"From Prescription to Toxicity: A Comprehensive Review of Drug-Induced Hepatotoxicity"

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ABSTRACT

The liver is the main organ responsible for controlling the internal environment of the body. At the moment, there is no way to compensate for liver dysfunction. Its main duty is to control the movement of nutrients and the metabolism of fats, proteins, and carbs. A primary cause of liver damage is drugs. Over 900 drugs, toxins, and plants have been connected to liver damage. Liver transplantation or death result from idiosyncratic drug responses in about 75% of cases.Acute fatty infiltration, cholestatic jaundice, liver granulomas, active chronic hepatitis, liver cirrhosis, acute-dose dependent liver damage, and liver cancers are a few examples of drug-induced liver diseases.

About 2000 cases of acute liver failure happen in the US each year, and more than half of these are caused by pharmaceuticals (37% from paracetamol and 13% from idiosyncratic reactions to other drugs). Drugs are the cause of 10% of all instances of acute hepatitis and 5% of hospitalisations related to jaundice. About 40,000 people die each year from chronic liver disease and cirrhosis, which account for about 2% of mortality in 17 countries. This study provides insight into the mechanisms of liver damage and clinical circumstances of numerous medications that cause hepatotoxicity, given the importance of drug-induced hepatotoxicity as a major cause of liver damage.

Keywords: Liver, hepatotoxicity, drug, mechanism

Objectives:

- Examine the potential for hepatotoxicity caused by drugs.
- Explain the clinical indicators and toxicity mechanism that are used to classify drug-induced hepatotoxicity.
- Identify the causes of hepatotoxicity caused by drugs.
- List the medications that caused hepatotoxicity in brief.

Introduction:

The liver plays a staggeringly large number of vital functions in the upkeep, operation, and control of the body's homeostasis. Almost every metabolic pathway that promotes development, resistance to disease, the provision of nourishment, energy, and reproduction involves it (Sharma et al., 1991). The primary functions of the liver are the metabolism of fat, protein, and glucose; detoxification; bile synthesis; and vitamin storage. For overall health and wellbeing, it is therefore crucial to keep the liver working (Subramaniam and Pushpangadan, 1999). Chemical-induced liver damage is referred to as hepatotoxicity. Certain pharmaceutical medications have the potential to injure organs, whether they are taken in excess or even at therapeutic dosages. Other chemical agents that can cause hepatotoxicity include those used in industry and laboratories, natural substances (such microcystins), and herbal remedies. Among the substances that harm the liver are hepatotoxins. Over a thousand drugs have been connected to liver damage, the most common cause for a drug to be taken off the market. The only indication of subclinical liver damage caused by chemicals is abnormal liver enzyme tests. Drug-induced liver injury is the cause of 50% of acute liver failures and 5% of all hospital admissions. Ostapowicz et al. (2002) found that over 75% of idiosyncratic pharmaceutical responses result in either liver transplantation or death. Acute liver injury without a known aetiology is frequently diagnosed as drug-induced liver injury (DILI). Understanding the agent's known and potential hepatotoxicity is an essential part of the diagnostic process, in addition to ruling out competing aetiologies. Hepatotoxicity data, however, are not always easily accessible. "Patient information" package inserts are included with every medication that has been approved by regulatory bodies. A number of case series and publications have unequivocally shown that certain medications cause liver injury. Positive rechallenge instances have demonstrated causality, and liver damage is a known clinical hallmark (phenotype) of many of these medications [4,5]. Amoxicillin-clavulanate, halothane, isoniazid, and chlorpromazine are a few examples. Halothane and chlorpromazine were frequently identified as hepatotoxic causes in early DILI investigations.

Etiology

Higher body mass index (BMI), advanced age, and feminine sex are risk factors for the development of DILI in patients.[8] [9] More than 1000 medications and herbal remedies that are known to cause hepatotoxicity are listed in the National Institute of Diabetes and Digestive and Kidney Diseases' (NIDDK) searchable database,LiverTox. While aspirin, tetracycline, and vitamin A are less common causes of intrinsic DILI, acetaminophen is the most common cause.

Causes of DILI instances include:

- The most commonly used antibiotics (45.4%) are amoxicillin-clavulanate, sulfamethoxazole-trimethoprim, ciprofloxacin, and isoniazid.
- NSAIDs, or nonsteroidal anti-inflammatory medications.
- 16.1% of herbal and dietary supplements (HDS) are made up of anabolic steroids, green tea extract, and multi-ingredient nutritional supplements.

- Medication for cardiovascular disease (10%) includes amiodarone and statins.
- Valproate and phenytoin are both medications that affect the central nervous system (CNS).
- Alpha inhibitors, methotrexate, tyrosine kinase inhibitors, and tumour necrosis factor inhibitors are examples of anticancer drugs.

Epidemiology

It is challenging to determine the true incidence of DILI because it is often underreported and multiple diagnostic criteria are used.[3]. Worldwide and in the United States, the annual incidence of DILI is fewer than 15–20 per 100,000 people.In [2][7].[11] Importantly, it is a much less common cause of acute liver injury overall, but it is the most common cause of acute liver failure episodes in the United States (13–16%).[1,]In [9] Women experience idiosyncratic DILI at a higher rate than men (59%) which may be due to pharmacokinetic differences or hormonal interactions with immunomodulating drugs. Individuals over 50 are more likely to experience DILI, which could be related to their increased use of prescription drugs.

Pathophysiology

There are two processes that define DILI pathogenesis: intrinsic and idiosyncratic. When medications cause dose-dependent liver damage with a brief latency period, the intrinsic mechanism is predictable and repeatable.[12][13] [7] [14] For instance, in paracetamol toxicity, the metabolism of the drug results in reactive metabolites that build up excessively, causing necrosis and hepatocyte death. The unique mechanism of DILI is distinguished by an unanticipated and non-replicable path. It affects vulnerable individuals regardless of the amount of medication taken, and its latency time varies, usually starting 7–14 days following the first dose. While the exact mechanism is unknown, it is thought to be caused by a confluence of environmental, drug, and host factors. The host factors include the patient's age, gender, immunological condition, metabolism, and genetic polymorphisms. Factors related to the drug include weight, duration, dose, and level of lipophilicity. Environmental influences include food, tobacco, pollutants, and concurrent alcohol usage. The two categories of idiosyncratic DILI mechanisms include immune-mediated (allergic) liver injury resulting from hypersensitivity and non-immune-mediated metabolic (non-allergic) processes resulting from mitochondrial injury.

Hepatotoxic Drugs (Antitubercular Drugs)

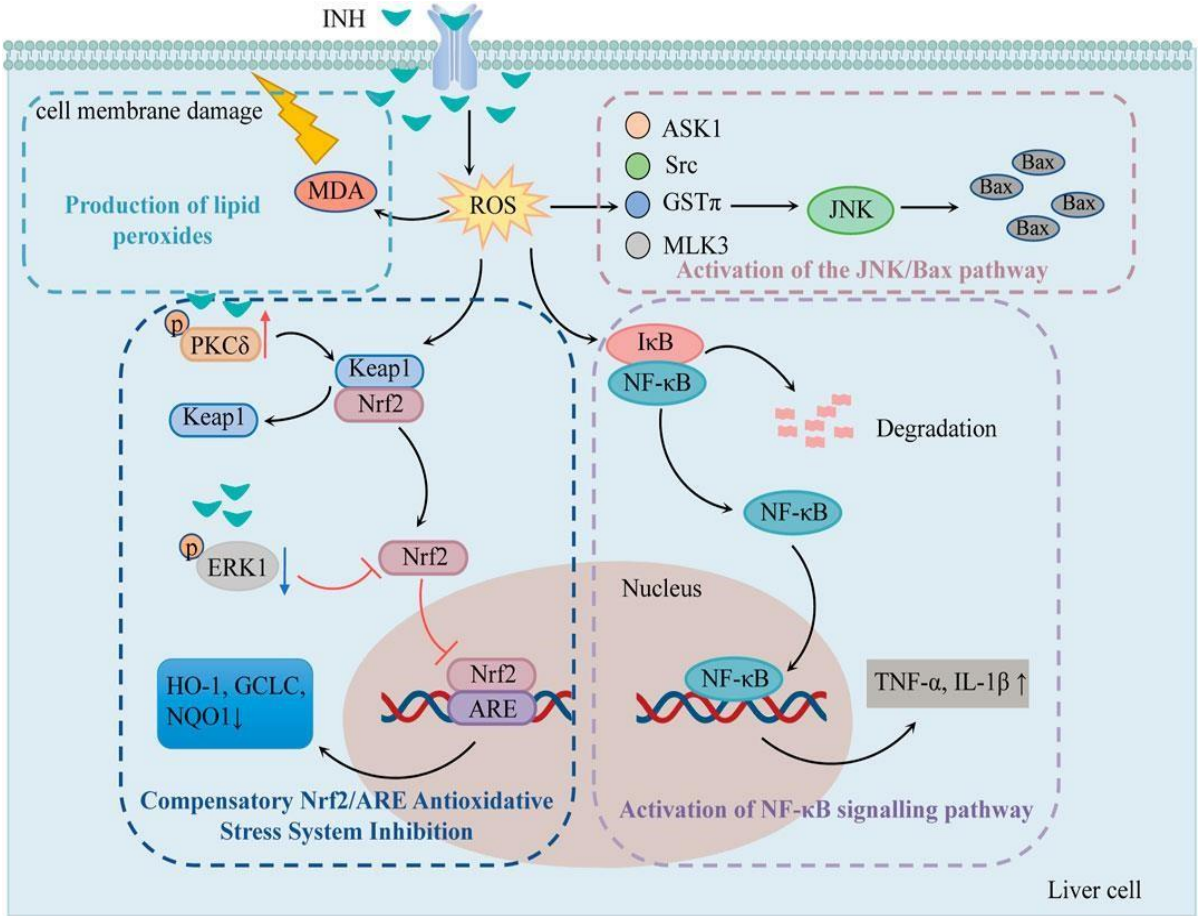
All of the first-line anti-tubercular medications—pyrazinamide, isoniazid, and rifampicin—have the potential to be harmful to the liver. These medications are broken down by the liver. Hepatotoxicity has not been demonstrated when ethambutol and streptomycin are used together. The side effects of antitubercular therapy may worsen if you take several different prescriptions. Consequently, while if INH, Rifampicin, and Pyrazinamide have the potential to be hepatotoxic, their harmful effects are exacerbated when taken together. The prevalence

of anti-TB-related hepatotoxicity varies between 2% and 28%, depending on the population being studied and the hepatotoxicity diagnostic criteria (Girling, 1978).

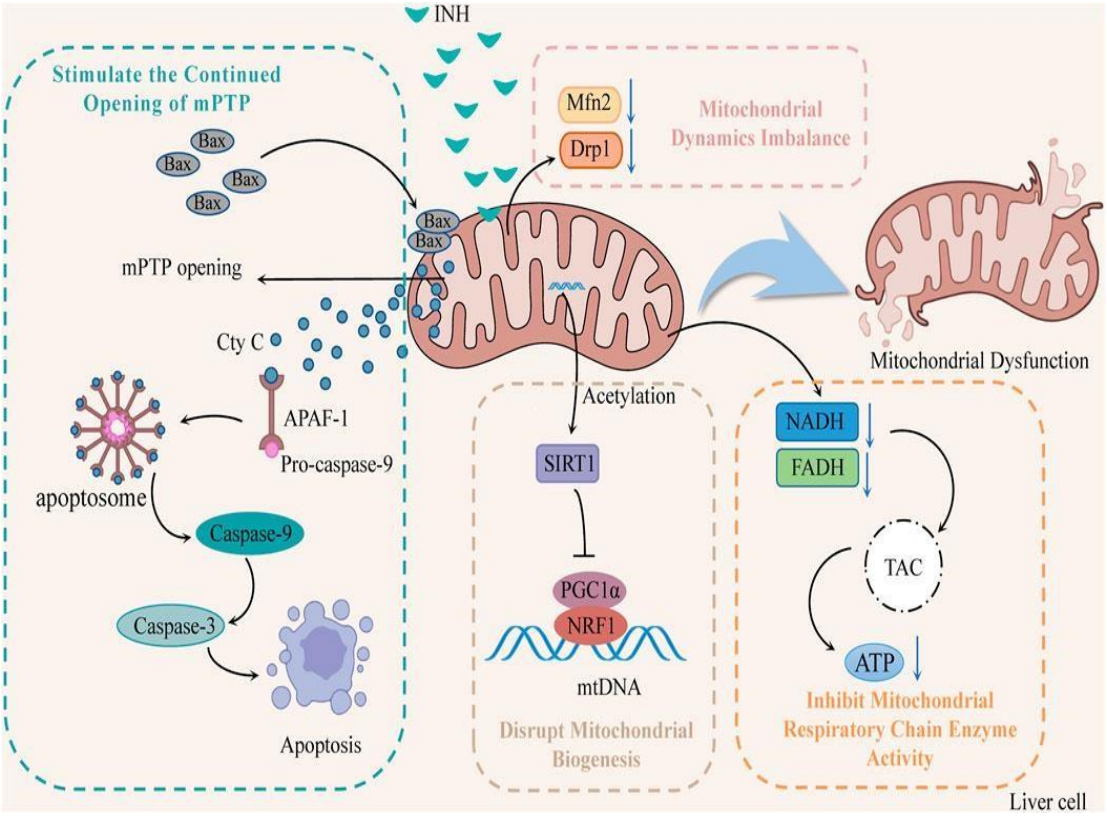
Rifampicin

The risk of hepatitis is increased in those taking Rifampicin concurrently. Rifampicin-induced overexpression of the cytochrome P450 enzyme is likely to be responsible for this, as it leads to a greater production of dangerous metabolites from acetyl hydrazine (AcHz). Moreover, rifampicin speeds up the hepatotoxic degradation of INH into nicotinic acid and hydrazine. INH and Rifampicin combined cause a higher incidence of liver necrosis, and Rifampicin shortens the plasma half-life of AcHz (an INH metabolite) and increases its oxidative elimination rate, which quickly converts AcHz to its active metabolites. Additionally, rifampicin's interactions with antiretroviral drugs impact plasma levels and hepatotoxicity risk (Padma et al., 1998; Tostmann et al., 2008). A higher CYP2E1 activity is associated with the CYP2E1 c1/c1 genotype, which could lead to a higher production of hepatotoxins. According to Jenner and Timbrell (1994) and (1995), CYP2E1 activity is stimulated by isoniazid and hydrazine in rat experiments. The activity of CYP1A2, 2A6, 2C19, and 3A4 is inhibited by isoniazid. Hydrazine detoxification is believed to include CYP1A2. Inhibiting or activating these enzymes may be how isoniazid produces its own toxicity (Wen et al., 2002; Desta et al., 2001).

The oxidative stress caused by isoniazid:



2.Mitochondrial dysfunctions:



Pyrazinamide

After being converted to pyrazinoic acid, pyrazinamide (PZA; pyrazoic acid amide) is oxidised by xanthine oxidase to 5-hydroxypyrazinoic acid. Pyrazinamide does not activate the enzymes involved in its metabolism, as evidenced by the fact that its serum half-life is independent of treatment duration. Uncertainty surrounds the enzymes implicated, the mechanism of pyrazinamide-induced toxicity, and whether pyrazinamide or its metabolites mediate the toxicity. There was no inhibitory effect of pyrazinamide on CYP450 isoenzymes in human liver microsomes, but it did reduce the activity of many CYP450 isoenzymes (2B, 2C, 2E1, 3A) in rat studies (Maffei and Carini, 1980; Nishimura et al., 2004).

Nonsteroidal anti-inflammatory drugs.

Nonsteroidal anti-inflammatory medications (NSAIDs) such as acetaminophen, mesulide, diclofenac, and ibuprofen form the basis of pharmacotherapy for most rheumatological conditions. Both over-the-counter and prescription medications are used extensively as analgesics and antipyretics. It is the most frequent cause of toxic damage caused by drugs to many organ systems, such as the kidneys and gastrointestinal tract. Centrilobular liver necrosis results after an overdose of paracetamol (Walker, 1997). There is very little epidemiological risk of liver damage that is clinically noticeable (1–8 cases per 100,000 patient years of NSAID use). However, when it does occur, it may be substantial and lead to confusion in the diagnosis (Sgro et al., 2002). On the other hand, ibuprofen use skyrocketed

between 1998 and 2000. Nearly all NSAIDs have been associated with liver injury, primarily hepatocellular in nature, with immunologic idiosyncrasy thought to be the cause. A number of NSAIDs have been taken off the market because of associated hepatotoxicity (Connor et al., 2003). Even though celecoxib is believed to carry a lesser risk, hepatotoxicity has been associated with the more recent, more selective COX-2 inhibitors (such as celecoxib, rofecoxib, and mesulide) (Benichou, 1990).

Examples of NSAIDs that were discontinued or eliminated due to hepatotoxicity include the following (Lewis, 2003): Glafanine and cinchophen are derivatives of anthranilic acid. Fenclozic acid, Amphenac, Isoxepac, and Bromofenac are examples of derivatives of acetic acid. The medications Benoxaprofen, Ibufenac, Pirprofenac, Suprofenac, and Fenbufen are derivatives of propionic acid. The pyrazolone chemicals oxyphenbutazone and phenylbutazone are examples. Sudoxicam is one of the oxicams. Quinazonlone derivatives include fluproquazone.

Mechanism of NSAID Toxicity

A number of in vitro animal models have recently been used to investigate the possible reasons of NSAID-related hepatotoxicity. Studies using freshly isolated rat hepatocytes and rat liver mitochondria have demonstrated that diphenylamine, which is present in the structure of NSAIDs, can uncouple oxidative phosphorylation, lower hepatic ATP levels, and increase hepatocyte damage. When mitochondria were incubated with diphenylamine, mefenamic acid, or diclofenac, the mitochondria grew. Additionally, a shift in the safranine-binding spectra to mitochondria was noted, suggesting that the membrane potentials of the mitochondria had been lost. Addition of oligomycin, which inhibits ATPase, protected cells from harm. No significant oxidative stress (reduction in glutathione and lipid peroxidation) or increase in intracellular calcium concentration was observed in diclofenac-induced hepatocyte injury. Administration of paracetamol causes centrilobular hepatocytes to necrotise, a condition marked by a nuclear lesion. Massive, severe hepatic necrosis follows pyknosis and eosinophilic cytoplasm. N-acetyl-P benzoquinoneimine, an oxidative derivative of paracetamol, covalently binds to protein sulfhydryl groups, causing lipid peroxidative degradation of glutathione levels and liver cell necrosis (Masubuchi et al., 2000; Bort et al., 1999).

Diclofenac

According to Mitchell et al. (1973), idiosyncratic DILI (drug-induced liver injury) includes diclofenac hepatotoxicity. High liver enzyme values are acquired by 15% of habitual diclofenac users, with 5% experiencing a threefold increase in transaminase levels. Although there have been reports of cholestatic liver disease and cases that may indicate autoimmune hepatitis, diclofenac is primarily associated with hepatocellular liver disease (Aithal, 2004). Diclofenac is glucuronidated by UDP-glucuronosyltransferase-2B7 and 4′-hydroxylated by cytochrome P450 2C9, producing an unstable acyl glucuronide. By using CYP2C8, the latter is further oxidised. By the way of CYP2C8 catalysis, 5-hydroxydiclofenac is also generated. Because 5 hydroxy diclofenac produces both diclofenac acyl glucuronide and benzoquinone imines, which change proteins covalently, CYP2C8 activity may be elevated or lowered,

which could increase the risk of hepatotoxicity. Since MRP2 is essential for the transport of diclofenac acyl glucuronide to biliary canaliculi, the metabolite builds up when MRP2 expression declines. Oxidative stress is brought on by the buildup of reactive compounds, and alterations in mitochondrial permeability harm cells. Neoantigens are also produced when reactive metabolites covalently bind to "self" proteins. In susceptible individuals and in a proinflammatory cellular environment, mild liver injury can progress to severe DILI. Additionally, APCs may phagocytose diclofenac adducts generated by dying hepatocytes and present them with MHC II molecules. When helper T cells identify neoantigens, they become activated and start an effector cell reaction. In addition to producing MHC I molecules on their surface, which rise with inflammation, hepatocytes may also carry diclofenac adducts, which can cause liver injury mediated by cytotoxic T cells. As an alternative, B cells might recognise diclofenac adducts on hepatocyte plasma membranes, which would allow them to develop into plasmacytes, release antibodies, and ultimately be eliminated by the immune system.

Antigen-presenting cell (APC), drug-induced liver damage (DIL), interleukin (IL), multidrug resistance protein 2 (MRP2), and T-cell receptor (TCR) are some examples of abbreviations (Aithal, 2011).

Sulindac

The medication most commonly associated with hepatotoxicity is sulindac. Of the 91 liver injury cases reported in the literature, 43% showed a cholestatic pattern (liver injury affects bile flow and is characterised by itching and jaundice), 25% showed a hepatocellular pattern, and the remaining cases showed a mixed pattern of injury (Tarazi et al., 1993). Four patients passed away, and the majority (67%) experienced jaundice.

Cholestatic liver injury may result from sulindac's competitive reduction of canalicular bile salt transport (Bolder et al., 1999).

Antiretroviral drugs

Deathly acute hepatitis has been associated with a number of antiretrovirals; asymptomatic transaminase elevations are the most frequent cause. Patients with chronic hepatitis C and/or B are at a higher risk of developing liver damage. Unknown is the frequency of drug-induced liver damage in the majority of antiretrovirals (Nunez, 1999). When co-infected individuals with HCV (Hepatitis C) and/or HBV (Hepatitis B) are treated with HAART (Highly Active Antiretroviral Treatment, generally a combination of two or three drugs), liver damage, especially severe toxicity, is evidently more common (Sulkowski et al., 2000; Wit et al., 2002).

Protease inhibitors

Ritonavir, Indinavir, Saquinavir, and Nelfinavir are a few examples. With the introduction of high-activity ART (antiretrovirals), which at first included a protease inhibitor (PI), hepatotoxicity became more noticeable. Nevertheless, no study has been able to show that there is a higher risk of liver damage associated with this particular drug family. According to certain research (Bonfanti et al., 2001), full dosage ritonavir (RTV) is more hepatotoxic than other PIs; however, other investigations have not confirmed these findings (Cooper and Aceti, 2002). RTV has occasionally resulted in acute hepatitis that is fatal (Pai et al., 2000). Additionally, reports of liver damage have been made in connection with the use of saquinavir (SQV) and indinavir (IDV) (Sulkowski, 2003). In a study of 1052 individuals, nelfinavir was found to be less hepatotoxic than the other PIs studied (RTV, IDV, SQV, and amprenavir (APV).

Nucleoside analogues are reverse transcriptase inhibitors (NRTI).

Tenofovir (TDF), Didanosine, Stavudine, Zidovudine, Lamivudine (3TC), and Abacavir (ABC) are a few examples. According to certain research, tenofovir and lamivudine (3TC) had a lower rate of hepatotoxicity (Nunez et al., 2001). But most NRTIs have the potential to damage mitochondria, which increases the risk of liver damage. Liver failure has occurred. While didanosine and stavudine are more commonly linked, severe hepatotoxicity has been documented in zidovudine users. Tenofovir (TDF) and abacavir (ABC), which have a low risk of mitochondrial damage, seem to be safer for the liver. Eliminating 3TC may trigger an HBV replication flare in people with chronic hepatitis B, which would raise transaminases (Brinkman et al., 1998).

Non-nucleoside analogues, reverse transcriptase inhibitors

Nevirapine, emtricitabine, and efavirenz are a few examples. There are a number of variables and processes that contribute to the risk of liver damage associated with non-nucleoside analogue reverse transcriptase inhibitors (NNRTI). People taking Nevirapine (NVP) as part of a post-exposure prophylactic regimen have experienced a number of cases of severe liver damage, some of which have been fatal (Bissuel et al., 1994; Gisolf et al., 2000). While some authors have found that NVP is more likely to cause liver damage than efavirenz (EFZ), others have not. Notably, one study (Sulkowski, 2002; Palmon, 2002) reported no cross-hepatotoxicity between NVP and EFZ. The rates of liver damage-related morbidity and death were the same for those receiving EFZ or NVP in the same experiment. Additionally, in studies on NVP hepatotoxicity, most patients who continued using the same medicine saw a decrease in transaminases (Carbonero et al., 2002; Martinez et al., 2001).

Mechanism of toxicity of antiretrovirals

Listed below are some possible routes that may contribute to the development of hepatotoxicity associated with antiretroviral medication. Certain people probably have multiple pathogenic pathways operating at the same time, which makes it challenging to pinpoint the exact mechanisms underlying the onset of hepatotoxicity.

Direct Toxicology

Like any other medication, antiretrovirals have the potential to directly harm the liver. If the enzymes involved in cytochrome-mediated drug processing in the liver are polymorphic, the result could be liver toxicity (Bissell et al., 2001). Idiosyncratic polymorphisms of the enzyme complexes may result in significant variance in drug metabolism, predisposing some individuals to hepatotoxicity because many antiretrovirals are metabolised in the liver via cytochrome pathways. Certain medications may make intracellular stress pathways and/or death receptors more active (Leist et al., 1998).

Hypersensitivity responses

Antiretrovirals can directly damage the liver, just like any other drug. Liver toxicity may result from polymorphism of the enzymes involved in cytochrome-mediated drug processing in the liver (Bissell et al., 2001). Since many antiretrovirals are metabolised in the liver via cytochrome routes, idiosyncratic polymorphisms of the enzyme complexes may create a substantial variation in drug metabolism and predispose some people to hepatotoxicity. According to Leist et al. (1998), several drugs may increase the activity of intracellular stress pathways and/or death receptors.

Mitochondrial toxicity

Hepatotoxicity of this rare but distinct type can cause sudden liver failure. Microvesicular steatosis accumulation in liver cells, together with mitochondrial depletion, is the primary characteristic of the hepatic lesion. The clinical manifestation of this early lesion may develop into macro vesicular steatosis with localised necrosis, fibrosis, cholestasis, biliary duct proliferation, and Mallory bodies, which resembles the symptoms of pregnant steatosis, Reye's syndrome, or alcohol-induced liver injury. It is noteworthy that this type of lesion is not predisposed by underlying hepatic disease (Bissell et al., 2001). Since lactic acidosis frequently appears after years of treatment and correlates with the number of concurrent NRTIs, it is believed to be caused by cumulative NRTI exposure. According to in vitro findings, a number of NRTI combinations result in long-term mitochondrial toxicity that is additive or synergistic (Chitturi and George, 2002).

Antihyperlipidemic drugs

Hepatocellular or mixed liver damage is frequently caused by anti-hyperlipidemic medications, with rare instances of pure cholestatic illness (Bertolami, 2007). Depending on the drug or class, different mechanisms of hepatotoxicity have been proposed. These include cytochrome P450 system effects, bile acid transport protein impairment, immune-mediated inflammatory response to the drug or its metabolites, immune-mediated apoptosis by tumour necrosis factor, and oxidative stress from intracellular damage. The antihyperlipidemic medication with the highest risk of liver damage is sustained release niacin. Although asymptomatic increases in amino transferases are common, HMG CoA reductase inhibitors, commonly referred to as statins, seldom cause clinically significant liver damage (Cohen et al., 2006).

Statins

Statins lower low-density lipoprotein (LDL) levels and increase the stability of atherosclerotic plaques by totally blocking 3-hydroxy-3 methylglutarylcoenzyme A (HMG-CoA) reductase, an enzyme necessary for the production of cholesterol (Jacobson, 2006). While very high dosages of statins can cause hepatotoxicity, ordinary therapeutic levels were not associated with substantial liver impairment, according to early animal studies on the medication (Horsmans et al., 1990). Rabbits treated with high doses of lovastatin had significant hepatocellular necrosis. A model of guinea pigs given large doses of simvastatin also showed same pattern of harm. But hepatocellular necrosis brought on by statins is quite rare in people (Alonso et al. 1999).

Atorvastatin

Hepatotoxicity from atorvastatin has been associated with a variety of liver damage patterns, typically appearing months after beginning the medication (Nakad et al., 1999; Pelli et al., 2003). In a recent case report, atorvastatin was also discovered to have underlying autoimmune hepatitis. After hundreds of thousands of patients were treated with this medication, only 0.7% of instances had significantly increased transaminase levels that were greater than three times the upper limit of normal (Grimbert et al., 2006).

Lovastatin

Lovastatin has been associated with cholestatic and hepatocellular forms of mixed hepatic injury. This type of liver disease involves varying degrees of cholestatic and cytotoxic involvement. The development or direct influence of enzyme-drug addiction results in cytotoxic T-cell response, membrane disruption, and cell dysfunction. A liver biopsy in one case that has been published showed histologic signs of cholestasis and centrilobular necrosis with a mixed inflammatory infiltrate (Ricaurte et al., 2006).

Simvastatin

Medication interactions are thought to be the cause of simvastatin hepatotoxicity. 1) Simvastatin in combination with flutamide, troglitazone, and diltiazem has been shown to cause hepatotoxicity (Kanathur and Caldwell, 2001).

Ezetimibe

According to recent studies, ezetimibe can occasionally result in hepatotoxicity, including acute autoimmune hepatitis and severe cholestatic hepatitis. According to Landmesser et al. (2005), the drug's metabolism may be the source of toxicity because it is rapidly absorbed, glucuronidated, and produces an active metabolite, and there is significant enterohepatic recirculation.

Anaesthetic Agents

These are the substances that cause reversible loss of emotion and discomfort. Anaesthetics can be classified as either local or general. Cholestasis is caused by these medications' interference with bilirubin metabolism and liver damage (direct toxicity and immune-mediated hypersensitivity) (Brody and Sweet, 1963).

Halothane

Halothane became the preferred anaesthetic in 1956, replacing ethylene. Acute hepatitis occurred in a few isolated cases during the two-year period (Brody & Sweet, 1963). Halothane can cause hepatotoxicity in two different ways: About 20% of patients treated with halothane experience type I, the first type of postoperative hepatotoxicity, which is mild and self-limiting and includes a minor amount of hepatic damage. It is thought that the modest hepatic damage results from halothane's direct impact on liver cells. There appear to be two clinically known causes of minor hepatic damage. According to electron microscopy, the first is a momentary increase in liver enzymes, while the second is a breakdown in the integrity of the cells.

Local hypoxia brought on by a shift in the hepatic oxygen demand and supply relationship, as well as the breakdown of halothane within cells through anaerobic and aerobic pathways, result in lesions (Conzen, 1993). Hepatitis caused by type II halothane is the second form of halothane-mediated hepatotoxicity. After halothane injection, this type of hepatotoxicity occurs in one out of every 10,000 to 30,000 adult patients. Immune-mediated hepatotoxicity is the most likely mechanism, where antibodies target altered liver microsomal proteins on the surface of hepatocytes (Fallahian, 2009). The patient's immune system is proven to be the cause of the fulminant form of halothane hepatitis. The generation of reactive intermediates during halothane metabolism usually results in tissue acetylation, in addition to signs of mild cellular damage (Satoh et al., 1985). Acetylation of intracellular proteins is thought to be the first step in the pathogenesis of severe liver injury. Producing antibodies that specifically target these acetylated neo antigens is the second stage. One important catalyst in the synthesis of trifluoro acetylated proteins, which have been connected to the pathophysiology of halothane hepatitis, is cytochrome P450 2E1 (CYP2E1) (Elisson, 1996; Reichle and Conzen, 2003).

Chloroform

Chloroform is just as dangerous as carbon tetrachloride. Chloroform's toxicity to the liver, kidneys, and nose depends on microsomal cytochrome P450 metabolism. It seems that inorganic chloride (expelled in urine), CO2 (exhaled), phosgene, and some hepatic covalently bound carbon are produced by the oxidative metabolism of chloroform, which is mediated by cytochrome P450. Hepatic centrilobular and renal proximal tubular necrosis have been found to be directly correlated with extensive covalent binding to kidney and liver protein (Njoku et al., 1997).

Isoflurane, Enflurane, and Desflurane

Anaesthesia using isoflurane, enflurane, and desflurane has been shown to cause hepatic damage. The immune reaction to liver proteins altered by trifluoroacetyl or trifluoroacetyl-like anaesthetic metabolites results in hepatotoxicity. Because isoflurane has a slower metabolism and produces less trifluoro acetyl proteins, there have only been a few documented occurrences of hepatotoxicity (Sipes and Brown, 1976). Desflurane, enflurane, and isoflurane undergo oxidative metabolism, which is catalysed by hepatic cytochrome P450 2EI. Rats' livers developed centrilobular necrosis as a result of reducing metabolites produced in hypoxic conditions (Ross JA et al. 1984).

Nitrous Oxide

According to one theory, nitrous oxide was used in nearly every instance of unexplained hepatitis (Horton et al., 1994). Methionine synthase inhibition and an elevated risk of hypoxia are potential roles. It has been demonstrated that increased NO production in the liver inhibits gluconeogenesis and mitochondrial respiratory chain enzymes (Curran et al., 1990). In cultured hepatocytes, NO inhibits bile canicular contraction as well as total protein synthesis (Dufour et al., 1995).

Anti-rheumatic drugs

A number of commonly used pharmaceuticals have been associated with adverse liver reactions, including anti-rheumatic treatments. Among the main causes of acute hepatotoxicity are azathioprine and sulfasalazine treatment. According to a population-based case-control study with 1.64 million patients, sulfasalazine and azathioprine were shown to be among the most hepatotoxic drugs of any class, with an approximate 1 in 1,000 user incidence of liver damage (Abajo et al., 2004).

Sulfasalazine hepatotoxicity

Psoriatic arthritis (PsA) and RA are frequently treated with the DMARD sulfasalazine. In a group of individuals with inflammatory arthritis, the estimated incidence of significant hepatotoxicity was greater (4 per 1,000 users). Both hepatocellular and cholestatic patterns of liver disease can manifest, with most occurrences occurring within the first month of beginning sulfasalazine medication. Approximately 25% of patients have jaundice, and some of them experience hepatic failure quickly (Jobanputra et al., 2008).

Gold salt-induced cholestasis

Although a wider range of DMARDs and biologic therapies have been developed, 7–11% of people with RA and PsA still use gold salts. After receiving gold-salt therapy, approximately 1% of people experience hepatotoxic consequences (Helliwell and Taylor, 2008). Following parenteral gold treatment, there have been reports of rapidly growing hepatocellular patterns of DILI, which can result in hepatic necrosis, liver failure, and death or transplantation (Watkins et al., 1988).

Azathioprine liver damage

RA and PsA are among the many inflammatory diseases that are treated with the immunosuppressant azathioprine. Acute DILI and vascular disorders such nodular regenerative hyperplasia (NRH), hepatic veno-occlusive disease, and peliosis hepatis have been associated with azathioprine use. Hypermethylation caused by increased thiopurine methyltransferase activity has been suggested as a potential hepatotoxic mechanism. On the other hand, the production of reactive oxygen species, which is linked to liver damage, may be connected to the oxidation of azathioprine or 6-mercaptopurine by xanthine oxidase.

Methotrexate liver damage

The use of methotrexate in clinical settings dates back nearly fifty years. With better clinical outcomes, methotrexate, a DMARD, has been used more frequently in PsA over the past ten years. It is still the first-line treatment for both early and established RA (Chandan et al., 2008). Although the mechanisms of methotrexate hepatotoxicity are unknown, they might be related to the drug's delivery system (Kremer, 2004). Methotrexate, a folate analogue, is taken up by the ATP-binding cassette (ABC) family of transporters after entering the cell through folate transporter 1. As a polyglutamate, methotrexate is kept in the cell and inhibits the formation of pyrimidines and purines by blocking the enzymes dihydrofolate reductase, thymidylate synthase, and AICAR (5aminoimidazole-4 carboxamide ribonucleotide) transformylase. Additionally, MTHFR (methylene-tetrahydrofolate reductase), which is in charge of converting homocysteine into methionine, is indirectly impacted by methotrexate. It has been shown that methotrexate treatment raises plasma homocysteine levels in RA patients; however, the effect differs based on whether folate is given. Overdosing on homocysteine can lead to oxidative stress and make the cell more vulnerable to its deadly consequences. It has been demonstrated that homocysteine induces endoplasmic reticulum (ER) stress, which leads to fatty infiltration of the liver if left untreated. Pro-inflammatory cytokines can also be stimulated by homocysteine. Liver fibrosis may result from the activation of hepatic stellate cells caused by the combination of these insults (Desouza et al., 2002).

Azathioprine-related NRH (Nodular Regenerative Hyperplasia)

Visible nodules caused by variations in liver cell plate thickness—some plates appear thinner and atrophic, while others are more than one cell thick—are a characteristic of NRH, an unusual condition. NRH is brought on by alterations in blood flow brought on by obliterative modifications in intrahepatic portal radicals. Atrophic patches indicate decreased blood flow in the acini, while nodular regions exhibit hypertrophic reactions. Vascular injury brought on by collagen deposited in the Disse gap between hepatocytes and sinusoidal endothelial cells has been connected to thioguanine, a product of azathioprine. Two patients who developed NRH were found to be heterozygous for the TPMT*3A mutation in the gene encoding thiopurine methyltransferase in a study of 65 liver transplant recipients undergoing azathioprine therapy. This suggests that differences in azathioprine metabolism could potentially increase the risk of developing this drug-induced liver disease (Breen et al., 2005).

TNF inhibitors caused hepatotoxicity

The three most studied TNF inhibitors, infliximab, etanercept, and adalimumab, have been associated with elevated transaminase levels. This criterion for defining hepatotoxicity determines the frequency of these events. 0.6% of anti-TNF-treated patients overall had enzyme levels that were more than twice the upper limit of normal in a study of 6,861 RA patients spanning 14,000 patient-years; 39 patients had ALT elevations that were three times the upper limit of normal, and nine patients had ALT levels that were more than five times the upper limit of normal. Hepatic sinusoids are involved in the removal of immunological complexes through interactions mediated by Fc receptors, which can either induce local hepatocyte damage or activate Kupffer cells to create reactive oxygen species. Because monoclonal antibodies (like infliximab and adalimumab) form immune complexes more easily than soluble receptors (like etanercept), the reported prevalence of hepatotoxicity with anti-TNF drugs may vary (Strand et al., 2007).

Anti-epileptic drugs (AED)

Liver damage from antiepileptic drugs (AEDs) is well recognised. Although the most common AED is rarely used, the acute liver failure these medications cause might have deadly consequences or necessitate liver transplantation. It is unknown what mechanisms underlie the hepatotoxicity brought on by AEDs. AED reactive metabolites may occasionally result in neoantigen formation, which triggers immunological allergic reactions, or they may infrequently induce direct cytotoxicity and liver cell necrosis (Bjornsson, 2008).

Carbamazepine (CBZ).

The best treatment for grandmal epilepsy is carbamazepine, a well-known antiepileptic drug. It decreases alkaline phosphatase (ALP) and raises gamma glutamyl transferase because it induces enzymes. According to Mitchell et al. (1988) and Forbes et al. (1992), CBZ can result in cholestatic and hepatic damage in addition to the development of liver granulomas. Carbamazepine metabolism is thought to be a key factor in the development of CBZ hypersensitivity and hepatotoxicity, with metabolites being suggested as the causative agents. According to in vitro metabolism studies employing pure enzymes and enzyme inhibitors, CYP 3A4 is involved in the synthesis of both stable epoxide and reactive metabolites. Ring hydroxyl metabolites 2 and 3 hydroxyl CBZ are produced when CBZ induces its own metabolism in vivo through CYP 3A4. These metabolites may be produced from an unstable arene oxide intermediate. Hapten development may result from the arene oxide metabolite. The hapten manufacturing sites, including the liver, suffer tissue damage as a result of the immune system's subsequent involvement (Steven Leeder and Pirmohamad, 2003).

Valproic Acid (VPA)

One commonly used antiepileptic drug that works well is valproic acid. Though up to 20% of individuals may see an initial increase in any liver enzyme, it is generally well tolerated. There is a theory as to how VPA is harmful. The main focus of this theory is how VPA interferes with endogenous lipids' β-oxidation. Carnitine and VPA form an ester conjugate, which could result in a secondary carnitine deficiency. In vitro studies and a number of

indirect evidence lines point to the possibility that the thioester derivative of coenzyme A and VPA functions as a metabolic bridge in liver tissue. Cell death may ensue from ATP depletion, mitochondrial metabolic limitation, or depletion of coenzyme A or the VPA CoA ester itself.

Felbamate

In 1993, the broad-spectrum anti-epileptic drug felbamate (FBM) received a licence to be sold in the US. It has been demonstrated to be successful in preventing both partial and total seizures. Liver damage and aplastic anaemia can be brought on by felbamate (2-phenyl-1, 3-propanediol dicarbamate, or FBM). Although the exact mechanism behind FBM-induced toxicities is unknown, 2-phenylpropenal, a reactive FBM metabolite, has been suggested as a potential culprit. FBM hydrolyses to 2-phenyl-1, 3propandiol monocarbamate (MCF), oxidises to 3-carbamoyl-2-phenylpropionaldehyde (CBMA), and spontaneously releases ammonia and carbon dioxide to form this metabolite (Popovic et al., 2004).

Phenytoin

A severe idiosyncratic reaction that affects fewer than 1% of people is phenytoin hepatotoxicity. Serum levels of lactic dehydrogenase, alkaline phosphatase, bilirubin, prothrombin time, and aminotransferases can all rise as a result of phenytoin hepatotoxicity. While the exact mechanism of phenytoin's hepatotoxicity is unknown, most research points to a hypersensitive mechanism (Smythe and Umstead, 1989).

Neuroleptics or anti-psychotic drugs

Unpredictable or idiosyncratic, hepatotoxicity from psychiatric medications affects a small but variable fraction of users. The first- and second-generation antipsychotics seldom cause mild, asymptomatic, transient, and reversible elevations of liver enzymes. After three months of treatment, these abnormalities start to show (Jeffrey and Allan, 2006).

Chlorpromazine (CPZ)

Most research has been done on chlorpromazine. It seems that both metabolite poisoning and hypersensitive reaction are responsible for the clinical features. Jaundice was demonstrated to be caused by chlorpromazine. The neuroleptic that has been studied the most is chlorpromazine, and the hepatic damage that CPZ causes is the model for hepatocellular cholestasis. (Ishak and Irey, 1972; Zimmerman, 1999) The mechanism of cholestatic sickness caused by phenothiazine is still unknown.

Haloperidol

Haloperidol is a very rare cause of overt liver damage, and it shares structural similarities with phenothiazines. The features resemble cholestatic damage brought on by phenothiazines. In rare instances, microvesicular steatosis has been connected to chlorpromazine and haloperidol, which have the same heptanoic acid side chain (Bricquir et al., 1994). β-oxidation of medium and short-chain fatty acids is inhibited by b oxidation of

the side chain. P450, thus, transforms both medications into reactive metabolites that may result in hypersensitivity reactions in individuals with hereditary susceptibility (Fromenty et al., 1989).

Risperidone & Quetiapine

Two of the most often given atypical antipsychotics are quetiapine and risperidone. Cholestasis caused by medication happens when a medication stops the liver's bile from flowing. This may occur when the drug explicitly prevents the intake of bile components, disrupts the excretions of bile canalicular substances, or eliminates components necessary for bile flow. When there is cholestatic damage, ALT and AST levels are usually normal or slightly elevated (Mohi-ud-din and Lewis, 2004).

Olanzapine

Olanzapine has been linked to reports of transient liver biochemistry abnormalities, while the cause of these issues is unknown. One case report describes a young guy who took olanzapine and had cholestatic jaundice and hepatosplenomegaly, among other serious abnormal liver biochemistry symptoms.

Clozapine

The atypical neuroleptic clozapine caused a moderate and transient increase in alanine transaminase (ALT) in 37% of patients. It is currently unknown what the possible mechanism of hepatotoxicity is (Hummer et al., 1997).

Anti-Depressants

The liver may be poisoned by the majority of tricyclic antidepressants. Even though amitriptyline, desipramine, and doxepin are among the other tricyclics that seldom harm the liver, their known cross-reactivity should be ruled out when sensitivity to one is suspected.

Amineptine

Even though there may be substantial necrosis, amineptine-induced liver damage is primarily cholestatic. A heptanoic acid side chain is included in the compound. Medium and short-chain fatty acid b-oxidation is inhibited by the β oxidation of the side chain. Both medications are thus transformed by P450 into reactive metabolites that may result in hypersensitivity reactions in those who are genetically sensitive (Fromenty et al., 1989).

MAO inhibitors

Every MAO inhibitor made from hydrazine has the potential to be harmful to the liver. P450 can break down hydrazine into dangerous intermediates. Another hydrazine that functions similarly to these is isoniazid. There are still instances of hepatitis with phenelzine, a substituted hydrazine MAO inhibitor (Bonkovsky et al., 1986).

Acetylcholinesterase inhibitors

Alzheimer's disease is treated with tacrine, a reversible cholinesterase inhibitor. Remarkably, the ALT exceeds the upper limit of normal in around half of the patients; in 25% of the patients, the value is more than three times the upper limit, and in 2%, it is 20 times higher (Selim and Kaplowitz, 2003). Because tacrine inhibits acetyl cholinesterase, it stimulates an afferent sympathetic route through the cholinergic coeliac ganglion. This leads to vasoconstriction, decreased sinusoidal perfusion, and reperfusion damage caused by reactive oxygen metabolites. Since the former process may make the later more sensitive, these concepts are not exclusive. Tacrine thus experiences high extraction, suggesting that periportal hepatocytes may absorb a significant amount of the drug; the uncoupling effect would increase respiration and O2 consumption in periportal hepatocytes, limiting O2 availability in the more distally perfused perivenular cells; and the superimposition of decreased O2 delivery due to the effect on the microcirculation would further limit O2 in the perivenular zone (Stachlewitz et al., 1997).

Antihypertensive medications

Methyldopa is used to treat high blood pressure. Liver damage in methyl dopa users has ranged from mild to severe. The former occurs in 2–10% of patients taking the drug and is characterised by asymptomatic and often transient elevations in serum transaminases (Rodman et al., 1976). The onset of overt clinical hepatic injury, which occurs in 50% of instances after four weeks, does not have the same strong temporal link with liver damage, which is more common in women and can present as acute hepatitis, chronic active hepatitis, or cholestasis. According to in vitro studies, the medication is metabolised by rat and human liver microsomes using the cytochrome P450 system, which causes covalent bonding with cellular macromolecules. This covalent binding is inhibited by a variety of chemicals, such as glutathione, ascorbic acid, and superoxide dismutase. This is consistent with methyl dopa being oxidised to a reactive quinone or semi-quinone by cytochrome P450-generated superoxide anions (Dybing, 1977).

HISTOPATHOLOGY

- Classifying drug-induced hepatotoxicity can be aided by histological findings, even though a liver sample is not required for diagnosis. Histological appearance can also be used to guide care by ruling out other diagnoses and identifying an aetiology. Additionally, it is a tool that can aid in prognosis.
- Acute hepatocellular injury: aspirin, phenytoin, and isoniazid (INH) have been linked to acute inflammation in addition to necrosis and apoptosis.
- The outcomes of chronic hepatocellular injury are as follows: fibrosis resembling those of other chronic liver diseases linked to amiodarone, valproic acid, and amoxicillin-clavulanate.
- The use of anabolic steroids is often associated with acute cholestasis, which is bile obstruction with hepatic cholestasis.
- Amoxicillin-clavulanate-induced chronic cholestasis, which includes bile stasis, portal inflammation, bile jury, bile plugs, and duct paucity.

- Steatosis: microvesicular, usually linked to tetracycline and valproic acid-induced mitochondrial damage.
- Zonal necrosis: generally in intrinsic DILI and linked with poor results; observed in acetaminophen toxicity.
- Granulomas are connected with milder harm and can arise from numerous medicines, including talc exposure through the bloodstream.

✓ **The top five implicated drugs in three prospective studies on DILI, in Spain (Andrade *et al.* [12] 2005), liver injury in drug-induced liver Injury (DILI) study from the US (Chalasani *et al.* [13] 2013) and a prospective study from Iceland (Bjornsson *et al.* [14] 2015).**

Spanish Registry	**DILIN Study**	**Icelandic Study**
Amoxicillin-clavulanate	Amoxicillin-clavulanate	Amoxicillin-clavulanate
Isoniazid	Isoniazid	Diclofenac
RIP + INH + PIZ	Nitrofurantoin	Azathioprine
Flutamide	SMZ/TMP	Infliximab
Ibuprofen	Minocycline	Nitrofurantoin

(RIP + INH + PIZ: Rifampin, Isoniazid and Pyrazinamide; SMZ/TMPSulfamethoxazole/Trimethoprim)

CONCLUSION

DILI is frequently brought on by antibiotics. According to a recent single-center experience, antibiotics were the class of drugs most frequently linked to non-fulminant drug-induced hepatitis.113 Amoxicillin/clavulanic acid, minocycline, nitrofurantoin, trimethoprim-sulfamethoxazole, and trovafloxacin were the antibiotics most frequently implicated. A recent study conducted in the United Kingdom, a French investigation, and a Spanish registry found antibiotics to be the primary cause of DILI.115 ALF (telithromycin), autoimmune hepatitis (minocycline), and cholestasis (amoxicillin/clavulanic acid) have all been shown to cause histological damage. With the introduction of new medications, clinical and regulatory issues regarding drug-induced hepatotoxicity will continue to exist. Unfortunately, because hepatotoxicity is generally not very common and underreporting is common, it is difficult to detect specific pharmaceutical toxicity. By using genetic predictors and toxicological models, toxicity can be avoided before it happens.

The Drug-induced Liver Injury Network6 and the Acute Liver Failure group are two cooperative initiatives that may help us better understand the hepatotoxicity associated with drugs. When there are clear indicators, as with statins, cautious use may be recommended. This is because drug administration in patients with underlying liver disease necessitates a balanced risk-benefit appraisal. It is particularly important for patients who have received liver transplants to closely monitor drug interactions. Giving thorough coverage of all the many hepatotoxic medications is difficult. In conclusion, a lot of prescribed medications are harmful to the liver and should be used carefully, particularly when taken in large quantities or for prolonged periods of time.

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