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Review Article:

Drug-Induced Liver Injury: Mechanisms and Counteracting Herbal-Derived Products

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Abstract

Background: Exposure to both synthetic and naturally occurring chemical substances can cause a wide range of reactions such as Drug-Induced Liver Injury(DILI). It is a serious problem due to the increasing number of substances being used for the treatment of different illnesses, coupled with the growing popularity of herbal products encourage self-medication but are not strictly regulated. It can be challenging to predict, diagnose, and treat (DILI) due to the wide range of underlying mechanisms and risk factors. DILI can range in severity from moderate transaminase elevation to potentially fatal acute liver failure. **Aim:** The purpose of this review article is to gain a better understanding of DILI , which includes its causes, classification, the more toxic medications, and chemicals that can lead to DILI. The purpose also covers the biomarkers and liver function tests that can help identify this condition, as well as the substances that are commonly used for liver protection. **Methods:** We made a worldwide search through well-known online databases such as PubMed, Science Direct, Elsevier, and others to keep going with related liver disease trials that have been approved in previous years. **Conclusion:** DILI is one of the leading causes of liver disease globally, resulting from the use of prescription, over-the-counter, and herbal medications. Due to the lack of a single clinical, laboratory, or histologic characteristic specific to the illness, diagnosing DILI can be challenging.For an accurate diagnosis, it is essential to establish a causal correlation between the suspected substances and other causes of liver injury.

1. Introduction

Drug-induced liver injury (DILI) is still a relatively common diagnosis and an issue in clinical practice. With a 50% fatality rate, DILI accounts for the majority of cases of acute liver failure while having little incidence in the general population. Despite the numerous reported causes of DILI, there is no conclusive link between medicines, risk factors, and mechanisms of DILI. Because of the important and multiple functions of the liver, drug-induced liver damage gained a lot of space in the animal and clinical studies.

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This review will discuss the classification, mechanisms, drugs that may be hepatotoxic, and herbal products to counter them. The liver is an essential metabolic organ unique to vertebrate animals and carries out a variety of vital biological processes, including the body's detoxification, the synthesis of the proteins and biochemicals required for growth and digestion (1-3). Other metabolic functions of the liver include the synthesis of hormones, the conversion and storage of resources like glucose and glycogen, and the metabolism of carbohydrates (4).

Additionally, the liver functions as an adjunct digestive organ through the production of bile, an alkaline fluid that contains cholesterol and bile acids that help break down dietary fat. The liver produces bile, which is drained to the duodenum to aid in digestion. The bile is stored and concentrated in the gallbladder (5). The highly specialized tissue of the liver, which is mainly made of cells known as hepatocytes, controls a wide range of high-volume metabolic reactions, such as the formation and degradation of complicated and tiny molecules, many of which are essential for regular bodily processes (6). The organ's overall number

of functions is estimated to be 500 or less, though figures vary widely **Figure 1** (7).

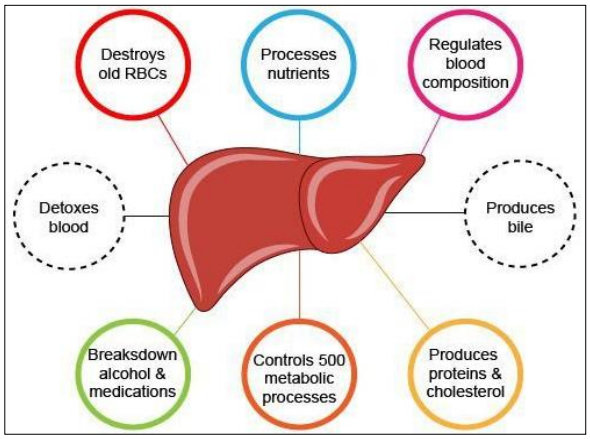

Figure 1. Essential liver functions (7)

1.1 Common biochemical and function tests of the liver

The term "liver function tests" can be misleading because many of the tests aim to identify the cause of liver damage instead of measuring the liver's function. Elevated levels of ALT and AST that are disproportionate to ALP and bilirubin indicate hepatocellular disease. Meanwhile, a cholestatic pattern is characterized by an increase in bilirubin and ALP that is out of proportion to ALT and AST. A mixed damage pattern is indicated by elevations in alkaline phosphatase activity and AST/ALT. On the other hand, isolated hyperbilirubinemia is identified by an increase in bilirubin coupled with normal levels of AST/ALT and alkaline phosphatase (7). The R ratio is used to determine the pattern of liver injury, whether it's cholestatic, hepatocellular, or mixed. The formula to compute the R ratio is R = (ALT value ÷ ALT ULN) ÷ (alkaline phosphatase value ÷ alkaline phosphatase ULN). A R ratio >5 indicates a hepatocellular pattern, <2 indicates a cholestatic pattern, and 2-5 indicates a mixed pattern (8). To assess the liver's true function, albumin and vitamin K-dependent clotting factor production by the liver can also be considered (9).

If the AST and/or ALT levels are less than two times the upper limit of normal (ULN), it indicates a borderline elevation. A mild elevation is indicated by 2 to 5 times ULN, while a moderate elevation is indicated by 5 to 15 times ULN. A severe elevation is indicated by 15 times ULN, and anything above 10,000 IU/l is considered a massive elevation (9). The extent to which AST and ALT are elevated depends on the underlying cause of the hepatocellular injury (10).

1.2 Drug-induced liver injury (DILI)

DILI currently represents a significant health concern, exacerbated the widespread use of medications and herbal treatments by individuals . Given the expanding commercialization of new pharmaceutical compounds, the ageing population's predisposition toward polymedication, and the increasing use of herbal and dietary supplementations (HDS), it is anticipated that the burden of DILI will escalate further in the future. Furthermore, pre- and post-marketing regulatory measures are primarily oriented towards DILI, which stands as the leading cause of acute liver failure in the USA and Europe (11-14). Remarkably, the development of liver toxicity accounted for 15% of the medications removed from the market between 1969 and 2002 (15).

1.3 Classification of drug-induced liver injury

DILI is classified as either an idiosyncratic or intrinsic adverse medication reaction. Intrinsic DILI is characterized by dose-dependency, predictability, and manifestation after a brief latency period. It originate from direct chemical damage to the medication or its metabolites. With acetaminophen (APAP) being a well-known contributor to such type of liver damage due to its hepatotoxicity. Most of the time, preclinical research and Phase 1 clinical trials detect intrinsic hepatotoxins. However, most hepatotoxicity cases are idiosyncratic, which makes them unpredictable, challenging to detect, and difficult to prevent. Notably, overdosage in most cases does not result in liver impairment, despite the apparent presence of a dosage threshold (16).

Given the limited number of volunteers enrolled in preclinical and clinical trials, instances of this form of DILI are infrequent. As a result, post-marketing surveillance may be necessary when the drug is distributed and used by a larger population. Because there are so many medications that can damage the liver, coupled with variations in the manifestation of this condition further there are currently no reliable diagnostic biomarkers, Presently, there is a lack of reliable diagnostic biomarkers, rendering idiosyncratic hepatotoxicity is one of the hardest diagnoses for medical professionals 11). As a result, a false diagnosis of DILI may lead to premature cessation of medications. Enhancing liver test monitoring systems and and the identification of specific and sensitive biomarkers for DILI diagnosis in preclinical and clinical settings could help partially deal with this issue (17).

1.4 Mechanisms of Drugs-induced Liver Injury

The mechanisms underlying Drugs-induced Liver Injury may be the consequence of immune-mediated processes causing damage or direct toxicity from the medication or its metabolites. These mechanisms are differed from one drug to another; however, may exhibit interrelated aspects . For instance, the inflammatory response triggered by a drug's direct toxicity can worsen the initial hepatocyte damage. It's also critical to understand that DILI is more likely to occur with oral drugs that undergo significant hepatic metabolism (18). Most medications are liposoluble, processed in the liver, and are ultimately eliminated in urine after metabolism into water-soluble metabolites or in bile for nonpolar medications. The hepatic cytochrome p450 system are enzymes mediate the phase I reaction, which is the initial stage of drug metabolism (19). This phase produces intermediate

bioactive molecules that may interact with different cellular organelles, such as mitochondria, causing hepatocyte malfunction and cellular death (20). Phase II reactions involve the conjugation of these potentially harmful intermediate compounds with glucuronic-, glutathione-, or sulfa-conjugate these possibly are harmful intermediate compounds to render them inactive. The rates at which phase I products are generated should not be greater than the liver's ability to inactivate them, to prevent hepatotoxicity. Toxic metabolites may build up if the substances crucial for the phase II conjugation processes are diminished or absent. This is the situation with patients who take acetaminophen and abuse alcohol (21). In this case, serious liver damage can be caused by acetaminophen, even at low doses (22).Mitochondrial dysfunction, a contributor to DILI, can result from various mechanisms. One of them is the inhibition of the mitochondrial respiratory chain, which lowers ATP synthesis and elevates reactive oxygen species levels as shown in **Figure 2** (23). Moreover, some medications, including amiodarone, perhexiline maleate, and diethylamioethoxyhexestrol can prevent fatty acid oxidation, which can lead to steatosis or steatohepatitis. Dideoxynucleotide analogs, which are frequently used to treat human immunodeficiency virus(HIV), could inhibit the replication of mitochondrial DNA (24,25).

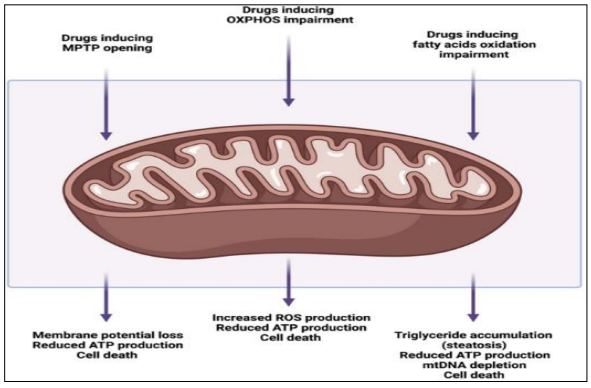

Figure 2. Mechanism of drug-induced liver injury on Mitochondria (23)

The opening of the mitochondrial permeability transition pore (MPTP), closely linked to cell death, may also lead to drug toxicity (26). Intracellular damage may be caused by a combination of the previously mentioned mitochondrial insults, ATP depletion, and ROS production. Hepatocytes eventually undergo apoptosis, but for this process to occur, energy (ATP) must be available, and this may not be the case because of mitochondrial malfunction and low ATP reserves. Here, the necrotic route leads to hepatocyte death, potentially increasing hepatic inflammation (27).

Furthermore, immune-mediated damage is recognized as another mechanism of DILI, . The liver houses elements of the innate and adaptive immune systems, which can react to drug metabolites that bind to major histocompatibility complex molecules on antigen-presenting cells and cause an immunological reaction against hepatocytes (28). This reaction can lead to liver toxicity, which is characterized by a prolonged period between medication delivery and the onset of liver damage. For example, halothane can induce the production of antibodies against cytochrome p450 CYP2E1. Detecting medication-induced antibodies in patient's serum can be useful diagnostic approach for DILI. Local cytokines and ROS produced during the immune-mediated damage process also contribute to liver injury (29). Notably, immune-mediated DILI can become more noticeable and severe with repeated exposure to a drug, similar to the case with halogenated anesthetics (30). Thus, a detailed medication history can be crucial in understanding potential side effects that may have occurred after previous drug administration.

1.5 Drugs having the potential to cause hepatotoxicity

1.5.1 Antitumor Drugs

Anticancer drugs can cause liver damage in a manner that is unique to each individual. Although liver tests can help identify changes in cellular damage, duct injury, or cholestasis, but they don't provide a complete picture of the damage caused (11).

Hepatotoxicity caused by chemotherapy often manifests as an unexpected or idiosyncratic reaction, as a result, the incidence is uncommon, the dosage of the medication, usually seen one to four weeks following the medication's administration, and more frequent following multiple exposures (31).

As previously mentioned, hepatotoxicity is frequently not the result of the drug itself but rather is generated by a metabolite that functions as an open source and damages the immune system (32). Nevertheless, hepatic tumor localization, genetic susceptibility to chemotherapy, and pre-existing liver disease all these factors can affect liver function. The extent of damage, whether permanent or reversible, depends on factors like liver adaptability, age, sex, and genetic diversity, the damage may be permanent or reversible. Risk factors such age, gender, and certain social behaviors like drinking alcohol and smoking can all raise the risk of liver toxicity (33).

Certain family groups when examined showed a 25% chance of experiencing medication responses (34). It is important to know that the immune system's reaction to medications and the cytochrome pathway's expression determine the particular genetic variabilities for particular pharmaceuticals (35).

I- Alkylating agents

Alkylating agents are a type of medication used in cancer treatment. They work by preventing DNA from being transcribed into RNA, which stops the synthesis of new proteins (36). Ifosfamide is a substance that belongs to the alkylating family and has similarities to nitrogen mustard. It is also an analogue of cyclophosphamide. The toxicity profiles of ifosfamide and cyclophosphamide appear to be comparable. A considerable number of individuals on ifosfamide experience slight, momentary increases in their serum aminotransferase levels. Usually, abnormalities are

temporary (36). However, the underlying cause of ifosfamide-induced idiosyncratic hepatotoxicity is unknown. Only a few instances of cholestatic liver disease that occurred just a few weeks after beginning ifosfamide have been associated with noticeable liver damage (along with other antineoplastic drugs). Syndrome of sinusoidal obstructions has only been documented in conditioning regimens before transplantation of hematopoietic cells and the degree of severity ranges from brief, self-limited harm to abrupt failure of the liver (11, 34).

II- Antibiotic anticancer drugs

Anthracycline antibiotics, such as doxorubicin and epirubicin are cytotoxic medications these medications mostly work by intercalating with DNA, disrupting the synthesis of RNA and DNA metabolism. The primary cause of cytotoxicity is suppression of topoisomerase 2 following DNA breakage caused by the enzyme, which prevents the break from being religated and ultimately results in cell death.These drugs are similar in their actions and toxicities to semisynthetic derivatives of daunorubicin. They are commonly used in the treatment of many types of tumors, serving both as adjuvants and for managing metastatic disease (37).Up to 40% of individuals receiving doxorubicin therapy may experience elevated serum aminotransferase levels, even with continuous therapy, these increases are usually asymptomatic and temporary. Unlike epirubicin, doxorubicin has been associated to significant liver impairment and jaundice. Doxorubicin and its analogues are metabolized by microsomal enzymes in the liver, which may generate a toxic or immunogenic intermediate, leading to liver damage (38). When doxorubicin and epirubicin are used together in therapy, the liver damage caused is usually minor and self-limiting. There is no concrete evidence linking the use of these medications alone to cases of sudden liver failure, persistent hepatitis, or disappearing bile duct syndrome. Singh Z (2019) first reported increased toxicity (pancytopenia, severe mucositis, and three drug-related deaths) due to anthracycline dose modification .This observation was made forty years ago in a small patient sample. The sample consisted of eight patients with liver impairment (bilirubin >3 mg/dl) who were receiving full-dose doxorubicin treatment (39).

To avoid toxicity caused by drug accumulation, a study was conducted on nine additional patients with liver dysfunction. The study concluded that the dose of doxorubicin should be reduced if the patient has hepatic dysfunction. According to the study, a 50% dose reduction is recommended for bilirubin levels between 2-3 mg/dl or for AST/ALT levels greater than three times the upper limit of normal (ULN). A 75% dose reduction is recommended for bilirubin levels between 3-5 mg/dl, and the medication should be stopped completely if bilirubin levels exceed 5 mg/dl. Although these suggestions were based on a very small number of patients with hepatic dysfunction of unknown cause, they have been widely adopted into clinical practice (39).

Several trials have reported contradictory outcomes with doxorubicin treatment in patients with hepatic dysfunction (40). However, a study by Krens (2019) found that patients with minor hepatic impairment (bilirubin ≤ 2x Upper Limit of Normal (ULN)) did not show any clinically significant increased toxicity when administered with full-dose doxorubicin (41). The authors suggested adjusting the dose (but didn't state how much) if serum bilirubin levels exceeded 3 mg/dl. However, only case reports have been published about the successful use of reduced dosages of doxorubicin in patients with more severe hepatic impairment (bilirubin > 5 mg/dl) (42). The dose-modification scheme in those investigations did not include transaminases. Certain studies have also assessed hepatoprotective drugs such as taurine while treating them with anthracycline. In a recent study, it was found that taurine can protect the liver against acute damage caused by doxorubicin. This protective effect is thought to be related to the inhibition of oxidative stress and apoptotic responses (43).

III- Antimetabolites

Antimetabolites are certain substances have similar framework but slightly different pathways of action. These substances are called Analogs. exhibit structural similarities to certain molecules. Notably, analogs of pyrimidines include a class of substances which interfere with or compete with nucleoside triphosphates in the synthesis of DNA, RNA, or both, and are known as nucleoside analogs or antimetabolites., Capecitabine and fluorouracil are uracil's substitutes and so they are uracil analogs or antimetabolites (44). Methotrexate, pemetrexed, and gemcitabine are other types of antimetabolites that are often found or utilized. Many of the medications in this class are metabolized by the liver, and when liver toxicity is identified, dose reduction is typically required (44).

Pyrimidine analogues can directly harm the liver to some extent. The present dosages and regimens usually cause minor hepatotoxicity, which is characterized by mild, and temporary increases in serum aminotransferase levels. However, some drugs, particularly fluorouracil, have been reported to cause more visible liver damage. High doses of fluorouracil can lead to the rapid development of hyperammonemia and coma. This condition can be due to hepatic dysfunction, it is usually reversible and not related to severe liver injury or jaundice. Additionally, biliary strictures and damage can occur due to fluorouracil, although this is a rare occurrence (less than 1% of patients treated) (45).

Capecitabine

Capecitabine is an oral prodrug of 5-fluorouracil (5-FU) that undergoes a three-step conversion process to become 5-FU, where the first step occurs in the liver. Once transformed into 5-FU, it inhibits cell division and interferes with the synthesis of DNA, RNA, and proteins. Capecitabine is taken orally, which is a significant advantage over 5-FU, which requires other methods of administration (46). The liver extensively metabolizes capecitabine through the microsomal enzyme system, predominantly 2C9, which may cause liver damage due to the formation of a toxic or immunogenic intermediate (47).

Some patients receiving conventional doses of capecitabine therapy experience serum aminotransferase elevation, but elevations above five times the upper limit of normal are rare, occurring in less than 1% of patients. Capecitabine has been reported to cause a similar hepatic steatosis to 5-FU. However, bilirubin elevation mostly occurs in the indirect (unconjugated) fraction and is often modest, self-limited, and isolated (i.e., not associated with other abnormalities in liver tests) (48, 49). Although product labels mention that,

isolated reports of cholestatic hepatitis have been observed in clinical studies (50). The clinical characteristics of liver injury caused by capecitabine are not well understood, including the time taken for the onset of symptoms, the pattern of elevated serum enzymes, the presence of immune-allergic or autoimmune symptoms, and the usual course and outcome. Despite this lack of comprehensive understanding , the liver damage caused by this medication is typically minor in severity. There have been no reported instances of vanishing bile duct syndrome, chronic hepatitis, or acute liver failure associated with its use, and therefore there is no need to adjust the dosage (51).

Fluorouracil

Fluoropyrimidine antimetabolites, such as 5-Fluorouracil (5-FU), are commonly used in cancer treatment. Studies have shown that the use of 5-FU can lead to elevated levels of hepatocyte steatosis. Steatosis occurs when the fat content in the liver exceeds 5% of its weight, which is a characteristic feature of non-alcoholic fatty liver disease (NAFLD). The severity of liver injury is determined by the percentage of fatty hepatocytes in total hepatocytes, ranging from mild (<30%), moderate (30–60%), and severe (>60%) (52). According to computed tomography, there is 30% to 47% rise in hepatic fat content following 5-FU administration (32, 53, 54). Given the infrequent use of 5-FU as a stand-alone treatment, determining the precise extent of liver damage can often pose a challenge it is frequently challenging to determine the precise level of liver damage (54).

Fluorouracil is linked to the disruption of the mitochondrial membrane and a decrease in membrane potential, which may hinder the oxidation of fatty acids and cause ROS to build up in the hepatocytes (55). The production of ROS by microsomal cytochrome P450 enzymes is also linked to fluorouracil. Moreover, fluorouracil is converted into catabolites such as fluoro-β-alanine, which may impair hepatocytes' ability to metabolize lipids and medications (53). Steatosis and lipid buildup are the results of damaged beta-oxidation and formation of ROS (55). Studies have shown that there is a significant connection between body mass index (BMI) and the development of steatosis during chemotherapy. Patients with a BMI above 25 are more than 20% likely to develop severe steatosis, while those with a BMI above 30 are even more susceptible to steatosis. The likelihood of developing steatosis remains unchanged by other patient factors such as age, gender, or diabetes (54).

Methotrexate

Methotrexate an antifolate medication with both antitumor and immunosuppressive properties (48), acts by inhibiting the synthesis of purines and pyrimidines, reducing the synthesis of DNA and RNA, and preventing the action of dihydrofolic acid reductase, which is involved in folate metabolism. In addition, it causes an increase in adenosine release, which may contribute to its immunosuppressive effects (58).

Methotrexate is a medication commonly used to treat non-oncologic diseases,it is known to increase blood aminotransferase levels. Long-term usage of this medication has been associated with the development of cirrhosis, fibrosis, and fatty liver disease. However, there is significant variation in the rates of abnormal liver tests and biopsies depending on the dosage, treatment regime, and length of treatment. Methotrexate is believed to cause liver damage through a direct toxicity mechanism that inhibits RNA and DNA synthesis in the liver, leading to cellular arrest. It is also known to increase the quantity of hepatic stellate cells, though the exact mechanism by which fibrosis is induced remains unclear. Concurrent folate medication reduces increased transaminase blood during low-dose methotrexate therapy (59).

IV- Platinum coordination complexes

The platinum coordination complexes are a class of antineoplastic substances that possess unique characteristics while typically being categorized as alkylating agents. Like typical alkylating drugs, their anticancer effect seems to be related to the cross-linking of DNA molecules. The platinum-containing complexes generate DNA adducts which impede DNA replication, induce strand breaks and leads to miscoding, these actions ultimately induce apoptosis and hinder the production of RNA and proteins (48). Cisplatin a commonly used chemotherapy medication acting as an alkylating agent, is a cytotoxic platinum derivative, the exact processes that lead to hepatotoxicity in cases where it occurs remain unclear. However, it is generally believed that increased production of ROS and reactive nitrogen species (RNS), along with decreased antioxidant defense components such as antioxidant enzymes (catalase and superoxide dismutase (SOD)) and the non-enzymatic molecule glutathione (GSH), are the main causes of cisplatin-induced liver toxicity (56). These pathways can lead to liver damage, including steatosis and cholestasis, even at typical dosages. Nonetheless, mild increases in AST levels are not uncommon (57). Abnormal liver tests, specifically AST and ALT, have been reported at high doses. No literature suggested dose reduction to mitigate liver damage (58). **Table 1** summarizes the toxic effect of some anticancer drugs.

1.5.2 Glucocorticoids

Steroids stimulate the liver to store glycogen, potentially result in hepatomegaly, an uncommon side effect of long-term steroid treatment especially in young people (65). Steatosis, on the other hand, is a common side effect of prolonged use of steroids affecting both adult and pediatric populations (66).

1.5.3 Isoniazid

One of the most commonly used drugs for treating tuberculosis is isoniazid (INH). While up to 20% of patients may experience a mild increase in liver enzymes, as few as 1% may experience severe liver damage (67).

1.5.4 Nonsteroidal anti-inflammatory drugs (NSAIDs)

Analgesics, which are commonly used to relieve pain, typically do not cause liver damage on their own. However, NSAIDs are a class of drugs, that can cause liver damage through both idiosyncratic and dose-dependent responses (68). Aspirin and phenylbutazone, in particular, are linked to intrinsic hepatotoxicity, while ibuprofen, sulindac, phenylbutazone, piroxicam, diclofenac, and indomethacin are associated with idiosyncratic reactions (69).

1.5.5 Acetaminophen (Paracetamol)

When taken as directed, acetaminophen, trade name Paracetamol is generally well-tolerated. However, overdosing on this medication is the primary cause of drug-induced liver damage and acute liver failure worldwide (70). The liver's cytochrome P-450 enzymes produce a toxic metabolite called N-acetyl-p-benzoquinone imine (NAPQI), which damages the liver instead of the medication itself (71). Normally, this metabolite undergoes phase 2 conjugation with glutathione for detoxification. However, during an overdose, excessive amounts of NAPQI are produced, which overwhelms the detoxification system and harms the liver cells. An additional factor that contributes to toxicity is nitric oxide (72).

The risk of liver damage depends on various factors, such as the quantity of consumption, the time between ingestion and the antidote, and the concomitant use of alcohol or other drugs. The amount of any substance that can harm the liver varies significantly from person to person and is usually assumed to be lower in individuals who are alcoholic for a long time (73, 74). Blood level measurement for liver functions is crucial for determining the prognosis, with higher values indicating a worse prognosis. The administration of acetylcysteine, (a precursor of glutathione), can reduce the extent of liver damage by neutralizing the harmful metabolite NAPQI. Patients with acute liver failure may recover on their own, but if they have poor prognostic indicators such as encephalopathy or coagulopathy, they may require a liver transplant, which is determined by King's College Criteria (75).

Table 1. A summary of some cytotoxic drugs and their effects on liver function

Drug name	Liver toxic effect	Frequency	Severity	Dose modification	Reference
Fluorouracil (5-FU)	Steatosis	Common Rarely	Classified as subclinical In most cases Subclinical	No adjustment in dose	(59)
Capecitabine	Hepatoxicity	Common (23-25%)	Grad 3–4 in approximately as 23% of cases	No dose adjustment	(60)
Cisplatin	increased aminotransferases	Common (with high doses)	Usually temporary	It's unlikely needing adjusting the dose,	(61)
Doxorubicin	Idiosyncratic reactions, such as elevated bilirubin and aminotransferases (myelosuppression, mucositis)	Rarely	Usually temporary	Dose adjustment with elevated bilirubin levels	(62)
Gemcitabine	A higher level of aminotransferases higher bilirubin levels Fatal cholestatic hepatotoxicity case reports	Very common (up To 60%) Rare	usually temporary and reversible Liver function degradation can be lethal.	No change in dosage,reduce the dosage by 20% and raise it if required	(63)
Imatinib	An increase in bilirubin or aminotransferases liver failure due to necrosis	5–8% Rare	2–8% grade 3–4 Case reports of Fatalities	Stop the drug, if hepatotoxicity appears.	(64)

1.6 Well-known hepatoprotective herbal-derived products

Herbal medications

There is growing interest among researchers in the use of herbal antioxidants to prevent DILI. Traditional medicines used in China and India to treat liver issues are potential sources of novel therapeutic compounds for this purpose. Studies have shown that natural products rich in flavonoids, polyphenols, or triterpenes can be effective hepatoprotective agents in animal and experimental liver injury models. The antioxidant properties of these natural products are believed to be the key to their protective effects. By neutralizing free radicals and shielding membrane lipids and macromolecules from damage caused by ROS, they can help prevent liver damage (73, 74).Various natural compounds have the potential to act as protective agents for the liver and prevent the entry of toxins into cells (73). Polyphenols are among the natural compounds that have been studied for their hepatoprotective and chemopreventive properties. These compounds interact with different CYP isoforms, boost GSH production, and help to produce Phase II/antioxidant enzymes. Over the past decade, numerous studies have explored the biochemical, genomic, and proteomic mechanisms of action of natural products. Curcumin, ginkgo, and silymarin are some of the most extensively studied natural products for their effectiveness, low toxicity, and easy availability in relation to hepatoprotection (75).

1.6.1 Curcumin

Curcumin, the main ingredient in turmeric, is a popular herbal formulation used to prevent drug-induced toxicity. It is known to have antioxidant, anti-inflammatory, choleretic, anti-carcinogenic, antiviral, and anti-infectious

properties (76). Once ingested, it gets converted into curcumin glucuronides, sulfates, tetrahydrocurcumin, and hexacurcumin in the colon and liver of both humans and rats. By inhibiting the activation of the transcription factor NF-kB, it reduces the production of the enzyme cyclooxygenase2, making it potentially hepatoprotective. Curcumin is a highly effective multi-drug resistance (MDR) modulator and can be used in combination with traditional chemotherapy drugs to reverse (MDR) in cancer cells (77).

Curcumin has immunosuppressive and anti-rheumatic properties. It also reduces the growth of human lymphocytes and the synthesis of several inflammatory mediators, including lipid mediators and cytokines. Oncochinoids have additionally been documented to prevent the development of pro-inflammatory through augmenting the activity of peroxisome proliferator-activated receptor-gamma (PPAR-gamma), Panaro MA. (2020) demonstrated how curcumin restored the liver's antioxidant activity, protecting against paracetamol-induced liver damage. They also demonstrated that curcumin successfully reversed the decline in the expression of antioxidant genes and counteracting paracetamol-mediated increases in matrix metalloproteinase-8 (MMP-8), interleukin-1b (IL-1b), IL-8, tumor necrosis factor-a (TNF-a), and acute phase proteins (81). Furthermore, curcumin provides hepatoprotection against animal liver damage caused by cisplatin, alcohol, and heavy metals (78).

1.6.2 Ginkgo

The extract of Ginkgo biloba has various properties, such as antiplatelet, immunomodulatory, and memory-improving (79). This herbal medicine has demonstrated potential benefit in the treatment of neurological disorders, chronic refractory schizophrenia, hepatotoxicity, and sleep disorders in individuals with memory-improving (80). The main components of ginkgo are flavonoids (such as kaempferol), terpenoids (like ginkgolides and bilobalaides), and organic acids (like ginkgolic acids and alkylphenols) (81).

Research suggests that Ginkgo biloba extract can be a helpful additional treatment for ischemic myocardial injury in diabetic patients. It is believed that the consumption of this extract can influence the metabolism of drugs The extract of Ginkgo biloba has various properties, such as antiplatelet, immunomodulatory, and memory-improving (79). This herbal medicine has demonstrated potential benefit in the treatment of neurological disorders, chronic refractory schizophrenia, hepatotoxicity, and sleep disorders in individuals with memory-improving (80). In the liver by affecting the enzymes responsible for their break them down, as well as changing the level of endogenous antioxidants such as GSH and antioxidant enzymes. It is important to note that administering multiple drugs together, particularly in cases where liver and kidney function are decreased, may be affected due to the altered hepatic metabolism (82).

1.6.3 Resveratrol

Resveratrol, is a natural polyphenol abundantly found in red wine, peanuts, and grape skins. Its potential health benefits have been extensively researched in recent years. Preclinical studies have shown that it can help prevent cancer, cardiovascular diseases, and neurodegenerative disorders (83). Previous studies have reported its activation of CYP2E1 and CYP1A2. Furthermore, it has been found that CYP1B1 metabolically hydroxylates resveratrol, converting it into piceatannol, a tyrosine kinase inhibitor with established anticancer properties. Resveratrol can enhance its lipophilicity by substituting its hydroxy groups with methoxy groups in its molecules, and it can attach to the active areas of CYPs (84).

Recent research demonstrated that resveratrol can protect the liver against damage caused by acetaminophen by blocking the CYP-mediated bioactivation of acetaminophen to promote liver regeneration. In a cat model, hepatic function significantly improved as a result of 2O3-induced liver toxicity indices. moderate consumption of resveratrol also reduced the generation of malondialdehyde and increased reactive oxygen species in liver tissues caused by Arsenic trioxide (As_2O_3). It also increased glutathione levels and antioxidant enzyme activity. Furthermore, resveratrol is protective against hepatotoxicity caused by azoxymethane, sodium fluoride, and methotrexate in animal models (85).

1.6.4 S-Adenosyl-L-Methionine (SAMe)

Adenosyl-L-methionine, also known as SAMe, is a natural chemical that can be found in several bodily fluids and tissues. SAMe synthetase converts methionine and ATP into SAMe. SAMe plays a critical role as a methyl group donor in transmethylation reactions, where the production of membrane phospholipids, particularly phosphatidylcholine, is essential for maintaining membrane fluidity. When methyl groups are released from the molecule, it leads to the formation of S-adenosyl-homocysteine, followed by homocysteine and cysteine, which is a precursor of glutathione (86).

Glutathione is the primary cellular antioxidant that detoxifies various substances and xenobiotics. This metabolic pathway involving SAMe is known as transsulfuration. Finally, SAMe is connected to the polyamine synthesis's aminopropylation step. The drug can now be used therapeutically in the treatment of various liver dysfunctions because of its formation of stable double salts of p-toluene sulphonic acid and sulphuric acid in SAMe (87).

It has been shown that SAMe can improve some biochemical parameters and pruritus in cholestasis caused by a variety of compounds (such as estrogens, lithocolate, etc. and in intrahepatic cholestasis superimposed on chronic liver disease in a variety of animal and human models, including controlled trials. Regarding alcohol toxicity, SAMe reduces the histological liver lesions, normalizes the mitochondrial enzymes, and keeps glutathione levels from declining in baboons given ethanol (88).

Studies have demonstrated that SAMe can significantly decrease the levels of acetaldehyde and ethanol in the blood following alcohol consumption in healthy individuals. Additionally, SAMe has been proposed as a better precursor to glutathione compared to N-acetylcysteine for individuals who experience delayed treatment after a paracetamol overdose (89).

1.6.5 Silymarin

Milk thistle seeds, also known as Silybum marianum, produce silymarin, a flavonoid complex that has been extensively researched. Silymarin consists of silybinin, silydianin, and silychristin, with libidin being a major component (90). Silymarin has two primary modes of action: facilitating cytoprotection through its direct interaction with cell membrane components and antioxidant qualities. It is recognized that one of silymarin's primary protective mechanisms is the inhibition of lipid peroxidation, as shown by various in vitro studies using erythrocytes, isolated and cultured hepatocytes, and human mesangial cells (90).

Silymarin has been documented to possess anti-inflammatory, anti-fibrotic, and anti-proliferative properties. Its protective potential is further enhanced by various biochemical processes, including the stimulation of ribosomal RNA (rRNA) synthesis rate through the induction of polymerase I and rRNA transcription. Silymarin also protects cells from damage caused by free radicals and obstructs the uptake of toxins. Silymarin prevents liver enlargement by blocking the synthesis of leukotrienes, free radicals, and five lipoxygenases in Kupffer cells. Moreover, in mouse hepatocytes, silybin, a crucial component of silymarin, guards against cellular damage and membrane lipid peroxidation (91, 92).

Silymarin has been found effective in preventing drug-induced liver damage in various animal models. Its hepatoprotective potential is believed to originate from its cytoprotective, antioxidant, and cell-regenerating properties. Silymarin works equally well in humans as it does in animals (73, 74). It has been observed to increase the concentration of glutathione and glutathione peroxidase in the serum of both animals and patients. Even though silymarin is not well absorbed, oral doses of 420 mg/day have displayed some therapeutic benefits and good tolerability in individuals suffering from alcoholic cirrhosis.Whereas Silybin, when taken in a daily dose of 20–48 mg/kg, is believed to be an effective remedy for acute poisoning caused by the Amanita phalloidesmushroom. Certain isoforms of silybin are known to have strong anti-nuclear factor kappa light chain enhancer of activated B cells (NF-kB) and anti-hepatitis C virus (HCV) properties (93).

Silymarin has also been shown to protect against prostate cancer _causing G1 arrest, and inhibiting the epidermal growth factor (EGF)signaling pathway. Additionally, silybin helps suppress the expression of tumor necrosis factor-amRNA and xanthine oxidase, which are essential for the development of skin tumors in mice. It has also been found to prevent transformation in cultured rat tracheal epithelial cells exposed to benzo[a]pyrene at lower, non-toxic concentrations. This makes it possible to identify chemopreventive substances that work in the early stages of the carcinogenic process (94).

Silymarin has been found to have a protective effect against hepatotoxicity caused by pyrogallol and rifampicin. This is due to its ability to modulate the increased level of CYPs and the decreased level of phase II and antioxidant enzymes (73). In a clinical study, almost two thousand patients with chronic liver diseases were given silymarin extract for eight weeks. Silymarin extract significantly decreased the index in about 88% of the patients. It is noteworthy that less than 1% of the participants experienced some mild side effects (95). **Table 2** presents a number of studies that showed the most often utilized hepatoprotective agent that reduces the effects of certain hepatotoxic substances.

Tables 2. Summary of studies that incorporate some of the treatments use as hepatoprotectants

Author	Published Time	Country	Hepatoprotective agent	Hepatotoxicics-ubastance	Intervention	Conclusion	Ref.
A Gupta	2023	India	Silymarin	Acetaminophen	Acute liver injury model with acetaminophen	Silymarin demonstrated significant hepatoprotective effects by reducing acetaminophen-induced liver damage. The study suggests its potential therapeutic use in acetaminophen toxicity.	(96)
Jian Li et al	2019	China	Curcumin	Carbon Tetrachloride (CCl4)	Animal model with CCl4-induced liver injury	Curcumin exhibited potent hepatoprotective properties, attenuating liver damage induced by CCl4 exposure. The findings support the idea of curcumin as a protective agent against chemical-induced liver injury.	(97)
Wang, Q. et al.	2023	Chaina	Schisandra chinensis	Alcohol	Chronic alcohol-induced liver injury model	Extract from Schisandra chinensis demonstrated hepatoprotective effects against chronic alcohol-induced liver damage. The study suggests the potential of Schisandra chinensis as a natural remedy for alcoholic liver disease.	(98)
Zhang, H. et al.	2022	China	Resveratrol	Carbon Tetrachloride (CCl4)	CCl4-induced liver injury model	Resveratrol exhibited significant hepatoprotective effects, reducing liver damage induced by CCl4. The study suggests its potential therapeutic application in chemical-induced liver injury.	(99)
Ganesh Rajaraman	2006	USA	Ginkgo biloba	Acetaminophen	Acetaminophen-induced liver injury model	Ginkgo biloba demonstrated hepatoprotective properties, mitigating liver injury caused by acetaminophen. The findings highlight its potential as a protective agent against drug-induced liver damage.	(100)

Mora, Silvia I	2018	Mexico	S-Adenosyl Methionine	Alcohol	Chronic alcohol-induced liver injury model	SAMe exhibited hepatoprotective effects in chronic alcohol-induced liver injury, suggesting its potential as a therapeutic agent for alcoholic liver disease.	(101)
Li, X.	2019	China	Licorice	Hepatitis C Virus (HCV)	Clinical trial in HCV-infected patients	Licorice supplementation showed potential hepatoprotective effects in patients with HCV infection, suggesting its role as a supportive therapy for liver health.	(102)

2. Conclusion

Drug-induced liver damage (DILI) is a broad category of reactions that can arise from exposure to any type of chemical, synthetic or natural substances. As many cases of DILI are asymptomatic, it is challenging to pinpoint the exact occurrence of the condition, and there are many unknowns when it comes to determine a drug's cause of liver damage. The majority of DILI cases are characterized by a little increase in blood transaminases levels that are found during standard biochemical laboratory tests which return to normal when the offending chemical agent is removed, also, many substances can play a beneficial role in ameliorating the toxic effects of these hepatotoxic substances. To improve our knowledge of the pathogenesis of DILI and create more accurate diagnostic and treatment strategies, more study is necessary.

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إصابات الكبد الناجمة عن الأدوية وآلياتها والمواد المضادة لها

الخلاصة

الخلفية: التعرض لكل من المواد الكيميائية الاصطناعية والطبيعية يمكن أن يسبب مجموعة واسعة من التفاعلات مثل إصابة الكبد الناجمة عن الادويه. إنها مشكلة خطيرة بسبب العدد المتزايد من المواد المستخدمة لعلاج أمراض مختلفة، فضلا عن القبول المتزايد لتلك المنتجات العشبية التي تشجع على العلاج الذاتي ولكن لا يتم تنظيمها بشكل صارم. قد يكون من الصعب التنبؤ بإصابة الكبد الناجمة عن الأدوية وتشخيصها وعلاجها بسبب النطاق الواسع من الآليات الأساسية وعوامل الخطر. يمكن أن تتراوح شدة الأصابه من الارتفاع المعتدل للترانساميناسات إلى الفشل الكبدي الحاد المميت. **الهدف:** الغرض من هذه المقالة المراجعة هو الحصول على فهم أفضل لاصابة الكبد الناجمة عن الادويه. ، والذي يتضمن أسبابه، تصنيفه، الأدوية والمواد الكيميائية التي يمكن أن تؤدي إليه. ويغطي الغرض أيضًا المؤشرات الحيوية واختبارات وظائف الكبد التي يمكن أن تساعد في تحديد هذه الحالة، بالإضافة إلى المواد المستخدمة بشكل شائع لحماية الكبد. **الطرق:** أجرينا بحثًا عالميًا من خلال قواعد البيانات المعروفة على الإنترنت مثل PubMed وDirect Science وElsevier وغيرها لمواصلة تجارب أمراض الكبد ذات الصلة التي تمت الموافقة عليها في السنوات السابقة. **الاستنتاج:** تعد اصابه الكبد الناتجه عن الادويه أحد الأسباب الرئيسية لأمراض الكبد على مستوى العالم، الناتج عن استخدام الأدوية الموصوفة طبيًا، والأدوية التي لا تستلزم وصفة طبية، والأدوية العشبية. بسبب عدم وجود خاصية سريرية أو مختبرية أو نسيجية واحدة محددة للمرض، فإن تشخيص إصابة الكبد الناجمة عن الادويه يمكن أن يكون صعباً. للحصول على تشخيص دقيق، من الضروري إنشاء علاقة سببية بين المواد المشتبه فيها والأسباب الأخرى لإصابة الكبد.