



Review Article

A COMPREHENSIVE REVIEW OF HEPATOTOXINS

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ABSTRACT

Liver has storage, filtration, excretory and metabolic functions. The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. More than 900 drugs have been reported to cause liver injury, and drugs account for 20-40% of all instances of fulminant hepatic failure. Other organic and inorganic substances used in laboratories and industries, natural chemicals (eg: microcystins) and some herbal remedies can also induce hepatotoxicity. Hepatic injury leads to disturbances the functions of hepatocytes resulting in leakage of plasma membrane thereby causing an increased enzyme level in serum. This review focus on various types of hepatotoxins involved in liver injury.

Key words: Liver, Hepatotoxicity, Drugs, Herbals, Chemicals.

INTRODUCTION

Toxic liver injury produced by drugs, chemicals and some herbs may virtually mimic any form of naturally occurring liver disease. Many chemicals damage mitochondria, an intracellular organelle that produce energy. Endogenous bile acids produce hepatocellular death by inducing fatty acid production from the cytoplasm to the plasma membrane where self aggregation stimulates apoptosis. Kupffer cell activation and penetration of neutrophils causes toxic damage. The liver conveys many cytochrome P450 isoforms, inclusive ethanol induced CYP2E1. This leads to the formation of ROS, activates many toxicological substrates, and ethanol can be a central pathway leading to oxidative stress. Hepatotoxicity occurs following mechanisms like disruption of liver cells, microvesicular steatosis, apoptosis of hepatocytes, injury to bile duct, cytolytic T-cell activation, including inhibition of mitochondrial respiration and damage to mitochondrial DNA. Induction of mitochondrial permeability

changes is another mechanism causing mitochondrial failure, which can lead to necrosis of ATP reduction or caspase-dependent apoptosis¹. Inorganic compounds like metals and metalloids causes cell damage by lipid peroxidation. Combination of cell damage and endotoxin also activate kupffer cells and neutrophils in the liver. Although it acts to removal cellular debris and part of the host's defense system, these inflammatory cells can cause more damage to the liver. The common symptoms of hepatotoxicity were hepatic necrosis, fibrosis, vomiting, haemorrhage, inflammation of feet and legs, loss of appetite, stomach pain, light coloured bowel movements, dark coloured urine, fever, malaise, pruritis, dyspepsia, weight loss and blood coagulation.

Classification of hepatotoxins

Hepatotoxins² are classified into

- a. Intrinsic
- b. Host Idiosyncrasy

Table 1. Classification of hepatotoxins

Category of agent	Mechanism	Histologic lesion	Example
Intrinsic Toxicity			
Direct	Direct physico-chemical distortion and destruction of structural basic cell metabolism.	Necrosis (zonal) and/(or) Steatosis.	Carbon tetrachloride, Chloroform, Phosphorous
Indirect cytotoxic	Interference with specific metabolic pathways leading to structural injury.	Steatosis (or) necrosis	Ethionine & Mycotoxins
Cholestatic	Interference with hepatic excretory pathways leading to cholestasis	Bile casts	Ictero-genin, 17a alkylated anabolic and contraceptive steroids
Host Idiosyncrasy			
Hyper sensitivity	Drug allergy	Necrosis (or) cholestasis	Sulphonamides, Para-aminosalicylic acid, Halothane
Metabolic abnormality	Production of hepatic metabolites	Necrosis (or) cholestasis	Iproniazid, Isoniazid, Halothane

Table 2. Some common types of hepatotoxic agents

Inorganic agents	
Metals & metalloids	Antimony, Arsenic, Beryllium, Bismuth, Boron, Cadmium, Chromium, Cobalt, Copper, Iron, Lead, Manganese, Mercury, Gold, Phosphorous, Selenium, Tellurium, Thallium, Zinc.
Organic agents	
Natural toxins	Albotocin, Cycasin, Icterogenin, Indospicine, Lantana, Agaione, Pyrrolizidines, Safrole, Tannic Acid and Microcystins
Mycotoxins	Aflatoxin, Cyclochlorotine, Ethanol, Luteoskyrin, Ochratoxin, Rubratoxins, Sterignatocystins, Griseofulvin, Sporidesmin, Tetracycline and other Antibiotics.
Bacterial toxins	Exotoxins (<i>Corynebacterium diphtheriae</i> , <i>Clostridium botulinum</i> , <i>Streptococcus haemolyticus</i>) and Endotoxins
Synthetic non-medicinal agents	Haloalkanes and Haloolefins, Nitroalkanes, Chloroaromatic compounds, Nitroaromatic compounds, Organic amines, Azo compounds, Phenol and its derivatives, Various other organic compounds.
Medicinal agents	Over 900 drugs used for treatment and diagnosis.

Table 3. Inorganic agents induced hepatotoxicity

Agents	Types of injury
Mercury	Hepatomegaly, centrilobular hepatic steatosis, decrease in the synthesis of hepatic coagulation factors ^{3, 4} and mitochondrial dysfunction ⁵ .
Lead	Portal inflammatory cell infiltration, apoptosis, biliary hyperplasia, cytoplasmic inclusions and swelling ⁶ , congestion, apoptotic and necrotic cells ⁷ .
Cadmium	Mitochondrial dysfunction and fragmentation ⁸ , apoptosis, neutrophil infiltration and proinflammatory cytokines and chemokines
Arsenic	Hepatocellular damage, hepatomegaly and oxidative stress
Copper	Hepatic failure, pericentral hepatic necrosis, Cholestasis and cirrhosis

Table 4. Common drugs associated with hepatotoxicity

DRUG OR CLASS	COMMON USES	TYPES OF LIVER INJURY
Allopurinol	Gout and Kidney Stones	HC or mixed, often with immunoallergic features
Amiodarone	Ventricular fibrillation and tachycardia	HC or mixed, or C
Amoxicillin- clavulanate	Bacterial infections	C; may be HCC
Anabolic steroids	Muscle building and increase male sex characteristics	C; may be contaminate in performance enhancing products
Androgen containing steroids	Impotence in men and breast cancer in women	C; may present with peliosis hepatitis, nodular regenerative hyperplasia, or HCC
Anti-TNF agents	Psoriatic-arthritis, spondylitis and crohn's disease	HC; may resemble Auto immune hepatitis
Azathioprine	rheumatoid arthritis	C or HC; may present with portal hypertension
carbamazepine	Seizures and trigeminal neuralgia	HC, mixed or C, often with immunoallergic features(AHS)
Flavocoxid	chronic osteoarthritis	Mixed, HC or C
Fluoroquinolones	Respiratory tract infections	C, HC or mixed
Inhaled anaesthetics	Analgesia and narcosis	HC; may have immunoallergic features
Interferon - α	Malignant melanoma	HC; AIH like
Interferon - β	Relapsing multiple sclerosis	HC
Isoniazid	Tuberculosis	Acute HC; resembles acute viral hepatitis
Lamotrigine	Seizures and bipolar disorders	HC; often with immunoallergic features (AHS)
Macrolides	Mycobacterial infections	HC; may be C
Methotrexate	Psoriasis and rheumatoid arthritis	Fatty liver and fibrosis
Minocycline	Bacterial, skin, respiratory and urinary tract infections and gonorrhea	HC; may resemble Auto immune hepatitis
Nitrofurantoin	Urinary tract infections	Acute form: C, chronic form: mostly HC, but may resemble Auto immune hepatitis
NSAIDs	Analgesic and anti-inflammatory	HC
Diclofenac	Antipyretic, Analgesic and anti-inflammatory	Hepatitis, jaundice and fatal hepatitis ⁹
Sulindac	Arthritis of the spine and gouty arthritis	Fatal hepatitis, C and hepatic injury ¹⁰
Nimesulide	Arthritis, acute pain, fever and primary dysmenorrhoea in adolescents	Hepatocellular necrosis and C ¹¹ .
Bromfenac	Eye swelling and inflammation	Fulminant hepatic failure ¹² .
Indomethacin	Arthritis, bursitis and tendonitis	HC necrosis ¹³ , Microvesicular steatosis and C
Phenytoin	Seizures	HC, mixed or C, often with immunoallergic features (AHS)
Proton pump inhibitors	Ulcers and gastroesophageal reflux disease	HC, but rare
Sulfasalazine	Bowel disease and ulcerative colitis	Mixed, HC or C; may have immunoallergic features
Trimethoprim-Sulfamethoxazole	Bacterial and pneumonia	C; may be HC, and/or may be associated with immunoallergic features
Valproate	Epilepsy and migrane	Hyperammonemia, HC and Reye like syndrome

Herbal drugs induced hepatotoxicity

Self medication is frequent and sometimes patients even increase the dosage because most of the herbal drugs are available without prescription and are low costs, this cause adverse reactions and worsen liver diseases.

Contamination of herbals with microorganisms, fungal toxins such as aflatoxin, with pesticide, heavy metals and synthetic drugs¹⁴ have been identified as a cause of hepatic diseases.

Interaction between herbs and chemical drug are another source of problems associated with the intake of herbal compounds that leads to liver impairment.

Table 5. Examples of common herbal medications associated with hepatotoxicity

HERB SCIENTIFIC NAME	COMMON USES	TYPES OF HEPATOTOXICITY
<i>Actaea racemosa</i>	Menopause symptoms	Acute autoimmune and fulminant hepatitis
<i>Atractylis gummifera</i>	antipyretic, emetic diuretic and chewing-gum ¹⁵ .	Inhibits mitochondrial functions, Glutathione depletion and increased lipid peroxidation
<i>Camellia sinensis</i>	Weight loss, mental alertness and lowering cholesterol	Cholestatic hepatitis and fulminant liver failure
<i>Symphytum officinale</i>	Back pain, Osteoarthritis and sprains	Veno-occlusive disease resulting in acute liver failure, fibrosis and cirrhosis
<i>Teucrium chamaedrys</i>	Fever, stomach-ache, diarrhea and digestive aid	Acute, chronic and fulminant hepatitis
<i>Chelidonium majus</i>	Dyspepsia, detoxification, irritable bowel syndrome and antispasmodic	Cholestatic hepatitis
<i>Piper methysticum</i>	anxiety and depression	Hepatic-necrosis, Cholestatic hepatitis and fulminant liver failure
<i>Larrea divaricata</i> and <i>larrea tridentata</i>	Common cold and pain	Cholestatic hepatitis and fulminant liver failure
<i>Hedeoma pulegioides</i> and <i>mentha pulegium</i>	Weight loss	Fulminant Hepatic necrosis
<i>Cassia angustifolia</i>	laxative	Acute hepatitis, Sub acute Cholestatic hepatitis and acute liver failure and portal vein thrombosis
<i>Ephedra sinica</i>	Asthma and hay fever	Acute hepatitis and liver failure
<i>Morinda citrifolia</i>	Weight loss	Severe acute hepatitis
<i>Usnea</i>	Immune stimulating and antioxidant	Acute liver failure

CONCLUSION

The liver is subject to potential damage from an enormous array of pharmaceutical agents, Natural toxins, metals and metalloids, mycotoxins, endotoxins and bacterial toxins. The injury may result from direct toxicity via hepatic conversion of xenobiotics to an active toxin through immune mechanism, usually by drugs or a metabolite acting as hapten to convert a cellular protein into an immunogen. Also these hepatotoxins are recognised as direct and indirect hepatotoxins. On the other hand, overdosage of herbal remedies also induced hepatotoxicity. In summary, several sources and its mechanisms initiates liver damage and aggravate ongoing injury processes. However cell injury and death is not only determined by the nature and dose of a medicinal agents but also by factors such as natural toxins, metals and metalloids, mycotoxins, endotoxins, bacterial toxins and overdosage of herbal drugs.

ABBREVIATIONS

CYP2E1	Cytochrome P450 2E1
ROS	Reactive Oxygen Species
ATP	Adenosine triphosphate
DNA	Deoxyribonucleic acid
H	Cholestatic
HC	Hepatocellular
HCC	Hepatocellular carcinoma
AHS	Anticonvulsant hyper sensitivity syndrome
AIH	Auto immune hepatitis
NSAID's	Non-Steroidal Anti-inflammatory Drugs
TNF	Tumor Necrosis Factor

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