**IASR J. Med. Pharm. Sci.**
**ISSN:** 2582-9343
**Website**: https://ijmps.com/
Open Access Journal
**Country**: India

IASR Journal of
Medical and Pharmaceutical
Science

ORIGINAL ARTICLE OPEN ACCES

# COMMON DRUGS CAN CAUSE HEPATOTOXICITY: A REVIEW

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*Received: 15-09-2024*
*Accepted: 24-10-2024*
*Available online: 25-11-2024*



## ABSTRACT

The liver is the top most organ and one of the most significant. It's top organ of the mortal body, tried and true for a grouping of capacities that offer help back digestion frame, immersion, vitamin capacity and detoxification. Hepatotoxicity, or liver damage due to exposure to chemicals and medicines, is a major concern in medicine remedy, leading to complications ranging from mild enzyme elevations to acute liver failure. liver This review focuses on common specifics associated with hepatotoxicity, their mechanisms of action, clinical counteraccusations, and strategies for forestallment and operation. specifics are a major beginning of acute hepatic injury. further than 700 medicines, poisons and herbal remedies are known to beget liver damage. The liver plays a vital part in the detoxification of colorful specifics. specifics that can be taken to treat the complaint can beget severe hepatotoxicity. Some medicines (troglitazone, trovafloxacin, etc.) can be move out of the request because of their acute or chronic liver injury. Thus, all in all the miracle of Drug cause liver damage (medicine- convinced hepatotoxicity), so many proved colorful aspects of DIHT, also agitating the medium of medicine toxin. remedial options for DIHT include medicine termination, conservative measures and liver transplantation in cases of non-paracetamol-induced hepatotoxicity. Technological advances since the coming from hereditary revolution now give unknown power to distinguish and measure the covalently linkage revision of independent selected proteins and their practical out- turn. The statistics should significantly ameliorate our understanding of medicine- convinced hepatotoxic responses.

**Key Words**: *Hepatotoxicity, liver, hepatotoxicity of medicines, antihypertensive, NSAIDs, contraceptive capsules, medium, Paracetamol.*

## INTRODUCTION

Unfavorable Medication reactions (ADRs) are vital wellbeing issues that contribute to persistent horribleness and mortality. There are a few sorts of ADR, which influence all organ frameworks in the body. still, medication- persuaded liver damage is the most common reason for the pullout of an affirmed pharmaceutical from the ask, and still accounts for encourage than 50 of cases of intense liver disappointment in the Joined together States minute (1). Liver harm persuaded by drugs and medications is a wellbeing issue that can lead to passing if ignored. pharmaceutical- persuaded hepatotoxicity( DIHT) is an unfavorable medication reaction that happens in clinical operations. DIHT can generate liver fibrosis, liver disappointment, and undoubtedly passing( 2, 3). A few specifics are dependable for liver harm. assist than 1, 000 medicinal, toxics and home grown cures have been detailed to breed hepatotoxicity. Around 85 of peculiar medicament reactions react in liver transplantation or passing. Due to underreporting and misdiagnosis, the appearance of DIHT is assumable created than the detailed extend of 1 in 10, 000 to 1 in 100, 000 cases( 4). One of the most common reasons for the pullback of a remedy from the ask is an increment in the serum drenching of liver chemicals( 5). It moreover influences the medicaments on the request and confines the utilize of certain medicaments and pharmaceuticals( 6). Liquor too causes liver clutter, which is the most common sort of medicament- changed over hepatotoxicity. DHIT alludes to liver brokenness or liver harm caused by medicine deadweight. mixes that can catalyze liver harm are called hepatotoxins ( 7). There are multifold medicaments that can bring on deep rooted liver clutter. A expansive number of pharmaceuticals utilized as sound supplements have been detailed to have unfavorable movables on the liver( 8).

A few commonly utilized clinical medicine for Drug causing hepatic injury therapy are (PPC) polyene phosphatidylcholine, ursodeoxycholic acid (UDCA) corrosive or tiopronin [9].

| | |
|---|---|
| Disulfiram | NSAIDs |
| Ketoconazole | Statins |
| Halothane | Birth Control Pills |
| Valproate | Phenobarbital |
| Methyldopa | Amiodarone |
| Phenytoin | Anabolic-Androgenic steroids |
| Ticlopidine | Heparin |
| Methotrexate | Tamoxifen |
| Hydralazine | Propylthiouracil |

**Category of hepatic Injury**

Hepatic Injury is classified into following broad types, each defined by a threefold increase in alanine aminotransferase (ALT) levels. Degree, a double over enhance in antacid phosphatase (high mountain) or a double over enhance in serum bilirubin (SBLN), if it is accompanied by high Alanine aminotransferace and high mountain level. Basically, high ALT or high altitude is known as liver cell damage; the increase of high levels of mountain and bilirubin is known as cholestatic; and in combined lesions, ALT and elevated levels are increased [10].

**PATHOLOGICAL SHOW OF DRUG INDUCED HEPATOTOXICITY**

Different medications have different components of action on the hepatic (liver) framework. There are drugs that cause hepatotoxicity that are taken after exhibits. Hepatotoxic drugs are those that damage the liver [11].

**1. Illustration of drugs that cause hepatotoxicity**

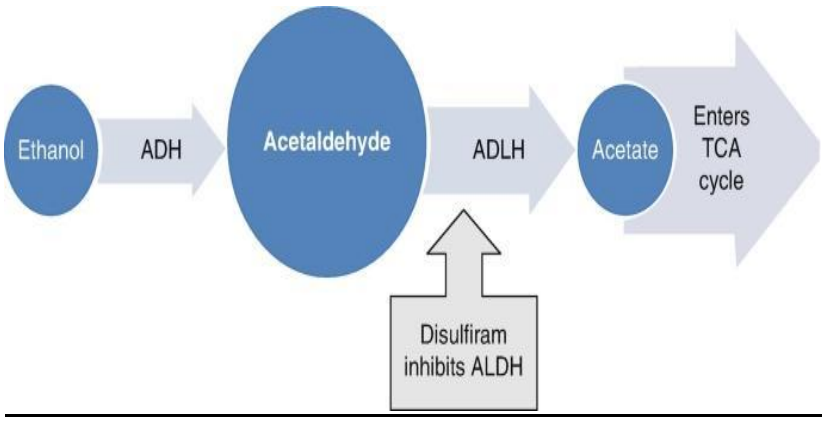
**1.1 ACETAMINOPHEN**

When taken in the right amounts to avoid gastrointestinal problems or adverse effects, acetaminophen is regarded as one of the most widely used antipyretic and analgesic drugs. By inhibiting the heart's cyclooxygenase (COX) activity, acetaminophen reduces fever and pain. However, a thorough investigation reveals the true cause of acetaminophen's activity [12].

Acetaminophen-induced liver damage is caused by an excess of the toxic metamorphosis N-acetyl-para-benzoquinone imine (NAPQI), which is then followed by oxidative stress and mitochondrial degradation, which ultimately results in the depletion of ATP stores. Numerous theories suggest that the destructive compound of paracetamol, NAPQI also known as NABQI, binds to a variety of biomolecule, particularly those found in mitochondria [13].

**1.2 DISULFIRAM**

Because of the limitations of chemical dehydrogenase, which can convert acetaldehyde to acetic acid during the liver's alcohol digestion process, disulfiram is regarded as a carbamate derivative used in alcohol-dependent patients [14].

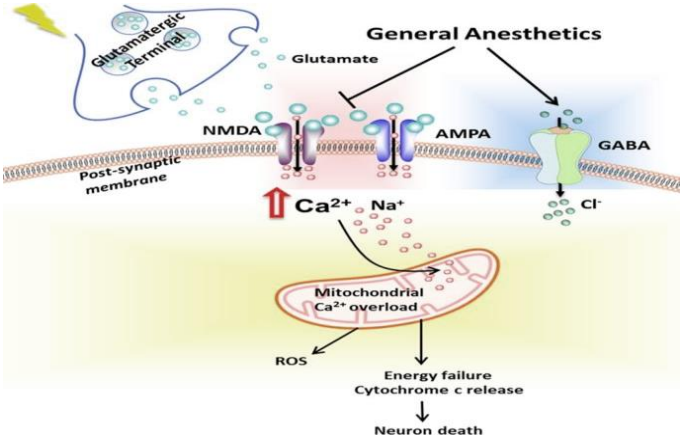



The process by which disulfiram causes chronic liver failure is unrevealed, however it could be due to excessive sensitivity and unfavorably susceptible reactions, as well as the producing of hazardous metamorphosis. Antabuse is broken down by RBC glutathione reductase enzyme (GR) to diethylthiocarbonate, which is metamorphosis in the hepatic using the amalgamation approach with glucoronic acid; the other component is converted to carbon bisulfide (CS2), which can produce toxic hepatitis and fringe neuropathy [15]. The approximate frequency of severe hepatotoxicity after disulfiram sedate therapy is one per 10,000 to 30,000 individuals per year [16].

### 1.3 KETOCONAZOLE

Ketoconazole is an antifungal drug/agent, a part of imidazole. Its helpful impacts incorporate avoiding the restraint of lanoesterol to ergosterol, which is leads to diminish the union of ergosterol, and the parasitic cellular porousness is increment since ergosterol is makes a difference to keep up the organism cell [17].

Recent studies on rodent liver cell cultures have revealed hepatotoxicity directly related to ketoconazole in a concentration-dependent manner. Several proteins, such as flavin-containing monooxygenases (FMOs), convert Levoketoconazole (KT) to metabolite N-diacetyl-ketoconazole (DAK), which has a higher natural toxicity than antifungal drug. Both levoketoconazole and N-diacetyl-ketoconazole (DAK) can form unbreakable bonds with liver proteins, leading to glutathione depletion and liver damage [18].




### 1.4 HALOTHANE

Halothane is a course of anesthesia drugs; it is utilized as a common inward breath anesthetic due to its activities on numerous receptors, such as actuating gamma-aminobutyric corrosive (GABA) glycine receptors and antagonizing the N-methyl-D-aspartate (NMDA) receptor [19].There are two components that can be considered for the toxicity of halothane to the liver. The first is the oxidation of the metabolic instrument, which is done through either reductive or oxidative pathways. The middle item of this pathway, which is focused on liver damage, is the authoritative role of the macromolecules and fatty acids in the liver cells.Moment is a pathological component; fluothane and its metamorphosis can cause extreme touchiness responses that are self-proof as a practical incitement examine when fluothane is taken in a little amount to tranquillizer who had scenes of jaundice and fever succeeding presentation to fluothane, or in different manifestation, the WBC change test (LTT) and white blood corpuscle movement restraint test are if spot as practical in separation with the standard bunch; both can be a section of primary prove supporting pathological component [20].

| Drug | Bioactivation | Immune Response | Reference |
|---|---|---|---|
| Halothane | Oxidative dehalogenation | Drug metabolite IgG, Anti-CYP2E1 IgG, Autoantibiotics | (21, 22) |
| Carbamazepine | Arene oxidation | Drug T cell | (23, 24) |
| Tienilic acid | Thiophene sulfoxidation | Anti-CYP2C9 IgG | (25) |
| Sulfamethoxazole | N-hydroxylation | IgG antibodies, Drug and metabolite, T cells | (26), (27) |

### 1.5 VALPROATE

Valproate is a medication often used to treat epilepsy and bipolar illness, as well as to avoid migraines. We do not fully understand how they work; nevertheless, they can increase GABA-ergic function by blocking GABA metabolism, boosting GABA release, and enhancing GABA-B receptors in the brain [28].
Sodium valproate can cause more liver damage due to mitochondrial dysfunction in liver cells. Several studies have shown the importance of oxidative stress and its consequences on valproate-induced liver injury. Several experimental models of valproate liver injury have shown the stage of oxygen radicals, lipid oxidation products (LOPs), modification in cellular antioxidant proteins, and glutathione depletion [29].

Yet, liver damage induced by valproate medicines can be reversed in 45% of patients by reducing the dose and discontinuing the drugs; yet, there is a not applicable condition distinguish by liver injury that is not so much prevalent, with a frequency ranging from 1 in 5,000 to 1 in 20,000 [30].

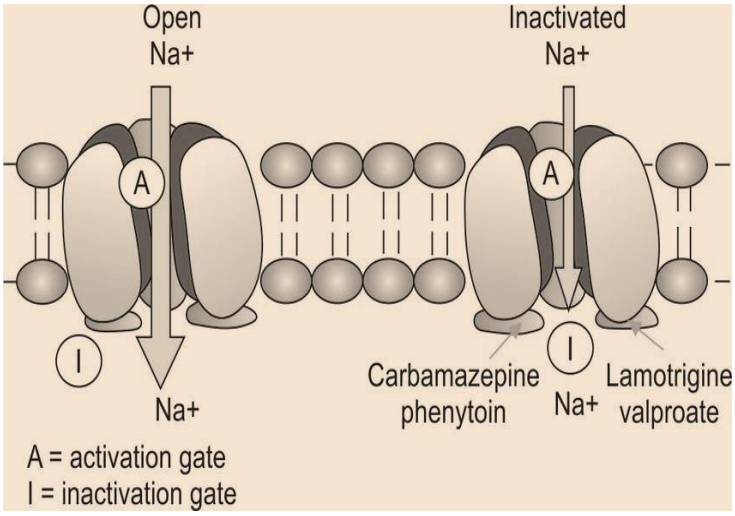
**1.6 METHYLDOPA**

Methyldopa has been used to treat easy hypertension associated with pregnancy. The sympathetic (anti-arenergic) activity of the drug alpha methyl dopa is accountable for its beneficial result in the therapy of raised blood pressure during parturiency, which lessen the mental force (fight or flight) in the heart and peripheral circulation, resulting in a decrease in heart rate and systemic vascular resistance (SVR) [31].

Although, alpha methyl dopa may additionally cause liver injury via an immune response, and few data supports this process, something like the lack of a portion-response connection and the non- appearance of septic in brute. Medical research revealed that a few individuals receiving alpha methyl dopa had hepatotoxicity coupled with fever or rash, signifying a hypersensitivity reaction [32].

A total of 5% of non-pregnant women who acquired methyldopa developed mild harm to their livers [33].

**1.7 PHENYTOIN**




One of the most widely used tranquilizers, phenytoin works by blocking presynaptic Ca++ channels and Na + channels, thereby helping to effectively control a variety of seizure disorders [34]. The fact that patients also experience fever and rash supports the theory that phenytoin's hepatotoxicity is the result of a hypersensitivity reaction. On the other hand, arene oxides might also be connected to the cytotoxic and immunological effects of phenytoin. These arene oxides are electrophilic and can acrylate cellular macromolecules like membrane lipids and DNA, impairing cellular function. Their presence is indicated by cytochrome P450 enzyme activity in phenytoin. When an exposed person's level of arene oxide surpasses their antioxidant capacity, oxidative stress results. This happens when phenytoin is provided at large doses that exceed therapeutic levels [35].

The prevalence of anticonvulsant-cause liver injury radius from one in 1,000 to in 20,000, and it may vary by contest and nationality [36].

**1.8 Ticlopidine**

Ticlopidine belongs to the thiopyridine family and is used as an antiplatelet. This powerful prodrug can inhibit the adenosine diphosphate receptor, which is responsible for activating the GPIIb/IIIa receptor that causes platelet aggregation [37]. Ticlopidine's exact mode of action is unknown. More research should be done to determine whether the cholestatic effects of ticlopidine are mediated by molecular alterations in the subcellular and ductal transport systems. Furthermore, an immunosuppressive mechanism is suggested by the dose-specific profile of granulomatous inflammation, biliary injury, peripheral plasma lymphocytic infiltration, and tissue eosinophilia. However, the outcomes of ticlopidine-induced hemostasis in mice suggest that ticlopidine and its metabolites, rather than hypersensitivity, are directly responsible for the negative effect [38].

Ticlopidine is known as an antiplatelet of the thiopyridine family. It is a potent prodrug, capable of blocking the adenosine diphosphate receptor involved in the activation of the integrin beta3 or antigen CD61 receptor accountable for abnormal thrombocyte aggregation [37]. The mode of action of ticlopidine is not known. Whether cholestatic effects are exerted by ticlopidine via molecular alterations in the subcellular and ductal transport systems requires further investigation. In addition, the dose-specific pattern of tissue eosinophilia, peripheral plasma lymphocyte infiltration, granulomatous inflammation, and biliary damage suggests an immunosuppressive mechanism. However, the results of ticlopidine hydrochloride-caused hemostasis in mice indicate that the negative effect is induced directly by ticlopidine hydrochloride and its metamorphosis rather than supersensitive [38]. A Canadian-American study of ticlopidine detected abnormal liver function tests in 4.4% of the patients [39].

**1.9 Antituberculosis agents**

Rifampicin is known to work by obstructing bacterial transcriptase, the catalyst necessary for DNA translation [40]. The mode of action of pyrazinecarboxamide and isonicotinylhydrazine is not fully acknowledge due to their different properties. These drugs are known to be anti-tuberculosis and undoubtedly liver failure medicine. Mechanism of liver disease:

**a) Rifampin:** An important cycle for histone deacetylase (HDAC) to acetyl rifampin and rifampicin-3 specific therapy. The impose mode of action of rifampin-caused hepatotoxicity is not known, and evidence for a liver metabolite does not exist.

**b) Unipyrazinamide:** It is converted over to pyrazinic acid and further disintergrated with the help of xanthine oxidase to 5-hydroxy-2-pyrazinecarboxylic acid. The mode of action by which pyrazinamide causes acute hepatic injury is not fully acknowledge.

**c) Isoniazid:** Isoniazid is metabolized into acetylhydrazine and isonicotinic acid after undergoing hydrolysis. However, isoniazid becomes acetyl isoniazid through acetylation when the hepatic enzyme N2methyltransferase 2 acts upon it. It has been surmised that the hepatotoxic metabolite is acetylhydrazine. However, current literature indicates that hepatotoxicity caused by isoniazid may be caused due to hydrazine instead of isoniazid or acetylhydrazine [41].

Generally, antituberculosis medicine have been outline to cause hepatotoxicity in 10%–30/% of sick person act towards with them [42].

**1.10 NSAIDs**

NSAIDs, including non-selective NSAIDs like diclofenac, ibuprofen, nimesulide, and sulindac, as well as selectivecyclooxygenase-2 (COX-2) inhibitors like celecoxib, are commonly used for their inflammation treating and pain treating effects. Non-steroidal-anti-inflammatory drugs (NSAIDs) work by inhibiting COX-2 to relieve pain and inflammation, but they also inhibit COX-1 in platelets, leading to decreased synthesis of thromboxane A2 and inhibition of platelet aggregation [43]. The main mode of action of NSAID-caused liver failure is not well understand, but it may be linked to the acidic nature of NSAIDs or responsive metabolites that bind to host proteins and cause damage to hepatocytes [44].

Clinically evident liver injury due to non-steroidal anti-inflammatory medicine is hardly seen, with about one to hundred cases per 100,000 recommendation [45].

**1.11 STATINS**

They are statins such as simvastatin and atorvastatin in the treatment of hypercholesterolemia that work via inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme that converts HMG-CoA to mevalonic acid, regarded as a cholesterol precursor [46].

Statins induce hepatotoxicity through undetermined mechanisms. Devices that could be incriminated in hepatic damage action of statins got to a prominent forefront of study, presenting mitochondrial dysfunction as the main suspect; statins cause an increase of superoxide dismutase biotechnology synthesis, leading to a significant increase in mitochondrial superoxide, ultimately causing mitochondrial impairment [47].

In a study involving 185 patients treated with statins, at clinical presentation, 57.8% were presented with a hepatocellular pattern, 18.3% a cholestatic pattern, and 23.2% a mixed one [48].

**1.12 CONTRACEPTIVE PILLS**

An increased risk of various presentations of liver damage has been associated with oral contraceptive use, including long-term intrahepatic canalicular cholestasis.

On the contrary, the cholestatic and hepatocellular elevations of liver enzymes have a comparable incidence from low dose estrogen oral contraceptives. In this case, it has been noted that the onset of liver injury may start between 3 days to 1 year following the treatment; however, the median is about 2 month [50].

An increased risk of several different presentations of liver injury, including intrahepatic canalicular cholestasis, has been associated with the long-term use of oral contraceptives [49].

However, cholestatic and hepatocellular liver enzyme elevations are equally frequent from low-dose estrogen oral contraceptives. The range of time between treatment and the onset of liver injury can range from 3 to 360 days, with a median time of 60 days [50].

**1.13 PHENOBARBITAL**

Phenobarbital, or 5-ethyl-5-phenylbarbituric acid, is an acidic derivative of barbituric acid, having a substituted form, its mechanism of antiepileptic action is through potentiation of GABA-activated inhibitory channel [51]. The antiepileptic action of phenobarbital is facilitated by GABA-mediated inhibition. Phenobarbital drugs can mostly cause hepatotoxicity and hypersensitivity reactions. Hepatotoxicity and hypersensitivity reactions can be caused by phenobarbital drugs.

These reactive compounds, among which are the arene oxides, are produced during the metabolism of phenobarbital in an action by the cytochrome P450 enzyme system. The cytochrome P450 enzyme system metabolizes phenobarbital and thereby produces arene oxides.

Arene oxides bind to cellular molecules and appear to elicit an immune response, which will cause hepatotoxicity. The binding of arene oxides to cellular molecules causes an immune response that leads to hepatotoxicity.

Phenobarbital-induced hepatitis comes along with fever, rash, and eosinophilia. Hepatic injury caused by phenobarbital is also presented by fever, rash, and eosinophilia [52].
A latest case control prospective study reported a figure of less than <1% of patients when having an increase in levels of serum aminotransferase during long periods of phenobarbital therapy.
According to a recent prospective study, an elevation in serum aminotransferase levels is developed by <1% of patients during long-term administration of phenobarbital [53].

### 1.14 AMIODARONE

Amiodarone is contemplete a class of antiarrhythmic agents. This drug is well known to block K currents that take part in the again polarization of the heart tissue during the third phase of the heart action potential. It is also an alpha and beta blocker of significant noncompetitive nature, although it lacks a clinically negative deterioration result [54].
Microscopic anatomy feature of this drug is to cause hepatotoxicity is a form of Mallory-Denk bodies (MDBs), white blood cell aggression, fatty change and increase size of hepatic cells similar to alcoholic liver diseases. This Microscopic anatomy effect is because the result of both amiodarone and its metamorphosis N-desethylamiodarone that brings out the accumulation in the hepatocytes, especially into the lysosomes. The result is the stop of both phospholipases Aa and Ab because of excrition of lysosomal lipids slowed down, which bring about phospholipases. This mechanism can lead to steatohepatitis and, accordingly, irreversible liver cirrhosis [55].
An elevation in liver enzymes, such as aminotransferases, was observed in 4-25% of patients treated with amiodarone [56].

### 1.15 ANABOLIC-ANDOGENIC STEROIDS

Constructive-sex hormone steroids such as stanozolol and nandrolone have been misused for a continously by both professional and amateur athletes to enhance muscle weight and movement performance [57]. They are synthetic derivatives of the male sex hormone androgenic hormone. Liver toxicity of AAS might be corrected to single vulnerability and genetic factors in hepatic cells. Oxidative factor could be a main causative of hepatic injury due to AAS misapply. It has been postulated that an increase in ROS caused by androgen receptor activation in hepatic cells may lead to mitochondrial degeneration, ultimately resulting in the clinical-trails signs of liver injury seen with the take of 17α-alkylated steroids [58]. 6.1% of 17-19-year-old children have been reported to use AAS. Therefore, liver injury caused with the misapply of AAS should be familiar to both adult and pediatric clinicians [59].

### 1.16 HEPARIN

Heparin is a composition of glycosaminoglycan of D-glucosamine and uronic acid, containing chains of both with molecular masses varying from 6 000 to 20 000 Dalton. Primarily, the oppose coagulant activity of heparin drug is mediated by the binding tom antithrombin-III [60]. The evidence in the literature supports the idea that heparin interacts with hepatocytes in more than just one way – it employs several avenues to injury the liver. Within investigation geared at determining the specific pathway of heparin mediated liver damage, it was observed that there was a marked increase in the High moving Group Box 1 Protein (HMGB1), which peaked 2 days after the last dose of heparin. The study found that anticoagulant is capable, and indeed was responsible, for inducing hepatocyte necrosis due to heparin-induced toxicity or hepatotoxicity and subsequent activation of the body's innate proximal immune response [61].

| **Mechanism** | **Description** |
|---|---|
| Hepatocyte Membrane Alteration | Heparin may directly interact with hepatocyte membranes, leading to damage and dysfunction. |
| Direct Toxicity | Heparin itself may have a toxic effect on hepatocytes, causing cellular injury. |
| Immune-Mediated Hypersensitivity | Heparin can trigger immune reactions, such as allergic responses, that contribute to liver damage. |
| HMGB1 Elevation | Heparin may induce hepatocyte necrosis, releasing HMGB1, which activates the innate immune system and exacerbates liver injury. |

It has been reported that transaminases elevations higher than 3 U/L are common in as high as 7% of patients who receive not separated anticoagulant medication. In 7.8% to 20% of ill person less concentrations of enoxaparin anticoagulant medication may be possible [62].

### 1.17 METHOTREXATE

Among different categories of weapons, MTX is widely integrated with the intolerance to folic acid. It has been demonstrated its usefulness in various clinical situations including inflammatory and autoimmune diseases ulcerative bowel disease including rheumatoid polyarthritis, psoriasis etc and also it can however be used as antineoplastic agent against leukaemia, osteogenic sarcoma, the cancer of head neck breast and lung [63]. Due to its properties MTX usage to

prevent autoimmune reaction may lead to hepatotoxicity. That is because, it less biosynthesis of methionine or through hampering of S-adenosyl methionine in CSF [64]. Since S-adenosyl methionine itself is an antioxidant its insufficiency in ill patient taking methotrexate will lead to an increase of reactive species of oxygen (ROS). At the same time MTX can possibly directly stimulate strong increases in ROS production [65].
The most recent systematic review of the literature concerning MTX and liver toxicity found that 49 % presented with elevated liver transaminases on treatment [66].

**1.18 HYDRALAZINE**

Hydralazine works primarily by preventing calcium channel blockers from releasing calcium into the muscles that cause contraction. So if it is blocked, the muscles have to remain relaxed and this dilation of the blood vessels to lower the blood pressure comes from this relaxation. Therefore, hydralazine is useful in the treatment of a following of cardiovascular state, such as extreme blood pressure, heart attack and congestive heart failure [67]. It is treated hydroponically in the liver where the hydralazine and acetyl-hydrazine forms are likely to participate in the toxicity of the liver and the destruction of the liver, and the risk of manifest liver damage can be compounded by the use of microsomal enzyme debaker in the context of these agents. [68]. However, some of the reductionist ideas about hydralazine liver damage suggest that it was mainly the immune system and its lupus-like mechanism that caused most cases of liver morbidity, since very few patients have been admitted with liver damage due to hydralazine [69].

**1.19 TAMOXIFEN**

Tamoxifen is a non-steroidal antiestrogen which has been used for the medication and prohibition of all phase of estrogen receptor-positive breast cancer by competing inhibiting the irrevocable of estrogens to their receptor [70]. Tamoxifen-induced liver injury has been attributed to abnormal mitochondrial β-oxidation of fatty acids, which leads to the generation of reactive oxygen species. Tamoxifen can interact with mitochondria by a reduction in phosphorylation efficiency; it can further impair the particle transfer in the chain of particle transport and further affect the mitochondrial membrane integrity. This leads to mitochondrial failure and ultimately results in increased ROS generation. Apart from this, the metabolic awakening of tamoxifen is attributed to the massive release of ROS. The prodrug, tamoxifen, is metabolized by CYP450 catalyst in the liver to produce its therapeutic action and in doing so, coproduces reactive oxygen species [71].

| **Effect** | **Mechanism** | **Outcome** |
|---|---|---|
| Inhibits estrogen binding | Competitive inhibition | Reduces estrogen's effects on breast cancer cells |
| Disrupts mitochondrial β-oxidation | Abnormal fatty acid metabolism | Increased ROS production |
| Reduces phosphorylation efficiency | Affects electron transport chain | Compromised mitochondrial function |
| Damages mitochondrial membrane | Disrupts mitochondrial integrity | Increased ROS production |
| Metabolic activation | Cytochrome P450 enzymes | Produces ROS |
| continuously use | Unknown mechanism | Increased chance of non-alcoholic fatty hepatic disease |

Although, lifelong tamoxifen drug use is associated with a 50-60% chance of developing non-alcoholic acute liver disease or non-alcoholic chronic hepatitis [72].

**1.20 PROPYLTIOURACIL**

Thioamide derivatives of the thioamide class propylthiouracil are used in treating thyrotoxicosis of hyperthyroidism and work through two primary mode of action: (a) its binding to thyroid peroxidase enzyme to prevents the oxidation of iodide converting to iodine; and (b) inhibiting the enzyme iodothyronine deiodinase type III responsible for converting T4 into its most active form, T3, in the periphery [73]. Several mechanisms have been suggested to cause hepatotoxicity for propylthiouracil, which includes glucosyltransferase inhibition, decreased synthesis of bile acids, and increased utilization of oxygen by the hepatocytes. Histopathological findings in the liver biopsy and postmortem studies from patients who experience hepatotoxicity associated with the use of propylthiouracil include inflammation and necrosis of the liver, which vary in severity. Histological findings included plasmacytic, eosinophilic, and lymphocytic infiltration and necrosis at various stages. However, the exact mechanism responsible for the hepatotoxicity associated with the use of propylthiouracil is not well understood [74], and the general occurrence of hepatic injury caused by any thyroid treatment drug such as propylthiouracil is minimum than 0.9%.

**Vitamin A (retinol)**

Excessive intake of vitamin A is a known cause of hepatic diseases leading to chronic with ascites or portal hypertension (75, 76, 77). Chronic exposure to large doses of vitamin A commonly used in the various popular megavitamin health protection programs leads to chronic poisoning and liver damage. Hypervitaminosis A occurs most commonly as the consequence of tonic medication. The recommended daily allowance of vitamin A for an adult is 5000 IU. Studies that administered from 15,000 units a day to more than 40,000 units per day for days evidenced some degree of liver damage. Highly advanced boluses could produce symptoms of toxicities in as short a time as a few months. The stellate cell, the liver is especially the main storage area of retinol and specifically. Most cases of vitamin A-induced liver damage are unsuspected and only an astute physician is likely to make the connection between regular vitamin A intake and unexplained advanced liver disease with ascites and portal hypertension. The clinical picture is more often that of cirrhosis with an insidious beginning. This medicine caused hepatic failure is associated with more than 70% of vitamin A injuries, where slight elevations in alkaline phosphatase occur with minimal or moderate elevations in the serum bilirubin content. Advanced cases of poisoning with vitamin A are noted with hypoalbuminemia and hypoprothrombinemia. Vitamin A has storage in stellate cells. These commonly are associated with a distribution of hepatoportal sclerosis that is characterized by the involvement of portal and perisinusoidal fibrosis, terminal venules' sclerosis, and atrophy of zone 3 of the hepatic lobule. Portal hypertension is attributed to the sinusoids compromised by enlarged stellate cells and deposited taxa in the sinusoids and terminal venules' sclerosis. This is accompanied by microvascular steatosis.

Sometimes microvascular steatosis develops. Vitamin A-induced liver injury results from natural vitamin A toxin, and the amount of damage depends upon recovery and duration of exposure. An increase in the levels of vitamin A in stellate cells leads to cell proliferation and conversion into myofibroblasts. Cases of alcoholic disease appear relatively sensitive to vitamin A poisoning. Alcohol potentiates the vitamin A toxin in experimental situations. Treatment is extractive and opinion depends on careful history and correct awareness.

**FURTHER DRUGS**

Several additional drugs have been described to cause hepatic failure and liver necrosis, the drugs are glucocorticoids, antibiotics (amoxicillin, metronidazole, doxycycline, ciprofloxacin, erythromycin), ibuprofen or albendazole.

**CASE HISTORY**

Romglitazone (rezulin) is introduced as a decrease the glucose level in blood in year 1997, but detail of hepatic injury accounted for 90 cases during just 3 days alone; the FDA had to temporarily stop the drug (79). Another non-steroidal anti-inflammatory drug, which came into use in orthopedic cases as a short-term analgesic, was bromfenac (durac), in overdose of which more than 50 cases were severely damaged in the liver followed by discontinuation of treatment. the time thereafter. Another highly liver toxic medicine, pemoline (Cylert), has been passed by the FDA commuttee since 1975 for arousal and attention disorders. More recently, it has been remove from the market by all its medicine making companies in 2005-2006 after 21 verified demonstration of pemoline-induced hepatic failure. Ximelagatran (exanta) was firstly tested as an anti-blood coagulating agent, but during trials on human, it was found that the absorption of ximelagatran increased hepatic enzyme conditions and caused hepatotoxicity. In 2004, rejected all applications to market ximelagatran. Approved in 1979 the antihypertensive drug ticrynafen (thienilic acid), but withdrew it in 1982 after many reports of failure of trails of hepatic failure and the syndicate of ticrynafen with liver disease. Withdrawn was a drug anti-anxiety, alpidem (anxyl), 1995 for the same cause (80). Many medicines with restricted action caused by the liver injury analog footprint are trovafloxacin (trovan), an antibiotic; tolcapone (tasmar), is known to treat Parkinson's disease; zileuton (zyflo), for COPD; felbamate (felbatol), used for partial epilepsy; isoniazid, an anti-tuberculosis drug; dantrium (dantrolene), used for unpleasant hyperthermia; normodine (labetalol), which is used in high blood pressure patients, etc. Interferon β-1a is another drug that is used in the management of multiple sclerosis. As is detailed in the book, it is reported to cause severe liver damage with total liver failure being the ultimate consequence (81). With interferon β-1a, the risk of liver damage increases several times if taken in combination with alcoholic products. During 2009, the FDA documented thirty-three confirmed reports of serious hepatotoxicity due to propylthiouracil. For safety reasons, the pharmaceutical companies issue warnings that some medications can cause hepatotoxicity. Similarly, the packaging of an antidepressant drug duloxetine states that "Cymbalta (duloxetine) should not be taken to ill person with significant alcohol consumption and liver dysfunction" (82).

**CONCLUSION**

Medicines are supposed to treat diseases, but their utility becomes useless if they present a poisionous makeup. There are many trade medicines with liver failure properties. Therefore, pharmaceutics business now turn to herbal medicine for their curative and hepatoprotectives role. Curcuma longa like other herbs have been found to possess potent hepatoprotective activity against different models of hepatotoxicity [83]. In most cases, the active principle of these plants responsible for their hepatoprotectives activity is the phytochemical content [84, 85]. Many plants have been studied for their potential as hepatoprotectives [86]. Plants possessing strong antioxidant capacity, such as Nerium indicum, were considered in its role as a hepatoprotector since the ability of acting as a hepatoprotector significantly depends on its antioxidant capacity. Increasing DIHT incidence continuously holds the promise for improved and better safer CAs in the future [87].

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