Hepatotoxicity as injury to the liver that is allied with diminished liver function caused by acquaintance to a drug. The dissimilarity between damage and function is important, because it is mainly when function is impaired that symptoms and clinically significant disease follow. The serious drug-related hepatotoxicity is incapacitating life-threatening. Drug-related hepatotoxicity is uncommon for many drugs, its true rate is difficult to determine. After acetaminophen overdose the use of N-acetylcysteine and intravenous carnitine for valproate-induced mitochondrial injury are allowances. Drug-related hepatotoxicity is now leading cause of acute liver failure, among patients referred for liver transplantation because of an intentional or unintentional overdose of acetaminophen. Hepatotoxicity leads to some liver disease such as:

- Hepatitis, inflammation of the liver, caused mainly by various viruses but also by some poisons (e.g. alcohol), autoimmunity (autoimmune hepatitis)
- Non-alcoholic fatty liver disease, a spectrum in disease, associated with obesity and characterized as an abundance of fat in the liver; may lead to hepatitis, i.e. steatohepatitis.
- Cirrhosis is the formation of fibrous tissue in the liver can be caused by viral hepatitis, alcoholism or contact with other liver-toxic chemicals.
- Haemochromatosis, a hereditary disease causing the accumulation of iron in the body, eventually leading to liver damage.
- Cancer of the liver (primary hepatocellular carcinoma or cholangiocarcinoma and metastatic cancers, usually from other parts of the gastrointestinal tract).
- Wilson's disease, a hereditary disease which causes the body to retain copper.
- Primary sclerosing cholangitis, an inflammatory disease of the bile duct, likely autoimmune in nature.
- Primary biliary cirrhosis, autoimmune disease of small bile ducts.
- Budd-Chiari syndrome, obstruction of the hepatic vein.
- Gilbert's syndrome, a genetic disorder of bilirubin metabolism.
- Glycogen storage disease type II, the build-up of glycogen causes progressive muscle weakness (myopathy) throughout the body and affects various body tissues, particularly in the heart, skeletal muscles, liver and nervous system.

**ETIOLOGICAL FACTORS FOR HEPATOTOXICITY**

Drugs directed orally or intravenously are focused to first pass metabolism in the liver results in their biological inactivation. When a drug leaks first pass metabolism its biological activity is maintained. Due to the absence of P450s and hepatic metabolic inactivation a stage will come when there is an exaggerated and prolonged response to a drug takes place. The composition of P450s in gut and liver can have a major influence on the efficacy and toxicity of a drug. Several of the xenobiotic metabolizing P450s, including CYP2A6, CYP2C9, CYP2C19 and CYP2D6; with the exception of CYP2A6 that are having the capability to activate certain nitrosamines. Functional polymorphisms occur with P450s that metabolize toxins and carcinogens for CYP1A2 and CYP1B1. Mutants in CYP1B1 cause hereditary glaucoma. From human liver specimens studies it was concluded that there is still a high degree of difference in their expression. When a limited number of P450s are involved in xenobiotic metabolism, Several P450s are involved in the synthesis of steroid hormones. When P450s is activating several genes like CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2E1 are involved in the process.

Drug interactions occur when two drugs are coadministered and both are processed by the same P450. One drug can then inhibit the metabolism of another drug significant to high serum levels and prolonged biological activity and occasionally toxicity. This depends on the drug activity as either inducer or inhibitor. When the effect is immediate, several P₄₅₀ enzymes block metabolic activity. On the other hand enzymes inducers chemical drug increase P₄₅₀ activity by cumulative its synthesis. Other factors are:-

- Inherited birth imperfections
- Metabolic complaints
- Bacterial infections.
- Alcohol or poisoning by toxins.
- Certain medications that is toxic to the liver.
- Nutritional paucities.
- Injury

**SYMPTOMS**

Jaundice or yellowing of the skin, darkened urine, loss of appetite, unusual weight loss or weight gain, vomiting, diarrhoea, light colored stools, abdominal pain in upper right part of the stomach, Varicose veins (enlarged blood vessels). ¹

**MECHANISM OF HEPATOTOXICITY CAUSED BY DIFFERENT AGENTS**

Several mechanisms are responsible for inducing hepatic injury. Many chemicals damage mitochondria, an intracellular organelle that produces energy. Its dysfunction releases excessive amount of oxidants which in turn injures hepatic cells. Activation of some enzymes in the cytochrome P-450 system such as CYP2E1 also leads to oxidative stress. ² Injury to hepatocyte and bile duct cells lead to accumulation of bile acid in liver. This endorses further liver damage. Non-parenchyma cells such as Kupffer cells also have role in the mechanism of hepatotoxicity. The Exact mechanism of drug induced liver injury remains largely unknown but it appears to involve two pathways — direct hepatotoxicity and adverse immune reactions.

**Direct Hepatotoxicity:** Drug induced liver injury is originated by the bio activation of drugs to chemically reactive metabolites, which have the ability to interconnect with cellular macromolecules such as proteins, lipids, and nucleic acids, leading to protein dysfunction, lipid per oxidation, DNA damage, and oxidative stress. These reactive metabolites may induce interruption of ionic gradients and intracellular calcium stores, resulting in mitochondrial dysfunction and loss of energy production. This damage of cellular function can dismiss in cell death and likely liver failure.

**Immunological Reaction:** Hepatic cellular dysfunction and cell death also have the ability to initiate immunological reactions, including both innate and adaptive immune responses. Damaging hepatocytes result in activation of innate immune system like Kupffer cells (KC), natural killer (NK) cells, and NKT cells and result in producing proinflammatory mediators and secreting chemokine to further recruit inflammatory cells to the liver. It has been confirmed that various inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and interleukin (IL)-1β produced during drug induced liver injury are involved in promoting tissue damage. ³ Innate immune cells are also the main source of IL-10, IL-6, and convinced prostaglandins, all have been shown to display hepatoprotective role. ⁴ It is the subtle equilibrium of inflammatory and hepatoprotective mediators produced after activation of the innate immune system that
determines an individual susceptibility and adaptation to drug induced liver injury. The major procedures of drug induced liver injury include acute hepatitis, cholestasis, and a mixed pattern.\textsuperscript{7}

**Hepatotoxic Agents (Hepatotoxicity) - CCl\textsubscript{4} Induced Hepatotoxicity:** Carbon tetrachloride (CCl\textsubscript{4}) induced liver damage has been lengthily used as an experimental model. CCl\textsubscript{4} is used as a model drug for the study of hepatotoxicity in acute and chronic liver failure. CCl\textsubscript{4} is metabolized by CYP2E1, CYP2B, and possibly CYP3A, to form the trichloromethyl radical, CCl\textsubscript{3}. This CCl\textsubscript{3} can also bind to cellular molecules damaging crucial cellular progressions. This radical can also react with oxygen to form the trichloromethylperoxy radical CCl\textsubscript{3}O\textsubscript{2}, a highly reactive species. The metabolites of CCl\textsubscript{4} cause the hepatic injury in the CCl\textsubscript{4} acute liver injury model.\textsuperscript{8}

Administration of a single dose of CCl\textsubscript{4} to a rat produces centrilobular necrosis and fatty changes. The poison reaches its maximum concentration in the liver within 3 hrs. of administration. Afterward, the level falls and by 24 hrs there is no CCl\textsubscript{4} left in the liver.\textsuperscript{9} Dose of CCl\textsubscript{4}: 0.1 to 3 ml/kg I.P.

**Galactosamine Induced Hepatotoxicity:** D-Galactosamine induced liver damage has been lengthily used as an experimental model. D-Galactosamine a discerning hepatotoxic, it induces a verbose type of liver injury closely like human biological hepatitis and approaching a drug induced disease in humans. The toxicity of D-Galactosamine is mainly due to the collapse of uridine ponds that are linked with ribonucleic acid (RNA) and altering hepatocellular function.\textsuperscript{10} This mechanism of toxicity increases in cell membrane porousness leading to cell death. The cholestasis caused by galactosamine may be from its negative effects on bile ducts. Galactosamine decrease the bile flow and it’s gratified i.e. bile salts, cholic acid and deoxycholic acid. Dose of D-Galactosamine: 400 mg/kg, I.P.\textsuperscript{11}

**Thioacetamide Induced Hepatotoxicity:** Thioacetamide, a selective hepatotoxic within a short period of time after the administration of the drug. It experiences an extensive metabolism to acetamide and thioacetamide S-dioxide by the mixed function oxidase system.\textsuperscript{12} Acetamide does not have liver necrotizing properties while thioacetamide S-oxide is further metabolized to cytochrome P-450 mono-oxygenase to sulfene, thioacetamide S-dioxide. The thioacetamide S-dioxide is a very extremely reactive compound. Thioacetamide is oxidized to a reactive metabolite that is further oxidized to thioacetamide S-dioxide, which covalently diles to liver, macromolecules and initiates liver injury. Chronic exposure of thioacetamide produced cirrhosis in rats.\textsuperscript{13} Mechanism of thioacetamide toxicity is due to the formation of thioacetamide S-oxide which is responsible for the amendment in cell permeability and the concentration of Ca++ increases intracellular in nuclear volume and also obstructs mitochondrial activity which clues to cell death.\textsuperscript{14}

**Alcohol Induced Hepatotoxicity:** Liver is the organ which is more prone to the toxic effect of ethanol. Alcohol ingesting is documented to cause fatty infiltration, hepatitis and cirrhosis. Hepatitis and cirrhosis may occur due to higher lipid per oxidative reaction during the microsomal breakdown of ethanol. It is usually putative that the alcohol can induce in vivo changes in membrane lipid composition. The mechanisms of alcohol lead to alteration in membrane phospholipid and increase in lipid peroxidation. The effect of ethanol is due to the higher generation of oxy free radicals during its oxidation in liver. The damaging effect of free radical is due to the decrease in catalase, superoxide dismutase and glutathione peroxidase or due to the direct effect of acetaldehyde formed by oxidation of ethanol.\textsuperscript{15}

**Paracetamol Induced Hepatotoxicity:** The mechanism of paracetamol induced hepatotoxicity is due to the formation of a hepatotoxic metabolite. A therapeutic dose of paracetamol is metabolized to sulphate and glucuronide conjugates and further is metabolized to a reactive midway which is depolluted by conjugation with glutathione. In overindulge, the sulphate and glucuronide conjugation pathways are drenched and drugs are converted to the reactive metabolite. The glutathione is rapidly exhausted and the metabolite accumulated and binds covalently to liver cell proteins, causing irreparable damage. Dose of Paracetamol: 1 gm/kg P.O.\textsuperscript{16}

**Antitubercular Drugs Induced Hepatotoxicity:** Antitubercular drug like Isoniazid (INH), Rifampicin and Pyrazinamide and their combination induced serious hepatotoxicity. Adverse effects of antitubercular therapy are occasionally potentiated by multiple drug regimens. INH is metabolized to monoacetyl hydrazine, which is metabolized to a toxic product by cytochrome P 450 leading to hepatotoxicity. Rifampicin also increases the breakdown of INH to nicotinic acid and hydrazine is hepatotoxic. When INH and rifampicin in combination the plasma half-life of INH is shortened and acetyl hydrazine is quickly converted to its active metabolites by snowballing the oxidative elimination rate. Rifampicin induces hydrolysis pathway of INH metabolism into the hepatotoxic metabolite hydrazine. When these drugs like rifampicin and pyrazinamide
administered parallel their Pharmacokinetic interactions exist in tuberculosis patients. Pyrazinamide decrease the blood level of rifampicin by decreasing its bioavailability and increasing its clearance.17

Lithocholic Acid Induced Hepatotoxicity: The mechanisms of hepatobiliary injury in the lithocholic acid progressively used model of cholestatic liver injury. The etiology of LCA-induced cholestasis in rat include biochemical alterations of the bile canicular membrane.18 Due to the poor solubility of LCA the crystalline plugs develop in bile canaliculi19 and impaired transferring.20 Administration of LCA can outcome in hepatocellular necrosis with significant reductions in basolateral bile acid uptake (Ntcp, Oatp1) and sinusoidal bile acid efflux transporters (Mrp3) increased. These changes in the liver represent an inherent toxicity of accumulating bile acids.

HEPATOPROTECTIVE AGENTS
(PHARMACOTHERAPY FOR HEPATOTOXICITY)
Allopathic Treatment: Ursodeoxycholic Acid, UDCA
(Ursodiol): At present UDCA is only one Allopathic compound approved by US FDA for the treatment of primary biliary cirrhosis (PBC) or hepatoprotection. It is increasingly being used to treat all cholestatic conditions because it improves serum liver.21 UDCA is a polar bile acid that may act by declining the hydrophobicity and toxicity of the bile. UDCA is a dihydroxy bile acid which is normally present in human bile in a little concentration of about 3% of total bile acids.22 (Figure No-1)

Multiple Action Of UDCA Are As Follows
1. Defence of Injured Cholangiocytes Against Toxic Effects Of Bile Acids: Hydrophobic bile acids damage cell membranes and use cytotoxicity at concentrations that are present in bile.24 UDCA may also protect cholangiocytes by falling apical uptake and UDCA encouraging basolateral efflux of bile acids from cholangiocytes and the concentration of hydrophobic bile acid decreasing intracellular thus reducing toxicity.

2. Inspiration Of Depollution Of Hydrophobic Bile Acids: It has been documented that UDCA stimulates steroid breakdown. UDCA activates PXR in rat hepatocytes and induces CYP3A4, which is a bile acid–metabolizing enzyme.25

3. Protection Against Bile Acid-Induced Apoptosis: Apoptosis is an important aspect of cell death in cholestasis liver diseases.26 Glycochenodeoxycholic acid induces apoptosis by ligand-independent activation of the Fas receptor in rat hepatocytes. UDCA shrinks Fas ligand–induced apoptosis in rat hepatocytes. It protects rat hepatocytes against bile acid–induced apoptosis by preventing bile acid–induced, c-Jun N-terminal kinase–dependent CD95 (Fas) trafficking to the plasma membrane.27

Clinical Uses of UDCA
1. Biliary cirrhosis
2. Biliary disease secondary to cystic fibrosis
3. Non-alcoholic steatohepatitis, idiopathic chronic hepatitis
4. Autoimmune hepatitis
5. Primary sclerosing cholangitis
6. Alcoholic hepatitis

AYURVEDIC OR HERBAL TREATMENT
These are generally classified into 3 categories without any strict delineation amongst them.
2. Hepatotropic Agents: Promote the healing process of the liver.
3. Hepatoprotective Agents: Prevent various types of liver affections.

(Table No-1)
CONCLUSION
Hepatotoxicity will remain a problem that carries both clinical and controlling significance. Future results from ongoing multicentre concerted efforts may help contribute to our current understanding of hepatotoxicity associated with drugs.

Credit of the antisocial drug is the vital in preventing a reappearance of the Drug Induced Liver Disease. Failure to differentiate an adverse drug reaction as the cause of liver disease may allow an initially minor reaction to progress to a serious illness. The practice strategies for causality valuation include reversal of liver test abnormalities when the suspected drug is withdrawn, corroborative evidence of an adverse drug reaction and the baring of other causes of hepato-biliary disease. Drug induced autoantibodies could be useful diagnostically but notwithstanding an increasing number of drugs associated with their formation they remain uncommon. Liver biopsy, potentially dangerous but may provide useful diagnostic information in many patients suspected of having DILD. Mixed cholestatic and hepatic reactions, granulomatous retorts combined with bile duct injury and fatty change together with zonal hepatic necrosis are all redolent of drug-induced liver disease. The gold standard for diagnosis remains rechallenge, which is neither often practical nor safe.

REFERENCES


Table 1: List of plants evaluate for hepatoprotective effect.

<table>
<thead>
<tr>
<th>S. no</th>
<th>Plants</th>
<th>Animal</th>
<th>P Value</th>
<th>Model</th>
<th>Part Used</th>
<th>Extract</th>
<th>Uses</th>
<th>Family</th>
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<tr>
<td>1</td>
<td>Aegle marmelos</td>
<td>Cross breed albino mice</td>
<td>&lt;0.01</td>
<td>CC14</td>
<td>fruit pulp</td>
<td>Ethanolic</td>
<td>dysentery and diarrhoea</td>
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<td>2</td>
<td>Aerva lanata Linn.</td>
<td>Wistar rats</td>
<td>&lt;0.001</td>
<td>Paracetamol</td>
<td>fresh plants</td>
<td>hydroalcoholic</td>
<td>Diuretic, Demulcent</td>
<td>Amaranthaceae</td>
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<tr>
<td>3</td>
<td>Annona squamosa Linn.</td>
<td>Wistar strains of rats</td>
<td>&lt;0.01</td>
<td>Isoniazid+Rifampicin</td>
<td>Leaves</td>
<td>Alcoholic</td>
<td>Cherimoya Custard-apple</td>
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<tr>
<td>4</td>
<td>Anogeissus latifolia</td>
<td>Albino rats of Wistar strain</td>
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<td>Bark</td>
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<td>respiratory diseases</td>
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<td>&lt;0.001</td>
<td>CC14</td>
<td>Stems</td>
<td>Aqueous and Methanolic</td>
<td>landscape gardening, afforestation and reforestation</td>
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<td>Chamomile capitula</td>
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<td>Fresh Plant</td>
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<td>swelling of inflamed tissues</td>
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<td>8</td>
<td>Plumbago zeylanicaLi.nn.</td>
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<td>&lt;0.05</td>
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<td>dyspepsia,</td>
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<td>9</td>
<td>Premna serratifolia</td>
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<td>CC14</td>
<td>Leaves</td>
<td>Ethanolic</td>
<td>Chicken pox and measles</td>
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<td>10</td>
<td>Rhododendron Arboreum</td>
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<td>Leaves</td>
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<td>Wistar albino rats</td>
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<td>Stem</td>
<td>Methanolic</td>
<td>Stomach ache, dysentery, rheumatism and swollen joints.</td>
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Figure 1: Mechanism of UDCA as hepatoprotective