

HEPATOTOXICITY V/S HEPATOPROTECTIVE AGENTS – A PHARMACOLOGICAL REVIEW

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ABSTRACT

Liver is the principle organ for maintaining the body's internal environment. Its major influence on the flow of nutrients, & control the metabolism of carbohydrate, proteins and fats. It is also the major reticulo- endothelial organ in the body as such has important immune function in maintaining body veracity. It plays a key role not only in metabolism and disposition of exogenous toxins or therapeutic agent, but also in the biochemical reaction. Many times liver is damaged due to overdose of drugs and alcohol consumption. Chemical driven liver damage is called hepatotoxicity. Chemical agents such as synthetic (CCl₄, galactosamine, lithocholic acid and anti-tuberculosis drugs), natural (microcystins) and herbal remedies (Cascara sagrada) can also induce hepatotoxicity. Such damaged liver will lead to many pathological conditions like hepatitis, cholestasis, steatosis, granuloma etc. Hepatoprotection or antihepatotoxicity is the ability to prevent damage to the liver.

KEYWORDS: Liver, Hepatotoxicity, Hepatoprotectivity, Pharmacotherapy.

INTRODUCTION

Liver is necessary for survival; there is currently no way to reimburse for the absence of liver function. This organ plays a major role in metabolism and has a number of functions in the body, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production, and detoxification. It produces and secretes bile into intestinal lumen and assists in digestion of fat and also helps in purifying the blood. Biochemical reactions, including the synthesis and breakdown of small and complex molecules, many of which are necessary for normal vital functions.¹

Hepatotoxicity

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 focus to first pass metabolism in the liver results in their biological inactivation. When a drug leaks first pass metabolism its biological activity is maintain. Due to the absence of P450s and hepatic metabolic inactivation a stage will come when there is 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 exemption 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.² 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 synthesis³. 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).³

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.⁴ 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)-1 β produced during drug induced liver injury are involved in promoting tissue damage⁵. Innate immune cells are also the main source of IL-10, IL-6, and convinced prostaglandins, all have been shown to display hepatoprotective role.⁶ 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.⁷

HEPATOTOXIC AGENTS (HEPATOTOXICITY) -

CCl₄ Induced Hepatotoxicity: Carbon tetrachloride (CCl₄) induced liver damage has been lengthily used as an experimental model. CCl₄ is used as a model drug for the study of hepatotoxicity in acute and chronic liver failure. CCl₄ is metabolized by CYP2E1, CYP2B, and possibly CYP3A, to form the trichloromethyl radical, CCl₃. This CCl₃ can also bind to cellular molecules damaging crucial cellular progressions. This radical can also react with oxygen to form the trichloromethylperoxy radical CCl₃OO, a highly reactive species. The metabolites of CCl₄ cause the hepatic injury in the CCl₄ acute liver injury model.⁸

Administration of a single dose of CCl₄ 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 CCl₄ left in the liver.⁹ Dose of CCl₄: 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.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.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.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 dilemmas to liver, macromolecules and

initiates liver injury. Chronic exposure of thioacetamide produced cirrhosis in rats.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.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.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.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 canalicular 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.

1. **Anti-Hepatotoxic Agents:** Antagonise the effects of any hepatotoxic causing hepatitis.
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 barring 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

1. Anthea Maton, Hopkins Jean, McLaughlin Charles William, Johnson Susan, Warner Maryanna Quon, LaHart David, Wright Jill D. Human Biology and Health.^{3rd} ed. Englewood Cliffs, New Jersey, USA: Prentice Hall. 1993.

2. D. WuDunn. Genetic basis of glaucoma. *Curr. Opin. Ophthalmol* 2002; 13: 55–60.
3. Lynch T, Price A. The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects. *Amer. Fam. Physician* 2007; 76(3): 391-396.
4. Jaeschke H, Gores GJ, Cederbaum AI, Hinson JA, Pessayre D, Lemasters JJ. Mechanisms of hepatotoxicity. *Toxicol. Sci.* 2002; 65 (2): 166–76.
5. Ishida Y , Kondo T , Ohshima T , Fujiwara H , Iwakura Y , Mukaida N .A pivotal involvement of IFN-gamma in the pathogenesis of acetaminophen-induced acute liver injury. *FASEB J.* 2002; 16: 1227 - 1236.
6. Masubuchi Y, Bourdi M, Reilly TP, Graf ML, George JW, Pohl LR. Role of interleukin-6 in hepatic heat shock protein expression and protection against acetaminophen-induced liver disease. *Bio. Chem. Bio. Phys. Res. Commun.* 2003; 304: 207 - 212.
7. Gunawan B, Kaplowitz N. Clinical perspectives on xenobiotic induced hepatotoxicity. *Drug Metab. Rev.* 2004; 36: 301 – 312.
8. Weber LW, Boll M, Stampfl A. Hepatotoxicity and mechanism of action of haloalkanes: carbon tetrachloride as a toxicological model. *Crit. Rev. Toxicol.* 2003; 33: 105-136.
9. Dawkins MJ. Carbon tetrachloride poisoning in the liver of the new-born rat. *J.Path. Bact.* 1963; 85: 189.
10. Keppler DO, Paush J, Decker K. Effect on ribonucleic acid synthesis: Selective uridine triphosphate deficiency induced by D-galactosamine in liver and reversed by pyrimidine nucleotide precursors. *J. Biol. Chem.* 1974; 249(suppl 1): 211-16.
11. Saraswat B, Visen PK, Dayal R, Agarwal DP, Patnaik GK. Protective action of ursolic acid against chemical induced hepatotoxicity in rats. *Ind. J. Pharmacol* 1996; 28: 232-237.
12. Chieli E, Malvadi G. Role of the microsomal FAD – containing mono-oxygenase in the liver toxicity of thioacetamide - S-oxide. *Toxicology* 1984; 31: 41-52.
13. Chieli E, Malvadi G. Role of cytochrome-450 dependent and FAA containing mono oxygenases in the bio activation of thioacetamide, thiobenzamide and their sulphoxides. *Biochemical and Pharmacology* 1985; 34:395-396.
14. Ambrose A.M, DeEds F, Rather L.J. Further studies on toxicity of thioacetamide in rats. *Proc. Soc. Exp.Biol. Med* 1950; 74: 134-140.
15. Sandhir R, Gill KD. Hepatoprotective effects of Liv-52 on ethanol induced liver damage in rats. *Ind. J. Expt. Biol.* 1999; 37:762-66.
16. Grahame-smith D.G, Azonson J.K. The drug therapy of gastro intestinal hepatic and biliary disorders .In: *Oxford Textbook of Clinical Pharmacology and Drug Therapy.* Oxford.1st Edition Oxford University Press; 1991. Page no. 383-385.
17. Padma VV, Suja V, Shyamala DCS, Prema. Hepatoprotective effect of Liv-52 on antitubercular drug-induced hepatotoxicity in rats. *Fitoterapia* 1998; 69(suppl 6):520-22.
18. Kakis G, Phillips MJ, Yousef IM. The respective roles of membrane cholesterol and of sodium potassium adenosine triphosphatase in the pathogenesis of lithocholate-induced cholestasis. *Lab Invest.* 1980; 43:73–81.
19. Bonvicini F, Gautier A, Gardiol D, Borel GA. Cholesterol in acute cholestasis induced by taurolithocholic acid: a cytochemical study in transmission and scanning electron microscopy. *Lab Invest.* 1978; 38:487–495.
20. Kubitz R, Sutfels G, Kuhlkamp T, Kolling R, Haussinger D. Trafficking of the bile salt export pump from the Golgi to the canalicular membrane is regulated by the p38 MAP kinase. *Gastroenterology* 2004; 126:541–553.
21. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: Mechanisms of action and therapeutic use revisited. *Hepatology* 2002; 36:525–531
22. Hagey LR, Crombie DL, Espinosa E, Carey MC, Igimi H, Hofmann AF. Ursodeoxycholic acid in the Ursidae: Biliary bile acids of bears, pandas, and related carnivores. *J. Lipid Res.* 1993; 34:1911 –7.
23. Paumgartner Gustav, Beuers Ulrich. Mechanisms of action and therapeutic efficacy of ursodeoxycholic acid in cholestatic liver disease. *Clin. Liver Dis.* 2004; 8: 67– 81.
24. Guldutuna S, Zimmer G, Imhof M, Bhatti S, You T, Leuschner U. Molecular aspects of membrane stabilization by ursodeoxycholate. *Gastroenterology* 1993; 104: 1736 –44.
25. Schuetz EG, Strom S, Yasuda K, Lecureur V, Assem M, Brimer C. Disrupted bile acid homeostasis reveals an unexpected interaction among nuclear hormone receptors, transporters, and cytochrome P450. *J. Biol. Chem.* 2001; 276:39411 –8.
26. Guicciardi ME, Gores GJ. Ursodeoxycholic acid cytoprotection: Dancing with death receptor and survival pathways. *Hepatology* 2002; 35:971– 3.
27. Graf D, Kurz AK, Fischer R, Reinehr R, Haussinger D. Taurolithocholic acid-3 sulfate induces CD95 trafficking and apoptosis in a c-Jun N-terminal kinase-dependent manner. *Gastroenterology* 2002; 122:1411 –27.
28. Kalaivani T., Premkumar N., Ramya S., Siva R., Vijayakumar V., Meignanam E., Rajasekaran C. ,Jayakumararaj R. Investigations on Hepatoprotective Activity of Leaf Extracts of *Aeglemarmelos* (L.) *Corr. (Rutaceae), Ethnobotanical Leaflets*2009; 13: 47-50.
29. Manokaran S, Jaswanth A, Sengottuvelu S , Nandhakumar J, Duraisamy R, Karthikeyan D ,Mallegaswari R. Hepatoprotective Activity of *Aervalanata*Linn. Against Paracetamol Induced Hepatotoxicity in Rats. *Res. J. Pharm. and Tech* 2008 ;(1, suppl 4):398-400.
30. Mohamed Saleem TS, Christina AJM, Chidambaranathan N, Ravi V, Gauthaman K. Hepatoprotective activity of *Annonasquamosa* Linn. On experimental animal model *Inter. J. of App. Res. in Nat. Prod.* 2008; (1, suppl 3): 1-7.
31. Pradeep H A, Khan S, Ravikumar K, Ahmed M F, Rao M S, Kiranmai M, Reddy D S, Ahamed S R, Ibrahim M. Hepatoprotective evaluation of *Anogeissuslatifolia*: In vitro and in vivo studies *World J. Gastroenterol* 2009;15(suppl 38):4816-4822.
32. Ali S.A., Al-Amin T.H., Mohamed A.H. and Gameel A.A. Hepatoprotective activity of aqueous and methanolic extracts of *Capparis decidua* stems against carbon tetrachloride induced liver damage in rats. *J. Of Pharmacol. And Toxic* 2009, 4(suppl4):167-172.
33. Gupta Ajay Kumar, Misra Neelam. Hepatoprotective activity of aqueous and ethanolic extract of Chamomile capitulain paracetamol-intoxicated albino rats *Amer. J. of Pharmacol. and Toxic* 2006; 1(suppl 1):17-20.
34. Chaudhari B. P., Chaware V. J., Joshi Y. R., Biyani K. R. Hepatoprotective activity of Hydroalcoholic extract of *Momordicacharantia* Linn. Leaves against Carbon tetra chloride induced Hepatopathy in Rats. *Inter. J. of Chem.Tech. Res.*2009; Vol 1(2):355-358.
35. Kumar Rajesh, Kumar Sushil, Arjunpatra, Jayalakshmi S. Hepatoprotective activity of aerial parts of *plumbago zeylanica*

- linn against carbon tetrachloride-induced hepatotoxicity in rats. *Inter. J. of Pharm. and Pharmaceut. Sc.* 2009; 1(suppl 1): 171-175.
36. Vadivu1 R., Suresh A. Jerad, Girinath K. , BoopathiKannan P., Vimala R., Kumar Sathish N. M. Evaluation of Hepatoprotective and In-vitro Cytotoxic Activity of Leaves of *Premnaserratifolia* Linn *J. Of Sci. Res.* 2009; 1(suppl 1):145-152.
37. T. Prakash, Snehal Dayalal Fadadu, Uday Raj Sharma, V. Surendra, DivakarGoli, Perfect Stamina and D. Kotresha. Hepatoprotective activity of leaves of *Rhododendron arboreum* CCl₄ induced hepatotoxicity in rat. *J. of Med. Plants Res.*2008; Vol. 2(11): 315-320.
38. Praveen TK, Dharmaraj S, Bajaj J, Dhanabal SP, Manimaran S, Nanjan MJ, RazdanRema. Hepatoprotective activity of petroleum ether, diethyl ether, and methanol extract of *Scopariadulcis* L. against CCl₄-induced acute liver injury in mice. *Ind. J. of Pharmacol.* 2009; Vol. 41(3): 110-114.
39. Rao B. Ganga, Jaya Raju N. Investigation Of hepatoprotective activity of *Spondiaspinnata*, *International Journal of Pharma Sciences and Research* 2010; Vol.1 (3): 193-198.

Table 1: List of plants evaluate for hepatoprotective effect.

S. no	Plants	Animal	P Value	Model	Part Used	Extract	Uses	Family	Ref.
1	<i>Aegle marmelos</i>	Cross breed albino mice	<0.01	CCl ₄	fruit pulp	Ethanollic	dysentery and diarrhoea	Rutaceae	28
2	<i>Aerva lanata</i> Linn.	Wistar rats	<0.001	Paracetamol	fresh plants	hydroalcoholic	Diuretic, Demulcent	Amaranthaceae	29
3	<i>Annona squamosa</i> Linn.	Wistar strains of rats	<0.01	Isoniazid+ Rifampicin	Leaves	Alcoholic	Cherimoya Custard-apple	Annonaceae	30
4	<i>Anogeissus latifolia</i>	Albino rats of Wistar strain	<0.05	CCl ₄	Bark	hydroalcoholic	respiratory diseases	Combretaceae	31
5	<i>Capparis decudua</i>	Wistar albino rats	<0.001	CCl ₄	Stems	Aqueous and Methanolic	landscape gardening, afforestation and reforestation	Capparaceae	32
6	<i>Chamomile capitula</i>	Albino rats	<0.001	Paracetamol	Fresh Plant	Aqueous ethanolic	swelling of inflamed tissues	Asteraceae.	33
7	<i>Momordica charantia</i> Linn.	Wistar albino rats	<0.01	CCl ₄	Leaves	Hydroalcoholic	Chicken pox and measles	Cucurbitaceae	34
8	<i>Plumbago zeylanica</i> Linn.	Wistar rats	<0.05	CCl ₄	Aerial Part	Methanolic	dyspepsia,	Plumbaginaceae	35
9	<i>Premna serratifolia</i>	Albino rats of Wistar strain	<0.001	CCl ₄	Leaves	Ethanollic	Chicken pox and measles	Lamiaceae	36
10	<i>Rhododendron Arboreum</i>	Wistar albino rats and albino mice	<0.05	CCl ₄	Leaves	Ethanollic	Headaches. coughs, diarrhoea and dysentery	Ericaceae	37
11	<i>Scoparia dulcis</i> L.	Swiss albino mice	<0.05	CCl ₄	Whole Fresh Plant	petroleum ether, diethyl ether, and methanol (PDM)	menstrual disorders, dysentery and fever	Scrophulariaceae	38
12	<i>Spondias pinnata</i>	Wistar albino rats	<0.01	CCl ₄	Stem	Methanolic	Stomach ache, dysentery, rheumatism and swollen joints.	Anacardiaceae	39

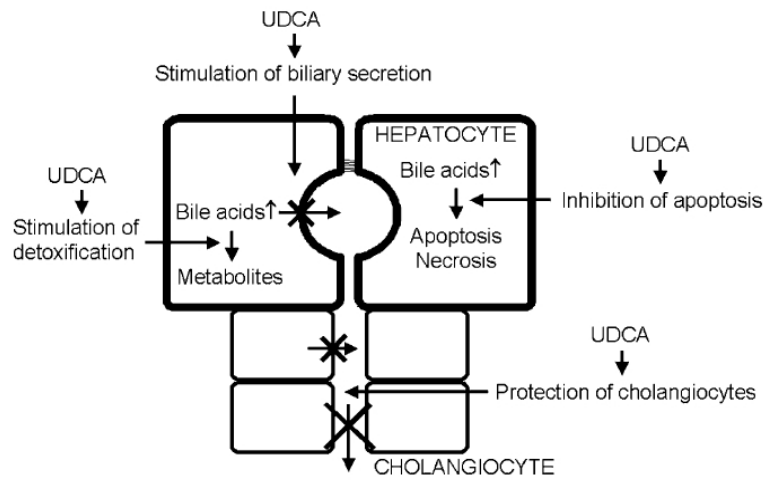


Figure 1: Mechanism of UDCA as hepatoprotective²³