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HEPATOPROTECTIVE ACTIVITY – A REVIEW

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Abstract:

Hepatoprotective agents are those compounds, which mitigate the liver injury caused by hepatotoxic agents. Hepatoprotective effects of plant drugs and herbal formulations are studied against chemicals (Alcohol, CCl₄, Beta galactosamine, Thioacetamide) and drugs (Paracetamol, Nimesulide, Antitubercular drugs like Isoniazid, Rifampicin etc.) induced hepatotoxicity in rats and mice as they virtually mimic any form of naturally occurring liver disease. All FDA approved NRTIs (Nucleoside reverse transcriptase), NNRTIs (Non-nucleoside reverse transcriptase inhibitor), and PIs (protease inhibitor) are associated with hepatotoxicity. Herbal drugs are significant source of hepatoprotective drugs. Mono and poly-herbal preparations have been used in various liver disorders. When compared with the allopathic medicine herbal drugs are more in number when it comes to hepatoprotective activity. According to one estimate more than 700 mono and poly-herbal preparations in the form of decoction, tincture, tablets and capsules from more than 100 plants are in clinical use. By understanding the mechanism of hepatotoxicity and pathophysiology of hepatotoxic agents the treatment can be made very effective and by knowing the mechanism of disease progression the drugs can be designed which target those steps to cure hepatic diseases.

Keywords: Hepatoprotective, CCl₄, Hepatitis, Thioacetamide, Galactosamine

Introduction:

Hepatoprotective drugs are defined as the drugs which prevent liver diseases. Many times liver is damaged due to chemicals, alcohol consumption and because of few drugs which are normally used for therapy. Chemical driven liver damage is called hepatotoxicity. Such damaged liver will lead to many pathological conditions like hepatitis, cholestasis, steatosis, granuloma etc. Many of the conventional drugs have the potential to cause hepatic damage, in such circumstances herbal medicine provide better therapy than conventional medicine when it comes to the adverse drug reactions which are caused by conventional medicine.

Liver:

Liver in normal adult weighs nearly three pounds. It produces and secretes bile into intestinal lumen and assists in digestion of fat. Liver helps in purifying blood.

Liver diseases:

Liver disease is a term for a collection of conditions, diseases and infections that affect the cells, tissues, structures or functions of the liver.¹

Liver functions:

Liver identifies xenobiotics and metabolize them and make them suitable for elimination. This involves chemical transformation (a) decreasing lipid solubility (b) change the biological activity. Mainly smooth endoplasmic reticulum of liver principally participates in metabolism. It is also called as metabolic clearing house of both exogenous and endogenous substances.² Drug metabolism takes place in 2 phases; Phase I and Phase II. Phase I reactions involve oxidation, reduction, hydrolysis, hydration which makes them water soluble and also generate metabolites which are more chemically active and potentially toxic. Phase II reactions takes place in cytosol and involve conjugation with endogenous compounds via transferase enzyme. A group of enzymes are located in endoplasmic reticulum, known as cytochrome P₄₅₀ enzymes. Cytochrome P₄₅₀ is a terminal oxidase component of electron transport chain. It is not a single enzyme but consists of a family closely related to 50 isoforms, 6 of them metabolize 90% of drugs.^{3,4}

Etiological factors:

There is a great diversity of individual P₄₅₀ gene products which allows liver to perform oxidation on vast array of chemicals in Phase I. Three important characteristics of P₄₅₀ system have role in drug induced toxicity. Genetic variations (polymorphism) in CYP450 metabolism should be considered when patients exhibit unusual sensitivity or resistance to drug effects at normal doses.

Change in enzyme activity:

This depends on drug's activity as either inducer or inhibitor. Enzyme inhibitors block metabolic activity of one or several P₄₅₀ enzymes, this effect is immediate. On the other hand inducers increase P₄₅₀ activity by increasing its synthesis.⁴ other factors are:

- Congenital birth defects or abnormalities of the liver present at birth.
- Metabolic disorders or defects in basic body processes.
- Viral or bacterial infections.
- Alcohol or poisoning by toxins.
- Certain medications that are toxic to the liver.
- Nutritional deficiencies.
- Trauma or injury.¹

Hepatotoxicity leads to necrosis, cirrhosis, hepatitis, hepatic failure, chemical/drug induced hepatotoxicity, liver disorders due to impaired metabolic functions.

Prevention:

- Avoiding toxic substances and excess alcohol consumption
- Eating a well balanced diet.
- Avoiding illegal drug use, especially sharing injection equipment.¹

Symptoms:

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

Diagnosis:

- Liver function tests
- A complete blood count (CBC)
- Abdominal X-rays
- Ultrasound
- ERCP or Endoplasmic retrograde cholangiopancreatography
- Abdominal CT scan or Abdominal MRI.¹

Mechanism of hepatotoxicity caused by different agents:

Damage to the liver is not due to the drug itself but to a toxic metabolite (N-acetyl-p-benzoquinone imine NAPQI or NABQI) which is produced by cytochrome P₄₅₀ enzymes in the liver.⁵ In overdoses large amount of NAPQI is generated which overwhelm the detoxification process and lead to damage to liver cells. Nitric acid also plays role in inducing toxicity.⁶The mechanism of hepatotoxicity caused by NSAIDs were documented to be both idiosyncratic and dose dependant. Aspirin and phenylbutazone are associated with intrinsic hepatotoxicity; idiosyncratic reaction has been associated with ibuprofen, sulindac, phenylbutazone, piroxicam, diclofenac and indomethacin. Enlarged liver is a rare side effect of long term steroid use in children.⁸

Carbon tetrachloride:

Liver injury due to carbontetrachloride in rats was first reported in1936⁹ and has been widely and successfully used by many investigators.^{10, 11} Carbontetrachloride is metabolized by cytochrome P₄₅₀ in endoplasmic

reticulum and mitochondria with the formation of CCl_3O^- , a reactive oxidative free radical, which initiates lipid peroxidation.^{12,13}



Administration of a single dose of CCl_4 to a rat produces, within 24 hrs, a centrilobular necrosis and fatty changes.⁹ The poison reaches its maximum concentration in the liver within 3 hrs of administration. Thereafter, the level falls and by 24 hrs there is no CCl_4 left in the liver.¹⁴ The development of necrosis is associated with leakage of hepatic enzymes into serum. Dose of CCl_4 : 0.1 to 3 ml/kg I.P.

Galactosamine:

Galactosamine produces diffuse type of liver injury simulating viral hepatitis. It presumably disrupts the synthesis of essential uridylylate nucleotides resulting in organelle injury and ultimately cell death. Depletion of those nucleotides would impede the normal synthesis of RNA and consequently would produce a decline in protein synthesis. This mechanism of toxicity brings about an increase in cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductules or canalicular membrane of hepatocytes. Galactosamine decrease the bile flow and its content i.e. bile salts, cholic acid and deoxycholic acid. Galactosamine reduces the number of viable hepatocytes as well as rate of oxygen consumption. Dose of D-Galactosamine: 400 mg/kg, I.P.¹⁵

Thioacetamide:

Thioacetamide interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury. A metabolite of thioacetamide (perhaps s-oxide) is responsible for hepatic injury. Thioacetamide reduce the number of viable hepatocytes as well as rate of oxygen consumption. It also decreases the volume of bile and it's content i.e. bile salts, cholic acid and deoxycholic acid. Dose of thioacetamide: 100 mg/kg, S.C.¹⁵

Alcohol:

The effects of ethanol have been suggested to be a result of the enhanced generation of oxygen free radicals during its oxidation in liver. The peroxidation of membrane lipids results in loss of membrane structure and integrity. This results in elevated levels of γ -glutamyl transpeptidase, a membrane bound enzyme in serum. Ethanol inhibits glutathione peroxidase, decrease the activity of catalase, superoxide dismutase, along with increase in levels of glutathione in liver. The decrease in activity of antioxidant enzymes superoxide dismutase, glutathione peroxidase are speculated to be due to the damaging effects of free radicals produced following ethanol exposure or alternatively could be due to a direct effect of acetaldehyde, formed by oxidation of ethanol.¹⁶ Alcohol pre-treatment stimulates the toxicity of CCl_4 due to increased production of toxic reactive metabolites of CCl_4 , namely trichloro-methyl radical by the microsomal mixed function oxidative system. This activated radical binds covalently to the macromolecules and induces peroxidative degradation of membrane lipids of endoplasmic reticulum rich in polyunsaturated fatty acids. This lipid peroxidative degradation of biomembranes is the principle cause of hepatotoxicity.¹⁷

Paracetamol:

Paracetamol, a widely used analgesic and antipyretic drug, produces acute liver damage in high doses. Paracetamol administration causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by large excessive hepatic lesion. The covalent binding of N-acetyl-P-benzoquinoneimine, an oxidative product of paracetamol to sulphhydryl groups of protein, result in lipid peroxidative degradation of glutathione level and thereby, produces cell necrosis in the liver. Dose of Paracetamol: 1 gm/kg P.O.^{17, 10}

Antitubercular drugs:

Though INH, Rifampicin and Pyrazinamide each in itself are potentially hepatotoxic, when given in combination, their toxic effect is enhanced. INH is metabolized to monoacetyl hydrazine, which is further metabolized to a toxic product by cytochrome P₄₅₀ leading to hepatotoxicity. Patients on concurrent rifampicin therapy have an increased incidence of hepatitis. This has been postulated due to rifampicin-induced

cytochrome P₄₅₀ enzyme-induction, causing an increased production of the toxic metabolites from acetyl hydrazine (AcHz). Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic. The plasma half life of AcHz (metabolite of INH) is shortened by rifampicin and AcHz is quickly converted to its active metabolites by increasing the oxidative elimination rate of AcHz, which is related to the higher incidence of liver necrosis caused by INH and rifampicin in combination. Rifampicin induces hydrolysis pathway of INH metabolism into the hepatotoxic metabolite hydrazine. Pharmacokinetic interactions exist between rifampicin and pyrazinamide in tuberculosis patients, when these drugs are administered concomitantly. Pyrazinamide decrease the blood level of rifampicin by decreasing its bioavailability and increasing its clearance. Pyrazinamide, in combination with INH and rifampicin, appears to be associated with an increased incidence of hepatotoxicity.¹⁸

Models to Evaluate Effect of Drugs on Liver

As liver is a multifunctional organ, a battery of liver function tests are employed to evaluate the effect of drug on liver, which are Non-invasive functional methods:

1. Ascorbic acid content in urine
2. Pentobarbitone induced sleeping time
3. Bromosulphthaline clearance test

Biochemical analysis of blood for

- a. SGPT (Serum glutamic-pyruvic transaminase)
- b. SGOT (Serum glutamic-oxaloacetic transaminase)
- c. Alkaline phosphatase
- d. Serum bilirubin
- e. Total proteins

Morphological test- Wet weight of liver/100 gm body weight

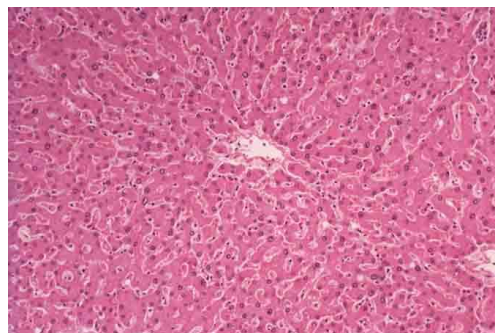


Figure:1 Biopsy of a normal liver

Free radical scavengers

a.Glutathione

b.Lipid peroxidation

c.Superoxide dismutase

d.Catalase

f.Glutathione peroxidase

g.Histopathology of liver ¹

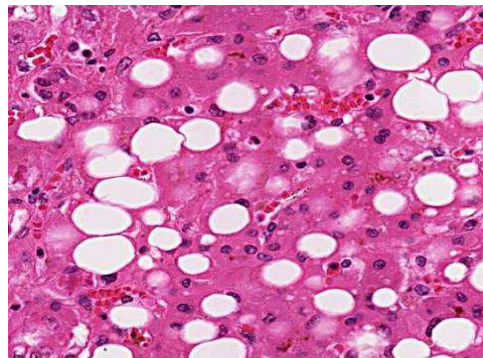


Figure:2 Biopsy of a fatty liver

Allopathic treatment:

1.Ursodeoxycholic acid (Ursodiol):

The immunomodulatory effects of ursodeoxycholic acid are believed to involve decreased immunoglobulin production by B lymphocytes, decreased interleukin-1 and interleukin-2 production by T lymphocytes, decreased expression of hepatocyte cell surface membrane HLA class I molecules and possibly stimulation of the hepatocyte glucocorticoid receptor.

Clinical applications:

biliary cirrhosis, biliary disease secondary to cystic fibrosis, nonalcoholic steatohepatitis, idiopathic chronic hepatitis, autoimmune hepatitis, primary sclerosing cholangitis, alcoholic hepatitis etc.

In recommended doses ursodeoxycholic acid be administered for 3-4 months after which the patient should be reassessed for improvement in biochemical markers of hepatocellular pathology.¹

2. Pencillamine:

Penicillamine is a degradation product of penicillin but has no antimicrobial activity. It was first isolated in 1953 from the urine of a patient with liver disease who was receiving penicillin

Penicillamine chelates several metals including copper, lead, iron, and mercury, forming stable water soluble complexes that are renally excreted. It also combines chemically with cystine to form a stable, soluble, readily excreted complex. Penicillamine induces hepatic metallothionein, which may bind and sequester copper in a

nontoxic form. It may also have antifibrotic effects as it inhibits lysyl oxidase, an enzyme necessary for collagen synthesis and directly binds to collagen fibrils, preventing cross-linking into stable collagen fibres. However, its efficacy as an antifibrotic agent in humans is doubtful and it has not been evaluated in veterinary medicine. Penicillamine may have immunomodulatory effects and has been demonstrated to reduce IgM rheumatoid factor in humans with rheumatoid arthritis. However, its mechanism of action in this disease remains uncertain.

Clinical applications:

Copper-storage hepatopathy (e.g., Bedlington Terriers), lead toxicity, cystine urolithiasis etc.

Dosage and formulations:

For management of copper associated hepatopathy, a dose of 10-15 mg/kg quarterly 12 hours PO is given on empty stomach. However if GIT adverse effects are experienced, those reactions may be reduced if it is given with food, although absorption may be reduced.¹

Herbal treatment:

These are generally classified into 3 categories without any strict delineation amongst them.

1. Anti hepatotoxic agents:

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

2. 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.

3. Hepatoprotective agents:

These generally prevent various types of liver affections prophylactically.

In general any hepatoprotective agent can act as an antihepatotoxic or hepatotropic agent but the vice versa is always not true.¹

Table 1

S.no	Plant	Animal	P Value	Model	Author
1.	<i>Abutilon indicum</i> ¹⁹	Wistar albino rats	<0.01	CCl ₄	E. Porchezian <i>et.al.</i>
2.	<i>Aegle marmelos</i> ²⁰	Cross breed albino mice	<0.01	CCl ₄	C.Rajasekaran <i>et.al.</i>
3.	<i>Aerva lanata</i> Linn. ²¹	Wistar rats	<0.001	Paracetamol	Manokaran S <i>et.al.</i>
4.	<i>Annona squamosa</i> Linn. ²²	Wistar strains of rats	<0.01	Isoniazid+ rifampicin	Mohamed Saleem TS <i>et.al.</i>
5.	<i>Anogeissus latifolia</i> ²³	Albino rats of Wistar strain	<0.05	CCl ₄	Ibrahim M <i>et.al.</i>
6.	<i>Capparis decudua</i> ²⁴	Wistar albino rats	<0.001	CCl ₄	S.A.Ali <i>et.al.</i>
7.	<i>Chamomile capitula</i> ²⁵	Albino rats	<0.001	Paracetamol	A K Gupta <i>et.al.</i>
8.	<i>Curcuma longa</i> ²⁶	Sprague Dawley rats	<0.05	Paracetamol	Somchit M.N <i>et.al.</i>
9.	<i>Embelia ribes</i> ²⁷	Albino mice	<0.05	Paracetamol	N Tabassum <i>et.al.</i>
10.	<i>Leucas ciliata</i> ²⁸	Albino rats	<0.001	CCl ₄	M N. Qureshi <i>et.al.</i>
11.	<i>Momordica charantia</i> Linn. ²⁹	Wistar albino rats	<0.01	CCl ₄	Chaudhari B. P. <i>et.al.</i>
12.	<i>Plumbago zeylanica</i> Linn. ³⁰	Wistar rats	<0.05	CCl ₄	Sushil kumar <i>et.al.</i>
13.	<i>Premna serratifolia</i> ³¹	Albino rats of Wistar strain	<0.001	CCl ₄	R.Vadivu <i>et.al.</i>
14.	<i>Pterocarpus marsupium</i> ³²	Wistar albino rats	<0.01	CCl ₄	V. Krishna <i>et.al.</i>
15.	<i>Rhododendron arboreum</i> ³³	Wistar albino rats and albino mice	<0.05	CCl ₄	T. Prakash <i>et.al.</i>
16.	<i>Saccharum officianarum</i> ³⁴	Wistar strain albino rats	<0.05	Ethyl alcohol	Bhavik A. Patel <i>et.al.</i>
17.	<i>Sarcostemma brevistigma</i> ³⁵	Albino rats	<0.001	CCl ₄	M. G. sethuraman <i>et.al.</i>
18.	<i>Scoparia dulcis</i> L. ³⁶	Swiss albino mice	<0.05	CCl ₄	MJ Nanjan <i>et.al.</i>
19.	<i>Spondias pinnata</i> ³⁷	Wistar albino rats	<0.01	CCl ₄	N. Jaya raju <i>et.al.</i>
20.	<i>Wedelia calendulacea</i> L. ³⁸	Albino rats	<0.05	CCl ₄	P.Murugaian <i>et.al.</i>

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