

Drug-induced Hepatotoxicity and Hepatoprotective Medicinal Plants: A Review

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ABSTRACT

The Liver, a paramount organ is the Chief site for metabolism of nutrients and energy production in the human body. It is also necessary for metabolism and elimination of exogenous drugs and harmful substances via kidney. Hepatotoxicity caused by a variety of environmental pollutants, pathogenic micro-organism, viruses, drugs and chemical agents may account for various hepatic diseases such as jaundice, necrosis, hepatitis, fibrosis and cirrhosis etc. Ayurveda is a traditional medicinal system of India and is being practiced continuously since ancient times and at present for the treatment of various human diseases. Medicinal plants as a significant source of therapeutic compounds used for the development of effective drugs against a variety of human diseases include liver ailments. Hence, therapeutic plants are becoming popular in the pharmaceutical industry to develop a safe and effective medicine for the treatment of the emerging new human diseases. Therefore, the present review is aimed to compiling data on hepatoprotective medicinal plants which have been investigated against drug-induced hepatotoxicity.

Key words: Medicinal Plants, Carbon tetrachloride, Paracetamol, Alcohol, Hepatotoxicity, Hepatoprotection.

INTRODUCTION

Liver is the principal and metabolic organ involved in the metabolism of vital molecules. Besides the metabolic role, it plays a central role in detoxification and excretion of endogenous and exogenous compounds thereby protecting body from the harmful substances.¹ In this process, the liver injury occurs due to prolonged exposure with xenobiotics and their metabolites.² Liver is also involved with almost all the biochemical pathways of growth, fight against diseases, nutrient supply and energy metabolism. Liver stands out from rest of the organs due to its regenerative property in response to liver damage.³ Apart from the drugs (paracetamol, antibiotic, anti-tuberculosis and chemotherapeutic drugs), there are various other chemicals account for liver injury including alcohol consumption, heavy metals used in industries like lead, arsenic etc (Figure 1).^{4,5} Chemical induced hepatotoxicity has been extensively

studied in animal model and the changes in biochemical pathways in association with pathological progress in the liver have been well documented.^{6,7} Hepatic damage results in necrosis, jaundice, fibrosis, cirrhosis, hepatitis, liver carcinoma etc.⁸ Liver diseases are one of the leading causes of illness and death globally. According to WHO estimates about 1.4 million deaths worldwide are due to the liver diseases. Although, modern medicine may treat to hepatic diseases, but they also cause numerous side effects in the human body.⁹

In the Ayurvedic system of Indian medicine, people used medicinal plants for centuries to manage the primary health care need. Plant-based therapy still rely for the prevention and treatment of health related problems for thousands years including liver diseases.¹⁰ Conventional medicine is now pursuing the use of natural products such as herbs to provide the support that

Submission Date: 28-09-2019;

Revision Date: 23-12-2019;

Accepted Date: 24-01-2020

DOI: 10.5530/ijper.54.2.28

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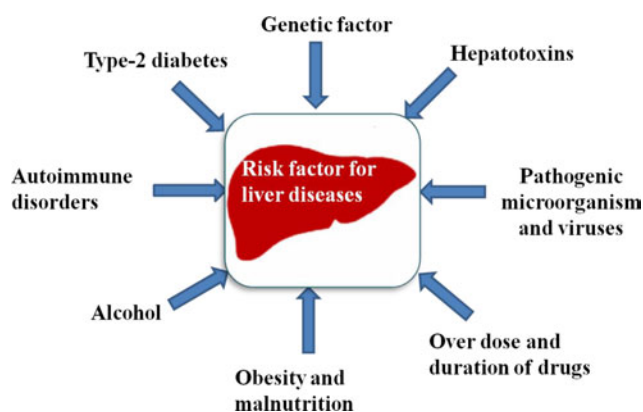


Figure 1: Possible risk factor for development of liver diseases.

the liver needs on a daily basis.¹¹ Therefore, it is essential to explore the suitable herbal drugs that could replace the chemical ones.

Indian medicinal plants also provide a rich source for antioxidants that are known to prevent different diseased states. The antioxidant protection is observed at different levels. The medicinal plants also contain other beneficial compounds like phytochemical ingredients for functional foods. Hence, the global knowledge about Ayurveda and Indian herbals will hopefully be enhanced by information on the evidence-base of these plants. This will yield rich dividends in the coming years. Plants with medicinal properties are considered as more reliable and efficient options and also reported to be used traditionally to treat liver ailments. Many traditional plants are being used traditionally to cure various ailments in rural and tribal villages in India.¹² Majorly plant-based preparations have been used to treat liver disorders. Herbal compounds perform natural process of healing in the human body. There has been a shift in universal trend from synthetic to herbal medicines for the prevention of diseases and ailments. The World Health Organization [WHO] estimates that 4 billion people use herbal medicines for some aspect of primary healthcare.^{13,14} A large experimental work is now being done on ethnopharmacology of herbal medicines. Search of new herbal drugs with better potential of healing and high safety profile is the current area of research interest. Numerous medicinal plants and their bioactive compounds have been studied and found to have hepatoprotective property against various types of drug-induced hepatotoxicity (Table 1, 2) and this review mainly summarized the drug-induced hepatotoxicity and hepatoprotective medicinal plants which have been evaluated *in vivo* and *in vitro* model.

Model Hepatotoxicants

Acetaminophen (Paracetamol)

Acetaminophen also known as paracetamol or *N*-acetyl-*p*-aminophenol [APAP]. A safe and effective analgesic and antipyretic drug under recommended.^{15,16} Recommended dosage of APAP ranges 325-650 mg every 4-6 hr in adults with a maximum of 4g a day and 10-15 mg/kg every 4-6 hr with maximum of 50-75 mg/kg in children.^{17,18} Under therapeutic dosage, APAP is generally metabolized in the liver (5-9%) by Cytochrome P-450 enzyme system into the reactive metabolite called *N*-acetyl-*p*-benzo-quinoneimine (NAPQI) but majority 80-90% was metabolised via phase II metabolic pathway (glucuronidation and sulfation) in which APAP-reduced glutathione (GSH)] conjugate is catalyzed by UDP-glucuronosyl transferases (UGT) and sulfotransferase (SULT), into non-toxic compounds: glucuronidated and sulfated metabolites which are eliminated through urine (Figure 2). Although, APAP's consumption for longer days may potentially harmful to the liver.¹⁹ Because NAPQI metabolite is produced in excess amount which caused lipid peroxidation and it may bind to cellular proteins forming protein adducts resulting in depletion of metabolic energy (adenosine triphosphate, ATP) and cell necrosis.²⁰ The APAP hepatotoxicity is the classical example of direct liver injury which can cause acute and severe liver injury in both human and experimental animals.²¹

APAP hepatotoxicity is currently the single most important cause for acute liver failure worldwide and is associated with significant number of deaths.²² Metabolic toxicity of APAP has been well studied in humans and experimental animals.²³ More than 50% of all cases of acute liver failure in the United States from 1997 to 2002 have been shown to result from exposure to drugs and 40% of these have been attributed to acetaminophen ingestion.²⁴ It has been studied that hepatotoxicity occurs following ingestion of a single

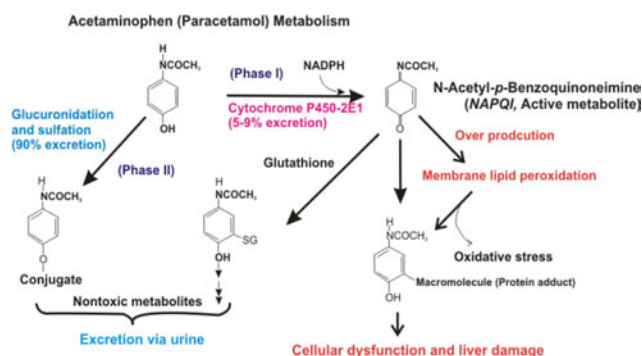
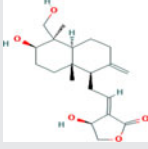

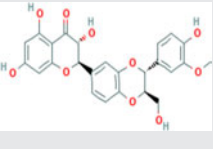

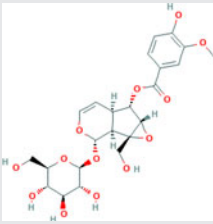



Figure 2: Metabolism of Acetaminophen with the hepatotoxicity.

Table 1: List of few hepatoprotective medicinal plants against toxic chemical induced liver damage in experimental animals.

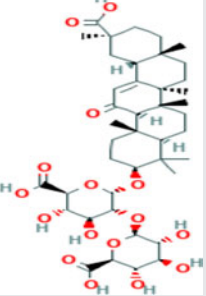

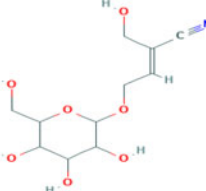
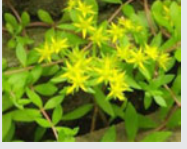
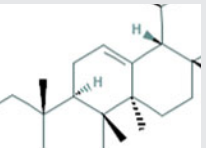

Medicinal Plants	Part used	Hepatotoxicants	Biochemical Parameters studied for hepatoprotection
<i>Sida acuta</i> ¹⁵⁷	Root	APAP	Hexobarbitone, <i>in vitro</i> LPO and histopathology
<i>Sphaeranthus indicus</i> ¹⁵⁸	Flower head	APAP	AST, ALT, ACP, SALP, bilirubin, protein, LPO, SOD, CAT and GPX, Histology
<i>Clausena dentata</i> ¹⁵⁹	Stem bark	APAP	AST, ALT, ALP, total bilirubin, GGTP and protein
<i>Cassia fistula</i> ¹⁶⁰	Root	CCl ₄	SGOT, SGPT, ALP and Total protein and histopathology
<i>Kyllinganemoralis</i> ¹⁶¹	Rhizomes	CCl ₄	ALT, AST, SALP, total bilirubin and histopathology
<i>Zanthoxylumarmatum</i> DC ¹⁶²	Bark	CCl ₄	ALT, AST, SALP, bilirubin total protein albumin, GSH and LPO, Histopathology
<i>Trichosanthes cucumerina</i> ¹⁶³	Whole plant	CCl ₄	ALT, AST, SALP, bilirubin total protein albumin, GSH and LPO, Histopathology
<i>Cichorium glandulosum</i> ¹⁶⁴	Root	CCl ₄	AST, ALT, SALP, DPPH inhibition and LPO
<i>Carissa carandas</i> Linn. ¹⁶⁵	Root	CCl ₄ and APAP	ALT, AST, SALP, bilirubin total protein Uric acid, GSH, LPO, SOD, CAT and histopathology
<i>Cassia occidentalis</i> ¹⁶⁶	Leaf	APAP and Alcohol	ALT, AST, SALP, bilirubin, albumin, serum cholesterol, serum total lipids and histopathology
<i>Vitis minifera</i> ¹⁶⁷	Leaf	Alcohol	AST, ALT, SALP, LDH, GGT, bilirubin, urea, creatinine, histopathological studies
<i>Azadirachta indica</i> ¹⁶⁸	Leaf	Alcohol	AST, ALT, ALP, protein, albumin, GSH, SOD and CAT
<i>Emblica officinalis</i> ¹⁶⁹	Fruit	Alcohol	AST, ALT, LPO, SOD, CAT, GST, SALP and histology

Table 2: Bioactive plant constituents with hepatoprotective potential.

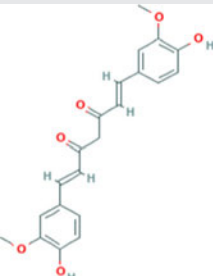

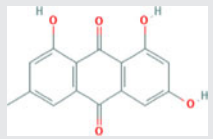

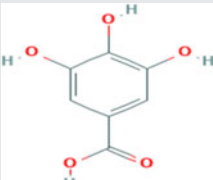

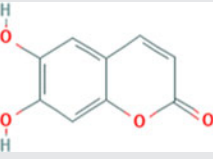

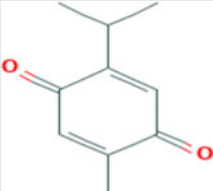

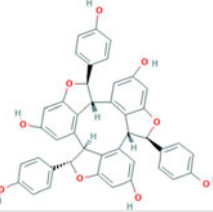

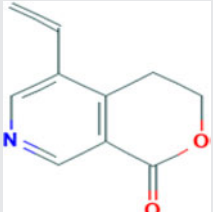

Bioactive constituents	Biochemical structure	Plants
Andrographolide ¹⁷⁰		<i>Andrographis paniculata</i> 
Silybin ¹⁷¹		<i>Silybum marianum</i> 
Picroside II ¹⁷²		<i>Picrorhiza kurroa</i> 

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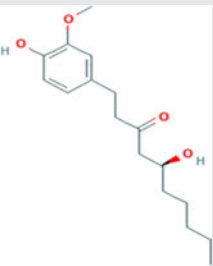

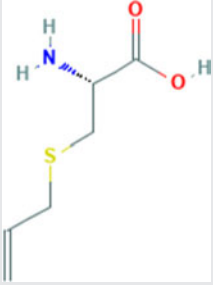

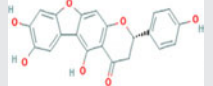

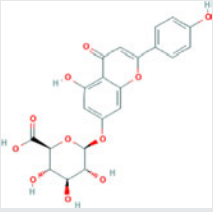

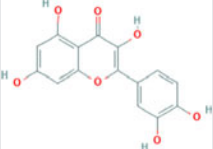

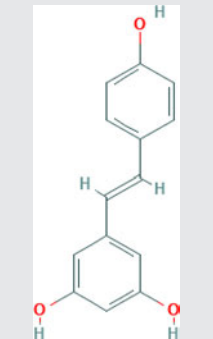

Table 2: Cont'd.

Bioactive constituents	Biochemical structure	Plants
Glycyrrhizin ¹⁷³		<i>Glycyrrhiza glabra</i> 
Sarmentosin ¹⁷⁴		<i>Sedum</i> 
Ursolic acid ¹⁷⁵		<i>Clerodendrum</i> 

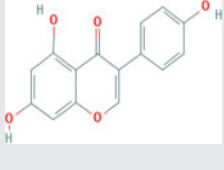

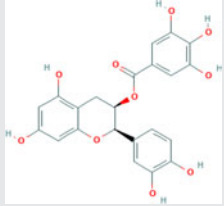

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Table 2: Cont'd.		
Bioactive constituents	Biochemical structure	Plants
Curcumin ¹⁷⁶		<i>Curcuma longa</i> 
Emodin ¹⁷⁷		<i>Ventilago madraspatana</i> 
Gallic acid ¹⁷⁸		<i>Acacia confusa</i> 
Esculetin ¹⁷⁹		<i>Cinchorium intybus</i> 
Thymoquinone (TQ) ¹⁸⁰		<i>Nigella sativa</i> 
α -viniferin ¹⁸¹		<i>Vitis coignetiae</i> 
Gentianine ¹⁸²		

Continued...

Table 2: Cont'd.		
Bioactive constituents	Biochemical structure	Plants
Gingerol ¹⁸³		<i>Gingerber officinalis</i> 
S-Allyl-L-Cysteine ¹⁸⁴		<i>Alium sativum</i> 
Anastatins A ¹⁸⁵		<i>Anastatica hierochuntica</i> 
Apigenin in-7-glucuronide ¹⁸⁶		<i>Cirsium japonicum</i> 
Quercetin ¹⁸⁷		<i>Capparis spinosa</i> 
Resveratrol ¹⁸⁸		<i>Vitis vinifera</i> 

Continued...

Table 2: Cont'd.		
Bioactive constituents	Biochemical structure	Plants
Genistein ¹⁸⁹		<i>Glycine max</i> 
Epicatechins gallate ¹⁹⁰		<i>Camelia sinensis</i> 

dose of APAP only when a dose >125 mg/kg [7.5 g in a 60 kg individual] is absorbed and the likelihood of toxicity increased substantially as the absorbed dose exceeds 250 mg/kg and LD₅₀ of APAP 3.7 g/kg in male rats.^{24,25}

Several investigators suggested that APAP toxicity was associated with increased level of hepatocellular enzymes *viz.*, AST, ALT, LDH and SALP into circulation.²⁶ It is well documented that the antioxidant enzymes (SOD, CAT, GPx, GR, G-6-PDH and GST) were decreased by APAP induced liver toxicity.^{27,28} Marked increased in serum globulin, bilirubin and total protein with significant decreased the albumin level after paracetamol administration were seen.²⁹ Some studies have implicated a role for mitochondrial damage in the toxic process initiated by APAP in hepatocytes.³⁰ Inhibition of cellular respiration due to impairment of mitochondrial function, DNA damage, decreased activity of Na⁺-K⁺ - ATPase were found in hepatocytes after paracetamol exposure.^{31,32} *In vivo* studies showed that APAP exposure induces DNA single-strand breaks in mice and rats, aneuploidy in rat embryo cells.³³

Carbon tetrachloride (CCl₄)

Carbon tetrachloride (CCl₄) is a chlorinated organic solvent and its overexposure may toxic to many organs. It is a colorless and highly volatile liquid with a sweetish [ethereal] odor. Upon heating, it breakdowns to highly toxic fumes of phosgene. It is primarily utilized for production of chlorofluorocarbons that are used as refrigerants. It has also been served as an antihelminthic, insecticide dispersant, dry-cleaning agent, grain-fumigant and fire extinguisher.³⁴ Carbon tetrachloride can be absorbed via oral (mouth) and inhalation (lungs) routes and dermal (skin) route both in humans and animals.

It is a well-known hepatic toxin used to induce liver damage in laboratory animals like mice and rat to evaluate hepatoprotective effect of medicinal plants. It is metabolized in the liver by an nicotinamide adenine dinucleotide phosphate [NADPH]-dependent CYP450-2E1 enzyme, forming free radicals, trichloromethyl (•CCl₃) radical and with further oxidation to trichloromethyl peroxy (•O-O-CCl₃).^{35,36} These free radicals attack on fatty acids in cell membranes and induce lipid peroxidation which cause further another reactive aldehydes (e.g., formaldehyde and acetaldehyde etc.). The aldehydes react with reduced glutathione [e.g., GSH], and reduces the GSH level in liver cells. GSH is an intracellular antioxidant which protects cells against free radical damage.³⁷ Over production of free radicals by CCl₄ metabolism may also induce DNA damage which contribute to the genotoxicity of CCl₄. Lipid peroxidation also causes cell membrane disruption thereby hepatic enzymes such as Aspartate transaminase [AST] and alanine transaminase [ALT] and bilirubin content released into the blood stream.³⁸ This in turn activates protein degradation inflammation and cell necrosis which can also contribute to cytotoxicity (Figure 3).³⁹

CCl₄ metabolites cause alteration in Ca²⁺ sequestration, lipid homeostasis and cytokines release and loss of energy metabolism.⁴⁰ The metabolism of CCl₄ has been investigated in the rat, rabbit, dog and human.⁴¹ Many investigators have utilized CCl₄ to induce liver cirrhosis in experimental animals.⁴²⁻⁴⁴ Administration of CCl₄ caused liver damage that mimics natural causes. It medicates changes in liver functions that ultimately lead to destruction of hepatocellular membrane. Peroxidation of lipids, covalent binding to macromolecules, disruption of metabolic mechanism in

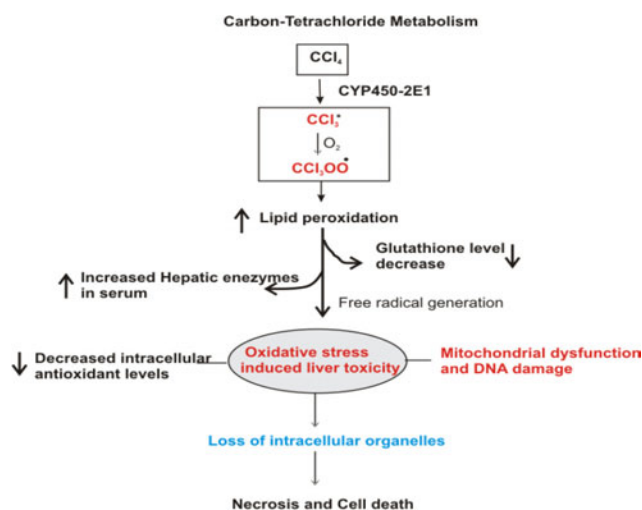


Figure 3: Metabolism of CCl₄ with the hepatotoxicity.

mitochondria, decrease levels of phospholipids, increase triglyceride levels, inhibition of calcium pump of microsomes and decreased activities of antioxidant enzymes Superoxide dismutase (SOD), Catalase, Glutathione peroxidase (GPx), Glutathione Reductase (GR) which may cause liver necrosis.⁴⁵⁻⁴⁷

The acute oral toxicity of CCl_4 is relatively low with a median lethal dosage LD_{50} -13,000 mg/kg for mice.⁴⁸ It is reported that liver is not only the target organ of CCl_4 but also causes toxicity in other tissues such as kidneys, heart, lung, testis, brain and blood.⁴⁹ An *in vitro* study indicated that the trichloromethyl radical also interacts with all four DNA nitrogenous bases and bound preferentially to guanine and adenine and produces a genotoxic response in liver.⁵⁰

CCl_4 intoxication causes significant reduction in the level of microsomal enzymes, aniline hydroxylase and p-aminopyrine-N-demethylase, glucose-6-phosphatase activity and protein synthesis.⁵¹ It also activates Kupffer cells that cause death of the hepatocytes.^{52,53} Histopathological studies reported that CCl_4 treated animals showed hydropic changes in centrilobular hepatocytes with single cell necrosis surrounded by neutrophils.^{54,55} Congestion of central vein and sinusoids were seen with acute and chronic inflammatory cells infiltrating sinusoids mainly in the central zone. The midzonal and periportal hepatocytes showed mild to moderate degree of fatty change. The most prominent of which are destruction of the smooth and rough endoplasmic reticulum and reduction of Golgi complexes and mitochondria, inhibition of protein synthesis⁵⁶ and its associated enzyme activities impaired secretion of triglycerides with resultant fat accumulation in liver.⁵⁷ The 3 mL/kg, *i.p.* dose of CCl_4 for 24 hr showed fatty changes and infiltration of lymphocytes around the central veins and loss of cellular boundaries.^{58,59}

Alcohol (Ethanol)

Alcohol addiction is a major public health burden and estimated to cause about 20–30% of liver cirrhosis. It also increased motor vehicle accidents worldwide. It is estimated that 15 to 30% of chronic heavy drinkers eventually develop severe liver diseases. Alcoholic fatty liver may progress to alcoholic hepatitis and finally to cirrhosis and liver failure.⁶⁰ In India, chronic alcohol abuse is the leading cause of liver cirrhosis. Alcohol, the most commonly consumed xenobiotic, generates ROS species whether it is used over a long period of time. ALD ranges from reversible fatty liver (steatosis), to more severe alcoholic hepatitis and fibrosis and cirrhosis and end stage liver disease. Also obesity with prolonged alcohol intake increases the risk of

irreversible liver damage.⁶¹ People who consume or addicted alcoholic have the major risk to develop alcoholic liver disease (ALD) such as hepatitis and cirrhosis.^{62,63} ALD pathway includes elevation of NADH/NAD⁺ ratio, causing lipid accumulation and up-regulation of cytochrome P4502E1 (CYP2E1), resulting in oxidative stress and cellular inflammatory.⁶⁴

Habitual consumption of Alcohol is one of the most common causes of liver disease in the world.⁶⁵ There is increasing evidence that the prenatal environment can influence the risk of developing some chronic diseases in the offspring's later in life.^{66,67} Alcohol-related disorders are one of the challenging current health problems with far reaching medical, social and economic consequences. Long-term alcohol use potentially results in serious illnesses, including fatty liver, diabetes, hypertriglyceridaemia, cirrhosis and cardiovascular disease and dementia.⁶⁸

In the hepatocyte, there are three systems that metabolize ethanol located in three different cellular compartments: alcohol dehydrogenase located in the cytosol, the microsomal ethanol oxidizing system situated in the ER and catalase located in the peroxisomes.⁶⁹ Alcohol is mainly metabolized in the liver. Normally about 10 gm of ethanol is metabolized in one hour. Phase I metabolism is involved in the induction of alcohol metabolism enzymes, especially in the gastrointestinal tract where it is converted to the acetaldehyde. Acetaldehyde is known to produce toxic effects on the liver cells and retard the rate of phase II metabolism. Accumulation of acetaldehyde leads to the formation of protein adducts, resulting in metabolic disturbances (Figure 4).⁷⁰

Recent studies have shown that cytochrome P-450 2E1 induced by ethanol has a high oxidase activity and plays

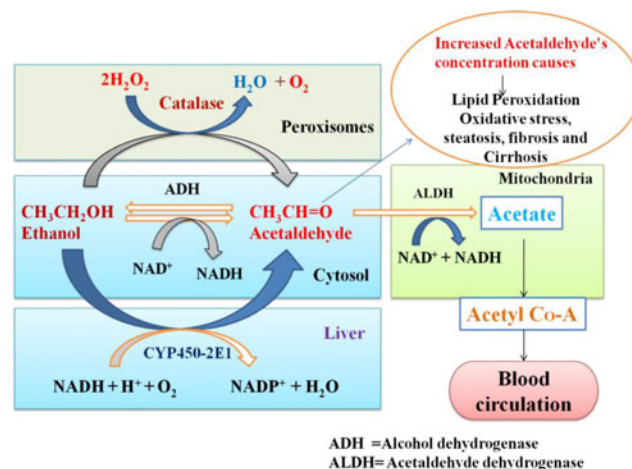


Figure 4: Oxidative pathway of Alcohol Metabolism with the hepatotoxicity.

a crucial role in the microsomal generation of ROS that initiates membranous lipid peroxidation (LPO).⁷¹⁻⁷³ This causes an imbalance between pro-oxidants and antioxidants. Enhanced oxidative stress in the liver due to chronic alcohol ingestion may be impaired antioxidant defense systems of the liver tissue.^{74,75} Free radicals or ROS such as hydroxy ethyl radical, superoxide and hydroxy radicals, which formed in ethanol mediated process, are responsible for alcohol induced oxidative stress and fatty liver.⁷⁶

Several studies have reported that daily consumption of alcohol intake is associated with changes in plasma lipid concentrations, increased cholesterol and triglycerides in serum.⁷⁷ It is reported that chronic alcohol intake leads to many cellular and tissue abnormalities such as alteration in liver enzymes (ALT, AST and SALP) which indicated the increased membrane permeability and necrosis in hepatocytes.⁷⁸

Kupffer cells have a direct regulatory role in hepatocyte injury caused by ethanol by expressing tumor necrosis factor-alpha (TNF- α). Ethanol ingestion may interrupt the pro-regenerative signal transduction that is initiated by injury-related cytokines such as TNF- α and interleukin-6 (IL-6) suggesting that TNF- α may have a critical role in pathogenesis of liver injury associated with alcoholic hepatitis. The biological actions of TNF- α include fever, neutrophilia and hypotension, clinical features that are also seen in patients with acute alcoholic hepatitis.⁷⁹ Chronic alcohol abuse provokes successive hepatic changes, consisting of alcoholic steatosis, fibrosis, hepatitis and cirrhosis. Ethanol exposure for 4 weeks showed obvious damaging effect on liver tissue in the form of dilatation with congestion of the portal vein, with thickening of its wall and marked fibrosis in the portal area.⁸⁰

Non-Alcoholic fatty liver disease

It is modern liver disease usually seen in obese or overweight people and children. Non-alcoholic fatty liver disease (NAFLD) refers wide a range of clinical conditions due to over accumulation of fat in the liver.⁸¹ In India, obesity is rising health problem particularly in urban areas which is more public health concerns including malnutrition. Overweight or obesity is reported about 30-65% of urban population of India. High-Fat Diet (HFD), unhealthy foods, physical inactivity and genetic factors. HFD is thought to be one of the main key factors for development of obesity. HFD is also main causative agent for nonalcoholic fatty liver diseases (NAFLD) leading to significant burden of morbidity and mortality in world population.⁸²

Some diabetic patients may have insulin resistance due to obesity. In India, the rate of hepatic diseases including fatty liver in obese people has been reported to be much higher about 8-30%.⁸³ It is a chronic liver disease that affects a high proportion of the world's population and represents a major cause of liver-related morbidity and mortality. Fatty liver is characterized by accumulation of fats (Triglycerides) in the liver resulting in oxidative stress, steatosis, fibrosis and cirrhosis.^{84,85}

Antituberculosis drugs

Tuberculosis (TB) is a serious infectious disease which can be fatal if not treated in time. TB is completely curable with regular and on time treatment with anti-Tuberculosis drugs like Isoniazid (INH), Rifampicin (RMP) and pyrazinamide (PZA).⁸⁶ However, these anti-TB drugs are associated with drug-Induced Liver Injuries (DILI) and thus have their own drawbacks and ill effects on health system. N-acetyl transferase metabolize Isoniazid (INZ) to acetyl-isoniazid which in turn form acetyl hydrazine and reactive acetyl species. Rifampicin (RMP) increases the rate of reactive acetyl species formation. These reactive acetyl species cause oxidative stress leading to hepatotoxicity.⁸⁷ Liver enzyme elevation is an indicator of Anti-TB DILI which ranges from 5-30%. Extreme effects of Anti-TB treatment are liver injury, neurological disfunctioning and gastrointestinal ailment etc.⁸⁸

Medicinal Plants with Significant Hepatoprotective Activity

Andrographis paniculata (Family: Acanthaceae)

Andrographolide, the active constituent isolated from the *Andrographis paniculata*'s leaf and aerial part, which showed a significant hepatoprotective activity against APAP induced toxicity on *ex-vivo* preparation of isolated rat hepatocytes.⁸⁹ Today, it is involved in about 26 different Ayurvedic formulations used to treat liver disorders such as jaundice and hepatitis. Andrographolide was reported to improve gall bladder function, increases bile flow and has been found to be as effective as silymarin in protecting the liver. It also has showed anti-diabetic effect in streptozocin-induced hyperglycaemic rats and diabetic nephropathy. It maintains the liver function enzymes (AST, ALT and LDH) by reducing the lipid peroxidation as well as regulate the level of glutathione and antioxidant enzymes (Superoxide dismutase, Catalase, Glutathione peroxidase and Glutathione reductase) in carbon tetrachloride induced toxicity.⁹⁰

Boerhaavia diffusa (Family: Nyctaginaceae)

It is known as Punarnava. The roots of *Boerhaavia diffusa* are known traditionally for liver cure and used for the treatment of various liver problems due to their safety and efficacy. The root contain various types of flavonoids, isoflavonoids, glycoproteins and steroids which make it potent free radical scavenger.⁹¹ The root extract has been reported to have potent antiviral efficacy of against hepatitis B and C viruses.⁹² Its extract also increases normal bile flow and antioxidant defence system with improving cellular morphology in hepatotoxicity in rats suggesting its strong hepatoprotective activity.⁹³

Eclipta alba (Family: Asteraceae)

In ayurvedic medicine, its leaf extract is considered a powerful liver tonic and rejuvenative. It also has traditional external uses, like athlete foot, eczema and dermatitis. The alcoholic extract of *Eclipta alba* exhibited antihepatotoxic effect in carbon tetrachloride and galactosamine induced acute liver damage. It showed significantly stimulatory effect on hepatocyte cell regeneration, regulates the levels of hepatic serum enzymes (AST and ALT) hepatic microsomal drug metabolizing enzymes and restores the normal architecture of liver cells against toxicity.⁹⁴ It has been reported that phytochemicals wedelolactone and demethylwedelolactone may possible components behind the hepatoprotective effect against liver disorders.⁹⁵

Picrorhiza kurroa (Family: Scrophulariaceae)

Current research studies reported that *Picrorhiza kurroa* has many pharmacological property such as hepatoprotective, anticholestatic, antioxidant and immune-modulating activity. It is reported that picroside-I and kutkoside, obtained from the ethanolic extract of the roots and rhizome of *Picrorhiza kurroa*, are good scavengers of free radicals [superoxide anion O^{2•-}] and inhibited Lipid peroxidation in liver tissue.⁹⁶ Ethanolic extract of this plant showed restoration of bilirubin and activity of AST, ALT, ALP and LDH against acetaminophen (APAP) induced liver toxicity. Its extract treated with APAP in experimental animals also showed protection on hepatic cells thereby confirming its hepatoprotective activity.⁹⁷ Its principal ingredient was used (50%) involved in a herbal formulation, known as Arogya-wardhani. A research study also reported its hepatoprotective efficacy against viral hepatitis and alcohol induced liver damage.^{98,99}

Tephrosia purpurea (Family: Fabaceae)

Tephrosia purpurea is locally known as Sarapunkha and used for diabetes mellitus in Ayurvedic medicine. It

is considered to be beneficial for liver, spleen and kidney disorders.¹⁰⁰ Experimental studies have demonstrated its antiulcer and hepatoprotective effects.¹⁰¹ Rats treated with *Tephrosia purpurea* at 500 mg/kg in thioacetamide induced toxicity resulted in a significant reduction in serum liver enzymes: AST, ALT and alkaline phosphatase and total bilirubin and significant improvement was seen in the levels of liver glutathione and MDA content (a Lipid peroxidation product) and antioxidant enzymes (SOD and Catalase). Histological examination confirmed the protection of liver by plant extract against toxicity.¹⁰² It was also found effective in cirrhosis and viral hepatitis in clinical trials.¹⁰³

Phyllanthus amarus (Family: Phyllanthaceae)

Phyllanthus amarus (PA) has been reported to possess hepatoprotective, antidiabetic, antihypertensive, analgesic, anti-inflammatory, antidiarrheal and antimicrobial properties.^{104,105} Its antiviral activity against hepatitis B virus has been well established.¹⁰⁶ *In vivo* studies demonstrated that the treatment of PA extract at 75 mg/kg p.o. for 7 days with ethanol exposure for 21 days restored the normal liver function by restoring the levels of AST, ALT and TNF- α towards toward control group. *In vitro* study demonstrated the hepatoprotective effects of aqueous extract of *Phyllanthus amarus* in ethanol-induced rat hepatic injury. MTT assay (2,5 diphenyl tetrazolium bromide) showed the good cell viability and protection of hepatocytes cell lines in alcohol treated rat primary cultured hepatocytes. Histopathological study also revealed the beneficial effect of PA with its potential antioxidant property.¹⁰⁷

Mimosa pudica (Family: Mimosaceae)

Mimosa pudica known as Chue Mue in Hindi, is a stout straggling prostrate shrubby plant. Leaves and stem of the plant have been reported to contain an alkaloid mimosine, leaves also contain mucilage and root contains tannins. The oral administration of the *Mimosa pudica* for 10 days in rat animals protected the levels of hepatic parameters such as total bilirubin, alkaline phosphatase (ALP), acid phosphatase (ACP), lipid peroxide (LPO) in tissue and serum, gamma glutamyl transferase (γ -GT), aspartate transaminase (AST) and alanine transaminase (ALT) against sub-acute toxicity induced by CCl₄ exposure.¹⁰⁸ *Mimosa pudica* is used for its anti-hyperglycemic, antidiarrhoeal, fever, piles, jaundice, leprosy, ulcers and small pox.¹⁰⁹ Histopathological studies revealed that the *M. pudica* extract exhibited protection of the liver tissue with the improvement in cellular morphology as compared to CCl₄ treated group.¹¹⁰

Hygrophila spinosa (Family: Acahaceae)

Its common name is Nirmulli or Gokulakanta. The plant has low molluscicidal activity against *Bulinus truncates* and antitumor activity.¹¹¹ Traditionally, the aerial parts and the roots are *Hygrophila spinosa* used as demulcent, aphrodisiac, diuretic, urinary and liver tonic, the root contains an alkaloid named hygrosterol rich in antioxidants. The pharmacological properties such as hepatoprotective, antibacterial, antitumor and antidiabetic of *Hygrophila spinosa* were investigated by various researchers. Carbon tetrachloride induced liver damage was protected by 15 days treatment of the aqueous extract of the plant root indicating its hepatoprotective activity. The increased level of serum marker enzymes Aspartate transaminase, Alanine transaminase and Gama Glutamyl in CCl₄ treated rats were found to be restored nearly to normal value after therapy of the plant root extract. The histological observations also proved the hepatoprotective action of the root of *Hygrophila spinosa*.¹¹²

Adhatoda vasica (Family: Acanthaceae)

A. vasica, an evergreen gregarious and perennial shrub. It is antioxidant and chemopreventive agent. It enhances the activities of glutathione-S-transferase in the liver of mice. Extract of leaves is extensively used in cough, asthma, bronchitis, tuberculosis, inflammation, allergy and jaundice.^{113,114} The hepatoprotective activity of Ethyl acetate extract of *Adhatoda vasica* (100 mg/kg and 200mg/kg) was also evaluated on CCl₄ (1ml/kg/bodyweight) induced liver damage in rat model. The statistically analysis of biochemical findings showed the significant lowered the increased the levels of serum Alanine aminotransferase, (ALT), Aspartate aminotransferase (AST), Alkaline Phosphatase (ALP) and also bilirubin when compared with CCl₄ treated animals. Histopathological observations also coincided with the biochemical findings results, however 200mg/kg dose was found to be more protective and suggested *Adhatoda vasica* possess pronounced hepatoprotective effect against CCl₄ induced liver damage.¹¹⁵ The treatment of aqueous extract of *Adhatoda vasica* leaf (100mg/kg and 200 mg/kg, p.o. for six days) with hepatotoxicity induced by paracetamol (2gm/kg) reduced the levels of serum ALT and AST same as positive control silymarin.¹¹⁶ Thus, the leaves of *Adhatoda vasica* have significant hepatoprotective activity.

Capparis sepiaria (Family: Capparaceae)

Capparis sepiaria is distributed in dry parts of India, in Deccan peninsula and Andamans. In Ayurveda, it is used in the treatment of tumors, prevents inflammation

and also acts as blood purifier. Local people used the root of this plant to cure from snake bite and skin diseases.¹¹⁷ The hepatoprotective effect of the alcohol extract of *Capparis sepiaria* (CS) Linn. (Capparaceae) stem was assessed in carbon tetrachloride (CCl₄)-induced toxicity in albino rats. The pretreatment with alcohol extract of *C. sepiaria* (100 mg/kg for 7 days) and the positive control silymarin (25 mg/kg) orally for 7 days against CCl₄ induced toxicity resulted in a significant protection of elevated levels of serum marker enzymes (AST and ALT) and bilirubin which is almost normal when compared with the effect of the positive control, silymarin. Histopathological observations was further confirmed the hepatoprotective effect of CS and proved the effect of CS in preventing hepatocellular necrosis and cellular degeneration caused by CCl₄ exposure.¹¹⁸ Thus CS extract may bring the almost normal histological architecture of the liver.

Aerva lanata (Family: Amaranthaceae)

Aerva lanata known as knot grass. It is an herbaceous perennial weed growing wild in the hot regions of India. It is claimed to be useful as diuretic, anthelmintic, antidiabetic, expectorant and hepatoprotective in traditional system of medicine.¹¹⁸ Antimicrobial, cytotoxicity and anti-inflammatory activity has been reported.¹¹⁹ It contains various flavanoid such as kaempferol, quercetin, isohamnetin, galactoside, flavanone glucoside pernisol, persinoside A and B. The hydro alcoholic extract of this plant has shown Hepatoprotective activity against carbon tetra chloride induced liver damage. The hepatoprotective activity of petroleum ether and methanolic extracts of the roots, stem bark and leaves root were studied in carbon tetrachloride induced hepatotoxicity in albino rats. The extracts at a dose of 200 and 300 mg/kg minimised the histopathological changes and reduced the raised hepatic serum marker enzymes (AST, ALT and serum alkaline phosphatase, SALP) and also decreased the levels of bilirubin and tissue lipid peroxidation. The plant extract also increased the activities of antioxidant enzymes (catalase, superoxide dismutase, glutathione-S-transferase, glutathione peroxidase, glutathione reductase) in CCl₄ treated animals.¹²⁰

Solanum nigrum (Family: Solanaceae)

Solanum nigrum is known as black night shade, makoy, deadly nightshade. It is folklore medicine used for the treatment of various ailments related to gastric and liver problem. The identified major phytochemical compounds are glycoalkaloids (solamargine, solasonine and solanine), glycoproteins and polysaccharides gallic acid, catechin, protocatechuic acid, caffeic acid,

epicatechin, rutin and naringenin).¹²¹ It is mainly used in polyherbal formulations targeting liver diseases problems. Previous studies have been reported that *S. nigrum* extract provides hepatoprotection by mitigating CCl₄ induced liver damage.^{122,123} The fruit extract of *S. nigrum* (100, 200, 300 mg/kg dose body weight/day) was administered for 30 days along with CCl₄ confirmed the antioxidant activity and hepatoprotective role of *S. nigrum* by restoring the liver function enzymes and reducing the oxidative stress caused by CCl₄ induced toxicity.¹²⁴

Liver histopathology result demonstrated that *Solanum nigrum* extract mitigated the changes of liver lesions including hepatic cells cloudy swelling, hepatic necrosis and fibrous connective tissue proliferation induced by CCl₄ intoxication in rats.¹²⁵ The hepatoprotective effect of plant extract might be associated to its modulation on cytochrome P-450 enzymes system with improving the antioxidant and free radical scavenger effects.

Wedelia chinensis (Family: Asteraceae)

Wedelia chinensis is a perennial herb. Traditionally, it is used as anti-inflammatory, antihelminthic, including respiratory infections and pain.¹²⁶ The ethanolic extract of *Wedelia chinensis* at doses of 250 mg/kg p.o and 500 mg/kg p.o. was evaluated for its hepatoprotection against carbon tetrachloride (CCl₄) induced hepatotoxicity in rat model. The CCl₄ administration significantly increased levels of biochemical parameters like aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate (ALP), total bilirubin and total protein along with histopathological changes which were protected by therapy of *Wedelia chinensis*.¹²⁷⁻¹²⁹ Hence, the results showed that *Wedelia chinensis* exhibits significant dose dependent hepatoprotective activity. The reducing cellular necrosis and fatty infiltration was seen in the histological findings indicating the recovery of hepatic cells.

Morus alba (Family: Moraceae)

It is known as white mulberry. All parts of this plant are useful to cure of cardiovascular disease, liver and spleen disorders. Recent research study has shown that this herb has free radical scavenging activity, hypolipidemic effect, antioxidant, antibacterial and anti-inflammatory properties. White mulberry leaf contains triterpenes, sterols, bioflavonoids, coumarins, alkaloids, amino acids and organic acids.¹³⁰ *Morus alba* showed the presence of various phytochemical compounds such as alkaloids, flavonoides, glycosides, tannins and steroids.¹³⁰ The hydroalcoholic extract at dose of 800mg/kg of *Morus alba* L. leaves was studied

for hepatoprotection against carbon tetrachloride induced hepatotoxicity. The hydroalcoholic extract of plant showed the significant liver protective effect by decreasing the hepatospecific serum marker enzymes: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and hexobarbitone induced sleep time. The treatment of *Morus alba* L. leaves resulted the less pronounced destruction of the liver, there was no fibrosis and inflammation were observed as compared with CCl₄ treatment group in experimental animals. Leaf extract of *Morus alba* found to be more hepatoprotective effect against carbon tetrachloride (CCl₄) induced hepatotoxicity. Its leaves extract is effectively prevented the CCl₄ produced biochemical and histological changes in the liver by reversing the biochemical and oxidative parameters toward normal group.¹³¹

Zingiber officinale (Family: Zingiberaceae)

It is known as ginger. The rhizome of *Z. officinale* is commonly used in cooking. It is being used in homes for curing cough, cold, fever and liver problems.¹³² Gingerols and shogaols are the main active chemical constituents present in ginger exhibited strong antioxidant activity, anti-inflammatory, antipyretic, antihepatotoxic and cardioprotective properties. It has been reported to have antioxidant and hepatoprotective agent against CCl₄ induced liver fibrosis.¹³³ The elevated levels of RBC counts and hemoglobin concentration with alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and gamma glutamyltransferase activities and the serum triglycerides and cholesterol concentration were observed in the CCl₄ treated animals as compared to control group. Methanol extract of ginger (250 and 500 mg/kg) significantly restored the carbon tetrachloride-induced above parameters. The hepatoprotective effect of ginger was also proved by the histopathological examination of liver tissue in CCl₄ treated rats. Ginger extract regulated the altered biochemical profile due to CCl₄ intoxication towards normalization.¹³⁴ Ginger maintained the integrity of plasma membrane and enhanced the liver regenerative capacity which might be due to its potent antioxidant activity against hepatotoxicity.

Rosa damascena (Family: Rosaceae)

Rosa damascena is an ornamental plant. It is generally used for the treatment of respiratory problem and headache and remedy for relaxing effects, anxiety and depression.¹³⁵ It is one of the ingredient used in the preparation of beauty cosmetics. It has many therapeutic effects, including laxative, antispasmodic and

cardiotonic.¹³⁶ The major compounds such as kaempferol, quercetin, glycosides, arabinosides, rhamnosides were found in flower parts of *Rosa damascena* exhibited free radical scavenging activity. Hepatoprotective and antioxidant property of *Rosa damascena* Mill. have been reported against acetaminophen-Induced hepatotoxicity in Albino Rats.

The flower extract of *Rosa damascena* Mill. Showed promising *in vitro* free radical scavenging potential. It neutralizes superoxide radical, hydroxyl radical and DPPH radical. Oral administration of *Rosa damascena* extract (50 mg/kg body weight) significantly reduced the levels of primary liver serum enzymes alkaline phosphatase (ALP), glutaminepyruvate transaminase (GPI) and glutamine oxaloacetate transaminase (GOT) activity along with tissue lipid peroxide level against CCl_4 induced acute liver damage in rats. These above results were further confirmed by histological examination of liver section indicated that that *R. damascena* could protect from the CCl_4 caused liver damage due to its free radical scavenging activity.¹³⁷

Rheum emodi (Family: Polygonaceae)

Rheum emodi is known as revan chini. It locally called Indian Himalayan Rhubarb is traditionally used as a medicine. The roots of this plant has been reported to possess hepatoprotective, antidiabetic, antioxidant, antifungal, antimicrobial and nephroprotective activities.^{138,139} The major phytochemicals present in root part are emodin, tannin, gallic acid and lignan. The root part is used to treat kidney stones, gout and jaundice by the local people. Its hepatoprotective effects (aqueous and methanolic extracts) were studied against liver damage induced by paracetamol in albino rats.¹⁴⁰

CCl_4 induced altered levels of hepatic serum markers i.e. ALT, AST, ALP, albumin and bilirubin were regulated by administration of *Rheum emodi* root extract. *Rheum emodi* extract also reversed the histological changes caused by CCl_4 induced toxicity which might be due to its antihepatotoxic effect.

Nymphaea alba (Family: Nymphaeaceae)

Nymphaea alba L. (*N. alba*), is known as the European water lily, White Lotus, or Nenuphar. Being as an aquatic flowering plant, *N. alba* was widely used traditionally as an antiseptic, an astringent, antioxidant and in insomnia.¹⁴¹ The *N. alba* flower is reported to have antioxidant, anti-inflammatory as well as hepatoprotective effect.^{142,143} There are many phyto-constituents such as ellagic and Gallic acid, quercetin, kaempferol, isokaempferide, apigenin and their glycosides have been identified in the flowers *Nymphaea alba* L. The

hepatoprotective effect of *N. alba* against CCl_4 -induced hepatotoxicity was studied and found good hepatoprotective agent.¹⁴⁴ It has also been reported to have ameliorative effect against isoniazid induced hepatotoxicity in rats.¹⁴⁵ The significant reduction in biochemical parameters (SGOT, SGPT, ALP, Bilirubin) and cholesterol level as compared to control group was seen after administration of ethanolic extract (200 and 400 mg/kg) of *Nymphaea alba*. Maximum inhibition was obtained at dose 400 mg/kg of Ethanolic Extract of *Nymphaea alba* in both model. The extract also prevented necrosis of the liver and promoted, to some extent liver regeneration.

Cichorium intybus (Family: Asteraceae)

It is known as Chicory. *Cichorium intybus* is a powerful hepatic stimulant that increases bile-secretion, promotes digestion. Experimental evidence has proved its action on liver glycogen.^{146,147} *Cichorium intybus* reported to have significant antihepatotoxic effect on CCl_4 induced biochemical and histological changes.¹⁴⁸ The aqueous-methanol seed extract of *C. intybus* has shown antioxidant and hepatoprotective effect on markers of liver function in the serum (AST and ALT), lipid peroxidation, antioxidant enzyme (SOD) levels and hepatic histopathology of the liver in rats with CCl_4 -induced hepatotoxicity against hepatotoxicants.¹⁴⁹

It is folklore medicine used as an antimalarial medicine. The sesquiterpene lactones lactucin and lactucopicrin have been identified in root of Chicory as an antimetastatic drug.¹⁵⁰ The flowers of the chicory plant are used as a tonic and appetite stimulant and for the treatment of gallstones, gastroenteritis, sinus problems, cuts and bruises. Jigrine is one of the main ingredients of Chicory seeds, a commercial product of India used for the treatment of various diseases of the liver.¹⁵¹

Silybum marianum (Family: Asteraceae)

A well-known Hepatoprotective plant and it is a flavonolignan derived from the seeds of *Silybum marianum* called as milk thistle. It has good hepatoprotection in various hepatotoxic models of experimental liver disease in laboratory animals.¹⁵² It has been clinically tested hepatoprotective drug and used for the alcoholic fatty liver, jaundice, viral hepatitis and drug-induced liver diseases. Hepatoprotective activity of silymarin has been reported in acute and chronic liver disease by various researchers across the world against carbon tetrachloride, alcohol, paracetamol, galactosamine and thioacetamide toxicity.¹⁵³ Scientific and clinical studies on Silibinin confirmed that it has *in vivo*, *in vitro* and *in silico* potential hepatoprotective, anti-inflammatory

and immune-modulating effects. It has anti-inhibitory effect on hepatitis C virus (HCV), NS5B polymerase and antioxidative stress, antifibrosis and anticancer activities.¹⁵⁴ Animal studies suggested that silymarin flavolignans increases hepatic glutathione and antioxidant enzymes levels generation in hepatocytes. It helps in drug detoxification and also acts positive modulator for liver regeneration against liver diseases. Silybin blocks the regulatory molecules such as CDK2, CDK4, cyclin E and cyclin D1 proteins in the cell division of cancer cells.¹⁵⁵

Silymarin is standard drug used to compare the hepatoprotective activity of the other plant extract. Its mechanism of action includes inhibition of hepatotoxin binding to receptor sites on the hepatocyte membrane, reduction of glutathione oxidation to enhance its level in the liver and intestine, antioxidant activity and stimulation of ribosomal RNA polymerase and subsequent protein synthesis leading to enhanced hepatocyte regeneration. Silymarin may make a breakthrough as a new approach to protect other organs in addition to liver. The most remarkable use of silymarin is in the treatment of mushroom poisoning, hepatitis, alcoholic liver disease and cirrhosis, psoriasis and hypercholesterolemia.¹⁵⁶

CONCLUSION

This study compiled the various pharmacological properties of medicinal plants which have been studied experimentally. However, there is urgent to identify and characterize the lead compound derived from the plants which can be potential candidates for hepatoprotection. The hepatoprotective action of medicinal plants may be related to its mitigation of oxidative stress and well as modulation of metabolic pathways involved in hepatotoxicity. Phytochemicals rich medicinal plants are source of good antioxidant activity which play an important role to combat against hepatic injury. These data may provide a rationale for further studies on pharmacological evaluation of hepatoprotective medicinal plants in systematic manner.

ACKNOWLEDGEMENT

The author expresses deep thanks to Indira Gandhi National Open University, Maidan Garhi, New Delhi -110068 (INDIA).

CONFLICT OF INTEREST

The author declares no conflict of interest.

ABBREVIATIONS

WHO: World Health Organisation; **APAP:** Acetaminophen; **NAPQI:** N-Acetyl-p-benzo-Quinone; **CCl₄:** Carbon Tetrachloride; **•CCl₃:** Trichloromethyl radical; **AST:** Aspartate transaminase; **ALT:** Alanin transaminase; **SALP:** Serum Alkaline transaminase; **SOD:** Superoxide dismutase; **GR:** Glutathione Reductase; **GPx:** Glutathione peroxidase; **CAT:** Catalase; **LD₅₀:** Lethal dose; **ALD:** Alcoholic liver disease; **CYP2E1:** Cytochrome P450-2E1; **ROS:** Reactive oxygen species; **LPO:** Lipid peroxidation; **TNF- α :** Tumor necrosis factor- α ; **IL-6:** Interleukin-6; **NAFLD:** Non alcoholic Fatty liver diseases; **HFD:** High Fat Diet; **TB:** Tuberculosis; **INH:** Isoniazid; **RMP:** Rifampicin; **PZA:** Pyrazinamide.

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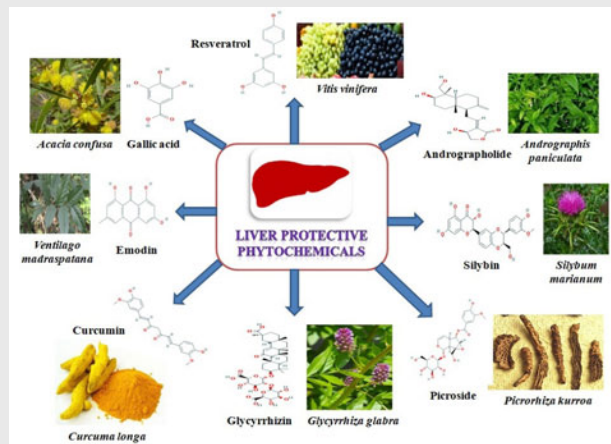
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SUMMARY

- The liver is the central organ for the metabolism and elimination of toxic agents from the human body.
- An imbalance between the antioxidant defence system and Oxidative stress (free radical species) leads to hepatic dysfunction.
- Hepatotoxicity is related to the toxic metabolites, over dose of drugs and pathogenic organisms.
- CCl₄, APAP and Alcohol are the experimental toxic agents metabolised by the liver CYP-450 enzymes system. They are widely used to hepatoprotective studies.
- Hepatotoxicity is characterized by the alteration of liver makers enzymes and histopathological changes in hepatocytes cells.
- Traditional medicinal plants are rich source of active phytochemicals that act as a therapeutic drug against hepatic disease/hepatotoxicity.
- Some hepatoprotective phytochemicals such as Andrographolide, Silybin, Picroside, Glycyrrhizin, Curcumin, Emodin, Gallic acid, Esculetin, Thymoquinone, Gingerol, S-Allyl-L-Cysteine, Apigenin, Quercetin, Resveratrol, Genistein, Epicatechins gallate etc. have been reported to offer promising hepatoprotection.
- By standardizing and evaluating the plant derived active phytochemicals can offer promising remedies in the healthcare system to treat human diseases in the future.
- Ensuring the safety, quality, standardisation and effectiveness of medicinal plants and herbal medicine are the key issue before the scientific communities and pharmaceutical companies.

PICTORIAL ABSTRACT



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Cite this article: Shakya AK. Drug-induced Hepatotoxicity and Hepatoprotective Medicinal Plants: A Review. Indian J of Pharmaceutical Education and Research. 2020;54(2):234-50.