# Drug Induced Hepatotoxicity and Hepatoprotective Drugs : A Review

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***Abstract*- Liver damage is a term for collection of conditions, diseases and infections that affect the cells, tissues, structures of function of hepatic cells. Hepatotoxicity is disorder which cause of mortality and morbidity due to environmental pollutants; hepatic cancer; alcoholic and intoxicants and other drug therapy. Drug-induced hepatotoxicity (DIH) / Drug-induced Liver injury (DILI) is the most common cause of acute hepatic failure. Drug-induced hepatotoxicity is a severe problem as it affects a huge population around throughout the globe, and it is the most highly cited reason for the failure of drugs.**

**Hepatoprotection is of intense interest and hepato-protective activity of a drug should be based on its ability to reduce the injurious effect or to preserve the architecture and physiological functions of the liver disturbed by a hepatotoxin. Hepatoprotective drugs are those compounds, which mitigate the liver injury caused by hepatotoxic agents. Liver injury treatments are important issue of today's research domain, because of many allopathic drugs and their toxic influence lead to liver damage. Modern treatment leads to serious adverse effects which eventually hepatic damage with symptoms include indigestion (constipation), fatigue, allergies and chemical sensitivities, jaundice, edema, body weight loss and neurological disorders. Further protective role of herbal drugs is not ignored because, herbal drugs are also acts by multiple pathways and shown full protection in liver disorders so there is a need to study different herbal drugs and their protective mechanism for liver disorders. Isolated active principles / secondary plant metabolites (SPMs) / phyto-pharmaceutical are to be treated like modern drugs and subjected to rigorous testing as required by the regulatory authorities.**

## 1. G eneral Introduction

### 1.1 Hepatic System : Anatomy & Physiology

As per Allen (2002), liver (Hepar) is cone shaped, dark reddish-brown, one of the largest solid glandular organs in the human body (weighing about 1.5 Kg / about 3 pounds in adults; representing approximately 2.5% of adult body weight) and essential for life. It is situated in the right upper quadrant of the abdomen (upper right hand portion of the abdominal cavity, under the diaphragm and on top of the stomach, right kidney and the intestines; in the protection of rib cage). It is covered by Glisson's capsule, a visceral continuation of the peritoneum (Moore, 2006)

There are two distinct sources that supply blood to the liver, including thefollowing:

- Oxygenated blood flows in from the hepatic artery
- Nutrient-rich blood flows in from the hepatic portal vein

The liver holds about 13 percent of the body's total blood supply at any given moment. The liver is divided into two lobar segments (right and left), and two accessory lobes. It is further subdivided into eight (Couinaud) segments based upon vascular supply and bile duct distribution. The right lobe is six times larger than left lobe. (Figure 1-2) (Sutherland *et al*., 2002; Kogure *et al*, 2007)

Vascular organ (Figure 1.3a and 1.3b)

Hepatic artery

- Supplies $O_2$ rich blood from heart to liver
- Provides 20-30% of blood supply to liver

Portal vein

- Supplies nutrient rich blood from the digestive tract
- Provides 70-80% of blood to liver

Nobili *et al*., 2011 stated that liver is a crucial organ for maintenance ofgastrointestinal homeostasis (optimal functioning is crucial for health and disease); a vital / essential sensitive organ of body responsible for multidimensional functions likemetabolic (biotransformation); secretory, detoxification from exogenous and endogenous challenges like xenobiotics, drugs, viral infections and chronic alcoholism (Torres *et al*., 2012; Sanchez *et al*., 2012)

Alonso *et al*., 2010 compiled the global causes for liver disease include :

- Viral hepatitis;
- HIV;
- Obesity with nonalcoholic fatty liver disease (NAFLD);
- Excessive chronic alcohol consumption;
- Immune and cholestatic disorders;
- Inherited metabolic disorders;
- Numerous medications
- Hemochromatosis;
- Schistosomiasis;
- Fungi infections;
- Fibrosis (Sanchez *et al*., 2012)

Several hepatoprotective / anti-hepatotoxic agents are reported to protect the liver from toxic insults and both synthetic and natural products are known to produce ameliorative effects both prophylactic and therapeutic.

Medicinal plants are important alternative/ complimentary sources for potential hepatoprotective agents, and their efficacy and safety have been documented in both experimental and clinical studies.

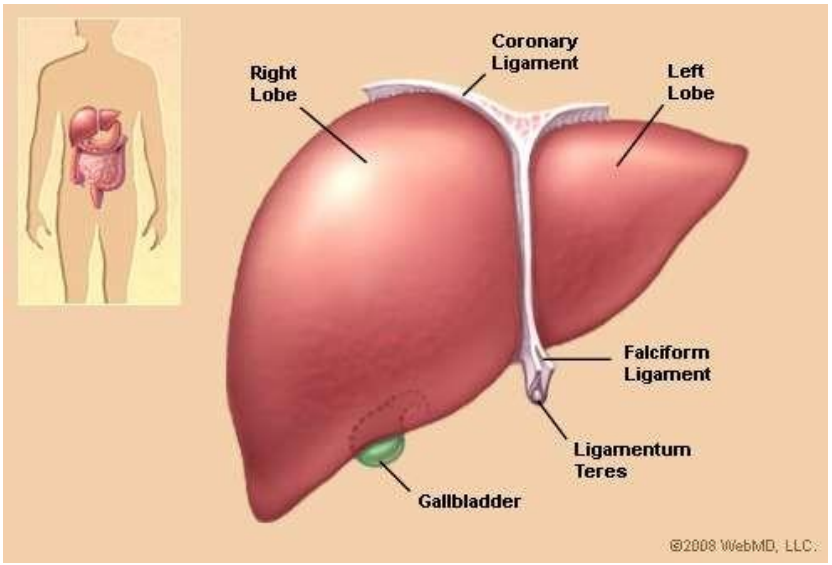


Figure 1 : Human Liver. (Brunicardi *et al*., 2010)

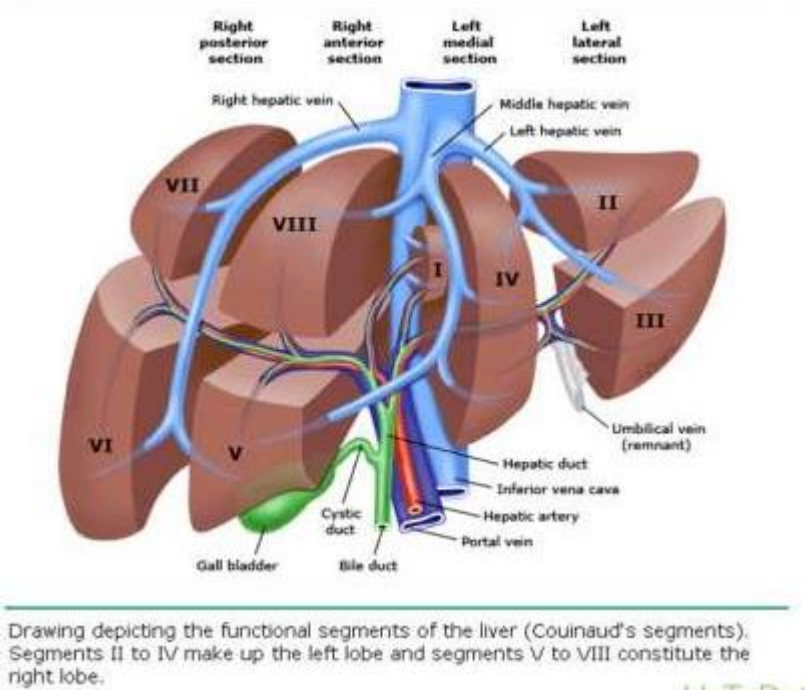


Figure 2 : Segmental anatomy of Liver.

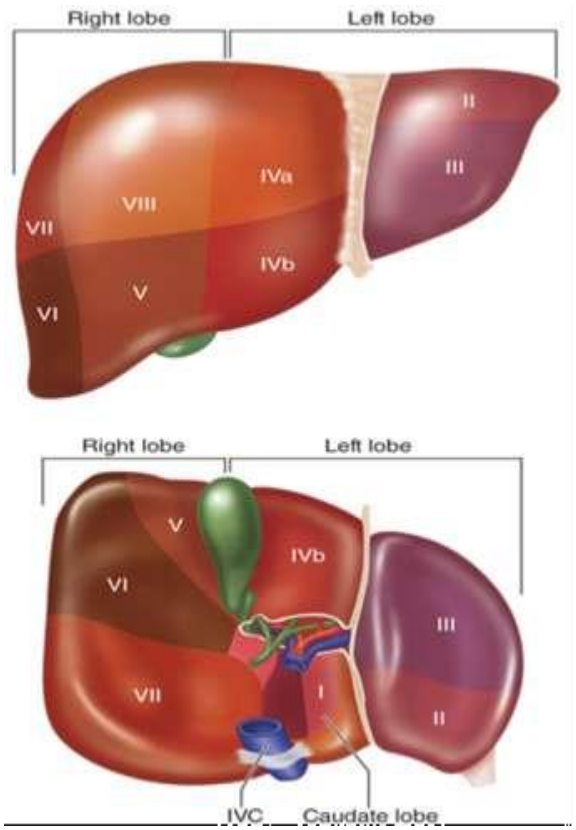


Figure 3a : Various lobes of the Liver.

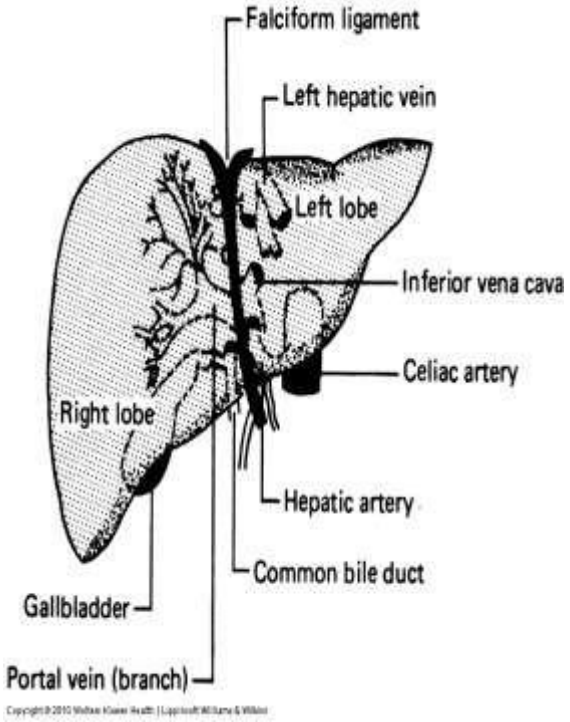


Fig. 3b : Various lobes and arteries of Liver.

**1.1.1 Microscopic Anatomy of Liver** (Figure 3a & 3b) (Grisham *et al*., 1983)

**1.1.2 Anatomy of Liver Cells** (Figure 4a &4b) (Wanson *et al*., 1979)

- Cell types
  - Hepatocytes
    - 70% of volume of liver
    - Regenerative
    - Perform major functions of liver
  - Kupffer cells
    - Macrophages acting as phagocytes

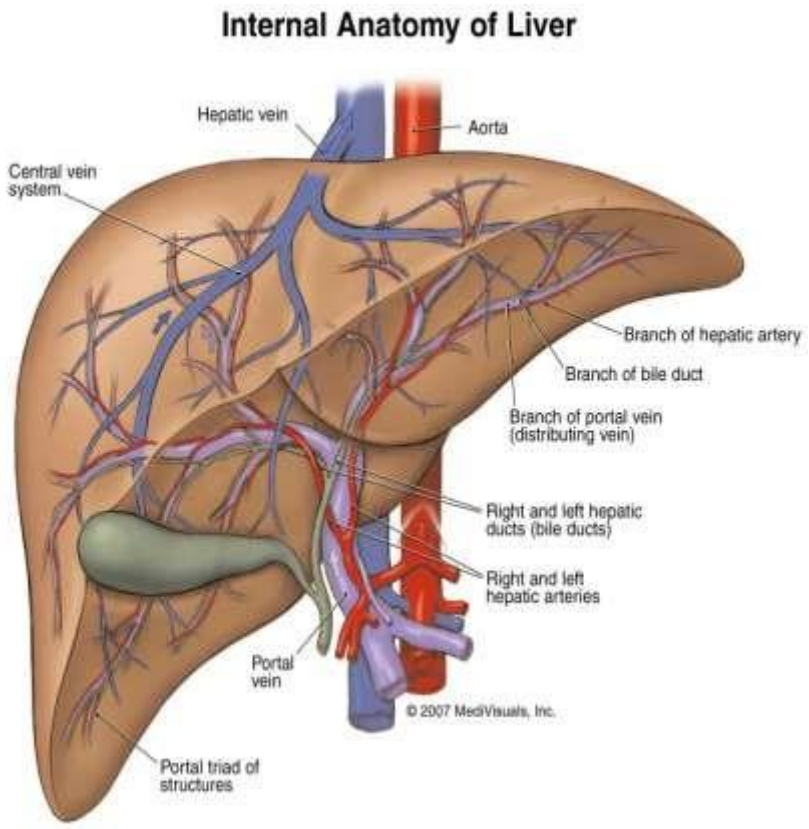


Figure 4a : Anatomy of Human Liver. (Bismuth *et al*., 1982)

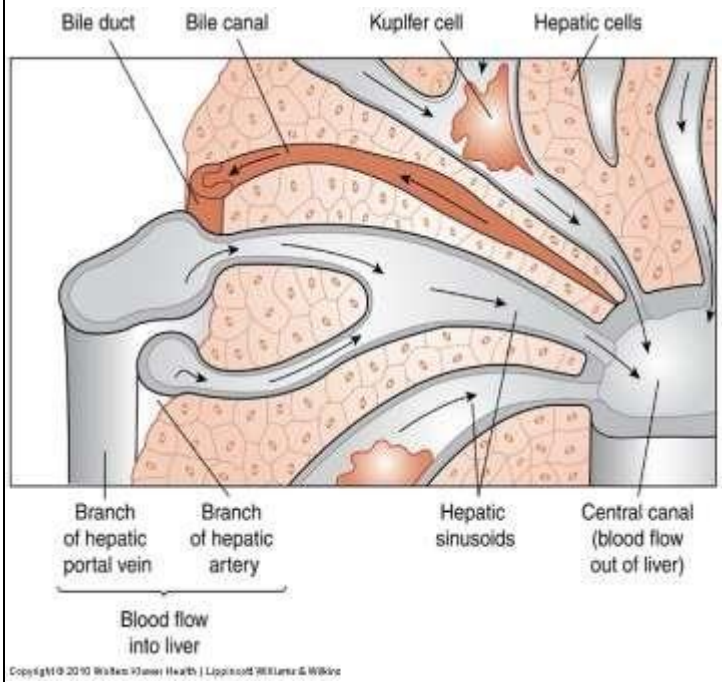


Figure 4b: Anatomy of the Liver Cells.

### 1.1.3 Functions of Hepatic System

Suman *et al*., 2011 summarised that it regulates chemical levels in the blood; excretes a product called bile, which helps carry away waste products; it processes blood and breaks down the nutrients and drugs into forms that are easier to use for the body. Some pronounced functions include the following:

- Bile production, which carries away waste and break down fats;
- Production of cholesterol and proteins to carry fats through the body;
- Conversion of glucose into glycogen for storage;
- Amino acids regulation, which form the building blocks of proteins;
- Haemoglobin processing. Storage of glycogen, vitamins, and minerals;
- Conversion of poisonous ammonia to urea;
- Detoxification of blood from drugs and other metabolites;
- Regulating blood clotting;
- Resisting infections by producing immune factors and removingbacteria;

This review article present intriguing information about the role of the liver and explain why a well-functioning liver is essential for overall health. It performs various interrelated functions. (Table 1) (Shivananda *et al*., 2011)

Table 1 : Important Biochemical Hepatic Functions.

**(1) Metabolic Functions** (Ozougwu, 2017)

Liver is the principal "metabolic clearing house" and its metabolic processes have a central role in metabolism carbohydrate ; protein; amino acid and ammonia; lipid ; bile salt; bilirubin **(**Figure 5-6; Hashmi, 2015)

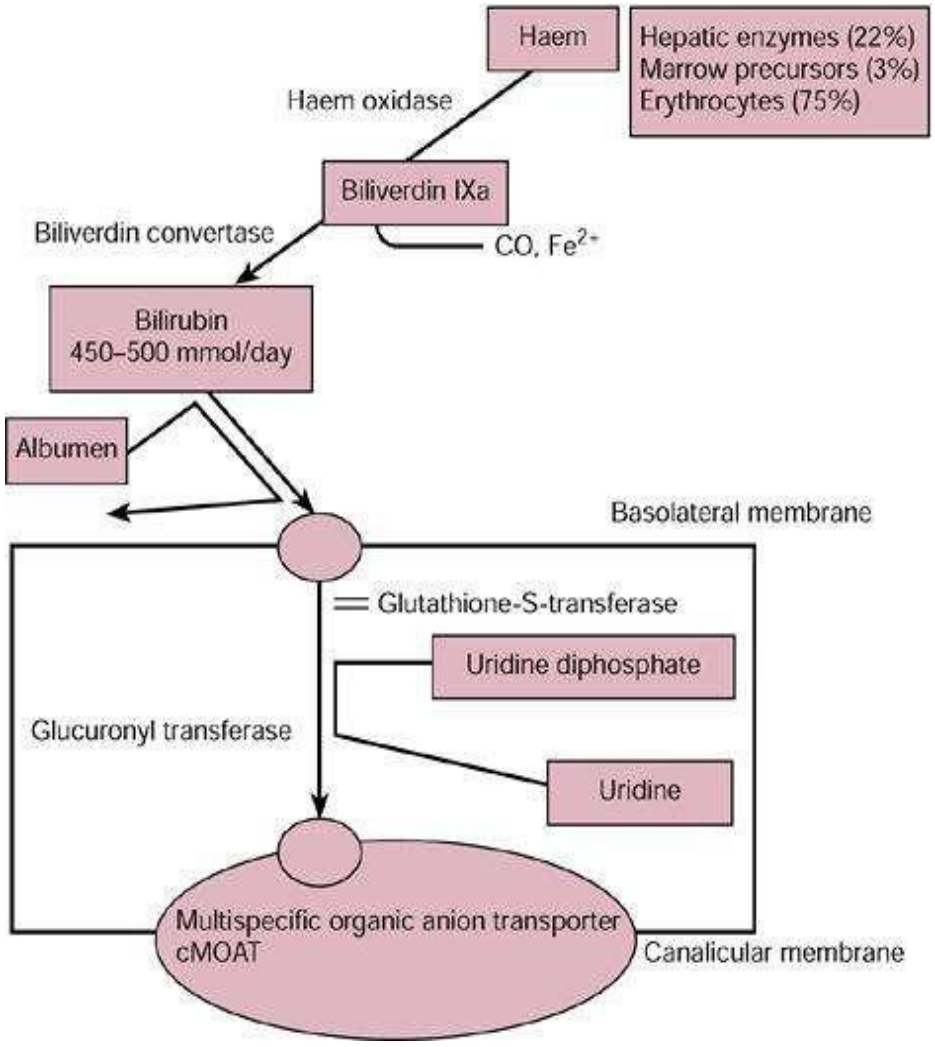


Figure 5 : Bilirubin Metabolism in Liver.

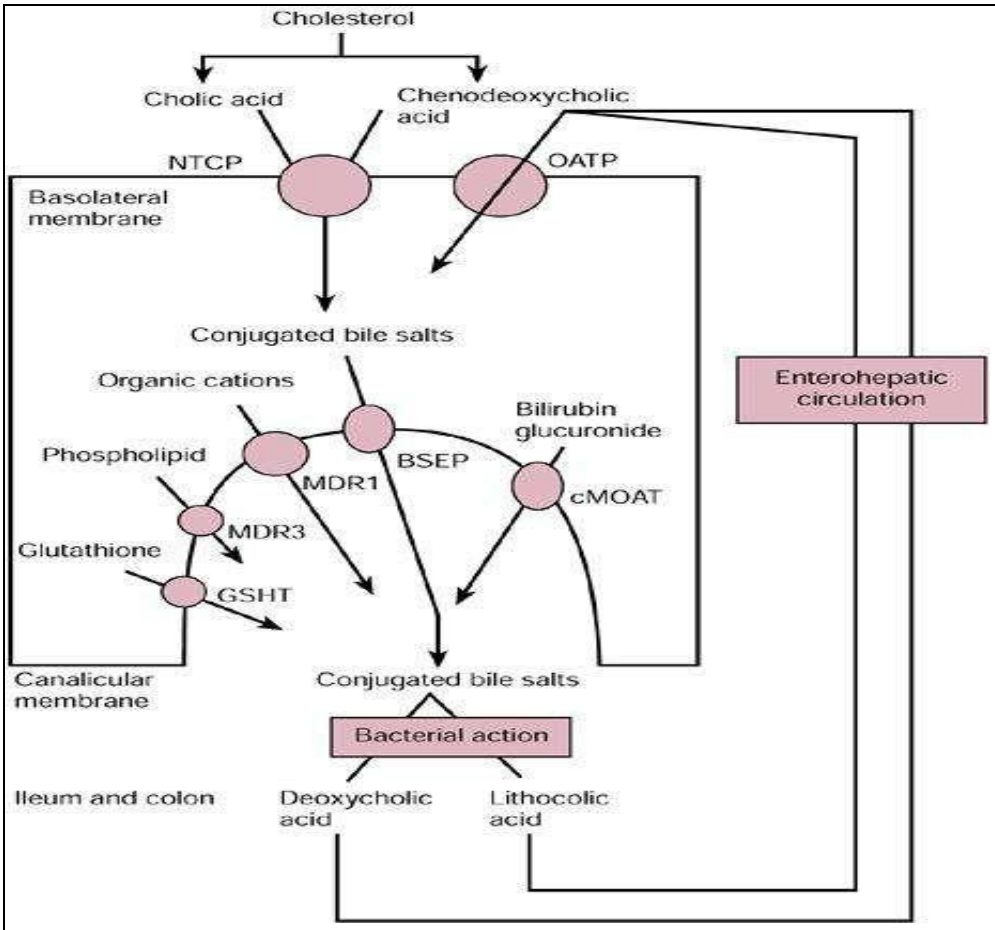


Figure 6 : Bile salt Metabolism in liver.

**(2)** Detoxication Functions of the Liver (Butura *et al*., 2008)

- In metabolism of many drugs; alcohol; and hormones:

(3) Storage Functions: a) Vitamins: B12, A & D

(4) Excretory and Secretory Function of Liver

(5) Blood Filtration Functions (Ozougwu, 2017)

**(6).** Immunologic Functions (Itoh *et al*., 1992; Mechal *et al*., 2001)

- In regulation of blood volume and participates in the immune mechanism.
- Phagocytosis of bacteria
- IgA secretion

## 1.2. Liver Degenerative Disease / Hepatotoxicity and Pathophysiology of Liver

Pradhan *et al*., 2006 emphasized on the maintenance of healthy liver for human health (Haidry *et al*., 2014).
Sudipta *et al*., 2012 illustrated that hepatotoxicity is a general term for liver damage and is the most important cause of mortality and morbidity (liver failure could leads to death within minutes).
Stickel and Schuppan, 2007 found that liver cirrhosis is the 9$^{th}$ leading cause of death in Western countries / among top ten killer diseases in India (highly vulnerable to damage by drugs and toxic metabolites).
Dienstag *et al*., 2001 reported hepatic injury accounts for 3.5%-9.5% of all ADRs and up to 14.7% of fatal adverse reaction.

Onkar *et al*., 2016 compiled hepatotoxicity caused due to following reasons:

- lipid- peroxidation;
- activation of pro-inflammatory mediators;
- induction of nitric acid synthase;
- mitochondrial dysfunction;
- Cytochrome P450 activation;
- Bile acid-induced hepatocyte death;
- congenital defects (malformed or absent bile ducts);
- obstructed bile ducts (cholestasis);
- autoimmune disorders;
- metabolic disorders (hemochromatosis, Wilson's disease);
- tumors; toxins (drugs, overdoses, poisons);
- alcohol-related conditions (cirrhosis);
- bacterial and parasitic infections; and viral infections (hepatitis B and C)

Subsequently, Nilesh *et al.*, 2012 illustrated the risk factors for hepatotoxicitywhich includes the following:

- race;
- age (geriatrics are at high risk due to reduced hepatic blood flow; decreased clearance; variation in drug binding; drug-to-drug interactions; lower hepatic volume);
- poor diet;
- infections;
- multiple drug therapy;
- gender (more common in females than in males);
- alcohol (due to depletion of glutathione);
- Genetic factors (idiosyncratic reactions);
- AIDS (low glutathione level);
- Drug formulations (long-acting drugs)
- global obesity epidemic (NAFLD);
- nonalcoholic steatohepatitis (NASH);
- cirrhosis and hepatocellular carcinoma;
- fibrosis

Piscaglia *et al*., 2010 found that liver pathologies affect hundreds of millions ofpatients worldwide and its common causes are as follows:

- chronic hepatitis B and C;
- alcoholism, non-alcoholic fatty liver disease;
- autoimmune and drug-induced hepatic disorders;
- liver fibrosis and ultimately cirrhosis;
- portal hypertension;
- liver failure;
- cancer.

Ward *et al*., 1999 found that liver cell suicide is mediated by proapoptotic signals, such as tumour necrosis factor (TNF). Hepatic diseases caused by a variety of factors as mentioned in Table 2.

Table 2: Liver diseases and its causes.

| Liver Diseases | Characteristics | Causes/Conditions |
|---|---|---|
| Active Liver failure | • Reduction in liver function | • Drugs<br>• Toxic Chemicals<br>• Various liver diseases. |
| Autoimmune disorders | • Abnormal immune response against heptic cells and development of antibodies against liver cells | • PBC<br>• Primary sclerosing cholangities<br>• Autoimmune hepatitis |
| Bile ducts obstruction | • Blockage of bile ducts | • Tumours<br>• Gallbladder stones<br>• Inflammations |
| Cirrhosis | • Surface injury of liver tissue chronic liver damage | • Alcoholism<br>• Chronic bile ducts obstruction<br>• Long term Hepatitis C infection |
| Genetic diseases | • Gene mutations that cause liver injury | • Hemochromatosis<br>• Wilsons's diseases<br>• Deficiency of α-1 antitrypsin |
| Hepatic vein obstruction | • Blood clots obstruct blood flow from the liver | • Thrombosis of hepatic vein<br>• Hepatic cancer<br>• Hypercoagulable disorder<br>• Parasitic infections |
| Hepatitis (A, B, C, D and E ) | • Acute or chronic liver damage | • Hepatotorpic viruses<br>• Alcohol consumption<br>• Drugs<br>• Xenobiotics<br>• Autoimmune diseases<br>• Non-alcoholic fatty liver diseases |
| Liver cancer | • Metastatic tumours in liver | • High possibility of chronic hepatitis<br>• Hepatocellular carcinoma |
| Liver infections | • Inffections that leads toseveral types of liver damage and bile ducts blockage | • Viral hepatitis (A, B C, D and E)<br>• Some parasitic infections (yellow fever virus, herpes virus) |

### 1.2.1 Hepatotoxicants

Thonda *et al*., 2012 revealed that hepatotoxins are the substances that causesliver damages (Table 3-4)

Table 3: List of Hepatotoxicants.

| Hepatotoxicants category | Examples | Hepatotoxicants category | Examples |
|---|---|---|---|
| Natural Products | | Drugs | |
| *Amanita phalloides* | • Amatoxins like α- amanitin phallotoxins | Anaesthesia | • Halothane |
| *Aspergillusflavus* | • Aflatoxins | Antibiotics | • Amoxicillin<br>• Clavulanate |
| Cyanobateria | • Microcystins<br>• Nodularins | Anti-convulsants | • Valproate<br>• Phenytoin |
| *Ecreinascidia turbinate* | • Ectenascidins | Anti-coagulants | • Heparin<br>• Warfarin |
| *Eupatorium adenophorum* | • 9-oxo-10,11-dehydroagera phoroe, a sesquiterpinet annin | Antiretroviral | • Protease inhibitors (PIs)<br>• NRTIs<br>• NNRTIs |
| *Fusarium moniliforme* | • Fumonisin | Aniline analgesics | • Acetaminophen |
| *Industrial toxins* | • Heavy metals( arsenic, lead, mercury)<br>• Vinyl chloride<br>• Trichloroethyl ene | Anti- hyperlipidaemias | • Atorvastatin<br>• Fenofibrate |
| *Lantana camara* | • Lantadenes | Anti-tuberculosis | • Isoniazid<br>• Rifampicin |
| *Penicilliumrubrum* | • Rubratoxins | Anti-malaria | • Iminoquinone(am oduaquine) |
| *Phompsis leptostromiformis* | • Phomopsin | Chemotherapy | • Imatinib<br>• Nilotinib |
| | | Corticosteroids | • Glucorticoids<br>• Anabolic androgenic steroids |
| | | NSAIDs | • Aspirin<br>• Diclofenac |
| | | Alcohol | • Alcohol |

Table 4 : List of hepatotoxic herbal plants.

| Hepato-toxic Plants | Hepatotoxicity |
|---|---|
| *Amanita Phalloides* (Amanitaceae) | Liver toxicity |
| *Atractylis gummifera* (Asteraceae) | Mitochondrial toxicity, Acute liver failure |
| *Callilepis laureola* (Asteraceae) | Hepatic necrosis, Oxidative phosphorylation inhibition |
| *Actaea Racemosa* (Ranunculaceae) | Hepatic necrosis and bridging fibrosis. |
| *Larrea tridentate* (Zygophyllaceae) | Inhibition of bile secretion and hepatotoxicity of liver cells |
| *Cycas revolute* (Cycadaceae) | Produces toxic intermediate by enzyme 450 |
| *Aesculus hippocastanum* (Sapindaceae) | Causes jaundice<br>Cause idiosyncratic |
| *Serenoa repens* (Arecaceae) | Glutathione depletion, cirrhosis, |
| *Teucrium chamaedrys* L (Lamiaceae) | Acute and chronic hepatitis, immunoallergic factor, hepatic failure |
| *Piper methysticum* (Piperaceae) | Glutathione depletion, immunoallergic factor, hepatic failure |
| *Cassia angustifolia* (Caesalpinaceae) | Acute hepatitis |
| *Symphytum officinale L.* (Boraginaceae) | Hepatic veno occlusive disease |
| *Chelidonium majus* (Papaveraceae) | Acute Hepatitis |

### 1.2.2. Pathophysiology of Drug Induced Hepatotoxicity (Figure 7)

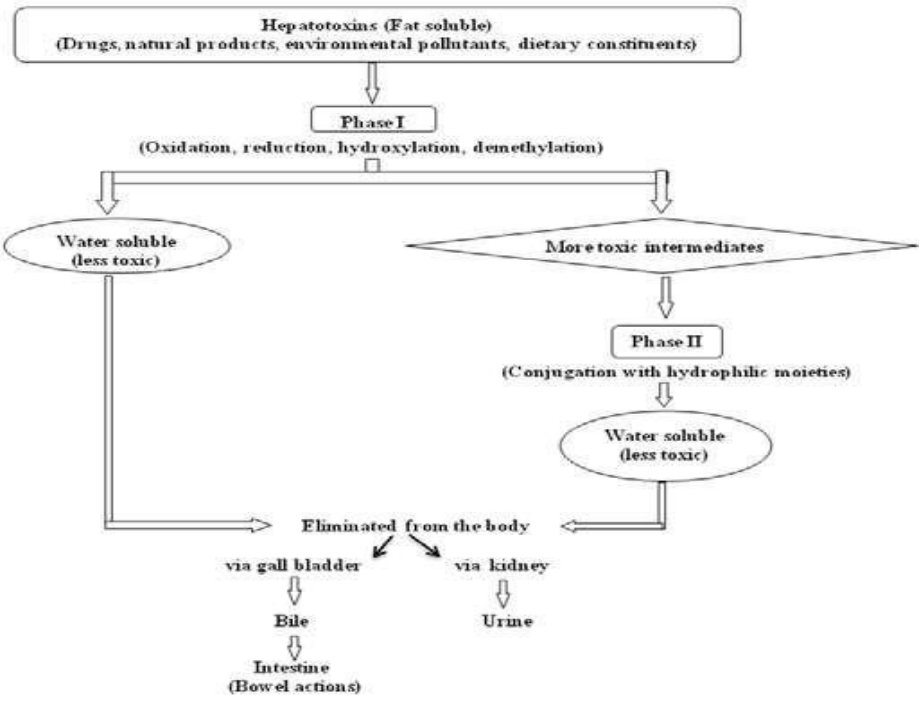


**Figure 1 Biotransformation of hepatotoxicants**

Figure 7: Biotransformation of hepatotoxins.

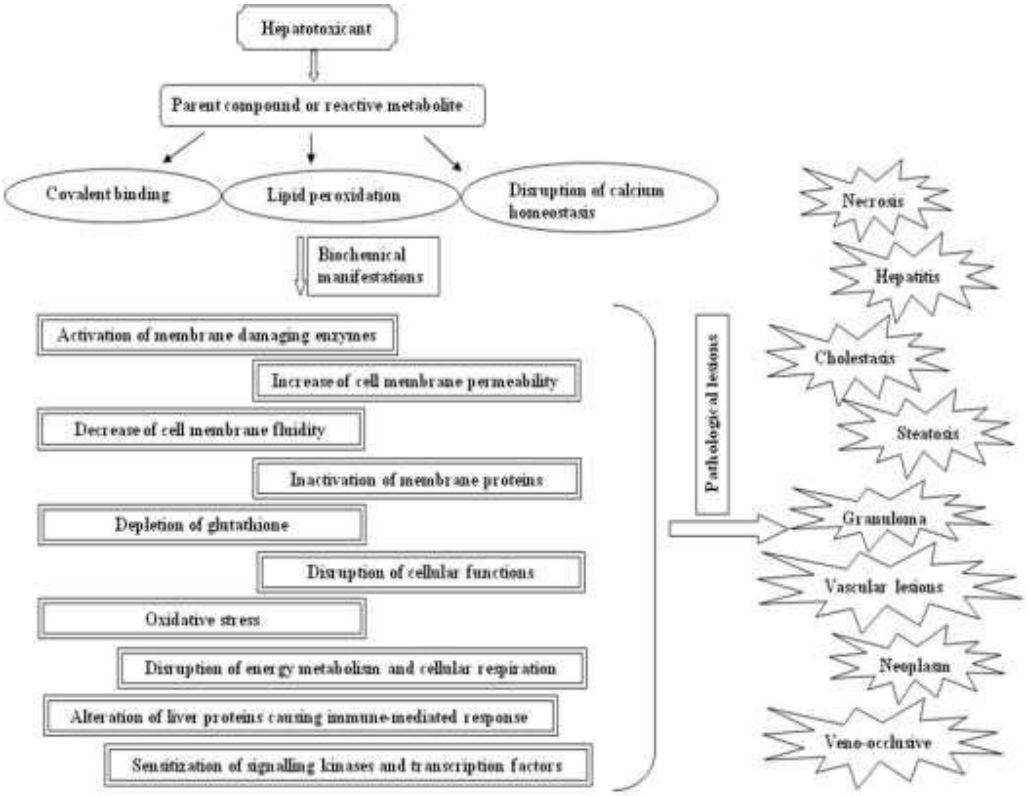


**Figure 2 Biochemical and pathological mechanism of hepatotoxicity**

Figure 8: Biochemical and pathological mechanism of hepatotoxicity.

Mohit *et al*., 2011 found that various hepatotoxins / chemicals (e.g. carbon- tetrachloride, alcohol, naturally-occurring plant toxins such as pyrrolizidine alkaloids, mycotoxins and bacterial toxins, inorganic compounds like arsenic, phosphorus, copper and iron) / drugs (e.g. paracetamol, anti-tuberculosis drugs e.g. rifampicin) in overdoses / within therapeutic ranges may induce hepatotoxicity (Figure 9-10).

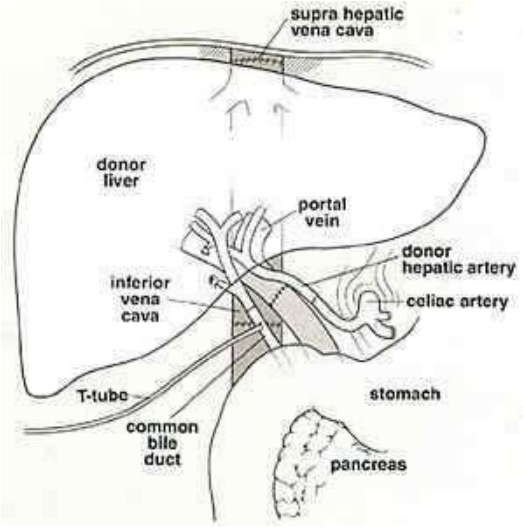


Figure 9: Pathophysiology of Liver Disease.

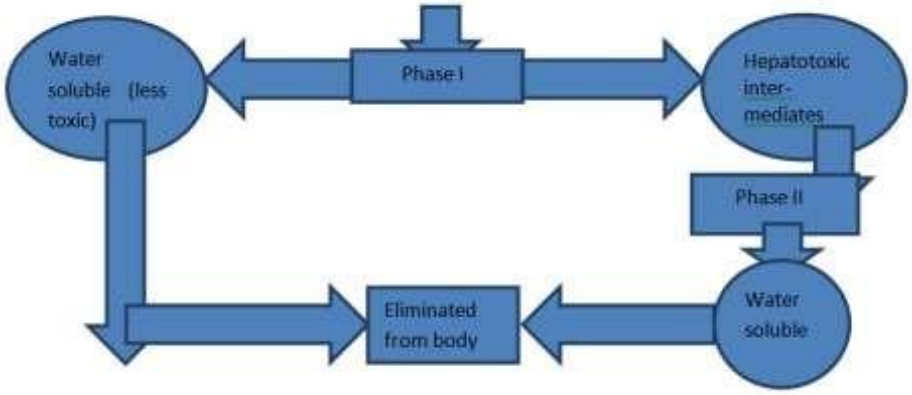


Figure 10 : Metabolism of xenobiotics in liver. (Preeti *et al*., 2016)

It is thus important to understand the mechansims of hepatotoxicity for devising pharmacological strategies for their prevention. Parabia *et al*., 2007 illustrated that Drug-induced hepatotoxicity (DIH) / Drug-induced Liver injury (DILI) is the most common and severe problem as it affects ahuge population around throughout the globe and may cause of acute hepatic failure (Davies, 1997; Dianzani *et al*., 1991)

**1.2.2.1. Hepatocellular Mechanisms** (Onkar *et al*., 2016)

- ❖ Rupture of hepatocyte membrane cause disruption of the hepatocyte.
- ❖ Disruption of the transport proteins.
- ❖ Apoptosis of hepatocytes.
- ❖ Mitochondrial disruption due to decreased ATP production.
- ❖ By induction of liver microsomal enzyme (P-450).

**1.2.2.2. Extra-hepatocellular Mechanisms**

- Toxic metabolites excreted in bile may cause injury bile duct injury.
- Drug toxicity mechanisms:

(a) drugs that directly affect the liver

(b) drugs that mediate an immune response.

**1.3 Symptoms of Liver Damage**

Symptoms of liver damage include digestive disturbances such as constipation; jaundice; edema; pruritus (itching), nausea and vomiting. This review article present intriguing information about the role of the liver and explain why a well-functioning liver is essential for overall health. Also identified will be environmental hazards that constantly challenge the detoxification capacity of the liver.

## 1.4. Screening Models for Anti-hepatotoxic / Hepatoprotective Drugs.

Muriel *et al*., 2008 stated that a successful development of therapy for the liverdepends on the availability of *in vitro* and *in vivo* test model systems for hepatic injury (Figure 11). Several models are available to screen the antihepatotoxic activity. Sincethere are limitations of the outcomes in each model, it is important to combine different methods for confirmation of the findings (Farghali *et al*., 2015)

i. Carbon tetrachloride ($CCl_4$) : Cause lipid peroxidation in hepatocytes.

ii. Meera *et al*., 2007, Galactosamine: Induce decrease the bile flow and its content, reduces rate of oxygen consumption, simulate viral hepatitis.

ii. Thioacetamide : Its metabolite (s-oxide) interferes with movement of RNA from the nucleus to cytoplasm which is responsible for hepatic injury.

iv. Paracetamol: hepatic necrosis (centrilobular), nuclear pyknosis.

v. Anti-tubercular Caused by multiple drug regimens.

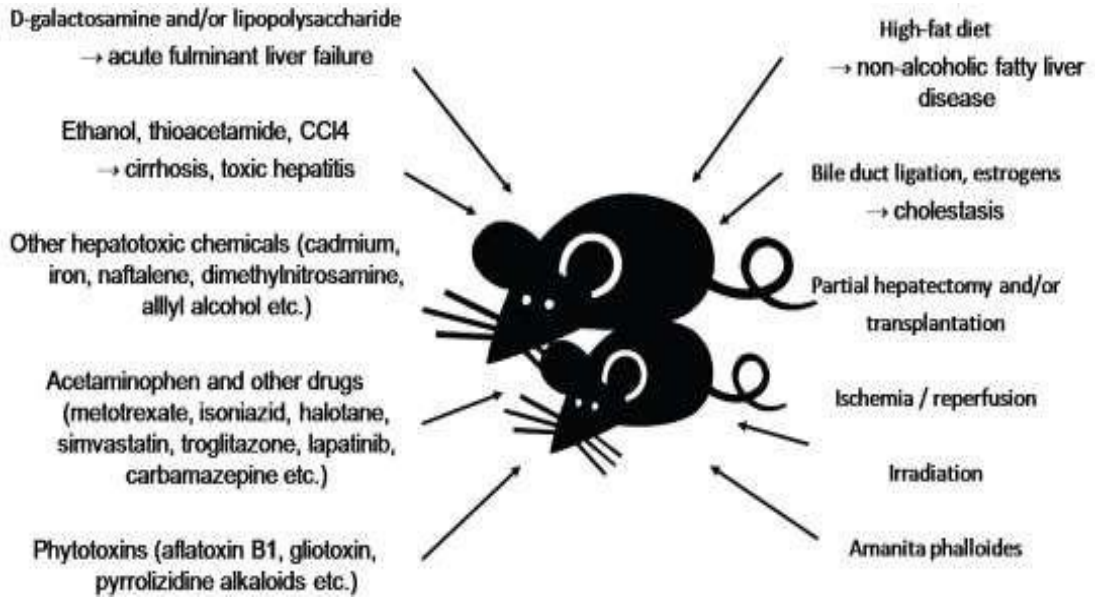


Figure 11: Common *in vivo* models of liver damage.

## 1.5. Biomarkers of Hepatotoxicity

Table 5: Hepatotoxicity Markers (Singh *et al*., 2011)

| Biochemical parameter | Histopathological lesion | Reason of abnormality |
|---|---|---|
| Alanine aminotransferase (ALT/SGPT) | • Hepatocellular necrosis | • Leakage from damaged tissue |
| Albumin | • Hepatic dysfunction | • Decreased synthesis |
| Alkaline phosphatise | • Hepatobilary injury<br>• Choleastasis | • Overproduction, releases in blood |
| Arginase | • Hepatocellular | • Release from injured hepatocytes |
| Aspaertate aminotransferase (AST/SGOT) | • Hepatocellular necrosis | • Damaged tissue leakage |
| Bile acids | • Hepatobiliary disease | • Regurgitation into blood |

| | | |
|---|---|---|
| Glumate dehydrogenase | • Hepatic necrosis | • Leakage from damaged tissue |
| Glutathione S-transferase | • Necrosis of hepatocytes | • Rapidly leaks from hepatocytes in reaction to liver injury |
| Lactate dehydrogenase | • Hepatocytes's necrosis | • Leaking damaged tissue |
| Sorbitol dehydrogenase | • Liver cell necrosis | • Damaged tissue leaking |
| Total bilirubin | • Hepatobiliary injury as well as cholestasis | • Hepatic clearance is decreased |
| Total protein | • Hepatic dysfunction | • Reduced synthetic capacity |

## 1.6. Hepatoprotection

Chattopadhyay *et al*., 2007 found that hepatoprotection is important because it plays a critical role in all aspects of metabolism and overall health (Jesika *et al*., 2016).

### 1.6.1. Hepatoprotection is achieved by following two categories of drugs:

**(i) Hepato-protective Drugs**: These drugs preserve the normal anatomical architecture and physiological functions of the liver and prevent toxic action of hepatotoxins (prophylactic action).

**(ii) Anti-hepatotoxic Drugs :** Drugs which reduce injurious effect caused by hepatotoxic agents, significant alleviation of the serum enzyme activities (Biochemical parameters like SGPT, SGOT etc.), increase glutathione store, membrane stabilization through increased protein synthesis (Therapeutic action; antagonise the effects of any hepatotoxin) (Figure 12-14).

In general any hepatoprotective agent can act as an anti-hepatotoxic orhepatotropic agent but the vice versa is always not true.

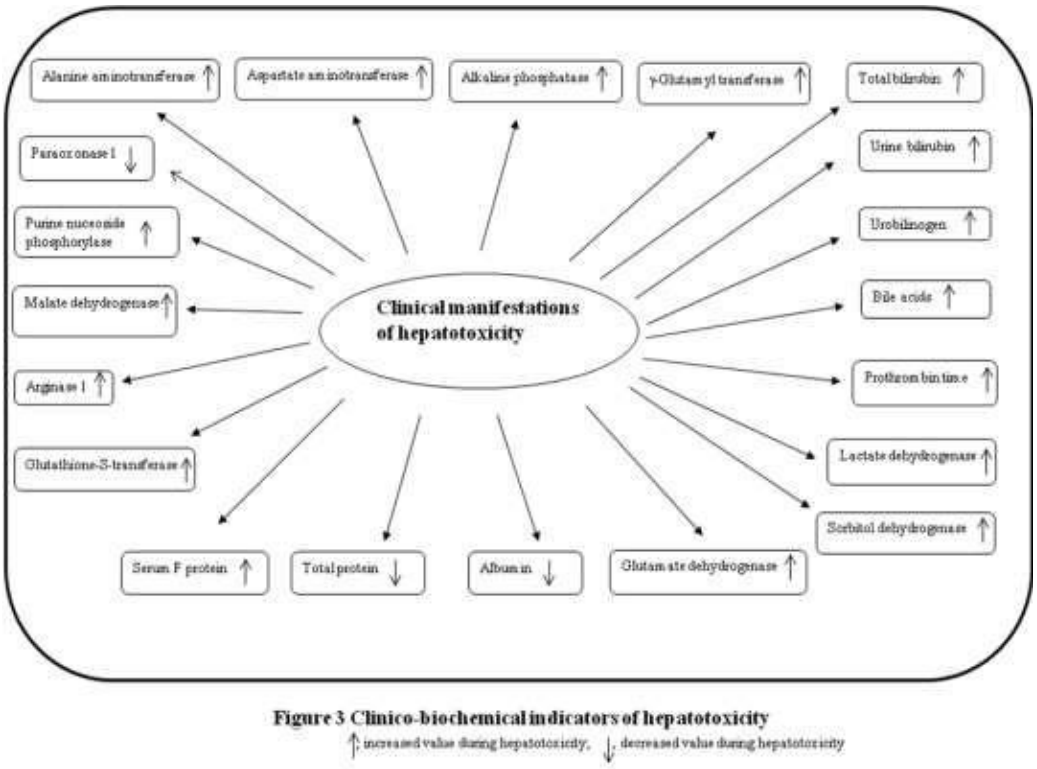


**Figure 3 Clinico-biochemical indicators of hepatotoxicity**

↑ increased value during hepatotoxicity; ↓ decreased value during hepatotoxicity

Figure 12: Clinico-biochemical indicators of hepatotoxicity.

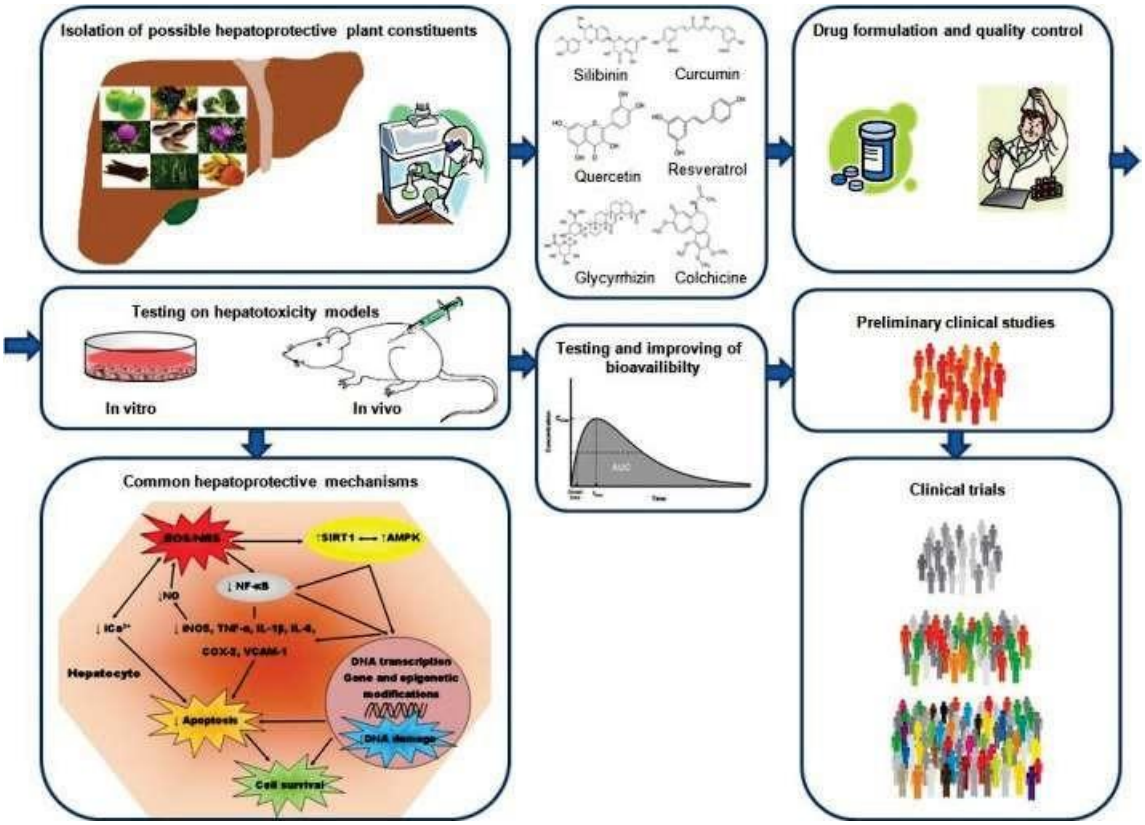


Figure 13 : Steps in development of hepatoprotective therapy for liver diseases.

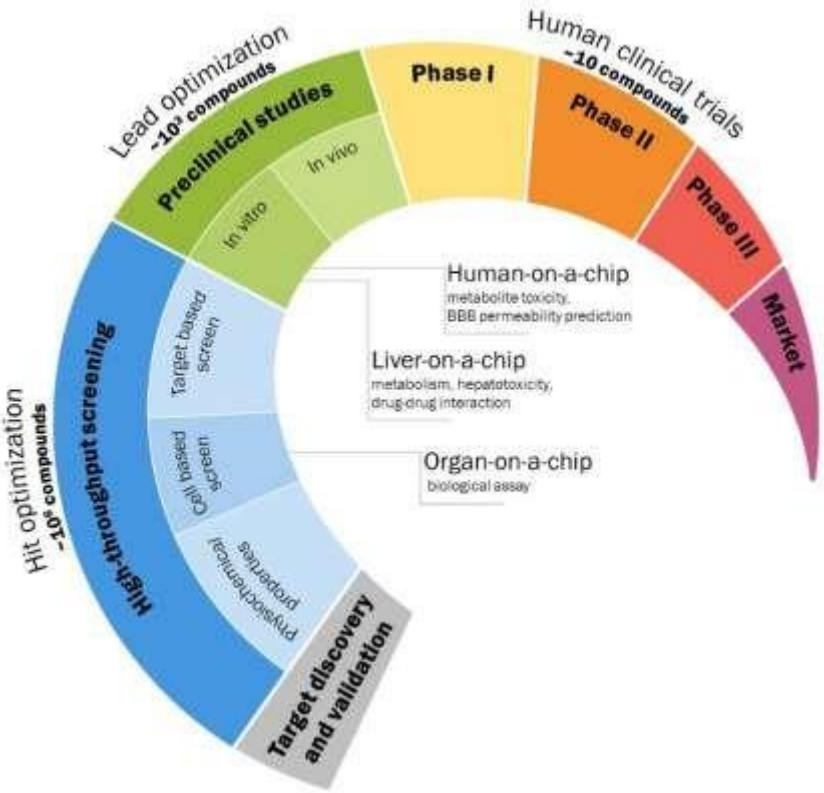


Figure 14 : HTS-based drug discovery paradigm.

### 1.6.2. Hepatoprotective Drugs

#### 1.6.2.1 Allopathic drugs

##### 1.6.2.1.1 Ursodeoxycholic acid (Ursodiol)

Gupta *et al*., 2009 found that ursodeoxycholic acid (a hydrophilic bile acid which protect the liver from the damaging effects of hydrophobic bile acids in cholestatic disorders) decreases intestinal absorption and suppresses hepatic synthesis and storage of cholesterol.

Gustav *et al*., 2002 reported that ursodeoxycholic acid is used in primary biliary cirrhosis, biliary disease secondary to cystic fibrosis, non alcoholic steatohepatitis, idiopathic chronic hepatitis, autoimmune hepatitis, primary sclerosing cholangitis, and alcoholic hepatitis.

Table 6: Allopathic hepatoprotective drugs with their adverse drug reactions (ADRs)

| S. No. | Allopathic medicine | Active constituents of Allopathic medicine | ADR (Adverse Drug Reactions) |
|---|---|---|---|
| 1 | Essentiale-L (Nicholas Piramal) | Essential phospholipids, linoleic acid, unseat fatty acid, Lecithin. Dose: 350 mg oral capsule | Nausea, stomach upset skinrash contraindicated during pregnancy |
| 2 | Mecolin (Stadmed) | Tricholine Citrate 0.55 gm and Sorbitol 7.15 gm in each 10 ml. Dose: 10 ml syrup | Abdominal pain, Diarrhea, Flatulence, Hyperuricaemia, Lactic acidosis, Urticaria |
| 3 | Sorbiline (Franco-Indian) | Sorbitol 7.15 gm, Tricholine citrate 550 mg Dose: 200 ml Syrup | Abdominal pain, Diarrhea, Flatulence, Hyperuricaemia, Lactic acidosis, Urticaria |
| 4 | Hepa Merz (Win-Medicare) | L-Ornithine, L-Aspartate Dose: 5 g/10 ml | Hyperuricaemia, Lacrimation, Skin rashes, Sneezing |
| 5 | Livosil Forte (Centaur) | Silymarin 140 mg, Thiamine 5 mg, Riboflavin 5 mg, Pyridoxine 1.5 mg, Niacinamide 7.5 mg, Pantothenic acid 25 mg, Vitamin B12.Dose : 250 mg Capsule | Bloating, dyspepsia, nausea and irregular stools, at high dose laxation. |

### 1.6.2.2. Herbals in the Treatment of Liver Diseases

Balunas *et al*., 2005 revealed that recent World Health Organization (WHO) studies indicate that over 30 percent of the world's plant species have at one time or another been in used for medicinal purposes. Of the 2,50,000 higher plant species on earth, more than 80,000 are medicinal. Herbal medicine is wide-spread throughout the world and it is an integral part of traditional systems of medicine.

Peter, 2001 further illustrated that World Health Organization (WHO) estimates that 4 billion people, 80% of the world population, presently use herbal medicine for some aspect of primary health care. Herbal medicine is a major component in all indigenous peoples' traditional medicine and a common element in Ayurvedic, homeopathic, naturopathic, traditional oriental, and.

Sheetal *et al*., 2004, summarised Alternative System of Medicine (ASM) / Complimentary System of Medicine (CAM) which include Ayurveda and Siddha (originated in India) Unani system (Persia). Ayurveda is also practiced in India and other neighboring countries mainly like Nepal, Bhutan, Srilanka, Bangladesh, Pakistan and also directly related to traditional systems of Tibet, Mongolia, Thailand etc.

Balandrin *et al*., 1993, assessed that Ayurvedic System is at least 5,000 years old and Chinese System is probably equally ancient whereas Unani and Tibetan Systems date back to about 3,000 years.

Suralkar *et al*., 2011compiled that in India, the traditional system of medicine is still widely practices by about 75% population because of either the lack of easy access to modern drugs or because of deliberate choice / faith in them and concluded that about 25% of the prescription drugs dispensed contain at least one active ingredient derived from plant material.

Walter *et al*., 1995 found that the use of herbal medicine has gained more momentum owing to the general awareness of its safety towards the human system in comparison to the synthetic drugs. Cragg *et al*., 1997, further, strongly believed that these systems possess drugs for chronic diseases.

Hikino *et al*., 1984 summarised various hepatoprotective medicinal plants like *Silybum marianum, Andrographic paniculata, Wedelia calendulacea, Phyllanthus emblica, Picrorhiza kurroa, and Eclipta alba* Linn. (Table 6)

Qiu (2007), articulated that there are various herbal formulations like Aclivan, Livatona, Liv. 52, Livotrit, Stimuliv, Amlycure, Tefroli and Vimliv which produce hepatoprotection.

### 1.6.2.3. Classification : They are generally classified into 3 categories:

**A. Anti hepatotoxic agents:**

These generally antagonise the effects of any hepatotoxin causing hepatitis or any liver disorder or disease.

**B. Hepatotropic agents:**

These generally support or promote the healing process of the liver. In practice these two activities cannot be easily distinguished from each other.

**C. Hepatoprotective agents:**

These generally prevent various types of liver affections prophilactically. In general any hepatoprotective agent can act as an antihepatotoxic or hepatotropic agent but the vice versa is always not true.

### 1.6.2.4. Hepatoprotective Polyherbal Formulations

Schuppan *et al*., 1999 reported that several herbs / herbal formulations claimed to possess beneficial activity in treating hepatic disorders. Herbal extracts have yielded molecules, often related to flavonoids. Plants are excellent sources of phenolic antioxidants. It has been assessed that these plants have been formulated together in different doses and combinations to achieve maximum synergistic antihepatotoxic / hepatoprotective activity.

In India, several polyherbal commercial formulations reputed to have hepatoprotective action are being available. The reputed ones among the formulations are Acilvan Hepa- 10, Liva-16, Livodin, Livosin, Livotrit, Livomap, Livocin, Vimliv, Livomycin, Livo-52, Amylcure, Sanliv, etc. Most of these formulations contain *Andrographis panuculata* Nees., *Boerrhaavia diffusa* Linn., *Astercantha longifolia* Nees., *Circhorium intybus* Linn., *Eclipta alba* Hask, *Oldenlandia corymbasa* Linn., *Picrorrhiza kurroa* Royle ex Benth, *Solarium nigrum* Linn., *Terminalia chebula* Retz, *Tinospora cordifolia* (Willd) Miers, etc. The quantity of herbal drugs varies in each formulation. Among various plants 33 plants were found to be there in most popular formulations available in India (Table 7, 8 and 9).

Table 7: Plant drugs with activity against liver disease (Saumendu *et al*., 2012)

| Plant Name / Family | Chemical Constituents | Uses |
|---|---|---|
| *Silybum marianum* (Asteraceae) | Flavonolignans : silybin, silydianin and silychristine,<br>- betaine | Hepatoprotective |

| | | |
|---|---|---|
| *Eclipta alba* (Asteraceae) | Alkaloid known as ecliptin, nicotin, glucoside | Viral hepatitis, liver disorder |
| *Picrorrhiza Kurrora* (Scrophulariaceae) | Iirridoid bitter substance picroside and kutkoside | Bitter tonic, in jaundice |
| *Andrographis paniculata* (Acanthaceae) | Andrographolides, kalmeghin (upto2.5%), deoxyandrographolide | Antipyretic, tuberculosis, anti-hepatotoxicity |
| *Curcuma longa* (Zingiberaceae) | Diaylheptanoids curcumin, volatile oil, curcuminoids, | Anti-inflammatory |
| *Tephrosia purpurea* (Fabaceae) | Tephrosin, deguelin and quercetin | In liver and spleen diseases. |
| *Solanum nigrum* (Solanaceae) | Solamargrine, andsolasonine | Hepatoprotective, diuretic, antiseptic. |
| *Taraxacum officinale* (Asteraceae) | Taraxecerin, taraxcin, sesquiterpene lactones. | Hepatic and biliary disorders, kidney stones |
| *Cichorium intybus* (Asteraceae) | Bitter glucoside, cichorin | Liver protection |
| *Peumus boldus* (Monimiacee) | Alkaloids, volatile oils, flavonols and their glycosides | Choleretic, diuretic, stomachic, mild sedative. |

Table 8: Plant drugs with activity against liver disease (Gupta & Singhvi, 2011)

| Plant Name / Family | Origin | Chem. Constituents | Uses |
|---|---|---|---|
| *Silybum marianum* (Cardus marianus, mariane thistle) Asteraceae | Indigenous to Mediterranean region, north Africa and western asia. | Flavonolignans including silybin, silydianin and silychristine, Seeds contain betaine (a hepatoprotector). | Liver disease, dyspepsia, disorders of biliary system, hepatoprotectiveand in chronic inflammatory, hepatic disorders. |
| *Eclipta alba* (*Eclipta prostata*)Compositae (Asteraceae) | | Alkaloid known as ecliptin, nicotin, glucoside | Viral hepatitis, liver disorder, skin and hair care, memory disorders, swollen glands, vision |
| *Picrorrhiza Kurrora* (Indian gentian, kutki) Scrophulariaceae | | Iirridoid bitter substance picrosideand kutkoside | Valuable bitter tonic, anti-peroidic, febrifuge and stomachic and laxative jaundice potent hepatopotectant |
| *Andrographis paniculata* (Kalmeg) Acanthaceae | Andrographis leaves, as well as the fresh juice of the whole plant | Andrographolides, kalmeghin (upto2.5%), deoxyandrographolide | Antipyretic, bacterial dysentery, tuberculosis, skin infection and hepatotoxicity |
| *Curcuma longa* (*Curcuma turmeric*) Zingiberaceae | | Diaylheptanoids curcumin, volatile oil, curcuminoids, | Protect animal livers as anti-inflammatory drug |
| *Tephrosia purpurea* (*Basterd indigo*) Fabaceae | | Tephrosin, deguelin and quercetin | Treatment of liver and spleen diseases. |
| *Solanum nigrum* (Black nightshade) Solanaceae | | Solamargrine, andsolasonine | Hepatoprotective diuretic, antioxidants. |
| *Taraxacum officinale* (Dandelion) Asteraceae | All parts of the northern hemisphere | Taraxecerin,taraxcin, sesquiterpene lactones. | Hepatic and biliary disorders, kidney stones, remedy for jaundice. |
| *Cichorium intybus* (Cichory) Compositae (Asteraceae) | | Bitter glucoside, cichorin | Liver diseases, liver protection, chlorpromazine induced hepatic damage |

Table 9: List of plants known to be used in more than four formulations.

| Plants / Used in Formulation (no.) | Formulation containing the Plant (Brand Name Manufacturer) |
|---|---|
| *Andrographis paniculata* (22) | Hepa-10 , Jaundex syrup, Kalmegh Compound, Lavarin, Lierin, Liva, Liva-16, Livatona, Livergen, Livin, Livodin, Livokin, Livol, Livomin, Livoped, Livosin, Livospin, Livotone, Livotrit, Stimuliv, Tefroli, Trisoliv |
| *Boerrhaavia duffusa* (16) | Acilvan, Amlycure, Hepex, Hipex, laundex syrup, Livarin, Liva, Liva-16, Livin), Livodin, Livomycin, Livomap, Liv-77, Neoliv- 100, Triguliv-15, Vimliv |
| *Eclipta alba* (16) | Acilvan , Amlycure, Hepa-10, Liv-77, Liva-16, Livin, Livodin, Livokin, Livol, Livomyn, Livosin, Livotrit, Stimulin, Tefroli,Trignliv-15, Vimliv |
| *Solatium nigrum* (15) | Acilvan, Amlycure, Hepa-10, Hepex, Hipex, Liv-52, Livarin, Livex, Liva, Liva-16, Livokin, Livomyn, Neoliv-100, Svliv, Triguliv-15 |
| *Tinospora cordifolia* (10) | Acilvan, Liv-77, Liva-16, Livin, Livodin, Livol, Livomap, Livomyn, Livotrit, riguliv-15 |
| *Astercantha tongifolia* (09) | Adliv-75, Biligen, Liva-16, Livatoma, Livergen, Livodin,Livokin, Livotone, Syliv |
| *Circhorium intybus* (09) | Acilvan, Amlycure, Hepex, Hipex, Liv- 52, Liv-77, Neoliv-100, Syliv, Vimliv |
| *Achillea millefoitium* (08) | Acilvan, Hefiaye, Amlycure, Liv-52, Livex, Suliv, Neoliv-100,Syliv |
| *Aphanomixis oolystachya* (08) | Biligen, Hepa-10, Jaundex syrup, Livin, Livodin, Livomyn, Livospin, Triguliv-15 syrup |
| *Berberis aristata* (08) | Amlycure, Liva, Liv-77, Livokin, Livol, Livomap, Livotrit, Triguliv-15 |
| *Cassia angustifolia* (08) | Adliv-75, Lierin, Liva, Liva-16, Livatona, Livergen, Livodin,Livosin |
| *Oldenlandia corymbasa* (08) | Lierin, Liva-16, Livatona, Livodin, Livokin, Livoped, Livospin,Syliv |
| *Picrorrhiza kurroa* (08) | Acilvan, Livarin, Lierin, Livertone, Livokin, Livol, Livotrit,Vimliv |
| *Terminalia chebula* (08) | Hipex, Livertone, Livin, Livokin, Livomap, Livol, Tefroli |

| | |
|---|---|
| *Cassia occidental* (07) | Acilvan, Hipex, Liv-52, Livex, Livomyn, Neoliv-100, Syliv |
| *Embelia ribes* (07) | Hipex, Livex, Livodin, Livomyn, Livosin, Livospin, Livotrit |
| *Tephrosia purpurea* (07) | Amlycure, Livin, Livokin, Livoraap, Livomyn, Livospin, Tefroli |
| *Trigonella foenum-graecum* (07) | Biligen, Liv-77, Livatona, Livergens, Livokin, Livoped, Livotone |
| *Apium graveolens* (06) | Liva, Livergen, Livokin, Livoped, Livotone |
| *Carum copticum* (06) | Livodin, Liva-16, Adliv-75, Kalmegh Compound, Livokin, Syliv |
| *Phyllanthus emblica* (06) | Hepex, Livertone, Livol, Livosin, Neoliv-100, Vimliv |
| *Plumbago zeylanica* (06) | Liva, Livin, Livokin, Livomyn, Livospin, Livotrit |
| *Terminalia arjuna* (06) | Acilvan, Liv-52, Liva, Livokin, Livosin, Neoliv-100 |
| *Tramhyspermum ammi* (06) | Biligen, Liva, Livatona, Livergen, Livin, Livoped |
| *Aloe barbadensis* (05) | Adliv-75, Amlycure, Biligen, Hepa-10, Livodin |
| *Fumaria officinalis* (05) | Amlycure, Hepa-10, Livomyn, Stimuliv), Trignliv-15 |
| *Holarrhena anti-dysenterica* (05) | Adliv-75, Livodin, Livosin, Livotone, Livotrit |
| *Ocimum sanctum* (05) | Acilvan, Amlycure, Livin, Livomyn, Tefroli |
| *Phyllanthus niruri* (05) | Amlycure,, Hepex, laundex syrup, Livomap, Trigulive-150 |
| *Tamarix gallica* (05) | Acilvan, Liv-52, Livex, Neoliv-100, Syliv |
| *Capparis spinose* (04) | Acilvan, Liv-52), Livomyn), Syliv |
| *Terminalia belerica* (04) | Amlycure, Livol, Livertone, Livosin |
| *Zingiber officinalis* (04) | Livin, Livomap, Livosin, Livomycin |

**REFERENCES:**

1. Allen SE. (2002) The liver: Anatomy, Physiology, Disease and Treatment. North Eastern University Press, USA.
2. Alonso FT, Garmendia ML, Searle J: *Rev Med Chil* 138: 1253-1258, 2010.
3. Balandrin, N.F., Kinghorn, A.D., and Farnsworth, N.R., 1993. Kinghorn, A. D., Balandrin, M. F., Eds., ACS Symposium Series, pp. 2-12.
4. Balunas M.J., and Kinghorn, A.D., 2005. *Life Sci.*, Vol. 8, 5, pp 431-41.
5. Bismuth H.(1982) *World J Surg.* 6(1): 3-9.
6. Brunicardi FC, Andersen DK, Billiar TR. (2010). 9th edition. New York: McGraw-Hill Publishing; 2010. p. 31–32.
7. Butura A. (2008) Ph.D Thesis Department of Physiology and Pharmacology Karolinska Institute, Stockholm, Sweden. 55 pp.1.

8. Chattopadhyay RR, Bhattacharyya SK (2007). *Pharmacog*. 1(1):439-445.
9. Cragg, G. M., Newman, D. J., and Snader, K.M., 1997. *J. Nat. Prod*., Vol. 60, pp 52-60.
10. Davies, S.E. (1997). *Current Diagnostic Pathology*, 4, 135-144.
11. Dianzani, M.U., G. Muzia, M. E. Biocca, R. A. Canuto. (1991) *Int. J. Tiss. Reac*., 13, 79-85.
12. Dienstag J.L., Isselbacher K.J., Braunwald E. The McGraw-Hill Companies, In, 2001; 2:737-1742.
13. Farghali H, Kutinová Canová N,: *Pharmaceut Biol* 53: 781-791, 2015.
14. Grisham JW. (1983). *Molecular and Cellular Biochemistry*. 53(2): 23 – 33.
15. Gupta Amartya K, Ganguly Partha, Ghosal Shibnath. (2009) *Pharmacology online*. 1: 757-768.
16. Gupta, S.K. and Singhvi, I.J. (2011) *International Journal of Pharmacy and Technology*. 3(1):824-853.
17. Gustav, Paumgartner (2002). *Journal of Hepatology.* 39 (2003) 112–114
18. Haidry M, Malik A T. (2014) *Biochem Pharmacol*. 3:1.
19. Hashmi Intkhab C., (2015). *Int. J. of Anat. Phy.and Biochemistry* (*IJAPB*),.*Vol. 2*,1-4.
20. Hikino H, Kiso Y. (1984) Vol. II, Academic Press, London. 39-67.
21. Itoh T, Okanoue M, Mori N, Hori K, Kashima K. (1992). *Liver*. 12 (1): 26 -33.
22. Jesika Rane, Rajesh Jadhao, R. L. Bakal (2016). *Journal of Innovations in Pharmaceuticals and Biological Sciences, Vol 3 (2), 24-36.*
23. Kogure K, Ishizaki M, Nemoto M. (2007) *J Hepatobiliary Pancreat Surg*. 14(3):297–301.
24. Mechal WZ, Azzaroli F,. (2001). *Gastroenterology.* 120: 250 - 260.
25. Mohit Dhingra, Nain Parminder, and Malik Manisha (2011). *International Research Journal of Pharmacy.*
26. Moore KL, Dalley AF. Clinically Oriented Anatomy. 2006 5th Edition Lippincott Williams and Wilkins. Pp. 1209.
27. Muriel P: *From Genomics to in vitro and in vivo Models. (1th edn)*. SAHU SC (ed.), John Wiley & Sons Inc, Chichester, 2008, pp 119-137.
28. Nilesh Mehta, Michael R Pinsky (2012): 2012, http://emedicine. medscape. com/article/169814-overview.
29. Nobili V, Carter-Kent C, Feldstein AE: *BMC Med* **9**: 70, 2011.
30. Onkar Bedi, Krishna Reddy V. Bijjem, Puneet Kumar, and Vinod Gauttam (2016). *Indian J Physiol Pharmacol*. 60(1): 6–21.
31. Ozougwu, Jevas C., (2017). Physiology of the liver. *International Journal of Research in Pharmacy and Biosciences*. V-4, I8, 13.
32. Parabia, MH, Adhvaryu MR, Reddy N. (2007). *World J Gastroenterol*, 13, 3199–205.
33. Peter, G., 2001. *Ann Intern Med*., Vol. 135, Issue 1, pp 594-600.
34. Piscaglia F, Gianstefani A, Ravaioli M, Golfieri R, Cappelli A, Pinna AD, Bolondi L. (2010) *Liver Transpl.* 2010 May;16(5):658-67.
35. Pradhan SC, Girish C. (2006). *Indian J Med Res*. 124, 491–504.
36. Preeti Chaudhary, Najam Ali Khan. (2016). *Asian J Pharm Clin Res, Vol 9, Issue 1, 2016, 37-40.*
37. Qiu. (2007). *Nature Drug Discov*. 6: 506–550.
38. Sanchez-Valle V, Chavez-Tapia NC, Uribe M, Mendez-Sanchez N: *Curr Med Chem* **19**: 4850-4860, 2012.
39. Saumendu Deb Roy, Dibyendu Shil, Koushik Nandan Dutta (2012), *World journal of Pharmaceutical research*. 6: 560–565.
40. Schuppan, D., Jia JD, Brinkhaus B, Hahn EG. (1999). *Hepatology*. 30(4):1099-104.
41. Singh, A., Tej K Bhat, O P Sharma. (2011) *Clinic Toxicol* 2011, S:4: 1-19.
42. Sheetal, V., and Singh, S.P., 2004. *Veterinary World*, 1(11), pp 347-350.
43. Shivananda Nayak B, Andrew Adogwa. (2011) *Evidence-Based Complementary and Alternative Medicine.* 1-5.
44. Sudipta, D.; Choudhury, M.D.; and Talukdar, A.D. (2012). *Indian Journal of Fundamental and Applied Life Sciences*, 2(1), 84-97.
45. Stickel F, Schuppan D., (2007). *Digestive and Liver Disease.* 39, 293–304.
46. Suman Pattanayak, Vikas Shende, Amol Jadav. (2011) *Asian J Pharm Biol Res*. 1(1): 22-27.
47. Suralkar U R., Kshirsagar A D, Mohite R, Aggrawal A S. (2011). *Asian Journal of Pharmaceutical and Clinical Research. Asian.* Vol 4, Issue 3, 18.
48. Sutherland F, Harris J. (2002). *Arch Surg.* 137(11):1305–1310.
49. Thonda VSS, Gowda S, Gowda S. *IJPCS* 2012;1(2):675-81.
50. Torres Dm, Williams CD, Harrison SA. *Clin Gastroenterol Hepatol*. 10: 837-858, 2012.
51. Walter, H.L., and Elwin, L., 1995. *Ann Missourie Bot Garden*., Vol. 82, pp 16-24.
52. Wanson JC, Bernaert, May C. (1979) *Progress in Liver Diseases*. 6: 1-22.
53. Ward FM and Daly MJ (1999). Churchill Livingstone, New York. 195-212.