity

Valproates are commonly used antiepileptic drugs to treat generalized seizures, schizophrenia, neuropathic pain, and prophylactic treatment of migraine. They are used by both adults and children under three years. The broad spectrum of antiepileptic efficacy of valproates has been demonstrated in a number of preclinical *in vivo* and *in vitro* models, including animal models of seizures [43]. Hepatotoxicity caused by valproate can occur for several reasons. One of them is increasing the dose of the drug to achieve the desired therapeutic effect. Another reason may be a normal total concentration of valproate, but a significantly increased level of free/ unbound drug. This occurs very often in the elderly, in the presence of hypoalbuminemia, pregnancy, renal failure, and concomitant use of drugs that bind to the same site of albumin [44]. The mechanism of hepatotoxicity is the mitochondrial damage in hepatocytes (Figure 5). It is caused by inhibition of beta-oxidation of fatty acids and reduced levels of tissue carnitine. As a result of that, microvesicular steatosis of the liver occurs [45]. In addition to the accumulation of intracellular lipids, valproate can also lead to accumulation of reactive oxygen species, which also lead to mitochondrial dysfunction. Acute valproate in most cases is manifested as reversible hepatotoxicity. Discontinuation of valproate therapy usually leads to normalization of abnormal liver function, but there is evidence that it can cause liver failure and death. Therefore, when prescribing this type of drug, patients should receive clear instructions on dosage and frequency of administration, as well as potential side effects [46].

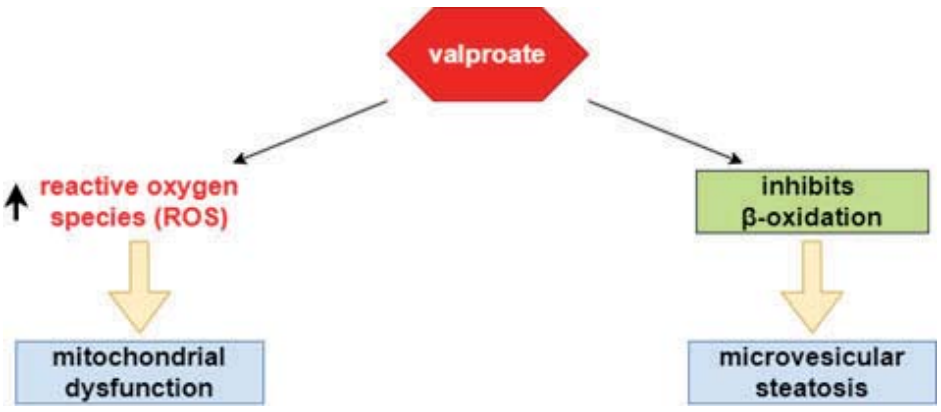

Fig. 5. Mechanism of valproate toxicity

Methotrexate-induced hepatotoxicity

Methotrexate is found effective in the treatment of cancer, inflammatory and autoimmune diseases, however, its application is limited due to the high incidence of liver toxicity. The drug could induce acute hepatocellular necrosis, cholestasis, nodular regenerative hyperplasia, fibrosis/cirrhosis, steatosis and steatohepatitis. The main risk factors, which are also related to the progression of liver injury are obesity, alcohol abuse, and diabetes. The complete mechanism of methotrexate-induced liver toxicity remains unknown. The role of oxidative stress induction has been widely discussed, and the role of methotrexate metabolites (methotrexate polyglutamates) as primary inducers of intracellular oxidative stress in hepatocytes was revealed. Recent research implies also the role of the suppressed activity of peroxisome proliferator-activated receptor-γ (PPARγ), antioxidant markers such as nuclear factor erythroid 2-related factor 2 (Nrf2), and heme oxygenase-1 (HO-1) and NADPH dehydrogenase (quinone) 1 (NQO1) activity in liver tissue damage [47-49].

Treatment of experimental animals with methotrexate induces elevated levels of pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α), nuclear factor- κB (NF-κB) and interleukin 6 (IL-6), IL-β1, IL-12, nitric oxide (NO), pro-inflammatory enzymes such as cyclooxygenase 2 (COX-2), nitric oxide synthase (NOS). Clinical biomarkers such as serum transaminases and bilirubin show increased blood levels, while intracellular superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities are decreased in rat liver tissue [48-50] (Figure 6).

Anti-tuberculosis drugs-induced hepatotoxicity

Treatment of pulmonary tuberculosis includes co-administration of drugs like Isoniazid and Rifampicin, which are known for their liver toxicity [51].

Isoniazid treatment could result in hepatocellular necrosis. The adverse drug reaction is of idiosyncratic type and usually occurs weeks to months after the start of the treatment. In

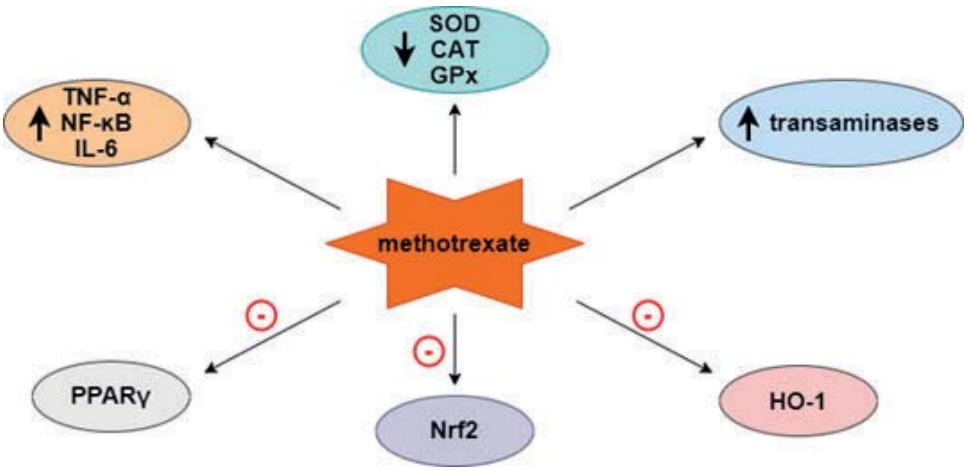

Fig. 6. Mechanism of methotrexate toxicity

some patients the condition remains asymptomatic, however, others may experience symptoms. The liver injury induced by isoniazid is usually mild and it is resolved even though the continuous treatment with the drug. In some cases, isoniazid evokes severe liver toxicity, manifested as severe hepatitis with possible progression to liver failure. The mechanism of toxicity remains unknown. The role of the metabolites (hydrazine, acetyl hydrazine, and radical metabolite) and the following immune response is implied. Recent research suggests the involvement of the transcription factors of glutathione synthesis and detoxification enzymes, including Nrf2. Other authors propose the role of oxidative stress and mitochondrial damage (electron transport chain interaction, lipid peroxidation, mitochondrial membrane potential change) as possible mechanisms of liver injury [52-54]. Isoniazid-induced hepatotoxicity is associated with polymorphisms of several genes including N-acetyltransferase II (NAT2), Cytochrome P450 2E1 (CYP2E1), and glutathione S transferases (GST1) [55]. The single nucleotide polymorphism in NAT2 affects the isoniazid metabolism rate. In addition, it affects the variations in treatment efficacy and frequency of adverse reactions. Populations with NAT2 enzymes in the slow acetylator group were shown to be susceptible to isoniazide-induced hepatotoxicity exposure [56]. The most important risk factors are genetic predisposition, advanced age, co-administration of enzyme inducers (eg. Carbamazepine, Rifampicin), or other substances with liver toxicity (eg. alcohol, azoles). Previous liver diseases also increase this risk. Other types of liver injury, associated with combined treatment with Rifampicin, Ethambutol, or Pyrazinamide are steatosis and cholestasis [52,54].

Rifampicin induces liver toxicity via the mechanism of hypersensitivity. Liver damage is rare in case of monotherapy, however, the risk increases if higher doses are taken. In case of combined therapy with Isoniazid, the risk increase greatly. The possible explanation is related to the induction of cytochrome enzymes, which occur during the treatment with Rifampicin. Increased activity of CYP450 intensifies the metabolism of Isoniazid, leading to increased production of toxic metabolites [51, 54].

CONCLUSION

There are many drugs that damage the liver and it is difficult to cover them all in detail. In conclusion, we can say that there is a wide range of drugs used for various indications that are toxic to the liver. A lot of them can cause liver damage even in therapeutic doses. For this reason, it is recommended to take hepatoprotectors and periodically monitor liver function biomarkers. When prescribing potentially hepatotoxic drugs, the dose and frequency of administration should be taken into account, as well as the benefit / risk ratio.

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Conflicts of interest

The authors declare no conflict of interest.

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