



HEPATOPROTECTIVE ACTIVITY: RECENT UPDATE

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ABSTRACT

Liver plays an important role in maintaining the biological equilibrium of vertebrates. Liver is the largest and almost complex organ in the body. It plays an important role in the maintenance of internal environment through its multiple and diverse function. It plays a central role in detoxification and excretion of many endogenous and exogenous compounds. Hence, any injury to it or impairment of its function has grave implication for the health of the affected person. Liver diseases possess complication in treating them throughout the world. Since, conventional or synthetic drugs used in treating of liver diseases are few & with the risk of serious side effects. This is the one of the reasons for many people all over the world including those in developed countries for turning towards complementary & alternative medicines.

Key words: Abacavir, Hydroxypropyl methyl cellulose, sodium alginate, direct compression technique, *in-vitro* drug release studies.

INTRODUCTION:

The liver is among the most complex and important organs in the human body. Its primary function is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances to the systemic circulatory system. A total loss of liver function leads to death within minutes, demonstrating the liver's importance.

General Description of Liver:

The liver is the largest gland in the human body, weighing approximately 3 pounds and occupying a large region mostly on the right side of the body, below the diaphragm and behind ribs 5 through 10.

Liver disease:

Liver disease is a term for a collection of conditions, diseases, and infections that affect the cells, tissues, structures, or functions of the liver. Some common liver disease symptoms include the following, each of which are described briefly below:

- Jaundice.
- Cholestasis.
- Cirrhosis.
- Fibrosis^[1]

Causes of liver disease:

- 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]

Diagnostic Procedures

The most commonly performed diagnostic procedures include the following:

- Cholecystography (also called oral cholecystography or gallbladder series).
- Computed tomography scan (CT or CAT scan).
- Endoscopic retrograde cholangiopancreatography (ERCP).
- Esophagogastroduodenoscopy (also called EGD or upper endoscopy).
- Hepatobiliary scintigraphy.
- Laparoscopy.
- Liver biopsy.
- Magnetic resonance imaging (MRI).

- Magnetic resonance cholangiopancreatography (MRCP).^[1]

Hepatotoxicity

Toxic liver injury produced by drugs and chemicals may virtually mimic any form of naturally-occurring liver disease. Hepatoprotective effect were studies against chemicals and drugs induced hepatotoxicity in rats like alcohol, CCl₄, Galactosamine, Thioacetamide, Paracetamol, Isoniazid, Rifampicin etc. ^[2]

Classification of hepatotoxins

Intrinsic:

It consists of agents that are predictable hepatotoxins. They are recognized by high incidence of hepatic injury in exposed individuals and in experimental animals. There is a constant latent period between exposure to a particular agent and the development of hepatic injury and the injury appeared to be dose related.^[3,4]

There are two types of intrinsic hepatotoxins:

Direct hepatotoxins:

It may be so called because they (or their metabolic products) produce direct injury to hepatocytes and its organelles, especially the endoplasmic reticulum. CCl₄, the prototype, produces peroxidation of the membrane lipids

and other chemicals that lead to degeneration of the membranes.^[3,4]

Indirect hepatotoxins:

They are anti-metabolites and related compounds that produce hepatic injury by interference with the specific metabolic pathway or processes, the structural injury produced by indirect hepatotoxins appear to be secondary to a metabolic region, while in that produced by direct hepatotoxins, the metabolic derangement is secondary to the structural injury. The hepatic damage produced by indirect hepatotoxins may be mainly cytotoxic injury (by interfering with metabolic pathway or processes essential for parenchyma integrity) expressed as steatitis or necrosis, or may be mainly cholestasis, interfering only or mainly with biliary secretion.^[3,4]

Host idiosyncrasy:

It consists of agents that are not predictably hepatotoxic, but produces hepatic injury in only a small portion of exposed individual, who are uniquely susceptible. In several instances auto antibodies directed against normal cellular constituents are detected. The injury does not appear to be dose related and is not reproducible in experimental animals and appears after a variable latent period.^[4,5]

Table no. 1: Classification of Hepatotoxin.

Sr no.	Category of Agent	Mechanism	Histological Lesions	Examples
1	Intrinsic Toxicity			
	a) Direct	Membrane injury, destruction of structural basis of cell	Necrosis and for stenosis	CCl ₄ , CHCl ₃
	b) Indirect	Metabolism interference with specific metabolic pathways lead to structural injury	Necrosis or Stetosis	Paracetamol, ethanol, Tetracyclin.
2	Host Idiosyncrasy			
	a) Hypersensitivity	Drug allergy	Necrosis or cholestetosis	Sulphonamide, Halothane.
	Metabolic abnormality	Production of the hepatic metabolites	Necrosis or Cholestelosis	Isoniazide

Mechanism of action in causing Hepatotoxins:

Chemically induced cell injury can be thought of as involving a series of events occurring in the affected animal and often in the target organ itself. The chemical agent is activated to form the initiating toxic agent, that either detoxifies or causes molecular changes in cell. The

cell recovers or there are irreversible changes, which may culminate cell death. cell injury can be initiated by a number of mechanisms, such as inhibition of enzymes, depletion of cofactors or metabolites, depletion of energy stores, interaction with receptors, & alteration of cell membranes.^[6]

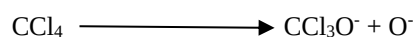
Table no. 2: Drug and Toxin–Induced Hepatic injury

Sr no.	Hepatocellular Damage	Examples
1	Microvesicular fatty change	Tetracycline, Salicylate, Ethanol
2	Macrovesicular fatty changes	Methotrate, Amidarone, Ethanol
3	Centrilobular necrosis	CCL ₄ , Rifampicin, Acetaminophen
4	Diffuse or massive necrosis	Isoniazid, Halothane, Acetaminophen, Methyldopa.
5	Hepatitis, acute and chronic	Methyldopa, Isoniazide, Phenytoin, Nitrofurantoin
6	Fibrosis –cirrhosis	Ethanol, Methotrexate, Amidarone.
7	Granuloma formation	Methyldopa, Isoniazide, Phenytoin, Nitrofurantoin
8	Cholestasis	Chlorpromazine, Erythromycin ^[6]

Mechanism of Action of Some selected Hepatotoxins**➤ CCL₄ induced hepatotoxicity**

The drug is metabolized in endoplasmic reticulum and mitochondria with the formation of CClO₃·, the reactive oxidative free radical intermediate generated by cytochrome P-450, the nascent oxygen O· resulted via lipoperoxidation causes rise in intracellular reactive Fe⁺²

ions, aldehyde and depletion GSH, and calcium sequestration. Oxidative CCl₃O· also by direct covalent interaction induces degeneration of Ca⁺² sequestration. Failure into sequestration results in increased intracellular Ca⁺², aggregation by proteolytic enzyme and causes an increase in Fe⁺² ions, which in turn by lipid peroxidation precipitates aldehyde cytotoxicity.^[7,8,9,10,11]

**➤ Galactosamine induced hepatotoxicity**

It resembles to that caused by acute human viral hepatitis. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductless or canalicular membrane of hepatocytes.^[12]

➤ Alcohol induced hepatotoxicity

Ethanol produces constellation of dose- related deleterious effects in the liver. the primary effects are fatty infiltration of the liver, hepatitis and cirrhosis. Because of its intrinsic toxicity, alcoholic injures the liver in the absence of dietary deficiencies. The accumulation of fat in the liver is an early event and can occur in normal individual after the ingestion of relatively small amount of ethanol. this accumulation results from inhibition of both the tricarboxylic acid cycle and oxidation of fat, in part owing to the degeneration of excess NADH produced by the action of alcohol dehydrogenase and aldehyde dehydrogenase.^[13,14]

➤ Paracetamol induced hepatotoxicity

The liver damage associated with paracetamol overdose is due to the formation of a hepatotoxic metabolite. Therapeutic doses of paracetamol are metabolized mostly to sulphate and glucuronide conjugates. The rest is metabolized to a reactive intermediate which is detoxified by conjugation with glutathione. In overdose, the sulphate and glucuronide conjugation pathways are saturated and more drug is converted to the reactive metabolite. The glutathione available for its detoxification is rapidly depleted and the metabolites accumulated and binds

covalently to liver cell proteins, causing irreversible damage.^[7,14]

Liver Function Test

In keeping with the multiplicity of the liver function, a variety of tests are available to access them. The choice of the test is influenced by its simplicity, reliability, and sensitivity as well as particular function one is interested in accessing.

➤ Test of bilirubin metabolism

- Estimation of serum bilirubin
- Urinary bilirubin
- Urine urobilinogen

➤ Test of protein synthesis and metabolism

- Estimation of plasma protein
- Albumin Globulin ratio (A/G ratio)

➤ Test based on excretory function

- Serum alkaline phosphatase
- Bromsulphthalein (BSP) Excretion

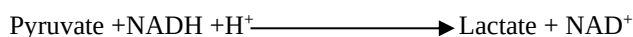
➤ Test to assess hepato- cellular damage

- Serum enzyme estimation^[15,16]

Parameters Reflecting Liver Condition and Their Interpretation**Transaminases**

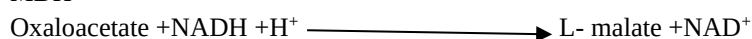
Transaminase is a process in which an amino group is transferred from an amino acid to an alpha – keto acid. It is an important step in the metabolism of amino acids. The enzyme responsible for transamination are called transaminases (now called amino-transferases). Two diagnostically useful transaminases are glutamate

➤ **SGPT (ALT)**



➤ **SGOT(AST)**

MDH



SGPT(ALT): 6–21 U/L [30,31]

➤ **Alkaline Phosphatase (ALP).**

$$\text{P-Nitrophenyl phosphate} + \text{H}_2\text{O} \longrightarrow \text{p-nitrophenol} + \text{H}_3\text{PO}_4$$

Colourless Yellow

Alkaline phosphatase (ALP): 20 to 100 U/L [31,32,33]

$$\text{g-glutamyl nitroanilide} + \text{glycylglycine} \longrightarrow \text{P-nitroaniline} + \text{Glutamyl glycylglycine}$$

Gamma-glutamyl transpeptidase (GGTP): 5–24 IU/L [31]

conjugation of bilirubin treatment such as Gilbert's disease.^[34,35]

The blood levels of these plasma proteins are decreased in extensive liver damage. A routinely estimated total protein is in the normal range of 5.5 to 8 gm/dl. Hypoalbuminemia may occur in liver disease having significant destruction of hepatocytes. [34,35]

Morphological like weight of the animals, weight and volume of the liver have also been used to evaluate the protective effect of the drug.^[35]

Normal Reference Range Table**Table of Normal Values**

Aspartate aminotransferase (AST)	7-21 U/L
Alanine aminotransferase (ALT)	6-21 U/L
Albumin	3.5-4.8 U/L
Alkaline phosphatase (ALP)	20-100 U/L
Bilirubin, direct	<0.3 mg/dL
Bilirubin, total	0.2-1.3 mg/dL
Gamma-Glutamyl Transpeptidase (GGTP)	5-24 IU/L

Experimental models for Hepatoprotective Screening:

Several chemical reagents and drugs which induce liposis, necrosis, cirrhosis, carcinogenesis and hepatobiliary dysfunctions in experimental animals are classified as hepatotoxins. The most important ones used are carbon tetrachloride (CCl₄), thioacetamide (TAA), D-galactosamine, Paracetamol, chloroform, ethyl alcohol and Pyridine. The following are some of the experimental rat models employing these hepatotoxins.^[16]

➤ **CCl₄ model:**

A number of CCl₄ models are devised depending upon its dosage through different routes of administration.

Acute Hepatic Damage:

Acute liver damage, characterized by ischemia, hydropic degeneration and central necrosis is caused by oral or subcutaneous administration of CCl₄ (1.25ml / kg). The biochemical parameters elevated are found to be maximum after 24 hours of CCl₄ administration. Normally administered as 50 % V/V solution in liquid paraffin or olive oil.^[17]

Chronic Reversible Hepatic Damage:

Administration of CCl₄ (1ml/kg s.c) twice weekly for 8 weeks produces chronic, reversible liver damage.^[18]

Chronic Irreversible Hepatic Damage:

Administration of CCl₄ (1ml/kg s.c) twice weekly for 12 weeks simulates chronic, irreversible liver damage.^[19]

➤ **Thioacetamide model:**

Thioacetamide (100 mg / kg s.c) induces acute hepatic damage after 48 hrs of administration by causing

sinusoidal congestion and hydropic swelling with increased mitosis.^[20]

➤ **D-Galactosamine model:**

D-galactosamine 800 mg /kg i.p induces acute hepatotoxicity after 48 hrs of administration with diffused necrosis and steatosis.^[21]

➤ **Paracetamol model:**

Paracetamol induces acute hepatotoxicity depending upon its dosage through different routes of administration, such as-

Paracetamol 800 mg/kg i.p. induces centrilobular necrosis without steatosis.

Paracetamol at a dose of 3 g/kg p.o stimulates acute hepatic damage.^[22,23]

➤ **Chloroform model:**

It produces hepatotoxicity with extensive central necrosis, fatty metamorphosis, hepatic cell degeneration and necrosis either by inhalation (for 1hr in atmosphere) or by subcutaneous administration. (0.4-0.5 ml/kg).^[24]

➤ **Ethanol model:**

Ethanol induces liposis to a different degree depending upon its dose, route and period of administration as follows-

A single dose of ethanol 1 ml/kg induces fatty degeneration.

Administration of 40 % (v/v) ethanol 2 ml/100g/day p.o for 21 days produces fatty liver.

Administration of country made liquor 3ml/100g/day p.o for 21 days produces liposis.^[25,26,27]

Table of Models & their Doses

Sr no	Name of model	Drug	Dose
1	CCl ₄ Model	CCl ₄	1ml/kg s.c
2	Thioacetamide Model	thioacetamide	100 mg/kg s.c
3	D-Galactosamine Model	D-Galactosamine	800 mg/kg i.p
4	Paracetamol Model	Paracetamol	800 mg/kg i.p
5	Chloroform Model	Chloroform	0.4-0.5 ml/kg
6	Ethanol Model	Ethanol	2ml/100gm/day p.o

➤ Treatment

Treatment for liver disease include allopathic and herbal drug treatment:

Hepatoprotective allopathic treatment

Allopathic Drugs:

Specific drugs used in the management of liver disease:

➤ Ursodeoxycholic acid (Ursodiol):

Mechanism of action:

Ursodeoxycholic acid, a relatively hydrophilic bile acid, is also believed to protect the liver from the damaging effects of hydrophobic bile acids, which are retained in cholestatic disorders. The hepatoprotective effect may however, be less in cats and dogs than in humans as the major circulating bile acid in dogs and cats is taurocholate. This is more hydrophilic and less hepatotoxic than the major circulating bile acids in humans.

Clinical applications:

Ursodeoxycholic acid has been used in the management of chronic hepatic diseases in humans such as primary biliary cirrhosis, biliary disease secondary to cystic fibrosis, nonalcoholic. However, its therapeutic efficacy in some of these disorders has not been firmly established.

Dose rate: It is recommended that ursodeoxycholic acid be administered for 3–4 months after which the patient should be reassessed for improvement in biochemical markers of hepatocellular pathology.

Adverse effects:

Ursodeoxycholic acid appears to be well tolerated by dogs and cats; vomiting and diarrhoea are reported rarely. There is some concern in human patients that taurine depletion may be potentiated by chronic treatment with ursodeoxycholic acid.^[28]

➤ Penicillamine:

Penicillamine induces hepatic metallothionein, which may bind and sequester copper in a nontoxic form. 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:

Penicillamine is a monothiol chelating agent which is used in veterinary medicine in the treatment of copper-storage hepatopathy (e.g., Bedlington Terriers), lead toxicity, and cystine urolithiasis. It has also been used in the management of rheumatoid arthritis in humans. Wilson's disease is treated by trientine or penicillamine.

Dosage and formulations:

For management of copper-associated hepatopathy, a dose of 10–15 mg/kg q12h PO is given on an empty stomach.

Adverse effects:

GIT adverse effects are common resulting in nausea and vomiting. Other adverse effects observed infrequently or rarely include:

Fever.

Lymphadenopathy.

Skin hypersensitivity reactions.

Immune-complex glomerulonephropathy^[28]

Herbal treatment:

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

➤ 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 can not 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^[28]

Table: Table shows liver protective Herbal Drug Along with Their Main Phytoconstituents.

Sr.no.	Main phytoconstituent	Liver Protective Drug	Part Used
1	Phenol	Arnica Montana Linn	Plant
		Cinchorium intybus Linn	Plant
		Picrorriza Kurroa Royle	Root
2	Coumarin	Armillaria tabescens scop	Fungus
		Artemisia capillaries herba	Plant
		Hermidesmus indicus	Roots
3	Lignans	Schisandra chinensis turcz	Fruit
		Schisandra sphenantra	Fruit
		Silybum marianum gaertn	Seed
4	Essential oils	Anethum graveolens Linn	Fruit
		Apium graveolens linn	Seed
		Azadirachta indica	Leaves
		Carapa guailanensi aublet	Seed
		Cynara solumus Linn	Leaves, Flower.

		Foeniculum vulgare Mill	Plant
		Petroselinum sativa Hoffm	Plant
		Pimpinella anisum Linn	Plant
5	Monoterpens	Murraya koenigii Linn	Rhizome
6	Sesquiterpenes	Atractylodis lanceae rhizome	Root
		Lindera strychnifolia	Leaves
7	Diterpens	Andrographis paniculata Nees	Whole plants
		Glycyrrhiza glabra Linn	Root
		Hedyotis corymbosa Linn	Whole plant, Trunkwood
		Protium hepatophyllum	
8	Carotenoid	Gardenia florida	Fruits
9	Glycosides	Aloe barbadensis Mill	Leaves
		Dianthus superbus linn.	Plant
		Polygonum cuspidatum	Root
		Panax ginseng	Rhizome
		Polygonum multiflorum Thunb	Plant
10	Flavonoids	Acacia catechu willd	Hard wood
		Aegiceras corniculatum	Stem
		Artemisia capillaries thunb	Root
		Calotropis gigantea R. Br.	Leaves
		Canscora decussate Roxb.	Plant and Juice
		Cassia occidentals linn.	Leaves
		Clausena dentate willd.	Plant
		Garcinia kola Hekel	inflorescences
		Helichrysum arenarium Linn.	Plant
		Mentha longifolia Linn.	Leaves
		Phyllanthus emblica linn.	Leaves
		Scrophularia grossheimi	Plant
		Tagetes patula linn.	Seeds
		Uncaria gambir(Hunter)Roxb	Heartwood
12	Alkaloids	Aristolochia clematis	Plant
		Fumaria parviflora Lam	Plant
		Fumaria officinalis linn	Plant
		Herniaria glabra linn.	Whole plant
		Peumus boldus Molina	Plant
		Physallis peruviana	
13	Xanthines	Thea sinesis	Leaves
		Coffea Arabica	Seed ^[29]

Hepatoprotective activity of crude plant extracts

The aetiology of liver diseases is diverse and a variety of plants has been reported to show hepatoprotective activity and so may be useful in the treatment of these diseases. A list of plants reported to have significant hepatoprotective

activity is shown in **Table 1** in alphabetical order of their family, together with their scientific names, origin, plant part used, kind of extract used, type of assay and inducer of liver damage.

S. No.	BOTANICAL NAME & FAMILY	PART USED	EXTRACT	MODEL	P VALUE	REFERENCE YEAR
1	Anisotes trisulcus (Forssk)	-	Ethanol	In vivo; CCL4 & PCM	< 0.01	Fleurentin et al. 1986
2	Crepis rueppelli (sch.) Bip.	-	Ethanol	In vivo; CCL4	< 0.001	Fleurentin et al. 1986
3	Hypoestes triflora (Forssk.) Roem. and Schult	Leaves	Aqueous	In vivo; CCL4	< 0.01	Van puyvelde et al 1989
4	Andrographis paniculate (Burm.f.)	Leaves	Alcohol	In vivo; CCL4	<0.05	Rana and Avadhoot 1991

	Nees					
5	Eclipta alba Hassk	-	Aqueous	In vivo; CCL4	<0.01	Singh et al. 1993
6	Wedelia chinensis (Osbeck) Merr.	-	-	In vivo; acetaminophen and GAIN	<0.01	Lin et al 1994
7	Hygrophila auriculata (K. Schum.) Heine	Seeds	Methanol	In vivo; & Thioacetamide	<0.01	Singh and Handa 1995
8	Apiaceae Apium graveolens L.	Seeds	Methanol	In vivo; & Thioacetamide	<0.001	Singh and Handa 1995
9	Artemisia absinthium L.	Aerial Parts	Aqueous - methanol	In vivo; CCL4 and PCM	<0.01	Gilani and Janbaz 1995
10	Artemisia maritima L.	Aerial Parts	Aqueous - methanol	In vivo; CCL4 and PCM	<0.05	Gilani and Janbaz 1995
11	Elephantopus Scaber L.	Whole plant	Aqueous	In vivo; acetaminophen And GAIN	<0.01	Lin et al. 1995
12	Elephantopus mollis kunth.	Whole plant	Aqueous	In vivo; acetaminophen And GAIN	<0.001	Lin et al. 1995
13	Pseudelephantopus spicatus (Juss.Ex Aublet) Gleason	Whole plant	Aqueous	In vivo; acetaminophen And GAIN	<0.05	Lin et al. 1995
14	Rhamnaceae Ventilago leiocarpa Benth	Bark	Methanol, ethanol, butanol and aqueous	In vivo; CCL4	<0.01	Lin et al. 1995
15	Daucus carota L.	Roots	Aqueous	In vivo; CCL4	<0.01	Bishayee et al. 1995
16	Bidens chilensis DC	-	-	In vivo; CCL4 and PCM	<0.01	Chih et al. 1996
17	Bidens pilosa L.	-	-	In vivo; CCL4 and PCM	<0.01	Chih et al. 1996
18	Fumaria parviflora Lam.	shoots	Aqueous-methanol	In vivo; PCM	<0.001	Gilani et al. 1996
19	Fumaria cee Fumaria Indica (Hauskn.) Pugsley	Whole plant	Methanol, Pet.Ether, Aqueous	In vivo; PCM, Rifampicin CCL4	<0.01	Rao and Mishra 1997
20	Swertia japonica (Roem.and Schult.) Makino	Whole plant	Butanol	In vivo; GAIN	<0.05	Haset et al. 1997
21	Nyctaginaceae Boerhaavia diffusa L.	Roots	Aqueous	In vivo; Thioacetamide	<0.01	Rawat et al. 1997
22	Cassia Fistula L.	Leaves	n-heptane	In vivo; CCL4	<0.001	Bhakta et al. 1999
23	Cassia occidentalis L.	leaves	Aqueous-ethanol	In vivo; PCM, Ethanol	<0.05	Jadri et al. 1999
24	Mitracarpus scaber Zucc	-	-	In vivo and invitro; CCL4	<0.01	Germano et al. 1999
25	Balanophoraceae Thonningia sanguinea vahl.	Roots, leaves	Aqueous	In vivo and invitro; GAIN and CCL4	<0.01	Gyamfi et al 1999
26	Piccorrhiza Kurroa (Roule.) Sans	Rhizome, Roots	Ethanol	In vivo; GAIN	<0.01	Anandan and Devaki 1999
27	Ficus hispida L	Leaves	Methanol	In vivo; PCM	<0.001	Mandal et al. 2000

28	Apocynaceae Apocynum	Leaf	aqueous	In vivo; CCL4 and GAIN	<0.05	Xiong et al. 2000
29	Glycine max (L.) Merr	Seed	Water	In vivo; acetaminophen	<0.01	Wu et al. 2001
30	Phaseolus aureus Roxb.	Seed	Water	In vivo; acetaminophen	<0.01	Wu et al. 2001
31	Compositae Ambrosia maritima L.	Whole plant	Aqueous methanol	In vivo; acetaminophen	<0.01	Ahmed and Kharter 2001
32	Phaseolus calcaratus Roxb.	Seed	Water	In vivo; acetaminophen	<0.01	Wu et al. 2001
33	Phaseolus radiatus L.	Seed	Water	In vivo; acetaminophen	<0.001	Wu et al. 2001
34	Araliaceae Acanthopanax senticosus (Rupr. and maxim.) Harms	-	-	In vivo; CCL4 & acetaminophen	<0.01	Lin and Huang 2002
35	Asteraceae Achyrocline satureioides	Aerial Parts	Aqueous	In vivo; Bromobenzene	<0.05	Kadarian et al. 2002
36	Oleaceae Phillyrea latifolia L.	Leaves	Aqueous	In vivo; CCL4	<0.01	Janakat and Al-Merie 2002
37	Croton oblongifolius Roxb	Aerial parts	Pet.ether, acetone, methanol.	In vivo; CCL4	<0.01	Ahmed et al. 2002
38	Feonculum vulgare Miller	Seeds	Essential oil	In vivo; CCL4	<0.001	Ozbek et al. 2003
39	Asteracantha longifolia L.	Whole plant	Aqueous	In vivo; CCL4 and PCM	<0.05	Hewawasam et al. 2003
40	Rhinacanthus nasuta(Linn)kurz	Root	Methanol	In vivo; CCL4	<0.01	Suja et al. 2003
41	Cinchorium intybus L	Seeds	Alcohol	In vivo; CCL4	<0.01	Ahmed et al. 2003
42	Crassulaceae Kalanchoe Pinnata Pers	Leaves	Juice of leaves; ethanol of marc	In vivo and invitro; CCL4	<0.01	Yadav and Dixit 2003
43	Combretaceae combretum kurz	Leaves	Methanol	In vivo and intro, GAIN	<0.01	Banskota et al, 2003
44	Solanum nigrum L.	Fruits	Ethanol	In vivo; CCL4	<0.001	Raju et al. 2003
45	Feoniculum vulgare Miller	Seeds	Essential oil	In vivo; CCL4	<0.01	Ozbek et al. 2003
46	Solanum pseudocapsicum Hassl	Leaves	Methanol	In vivo and in vitro; CCL4	<0.05	Vijayan et al. 2003
47	Phaseolus aureus Roxb.	Seed	Water	In vivo; acetaminophen	<0.01	Wu et al. 2001
48	Compositae Ambrosia maritima L.	Whole plant	Aqueous methanol	In vivo; acetaminophen	<0.01	Ahmed and Kharter 2001
49	Phaseolus calcaratus Roxb.	Seed	Water	In vivo; acetaminophen	<0.001	Wu et al. 2001
50	Phaseolus radiatus L.	Seed	Water	In vivo; acetaminophen	<0.05	Wu et al. 2001
51	Araliaceae Acanthopanax senticosus (Rupr. and maxim.) Harms	-	-	In vivo; CCL4 & acetaminophen	<0.01	Lin and Huang 2002
52	Asteraceae Achyrocline satureioides	Aerial Parts	Aqueous	In vivo; Bromobenzene	<0.01	Kadarian et al. 2002
53	Oleaceae Phillyrea latifolia L.	Leaves	Aqueous	In vivo; CCL4	<0.01	Janakat and Al-Merie 2002

54	<i>Croton oblongifolius</i> Roxb	Aerial parts	Pet.ether, acetone, methanol.	In vivo; CCL4	<0.01	Ahmed et al. 2002
55	<i>Feonculam vulgare</i> Miller	Seeds	Essential oil	In vivo; CCL4	<0.001	Ozbek et al. 2003
56	<i>Asteracantha longifolia</i> L.	Whole plant	Aqueous	In vivo; CCL4 and PCM	<0.01	Hewawasam et al. 2003
57	<i>Rhinacanthus nasuta</i> (Linn)kurz	Root	Methanol	In vivo; CCL4	<0.05	Suja et al. 2003
58	<i>Cinchorium intybus</i> L	Seeds	Alcohol	In vivo; CCL4	<0.01	Ahmed et al. 2003
59	<i>Crassulaceae Kalanchoe Pinnata</i> Pers	Leaves	Juice of leaves; ethanol of marc	In vivo and invitro; CCL4	<0.01	Yadav and Dixit 2003
60	<i>Combretaceae combretum</i> kurz	Leaves	Methanol	In vivo and intro, GAIN	<0.001	Banskota et al, 2003
61	<i>Solanum nigrum</i> L.	Fruits	Ethanol	In vivo; CCL4	<0.05	Raju et al. 2003
62	<i>Feoniculum vulgare</i> Miller	Seeds	Essential oil	In vivo; CCL4	<0.01	Ozbek et al. 2003
63	<i>Solanum pseudocapsicum</i> Hassl	Leaves	Methanol	In vivo and in vitro; CCL4	<0.01	Vijayan et al. 2003
64	<i>Nymphaeaceae Nymphaea stellata</i> willd	Roots	Alcohol	In vivo; CCL4	<0.01	Bhandarkar and Khan 2004
65	<i>Ophioglossaceae Helminthiostachys zeylanica</i> (L.) Hook	Rhizome	Methanol	In vivo; CCL4	<0.001	Suja et al. 2004
66	<i>Solanum trilobrtum</i> L.	Whole plant	Methanol	In vivo; CCL4	<0.01	Shahjahan et al. 2004
67	<i>Erycibe expansa</i> Wall and G. Don	Stem	Methanol	In vitro; GAIN	<0.05	Matsuda et al. 2004
68	<i>Epaltes divaricata</i> (L) cav.	-	Alcohol	In vivo; CCL4	<0.01	Hewawasam et al. 2004
69	<i>Burseraceae Commiphora opobalsam</i> (L)	Aerial Parts	Ethanol	In vivo; CCL4	<0.001	AL-Howiriny et al. 2004
70	<i>Caesalpiniaceae Bauhinia racemosa</i> Lam	Bark	Methanol	In vivo; CCL4 and PCM	<0.05	Gupta et al 2004
71	<i>Flaveria trinervia</i> (Spreng) c. Mohr	Leaf	Methanol	In vivo; CCL4	<0.01	Umadevi et al. 2004
72	<i>Aizoaceae trianthema portulacastrum</i> L.	Leaves	Ethanol	In vivo; PCM and Thioacetamide	<0.01	Kumar et al. 2004

Where CCL4; Carbon tetrachloride; PCM; Paracetamol, LPS; Lippopolysaccharide, TB; tuberculosis; DMN; dimethylnitrosamine; Pet.ether; Petroleum ether.

Chemically defined molecules with hepatoprotective activity

Several chemically defined molecules have been isolated from crude plant extracts with proven hepatoprotective activity.

A list of these compounds is shown in **Table 2** with information on the chemical name and class of the compounds.

Sr no.	Chemical Substances	Plant	Plant part	Class	References Year
1.	Picroliv	<i>Picrorrhiza kurroa</i> Royle ex Benth	a	Iridiod glycoside	Visen et al. (1991)
2.	Agathisflavone	<i>Canarium manii</i> king	a	Biflavonoid	Anand et al. (1992)
3.	Scropolioside-A	<i>Scrophularia Koelzii</i> pennell	a	Iridiod Glycoside	Garg et al. 1994

4.	Neoandrographolide	Andrographis Paniculata (Burm.f.) Wall. Ex Nees	a	Diterpene	Chander et al. (1995)
5.	Wighteone	Cudrania cochinchinesis(Lour) Kudo et masam	Roots	Flavonoid	Lin et al. (1996)
6.	Naringenin	Cudrania cochinchinesis(Lour) Kudo et masam	Roots	Flavonoid	Lin et al. (1996)
7.	Quercetin -3- O-β-D-glucuronopyranoside	Saururus chinesis(Lour) Baill	a	Flavonol glycoside	Sung et al. (1997)
8.	Quercetin -3- O-β-D-glucuronopyranosyl methyl ester	Saururus chinesis(Lour) Baill	a	Flavonol glycoside	Sung et al. (1997)
9.	Tetrahydroswertianolin	Swertin Japonica Makino	a	Xanthione	Hase et al. (1997)
10.	Gentiopicroside	Swertin Japonica makino	a	Iridiod	Hase et al. (1997)
11.	Andrographolide	Andrographic Paniculata(Burm.f)	a	Iridiod	Hase et al (1997)
12.	Lithospermate B	Salvia miltorhiza Bunge	roots	Caffeine acid	Hase et al (1997)
13.	¥-Amyrone	Sedum sarmentosum Bunge	a	Triterpene	Amin et al. (1998)
14.	3-epi-¥-amyrin	Sedum sarmentosum Bunge	a	Triterpene	Amin et al. (1998)
15.	¥-amyrin	Sedum sarmentosum Bunge	a	Triterpene	Amin et al. (1998)
16.	Monomethyl fumarate	Fumaria indica pugsley	Whole plant	Fumaric acid	Roa and Mishra (1998)
17.	18β-hydroperoxy-olean,2-en-3-one	Sedum sarmentosum Bunge	a	Triterpene	Amin et al. (1998)
18.	Thymoquinone	Nigella sativa L.	a	Quinone	Daba and abdel-Rahman 1998
19.	3-(S)-3-β-D-glucronopyranosyloxybutanolide	Goodyera schlechtendaliana Reichb G. matsumurana Schltr. G. discolor kergawl	Whole plants	Aliphatic glycoside	Du et al. (2000)
20.	3-(S)-3-β-D-glucronopyranosyloxy-4-hydroxybutanoic acid	Goodyera schlechtendaliana Reichb G. matsumurana Schltr. G. discolor kergawl	Whole plants	Aliphatic glycoside	Du et al. (2000)
21.	18 β-glycyrrhetic acid	Glycyrrhiza uralensis Fisch	Rhizomes	Glycyrrhetic acid	Shim et al. 2000
22.	1-O-galloyl-6-O(4-hydroxy-3,5-dimethoxy)benzoyl-β-d-glucose	Combretum quadrangulare kurz	seeds	Gallic acid	Adnyana et al. (2001)
23.	Indigtone	Indigofera tinctoria L.	Aerial parts	Aliphatic Nitro-compound	Singh et al. (2001)
24.	(S)-bakuchiol	Psoralea corylifolia Babchi	a	Monoterpene phenol	Hyun et al. (2001)
25.	Rutin	Artemisia Scroparia Waldst.and kit	a	Flavonoid	Janbaz et al. (2002)
26.	Troxeutin	Artemisia Scroparia Waldst.and kit	a	Flavonoid	Zhang et al. (2002)
27.	Mangiferin	Salacia reticulate abst	Roots	Phenolic compound	Yoshiwaka et al 2002

28.	(-)-4'-O-Methylepigallocatechin	Salacia reticulata abt	Roots	Phenolic compound	Yoshiwaka et al 2002
29.	Torilin	Cridium monnieri(L)Cusson	a	Sesquiterpene	Oh et al. (2002)
30.	Torilolone	Cridium monnieri(L)Cusson	a	Sesquiterpene	Oh et al. (2002)
31.	Myristin	Myristin fragrans Houtt	a	Cetyl ester	Morita et al. (2003)
32.	Anastatin A	Anastatica hierochuntica L.	Whole Plant	Flavonoid	Yoshikawa et al 2003
33.	Anastatin B	Anastatica hierochuntica L.	Whole Plant	Flavonoid	Yoshikawa et al 2003
34.	Kaempferol	Rhodiola sachalinesis A. Bor	Roots	Phenolic compound	Song et al. (2003)
35.	Salidroside	Bo r	Roots	Phenolic compound	Song et al. (2003)
36.	Acanthoic Acid	Acanthopanax koreanum Nakai	Roots bark	Diterpene	Park et al. (2004)
37.	Allicin	Allium sativum	Cloves	Allyl thiosulfinate	Vimal and Devki (2004)
38.	Luteolin	Eqisetum arvense L.	Aerial parts	Phenolic Compound	Oh et al. 2004
39.	(7'R)7'Hydroxylariciresinol	-	-	Tetrahydrofuran	Nguyen et al. 2004
40.	Taxiresinol	-	-	Tetrahydrofuran	Nguyen et al 2004
41.	orobol	Erycibe Expansa Wall.	Stem	Isoflavones	Matsuda et al. 2004
42.	Genistein	Erycibe Expansa Wall.	Stem	Isoflavones	Matsuda et al. 2004
43.	5,7,4-trihydroxy-3'-methoxyisoflavone	Erycibe Expansa Wall.	Stem	Isoflavones	Matsuda et al. 2004
44.	Erycibenin A	Erycibe Expansa Wall.	Stem	Pterocarpane	Matsuda et al. 2004
45.	5-O-methyl-(E)-resveratrol.3-0-β-D-apiofuranosyl-1->6)-β-D-glucopyranoside	Acer mono Maxim	Leaves	Stilbene glycoside	Yang et al (2005)
46.	5-O-methyl-(E)-resveratrol.3-0-β-D-glucopyranoside	Acer mono Maxim	Leaves	Stilbene glycoside	Yang et al (2005)
47.	Rubiadin	Rubia cordifolia L.	Roots	Anthraquinone	Rao et al. (2006)
48.	Corilagin	Terminalia catappa L.	Leaves	Tannin	Kinoshita et al. (2007)
49.	3,4,5-trihydroxybenzoic acid	Terminalia belerica Roxb.	Fruit	Gallic acid	Jadon et al. (2007)
50.	Kinsenoside	Anoectochilus formosanus Hay	Whole Plant	Furanone	Wu et al. (2007)
51.	3,4 -di-O-caffeoylquinic acid	Lactuca indica L.	Aerial Parts	Quinic Acid	Kim et al. 2007
52.	3,4 -di-O-caffeoyl -muco -quinic acid	Lactuca indica L.	Aerial Parts	Quinic Acid	Kim et al. 2007

53.	5-O-(E)p-coumaroylquinic acid	<i>Lactuca indica</i> L.	Aerial Parts	Quinic Acid	Kim et al. 2007
54.	Kinsenoside	<i>Anoectochilus formosanus</i> Hay	Whole Plant	Furanone	Wu et al. (2007)

List of commercially available Polyherbal liquid formulations investigated for Hepatoprotective Activity ^[29]

Sl. No	Name of the formulation	Plants used in the formulation	Indication	Dose
1	Liv 52 (Himalaya Drug Co, Bangalore)	<i>Achillea millefolium</i> , <i>Capparis spinosa</i> , <i>Cassia occidentalis</i> , <i>Cichorium intybus</i> , <i>Solanum nigrum</i> , <i>Tamarix gallica</i> , <i>Terminalia arjuna</i>	Ayurvedic medicine, protects liver against various hepatotoxins, promote appetite and growth	2-3 teaspoon 2 to 3 times daily
2	Livergen (Standard Pharmaceuticals, Serapore, West Bengal)	<i>Andrographis paniculata</i> , <i>Apium graveolens</i> , <i>Asteracantha longifolia</i> , <i>Cassia angustifolia</i> , <i>Trachyspermum ammi</i> , <i>Trigonella foenumgraecum</i>	Ayurvedic medicine, gastrointestinal and hepatic regulator	2-4 teaspoon twice Daily ^[25]

CONCLUSION:

The present study reveals plant extracts with hepatoprotective properties against toxic chemicals that cause liver injury, seeming to validate their use in folk medicine. These plants may offer new alternatives to the limited therapeutic options that exist at present in the treatment of liver diseases or their symptoms, and they should be considered for future studies.

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