EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 12
164-179
Year: 2017

HEPATOPROTECTIVE ACTIVITY AND MEDICINAL PLANTS- A REVIEW

M. P. Khinchi and Nishant Singh Katiyar*

Kota College of Pharmacy, Kota, Rajasthan- 325003, India.

***Corresponding Author: Nishant Singh Katiyar**
Kota College of Pharmacy, Kota, Rajasthan- 325003, India.

Article Received on 15/10/2017 **Article Revised on 06/11/2017** **Article Accepted on 26/11/2017**

ABSTRACT
Liver plays a pivotal role in metabolism, secretion and storage and is sometimes referred as the "great chemical factory" of the body, because the body depends on the liver to regulate, synthesize, store and secrete many important proteins, nutrients, chemicals and to purify and clear toxins or unnecessary substances from the body.[1] The risk of the liver intoxication has recently increased by the higher exposure to environmental toxins, pesticides and frequent use of chemotherapeutics. Liver damage is always associated with cellular necrosis, increase in tissue lipid peroxidation and depletion in the tissue glutathione (GSH) levels. In addition, serum levels of many biochemical markers like serum glutamate oxaloacetate transaminase (SGOT/AST) and serum glutamate pyruvate transaminase (SGPT/ALT) triglycerides, cholesterol, bilirubin and alkaline phosphatase are elevated.[2,3] Hepatoprotective effect was studied against chemicals and drugs induced hepatotoxicity in rats like alcohol, carbon tetrachloride, galactosamine, paracetamol, isoniazid and rifampicin, antibiotics, peroxidised oil, aflatoxin etc. AYURVEDA, an ancient Indian system of medicine, described various plants for the treatment of hepatotoxicity. Since times immemorial plants have been used therapeutically in a variety of conditions and with the advent of modern synthetic drugs and their convenience of standardized dosage forms, dramatic efficacy in acute conditions and most of all simplicity of usage, there was a decline in the use of plant medicines till the herbal revolution. In contrast to the narrow spectrum of activity of synthetic drugs with their possible risk of side effects and also chemophobia, herbal drugs as traditionally preferred however, herbal drugs are often mild in action and need to be taken for a long period to be effective especially in chronic conditions. Herbal medicines have been used in the treatment of liver diseases for a long time. A number of herbal preparations are available in the market. The present review is aimed at compiling data on different medicinal plants with hepatoprotective activity on various models of hepatotoxicity.

KEYWARDS: Hepatoprotective activity, Medicinal plants, Hepatotoxicity, Liver diseases, CCl_4, Thioacetamide, Paracetamol.

INTRODUCTION
Hepatotoxicity may be defined as the effect of any agent on liver results in a deviation from normal function, morphology and implies chemical/drug/microbial-driven liver-damage.[4] As some agents lead to necrosis, steatosis, cirrhosis, carcinoma, other cause is jaundice or with little or no overt injury to the hepatic parenchyma and some agents produce degenerative or vascular lesions. Hepatotoxicity related to many drugs or their transformation to chemically reactive metabolites that may be influenced by therapeutic, physiological or nutritional factors interfering with drug elimination or formation of a reactive metabolite or their detoxification. It is caused by drug accumulation or may be due to metabolic inhibition by other drugs or liver damage.

The aspects of chemical induced hepatotoxicity include the nature of the hepatotoxic agents, character of the injury, mechanism for the hepatotoxic effects and the circumstances of the exposure and the medical and social importance.

Domestic exposure to hepatotoxins includes accidental exposure to ccl_4, phosphorous, toxic/over doses of hepatotoxic medicinal agents such as acetaminophen or ferrous sulphate, ingestion of hepatotoxic mushrooms.

Liver plays an important role in regulation of physiological processes, involved in several vital functions such as storage, secretion and metabolism. It also detoxifies a variety of drugs and xenobiotics and secretes bile that has an important role in digestion.

The liver plays a central role in transforming, clearing the chemicals and insusceptible to the toxicity from these agents. Certain medicinal agents when taken in overdoses and sometimes even when administered within therapeutic ranges may injure this organ. Other chemical

agents such as those used in laboratories, industries, natural chemicals and herbal remedies can also induce hepatotoxicity and chemicals that cause liver injury are called hepatotoxins.

Liver diseases are among the most serious ailments classified as acute or chronic hepatitis (inflammatory liver diseases), hepatosis (non inflammatory diseases) and cirrhosis (fibrosis of liver).[5] Liver diseases are mainly caused by toxic chemical drugs e.g. paracetamol, anti-tubercular, anticancer agents or alcohol, some natural toxins such as peptides of *Amanita phalloides*, pyrrolidizines and the toxin of cycad nut. Most of the hepatotoxic chemicals damage liver cells by inducing lipid peroxidation and others by oxidative cell damage. It has been estimated that about 90% of acute hepatitis is due to viruses and major viral agents involved are hepatitis A, B, C, D, E and G. Among these, hepatitis B infection often results in chronic liver diseases and cirrhosis of liver.[6]

More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. Chemicals often cause subclinical injury to liver which manifests only as abnormal liver enzyme tests. Drug induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures.[7] AYURVEDA, an ancient Indian system of medicine, described various plants for the treatment of hepatotoxicity. Since times immemorial plants have been used therapeutically in a variety of conditions and with the advent of modern synthetic drugs and their convenience of standardized dosage forms, dramatic efficacy in acute conditions and most of all simplicity of usage, there was a decline in the use of plant medicines till the herbal revolution. In contrast to the narrow spectrum of activity of synthetic drugs with their possible risk of side effects and also chemophobia, herbal drugs as traditionally preferred however, herbal drugs are often mild in action and need to be taken for a long period to be effective especially in chronic conditions.

LIVER DISEASES AND MEDICINAL PLANTS

In India, more than 87 plants are used in 33 patented & proprietary multi-ingredient plant formulations & about 40 polyherbal commercial formulations reputed to have hepatoprotective action are being used. It has been reported that about 160 phytoconstituents from 101 medicinal plants have hepatoprotective activity.[8]

Many herbs have been used to alleviate various liver diseases, of which the most popular ones include Silymarin from *Silybum marianum, andrographolide* and neoandrographolide from *Andrographis paniculata*, curcumin from *Curcuma longa*, picroside and kutkoside from *Picrorrhiza kurroa*, phyllanthin and hypophyllanthin from *Phyllanthus niruri*, glycyrrhizin from *Glycyrrhiza glabra*, etc.[9]

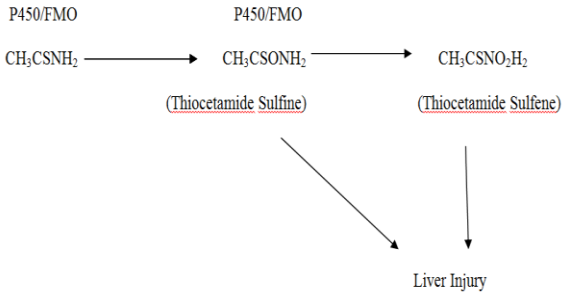
Mechanism of drug induced hepatotoxicity

1. Thioacetamide induced hepatotoxicity

Thioacetamide, originally used as a fungicide, is a potent hepatotoxicant, bioactivated by CYP450 and/or Flavin-Containing Monooxygenase (FMO) systems to sulfine (sulfoxide) and sulfene (sulfone) metabolites, which cause centrilobular necrosis. Thioacetamide sulfoxide, a relatively stable intermediate of thioacetamide is the penultimate reactive, is obligatory for the hepatotoxic effects.[10]

Since much of the TA transformation mechanism and toxicity study was conducted largely prior to the advent of the discovery of CYP450 isozymes and information on specific isozymes involved in the bioactivation of TA has remained completely blurred and uninvestigated.

A single large dose 100 mg/kg p.o is followed by degenerative changes in 6-8 h. By 24 h this dose in rats leads to centrizonal necrosis and in 24-30 h the effect will be maximal. The prenecrotic changes include loss of glycogen by 6 h and acidophilic degeneration of cells in the central zone by 8 h. By 9th h this is accompanied by the dilatation of sinusoids to form pathways between the central veins of contiguous lobules. Hepatocytes of central zone contain a few lipid droplets and repair begins at 37 h and the liver will return to normal by 7 days.



Mechanism-based thioacetamide induced liver injury

2. Ranitidine induced hepatotoxicity[11, 12]

Liver injury induced by ranitidine is due to its metabolite which may leads to hepatic oxidative damage and one of its metabolite is generating immunoallergic reaction. Ranitidine with dose of either 30 or 50 mg/kg it also produces an reaction as reflected by infiltration of hepatocytes. Severe inflammatory changes with collagenous septa beginning to form after pronounced centrilobular and bridging necrosis. In the parenchyma there was focal liver cell necrosis with some accumulation of histocytic elements and slight steatosis and cholestasis. Portal tract shows fibrosis, bile duct proliferation and infiltrate consisting of lymphocytes, plasma cells, polymorphs and eosinophils. Liver injury is manifested in terms of increase in levels of serum aminotransferases, modest hepatic infiltration by both lymphocytes and eosinophils and slight focal hepatocellular necrosis also causes liver cholestasis

associated with increased plasma bilirubin and alkaline phosphatase.

3. Paracetamol induced hepatotoxicity[13, 14, 15]

N-Acetyl-para-aminophenol [APAP], is metabolized in the liver primarily by glucuronidation and sulfation and with therapeutic doses (<4 g daily), only 4% is converted by the cytochrome P450 system to the reactive toxic intermediate N-acetyl-p-benzoquinoneimine (NAPQI). This toxic metabolite is rendered nontoxic by binding to glutathione. In case of APAP overdose due to CYP enzyme induction and glutathione depletion or the inhibition of glucuronidation this reactive metabolite cannot be sufficiently neutralized. Instead, NAPQI reacts with the cysteine group of hepatocellular proteins which lead to the loss of cell function and cell death.

NAPQI-protein adducts, released into the circulation from the injured liver in patients who overdosed APAP, can be detected even if there are no large increases in transaminase levels. The NAPQI-protein adducts serum concentration also correlates significantly and positively with serum Aspartate aminotransferase (AST) activity. These patients had higher alanine aminotransferase (ALT) levels, a higher prothrombin international normalized ratio (INR) and a higher death rate compared with the non-APAP group, suggesting an APAP injury.

4. D-galactosamine induced hepatotoxicity

Galactosamine administration induces an inflammatory response in liver that biochemically and histologically resembles viral hepatitis 13. A single administration causes hepatocellular necrosis and fatty liver.[16]

It causes appearance of specific lesions in liver cells, characterized by inhibition of nuclear RNA and protein synthesis.[17]

5. Carbon tetrachloride (CCl4) induced hepatotoxicity

Liver injury due to CCl4 in rats was first reported in 19365 and has been widely and successfully used by many investigators.[18,19] Carbon tetrachloride is metabolized by cytochrome P-450 in endoplasmic reticulum and mitochondria with the formation of CCl3O-, a reactive oxidative free radical, which initiates lipid peroxidation.[20, 21] Administration of a single dose of CCl4 to a rat produces, within 24 hrs, a centrilobular necrosis and fatty changes. 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 CCl4 left in the liver.[22] The development of necrosis is associated with leakage of hepatic enzymes into serum. Dose of CCl_4 that induces hepatotoxicity ranges from 0.1 to 3 ml/kg administered intraperitoneally.

Methods of pharmacological evaluation of hepatoprotective plants

***In- vivo* models**

Toxic chemicals-induced liver damage

A toxic dose or repeated doses of a known hepatotoxin (carbon tetrachloride, alcohol, D-galactosamine, Allyl alcohol, paracetamol, thioacetamide, etc) is administrated to induce liver damage in experimental animals. The test substance is administered along with, prior to and after the toxin treatment. If the hepatotoxicity is prevented or reduced the test substance is deemed to be effective.

Liver damage and recovery from damage are assessed by measuring serum marker enzymes, bilirubin, histopathological changes in the liver, biochemical changes in liver (eg: hydroxyproline, lipid etc) and bile flow. When liver is damaged liver enzyme such as Glutamate Pyruvate Transaminase (GPT), SGOT and Alkaline Phosphatase enter into the circulation. An increase in the levels of these marker enzymes in the serum is an indication of liver damage. Other effects of induced liver damage are reduction of prothrombin synthesis there by extended prothrombin time and reduction in clearance of certain substances such as bromsulphapthalein can be used as some of experimental models in the evaluation of hepatoprotective plants.

The hepatoprotective effect of a drug against different hepatotoxins differ especially when the mechanism of action of toxins are different. Therefore the efficacy of each drug has to be tested against hepatotoxin that acts by different methods.

Reduction in drugs-induced prolongation of thiopentone induced sleeping time

This method is used to screen anti-hepatotoxic effect (thioacetamide, ranitidine, paracetamol etc.) of drugs in animals. Hepatotoxic drugs like thioacetamide, ranitidine, paracetamol etc. reduces the levels of drug metabolizing enzymes in liver. Therefore metabolism of thiopentone is reduced resulting in prolongation of its sleeping time. If a plant drug reduces this drugs-induced prolongation of “sleeping time” by improved functional status then the drug administered can be considered hepatoprotective against drugs induced hepatotoxicity.

Anti-hepatitis virus activity

At present, simple *in vivo* test systems are not available to determine anti-hepatitis virus activity in rodent models. However duck and monkey models have been introduced to test anti-hepatitis B activity.

Choleretic activity

Techniques are available to collect bile by cannulating the bile duct in anaesthetized as well as conscious animals to study the effect of drugs on the secretion.

Regeneration of hepatocytes
The effects of drugs on hepatocyte regeneration can be tested by surgical removal of a portion of the liver in experimental animals followed by autopsy.

***In-vitro* studies**
Fresh hepatocyte preparations and primary cultured hepatocytes are used to study direct anti-hepatotoxic activity of drugs. Hepatocytes are treated with hepatotoxin and the effect of the plant drug on the same is evaluated. The activities of the transaminases released into the medium are determined. An increase in the activity of transaminases in the medium indicates liver damage. Parameters such as hepatocyte multiplication, morphology, macromolecular synthesis and oxygen consumption are determined.

Biochemical assays
Since, many toxic chemicals induce liver damage by lipid peroxidation or oxidative damage to DNA and reduction in the levels of glutathione and assessment of antioxidant property is useful. Antioxidant property of plant drugs is studied using liver homogenates, isolated liver cell membranes and DNA etc. in the process leading to cirrhosis, accumulation of connective tissue and parenchymal regeneration are competing events. Therefore, the search for agents to prevent liver cirrhosis is also focused on inhibition of excessive connective tissue formation in the liver. Fibrosuppressive effects on protein hydroxylation by inhibitors also can be screened.

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 following are some of the experimental models explained by employing some of the important hepatotoxins.

1. CCl_4 model: A number of CCl_4 models are devised depending upon its dosage through different routes of administration.

a) Acute hepatic damage: Acute liver damage, characterized by ischemia, hydropic degeneration and central necrosis is caused by oral or subcutaneous administration of CCl_4 (1.25ml/kg). The maximum elevation of biochemical parameters are found to be 24 hours after the CCl_4 administration normally administered as 50% v/v solution in liquid paraffin or olive oil.
b) Chronic reversible hepatic damage: Administration of CCl_4 (1ml/kg S.C.) twice weekly for 8 weeks produces chronic, reversible liver damage.
c) Chronic, irreversible hepatic damage: Administration of CCl_4 (1ml/kg S.C.) twice weekly for 12 weeks simulates chronic, irreversible liver damage.[23]

2. Thioacetamide model: Thioacetamide (100mg/kg s.c.) induces acute hepatic damage after 48 hrs of administration by causing sinusoidal congestion and hydropic swelling with increased mitosis.[24]

3. D-galactosamine model: D-galactosamine (800mg/kg i.p.) induces acute hepatotoxicity after 48 hrs of administration with diffused necrosis and steatosis.[25]

4. Paracetamol model
Paracetamol induces acute hepatotoxicity depending upon its dosage through different routes of administration; such as
a. Paracetamol (800mg/kg i.p.) induces centrilobular necrosis without steatosis.[26]
b. Paracetamol at a single dose of 3g/kg p.o. stimulates acute hepatic damage. It takes 48 hrs to induce the toxicity.[27]

5. Chloroform model
It produces hepatotoxicity with extensive central necrosis, fatty metamorphosis, hepatic cell degeneration and necrosis either by inhalation or by subcutaneous administration (0.4-1.5ml/kg).[28]

6. Ethanol model
Ethanol induces liposis to a different degree depending upon its dose, route and period of administration as follows:
a. A single dose of ethanol (1ml/kg) induces fatty degeneration.[29]
b. Administration of 40%v/v ethanol (2 ml/100g/day p.o.) for 21 days produces fatty liver.[30]
c. Administration of country made liquor (3ml/100 g/day p.o.) for 21 days produces liposis.[31]

Analysis of parameters to assess liver function

A. Functional parameter (Thiopentone induced sleeping time in rats)

After last dose of drug/extracts administration, rats were fasted for 18 h prior to recording of thiopentone induced sleeping time. Animals on 25th day all groups received thiopentone sodium (40 mg/kg, i.p). The time interval between the loss and the regaining of the righting reflex was measured as sleeping time.

B. Physical parameters

Determination of wet liver weight
Livers isolated from the animals were washed with alcohol and dried with filter paper strips and weighed on an electronic balance (Dhona, Calcutta) and were expressed with respect to their body weight i.e. g/100 gm.

Determination of wet liver volume
After recording the liver weights, the livers were individually dropped into a measuring cylinder containing a fixed volume of distilled water and the volume displaced was recorded and expressed as ml/100 g body weight.

C. Biochemical parameters

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

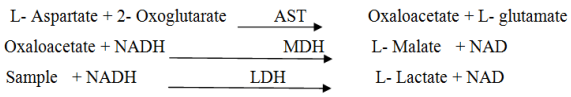
1. Serum enzyme parameters Transaminases[32]

Transamination 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 enzymes responsible for transamination are called transaminases or amino-transferases. Two diagnostically useful transaminases are glutamate oxaloacetate transaminase SGOT/AST and glutamate pyruvate transaminase SGPT/ALT. These two enzymes are sensitive markers of hepato-cellular injury.

A. Estimation of SGOT/AST

SGOT is an enzyme found mainly in heart muscle, liver cells, skeletal muscle and kidneys. Injury to these tissues results in the release of the enzyme in blood. Elevated levels are found in myocardial infarction, cardiac operations, hepatitis, cirrhosis, acute pancreatitis, acute renal diseases and primary muscle diseases. Decreased levels may be found in pregnancy, Beri Beri and Diabetic ketoacidosis. Its normal serum level is 5-40 units/l.

Principle: SG0T catalyses the transfer of amino group from L- Aspartate to 2-Oxo glutarate with the formation of oxaloacetate and L-glutamate. The rate of this reaction is monitored by an indicator reaction coupled with Malate dehydragenase (MDH) in which the oxaloacetate formed is converted to malate ion in the presence of NADH (Nicotinamide Adenine Dinucleotide). The oxidation of NADH in this reaction is measured as a decrease in the absorbance of NADH at 340 nm, which is proportional to SGOT activity.



Where:-
AST: Aspartate amino transferase
MDH: Malate dehydragenase
LDH: Lactate dehydragenase

Procedure

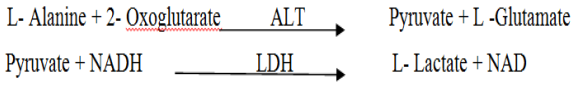
Pipette	Sample (µl)
Working reagent	500
Sample	50

SGOT levels are 10-200 fold elevated in patients with acute hepatic necrosis, viral hepatitis and drug induced poisoning. SGOT levels are also elevated by 10 fold in patients of post hepatic jaundice, intra hepatic cholestasis and less than 10 fold in alcoholic and hepatic steatosis. Very high levels are seen in extensive acute hepatic necrosis such as in severe viral hepatitis and acute cholestasis.

B. Estimation of SGPT/ALT

ALT or SGPT is a cytosolic enzyme primarily present in the liver. Its normal serum level is 7-56 units/l.

Principle: SGPT catalyses the transfer of amino group from L- Alanine to 2-Oxoglutarate with the formation of pyruvate and L-glutamate. The pyruvate so formed is allowed to react with NADH to produce L-lactate. The rate of this reaction is monitored by an indicator reaction coupled with LDH in the presence of NADH (Nicotinamide Adenine Dinucleotide). The oxidation of NADH in this reaction is measured as a decrease in the absorbance of NADH at 340 nm, which is proportional to SGPT activity.



ALT: Alanine amino transferase
LDH: Lactate dehydrogenase

Procedure

Pipette	Sample (µl)
Working reagent	500
Sample	50

As mentioned in the above table blank, standard and sample was prepared by considering 500 µl of working reagent and 50 µl each of distilled water, standard and sample respectively, later all the samples were incubated at 37^0c, aspirated individually and absorbance was recorded at 340 nm.

ALT activity is predominantly associated with liver tissues followed by comparatively lower levels in heart, muscles and kidneys. Quantitation of ALT is a useful parameter in evaluating liver function. Elevated levels of this enzyme are found in liver and kidney diseases such as infectious or toxic hepatitis, infectious mononucleosis and cirrhosis. Moderate increase is also found in obstructive jaundice, metastasis carcinoma, hepatic congestion and myocardial infarction.

Phosphatases[32]

Phosphatases belong to the class of enzyme called hydrolases and they are characterized by their ability to hydrolyse a large variety of organic phosphate with the formation of an alcohol and phosphate ions.

Phosphatases of diagnostic significance are alkaline phosphatase and acid phosphatase. These are differentiated by their reaction in alkaline and acidic medium. The P_H for measuring the alkaline phosphatase activity is 10 and for acid phosphatase are 5.

C. Alkaline phosphatase (ALP)[32]

ALP is a membrane bound glycoprotein enzyme, produced by many tissues, especially bone, liver, intestine, placenta and is excreted into the bile. Elevation in activity of the enzyme can thus be found in diseases of bone, liver and in pregnancy. ALP levels in serum are abnormally high in biliary obstruction. Slight to moderate increase is seen in parenchymal liver diseases such as in hepatitis and cirrhosis and in metastatic liver disease. Its normal serum level is 20-100 U/L.

Principle: Serum alkaline phosphatase hydrolyses p-Nitro phenyl phosphate in the presence of oxidizing agent Mg^{+2}. This reaction is measured as absorbance is proportional to the ALP activity.

Where :-
ALP : Alkaline phosphatase

Procedure

Pipette	Sample (µl)
Working reagent	500
Sample	10

As mentioned in the above table blank, standard and sample was prepared by considering 500 µl of working reagent and 10 µl each of distilled water, standard, sample respectively, later all the samples were incubated at 37^0c, aspirated individually and absorbance was recorded at 405 nm.

Increased alkaline phosphatase activity may be related to hepatobiliary and bone disease. Very high alkaline phosphatase activity in serum is seen in patient with bone cancer and marked increased also occur in obstructive jaundice and biliary cirrhosis. Modetrate elevations have been noted in case of Hodgkin's disease, congestive heart failure, infective hepatitis and abdominal problems.

2) Bile pigments

Bilirubin or hematoidin is the yellow breakdown product of normalheme catabolism. Heme is found in hemoglobin, a principal component of red blood cells. Bilirubin is excreted in bile and urine, and elevated levels may indicate certain diseases. It is responsible for the yellow color of brusis, urine and the yellow discoloration in jaundice.

Bilirubin in serum would only react with diazo reagent in the presence of alcohol, after the proteins had been removed by precipitation. Normally 0.25mg/dl of conjugated bilirubin is present in the blood of an adult. Bilirubin rises in disease of hepatocytes, obstruction to biliary excretion into duodenum, in haemolysis and defects of hepatic uptake and conjugation of bilirubin pigment such as Gilbert's disease. Estimation of bilirubin is one of the better liver function tests because the liver must take bilirubin away from the albumin to which it is bound in the circulation, conjugate it and excrete it into the bile-a truly complex series of reaction.[33, 34, 35]

Estimation of serum Total Bilirubin (TB)[36, 37]

The serum bilirubin level is one of the best tests of liver function. Bilirubin is the metabolic product of the breakdown of heme derived from senescent red blood cells. Each day about 7.5g of hemoglobin is catabolized with the corresponding production of 250 mg bilirubin.

Normally, 0.25 mg/dl of conjugated bilirubin is present in the blood of an adult. Bilirubin level rises in diseases of hepatocytes, obstruction to biliary excretion into duodenum, in hemolysis and defects of hepatic uptake and conjugation of bilirubin treatment such as Gilbert's disease.

Principle

Bilirubin reacts with diazotized sulphanilic acid to form an azo compound, the color of which is measured at 546 nm (536-560 nm) and is proportional to the concentration of bilirubin. The stability of final color of reaction of mixture is 10 minutes for total bilirubin and 5 minutes for direct bilirubin.

Hepatoprotective medicinal plants

Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. The Indian Traditional Medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials. The association of medical plants with other plants in their habitat also influences their medicinal values in some cases. One of the important and well documented uses of plantproducts is their use as hepatoprotective agents. Hence, there is an ever increasing need for safe hepatoprotective agent.[38] In spite of tremendous strides in modern medicine, there are hardly any drugs that stimulate liver function, offer protection to the liver from damage or help regeneration of hepatic cell. Many formulations containing herbal extracts are sold in the Indian market for liver disorders.[39] But management of liver disorders by a simple and precise herbal drug is still an intriguing problem. Several Indian medicinal plants have been extensively used in the Indian traditional system of medicine for the management of liver disorder. Some of these plants have alreadybeen reported to posse's strong antioxidantnactivity.[40,41]

In India, more than 87 plants are used in 33 patented & proprietary multi-ingredient plant formulations & about 40 polyherbal commercial formulations reputed to have hepatoprotective action are being used. It has been reported that about 160 phytoconstituents from 101 medicinal plants have hepatoprotective activity.[42]

Many herbs have been used to alleviate various liver diseases, of which the most popular ones include Silymarin from *Silybum marianum, andrographolide* and neoandrographolide from *Andrographis paniculata*,

curcumin from *Curcuma longa*, picroside and kutkoside from *Picrorrhiza kurroa*, phyllanthin and hypophyllanthin from *Phyllanthus niruri*, glycyrrhizin from *Glycyrrhiza glabra*, etc.[43]

The literature review reveals that a large number of drugs of plant origin are endowed with hepatoprotective claims either directly or indirectly. In recent years, the usage of herbal drugs for the treatment of liver diseases has increased all over the world. The herbal drugs are believed to be harmless and free from serious adverse reactions, as they are obtained from nature and are easily available. Also, the limited therapeutic options and disappointing therapeutic success of modern medicine including herbal preparations.

Liver protective herbal drugs contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthenes derivatives.[44] Studies carried out in China and Japan resulted in the isolation of a hepatoprotective lignan, gomishin from the fruits of Chinese medicinal plant *Schizandra chinensis*. Gomishin is used for the treatment of chronic hepatitis. Studies carried out at Tropical Botanic Garden and Research Institute (TBGRI) have shown that *Trichopus zeylanicus*, *Phyllanthus maderaspatensis* and *P. kozhikodianus* are extremely active against paracetamol-induced liver damage in rats.[45,46,47] A recent report indicates that fumaric acid obtained from *Sida cordifolia* has significant anti-hepatotoxic activity in rat.[48] Ursolic acid which occurs in many plants also showed promising hepatoprotection against paracetamol and CCl_4 induced liver damage in rats.[49,50] Some of the reported constituents with pharmacologically/therapeutically proved claims may be enlisted as silymarin, (+)- catechin, saikosaponins, curcumin, glycyrrhizin, picroside I and II gomisin etc[51], acetyl bergenin[52] and kolaviron.[53] Most commonly used plants in herbal formulations in India and scientifically validated in experimental animals are *Andrographis paniculat*)[54], *Boerhaavia diffusa*, *Eclipta alba*, *Picrorrhiza kurroa*[55], Cichorium intybus, Tinospora cordifolia.[56] Some of the polyherbal formulations are verified for their hepatoprotective action against chemical induced liver damage in experimental animals: Liv. 52, Liver cure, Tefroli, Livol, Hepatomed, Jigrine, Stimuliv, Koflet and Icterine.

Antioxidants can protect experimental animals and humans from oxidant mediated liver damages. This effect can be seen even in certain common vitamins, spices and vegetables (e.g. Vitamin-E and turmeric). Efficacy of the traditional and new herbal products should be tested by standard experimental methods. Also, there should be adequate data from *in vivo* and *in vitro* studies to validate the therapeutic potential claimed.[57]

Several plants have been reported to have hepatoprotective activity among those; a few plants tested against different experimental models are listed in below table.

Name of Plant	Family	Plant Parts Used	Screening Models
Arachniodes exilis[58]	Dryopteridaceae	Rhizomes	Carbon tetrachloride
Asparagus racemosus[59]	Liliaceae	Whole plant	Carbon tetrachloride
Amaranthus spinosus[60]	Amaranthaceae	Whole plant	Carbon tetrachloride
Aloe barbadensis Mill[61]	Liliaceae	Dried aerial parts	Carbon tetrachloride
Artemisia absinthium[62]	Asteraceae	Powdered aerial parts	Carbon tetrachloride
Azadirachta indica[63]	Meliaceae	Leaf	Paracetamol
Aerva lanata Linn[64]	Amaranthaceae	Coarse powder plant material	Paracetamol
Acacia confuse[65]	Leguminosae	Bark	Carbon tetrachloride
Alocasia indica Linn.[66]	Araceae	Leaves	Paracetamol
Acacia Catechu[67]	Leguminosae	Powdered pale catechu	Carbon tetrachloride
Argemone Mexicana[68]	Papavaraceae	Leaf & flower	Carbon tetrachloride
Ardisia solanacea[69]	Myrsinaceae	Leaves	Carbon tetrachloride
Aphanamixis polystachya[70]	Meliaceae	Leaves	Carbon tetrachloride
Alchornea cordifolia[71]	Euphorbiaceae	Leaves	Carbon tetrachloride
Apium graveolens[72]	Apiaceae	Seeds	Carbon tetrachloride
Asteracantha longifolia[73]	Acanthaceae	Whole plant	Carbon tetrachloride
Azima tetracantha[74]	Salvadoraceae	Leaves	Paracetamol
Aloe vera[75]	Xanthorrhoeaceae	Leaves	Paracetamol
Aerva lanata[76]	Amaranthaceae	Whole plant	Paracetamol
Aerva sanguinolenta[77]	Amaranthaceae	Leaves	Paracetamol
Asparagus racemosa[78]	Liliaceae	Roots	Paracetamol
Albizzia lebbeck[79]	Fabaceae	Leaves	Thioacetamide
Anisochilus carnosus[80]	Nyctaginaceae	Leaves	Thioacetamide
Aegle marmelos Correa[81]	Rutaceae	Leaves	Paracetamol
Andrographis paniculata[8]	Acanthaceae	Aerial parts	Ethanol
Boerhaavia diffusa[83]	Nyctaginaceae	Roots	Carbon tetrachloride

Byrsocarpus coccineus[84]	Connaraceae	Leaf	Carbon tetrachloride
Bixa orellana[85]	Bixaceae	Seed	Methanol
Berberis tinctoria[86]	Berneridaceae	Leaves	Methanol
Betula utilis[87]	Betulaceae	Bark	Ethanol
Baliospermum montanum[88]	Euphorbiaceae	Roots	Paracetamol
Bupleurum kaoi[89]	Umbelliferar	Dried roots	Carbontetra chloride
Cordia macleodii[90]	Boraginaceae	Leaves	Carbon tetrachloride
Cassia fistula[91]	Leguminosae	Leaf	Carbon tetrachloride
Clerodendrum inerme[92]	Verbenaceae	Leaves	Carbon tetrachloride
Cassia occidentalis[93]	Caesalpiniaceae	Leaves	Paracetamol and ethyl alcohol
Croton oblongifolius[94]	Euphorbiaceae	Aerial parts	Carbon tetrachloride
Cochlospermum vitifolium[95]	Cochlospermaceae	Bark	Carbon tetrachloride
Cassia tora[96]	Caesalpiniaceae	Leaves	Carbon tetrachloride
Carum copticum[97]	Apiaceae	Seed	Paracetamol And ccl4
Chamomile capitula[98]	Asteraceae	Fresh natural mature capitula	Paracetamol
Calotropis procera[99]	Apocynaceae	Flowers	Paracetamol
Capparis spinosa[100]	Capparidaceae	Root bark	Carbon tetrachloride
Cleome viscose Linn.[101]	Capparidaceae	Leaf powder	Carbon tetrachloride
Casuarina equisetifolia[102]	Casuarinaceae	Leaf & bark	Carbon tetrachloride
Cajanus cajan[102]	Papilionaceae	Whole plant	Carbon tetrachloride
Coriandrum sativum[103]	Apiaceae	Whole plant	Carbon tetrachloride
Carissa carandas[104]	Apocynaceae	Roots	Carbon tetrachloride
Cinnamomum zeylanicum[105]	Lauraceae	Bark	Carbon tetrachloride
Carica papaya[106]	Caricaceae	Seed	Carbon tetrachloride
Capparis spinosa[107]	Capparidaceae	Root bark	Carbon tetrachloride
Carissa opaca[108]	Apocyanaceae	Leaves	Carbon tetrachloride
Coccinia indica[109]	Cucurbitaceae	Fruits	Paracetamol
Carissa carandas[110]	Apocyanaceae	Roots	Paracetamol
Cyperus articulates[111]	Cyperaceae	Rhizome	Paracetamol
Ceiba pentandra[112]	Bombacaceae	Stem bark	Paracetamol
Calotropis gigantean[113]	Ascelpiadaceae	Root bark	D-galactosamine
Coldenia procumbens[114]	Boraginaceae	Whole plant	D-galactosamine
Crassocephalum crepidioides[115]	Asteraceae	Whole plant	D-galactosamine
Clitoria ternatea Linn[116]	Fabaceae	Leaves	Paracetamol
Decalepis hamiltonii[117]	Asclepiadaceae	Roots	Carbon tetrachloride
Delonix regia[118]	Caesalpiniaceae	Aerial parts	Carbon tetrachloride
Diteracanthus patulus[119]	Acanthaceae	Leaves	Carbon tetrachloride
Dragea volubilis[120]	Asclepiadaceae	Fruits	Paracetamol
Desmodium oojeinense[121]	Fabaceae	Bark	Paracetamol
Elephrantopus scaber Linn[122]	Asteraceae	Whole plant	D-galactosamine
Equisetum arvense[123]	Equisetaceae	Aerial parts	Carbontetra chloride Induced
Embelia ribes[124]	Myrsinaceae	Fruits	Paracetamol
Enicostemma axillare[125]	Gentianaceae	Whole plant	D-galactosamine
Euphorbia fusiformis[126]	Euphorbiaceae	Tubers	Rifampicin
Fumaria indica[127]	Papaveraceae	Whole plant	D-galactosamine
Ficus religiosa Linn[128]	Moraceae	Stem bark	Paracetamol
Glycyrrhiza glabra Linn.[129]	Fabaceae	Root powder	Carbon tetrachloride
Gentiana olivieri[130]	Gentianaceae	Aerial parts	Carbon tetrachloride
Ginkgo Biloba[131]	Ginkgoaceae	Dried extracts	Carbon tetrachloride
Gundelia tourenfortii[132]	Asteraceae	Footstalks	Carbon tetrachloride
Hygrophila auriculata[133]	Acanthaceae	Root	Carbon tetrachloride
Halenia elliptica[134]	Gentianaceae	Whole plant	Carbon tetrachloride
Hypericum japonicum[135]	Hypericaceae	Whole plant	Carbon tetrachloride
Hippophae rhamnoides[136]	Elaegnaceae	Leaves	Carbon tetrachloride
Juncus subulatus[137]	Juncaceae	Powdered tubers	Paracetamol
Kalanchoe pinnata Pers.[138]	Crassulaceae	Leaves	Carbon tetrachloride
Kigelia Africana[139]	Bignoniaceae	Leaves	Paracetamol
Luffa echinata[140]	Cucurbitaceae	Fruits	Carbon tetrachloride
Laggera pterodonta[141]	Asteraceae	Whole herb	Carbon tetrachloride
Lactuca indica[142]	Compositeae	Aerial parts	Carbon tetrachloride

Launea intybacea[143]	Asteraceae	Aerial parts	Carbon tetrachloride
Leucas lavandulaefolia[144]	Labiatae	Leaves	Paracetamol
Momordica dioica[145]	Cucurbitaceae	Leaves	Carbon tetrachloride
Mallotus japonicas[146]	Euphorbiaceae	Cortex	Carbon tetrachloride
Morus alba[147]	Moraceae	Leaves	Carbon tetrachloride
Mimosa púdica[148]	Mimosaceae	Leaves	Carbon tetrachloride
Momordica tuberose[149]	Cucurbitaceae	Tubers	Paracetamol
Nelumbo nucifera Gaertn[150]	Nelumbonaceae	Leaves	Carbon tetrachloride
Nilgirianthus ciliates[151]	Acanthaceae	Bark	Paracetamol
Nigella sativa[152]	Ranunculaceae	Seed oil	D-galactosamine
Orthosiphon stamineus[153]	Lamiaceae	Leaves	Acetaminophen
Ocimum snctum[154]	Lamiaceae	Leaf	Paracetamol
Operculina turpethum[155]	Convolvulaceae	Roots	Paracetamol
Olenlandia herbaceae[156]	Rubiaceae	Whole plant	D- galactosamine
Phyllanthus niruri[157]	Euphorbiaceae	Leaves and fruits	Carbon tetrachloride
Piper chaba[158]	Piperaceae	Fruit	D-galactosamine
Picrorrhiza rhizome[159]	Scrophulariaceae	Dried underground stems	Poloxamer (px)-407
Piper longum[160]	Piperaceae	Fruits and roots powder	Carbon tetrachloride
Picrorhiza Kurrooa[161]	Scrophulariaceae	Root and rhizome	Carbon tetrachloride
Rubia cordifolia Linn.[162]	Rubiaceae	Roots	Carbon tetrachloride
Ricinus Communis[163]	Euphorbiaceae	Leaves	Carbon tetrachloride
Schouwia thebica[164]	Arecaceae	Aerial parts	Carbon tetrachloride
Silybum marianum[165]	Asteraceae	Leaves	Thioacetamide
Scoparia dulcis[166]	Scrophulariaceae	Whole plant	Carbon tetrachloride
Sesamum indicum[167]	Pedaliaceae	Seeds	Carbon tetrachloride
Tridax procumbens[168]	Asteraceae	Leaves	Carbon tetrachloride
Tylophora indica[169]	Asclepiadaceae	Leaf powder	Ethanol
Thymus capitatus[170]	Lamiaceae	Essential oils	Paracetamol
Tamarindus indica[171]	Caesalpiniaceae	Fruits, seeds, leaves	Paracetamol
Vitis vinifera[172]	Vitaceae	Leaves	Carbon tetrachloride
Vitex trifolia[173]	Verbenaceae	Leaves	Carbon tetrachloride
Vanilla planifolia[174]	Orchidaceae	Beans	Paracetamol
Woodfordia fruticosa Kurz[175]	Lythraceae	Flowers	Carbon tetrachloride
Wedelia calendulaceae[176]	Compositae	Leaves	Thioacetamide
Zanthoxylum armatum[177]	Rutaceae	Bark	Carbon tetrachloride
Zizphus rotundifolia[178]	Rhamnaceae	Leaves	Carbon tetrachloride
Zizyphus jujube[179]	Rhamnaceae	Fruits	Thioacetamide

REFERENCES

1. Garba, S.H., Sambo, N., and Bala, U., T he effect of the aqueous extract of *Kohautia grandiflora* on paracetamol induced liver damage in albino rats., Nigeria journal of physiological Sciences., 2009; 24(1): 17-23.
2. Mossa, J.S., Tariq, M., Mohsin, A., Aqeel, A.M., al-Yahya, M.A., al-Said MS., et al., Am J Chin Med., 1991; 19: 223.
3. Mascolo N., Sharma, R., Jain SC., Capasso F., Jethnopharmacol, 1998; 22: 211.
4. Guyton H. Textbook of medical physiology, 10th edn, Philadelphia, The Curtis Center Saunders, 2000: 798-801.
5. Zimmerman Hyman J, Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver, Lippincott Williams & Wilkins, 1978: 26-31.
6. Sampath KP. *Swertia chirata*, A traditional herb and its medicinal uses, J Chem Pharm Res, 2010; 2(1): 262-266.
7. Ostapowicz G, Fontana RJ, Schiodt FV, Larson A, Davron JT, Steven HB, Timothy M and Reish J. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002; 137: 947–954.
8. TS Mohamed Saleem, C Madhusudhana Chetty, S Ramkanth, VST Rajan, K Mahesh Kumar, Gauthaman K: Hepatoprotective Herbs – A Review International Jouranal of research in Pharmceutical Sciences, 2010; 1(1): 1-5.
9. Arvind S Negi, JK Kumar, Suaib Luqman, Karuna Shanker, MM Gupta, SPS Khanuja: Recent Advances in Plant Hepatoprotectives: A Chemical and Biological Profile of Some Important Leads. Medicinal Research Reviews, 2008; 28(5): 746 -772.
10. Kirchain W R, Gill MA. "Drug –Induced Liver Disease", Pharmacotherapy a pathophysiological approach. London Appleton and Lange, 1999; 4: 628-636.
11. Valois M, Copper MA, Shear NH, An organized approach to drug induced hepatitis, Can J Clin Pharmacol, 2003; 10: 59-62.
12. Faried AE, El Sayed AH, Biochemical and histological studies on H_2-receptor antagonist

ranitidine-induced hepatotoxicity in rats. Indian J Exp Biol, 2005; 43: 782-785.
13. Kim YW, Ki SH, Lee JR, Lee SJ, Kim CW, et. al. *Glycyrrhizae radix* prevents acute liver injuries in rats induced by acetaminophen. J Ethnopharmacol 2006; 161: 125-138.
14. Masubuchi KM, Kim YM, Possible mechanism of hepatocytes injury induced by Diphenylamine and its structurally related nonsteroidal drugs. J Pharmacol Exp Therap, 2000; 292(3): 982-988.
15. Tripathi KD. Essential of medical pharmacology, 6th edn, New Delhi, Jaypee brothers medical publishers (P) Ltd., 2008: 198-200.
16. Wojcicki J, L Samochowlec & A Hinek: The effect of cernitin TM on galactosamine-induced hepatic injury in rat. Graminex: ‘‘Your Botanical source’’, 1984; 2: 1–5.
17. Koff RS, Gordon G, and Sabesin SM: D-Galactosamine hepatitis: 1. Hepatocellular injury and fatty liver follow a single dose. Proceedings of the society of experimental biology and medicine, 1971; 137: 696.
18. Handa SS, Sharma A. Hepatoprotective activity of Andrographolide from *Andrographis paniculata* against carbon tetrachloride. Ind J Med Res., 1990; 92: 276-92.
19. Shirwaiker A, Sreenivasan KK, Krishnanand BR, Kumar AV. Chemical investigation and antihepatotoxic activity of the root bark of *Caparis spinos*. Fitoterapia, 1996; 67: 200-204.
20. Zimmerman MD, Hayman J. Function and integrity of the liver. In: Richard A McPherson, Matthew R Pincus, John Bernard Henry. Clinical diagnosis and management by laboratory methods. Edn 17, Saunders Elsevier, New York, 1976; 217-50.
21. Agarwal AK, Mehendale JK. Potentiation of carbon tetrachloride hepatotoxicity and lethality by chlordecone in female rats. Toxicology. 1983; 26: 231-42.
22. Dawkins MJR. Carbon tetrachloride poisoning in the liver of the new born rat. J Path Bact., 1963; 85: 189-196.
23. G. Sowjanya, D.Swarnalatha, T.Shivakala and SK.Mobeena. International Journal of Phytopharmacy. Mar-Apr 2013; 3(2): 37-49.
24. Saraf, S., Dixit, V.K., Thripati, S.C., and Patnaik, G.K., Fitoterapia, 1992; 63: 414.
25. Kiso, Y., Thokkin, M., Hikino, H., Assay method for antihepatotoxic activity using galactosamine-induced cytotoxicity in primary cultured hepatocytes. J.of Natural Prod., 1983; 46: 841-847.
26. Rachmilewitz, M., Rosin, A. and Doljanski, L., Observations on the mitotic reaction induced in the livers of rats by thiourea, Amer. J. Pathology, 1950; 26(5): 937-949.
27. Handa, S.S. and Anupama, S., Hepatoprotective activity of andrographolide against galactosamine and paracetamol intoxication in rats. Indian J. of Medical Research, 1990; 92(B): 276-283.
28. Goldschmidt, S., Var, H.M., Ravdin IS: The influence of the foodstuffs upon the susceptibility of the liver to injury by chloroform, and the probable mechanism of action of them. J.of Clinical investigation, 1939; 80: 277-289.
29. Goodell, J.P.B., Hawkins., W.B., and Hanson, PC: Methionine protects against mepharsen liver injury in protein depleted dogs, J.of Experimental Medicine, 1944; 79: 625-632.
30. Thripati, S.C., Patnaik, G.K., and Dhawan, B.N., Hepatoprotective activity of Picroliv against alcohol-carbon tetrachloride induced damage in rats, Indian J. Pharmacology, 1991; 23: 143-148.
31. Gulati, R., Agarwal, S., and Agarwal, S.S., Hepatoprotective activity of *Boerhaavia diffusa Linn.* Against country made liquor induced toxicity in albino rats fed on controlled calorie diet, Indian J. of Pharmacology, 1991; 23: 264-266.
32. Joshi A. Rashmi, Saraswat Rashmi A Textbook of Practical Biochemistry, 1st edi. B. Jain Publishers Pvt Ltd, 2002: 147-152.
33. Geeta MB. How do I evaluate a liver profile: Hepatologist‘s perspective. Clin. Labtecnology, 2000; 1(5): 114.
34. Harsh Mohan. Textbook of Pathology, Jaypee brothers Medical Publishers Ltd., New Delhi. 2002; 4: 22-24, 569-630.
35. Malloy HT, Evelyn KA. The Determination of Bilirubin with the Photoelectric Colorimeter. J. Biol. Chem., 1936; 119: 481-490.
36. Harshmohan. Textbook of Pathology. Edn 5, Jaypee Brothers: Medical Publishers (P) Ltd., New Delhi, 2005; 22-24 and 608-668.
37. Lehrer JK. Medical Encyclopedia: Albumin-Serum. Available from: www.nlm.nih.gov/medlineplus/ency/article/003480.htm. [Accessed on 29 July 2009].
38. Ward FM, and Daly MJ, Hepatic Disease, Clinical Pharmacy and Therapeutics, Churchill Livingstone, New York, 1999; 195-212.
39. Achuthan CR, et.al. Antioxidant and Hepatoprotective effects of *Rosa damascene*, Pharmaceut. Biol., 2003; 41: 357-361.
40. Aniya Y, et.al. Free radical scavenging action of the medicinal herb *Limonium wrightii* from the Okinawa islands, Phytomedicine, 2002; 9: 239-244.
41. Gupta AK, Antioxidant activity of *Chamomile recutita capitula* methanolic extracts against CCl4-induced liver injury in rats Journal of Pharmacology and Toxicology, 2006; 1: 101- 107.
42. TS Mohamed Saleem, C Madhusudhana Chetty, S Ramkanth, VST Rajan, K Mahesh Kumar, Gauthaman K: Hepatoprotective Herbs – A Review International Jouranal of research in Pharmceutical Sciences, 2010; 1(1): 1-5.
43. Arvind S Negi, JK Kumar, Suaib Luqman, Karuna Shanker, MM Gupta, SPS Khanuja: Recent Advances in Plant Hepatoprotectives: A Chemical and Biological Profile of Some Important Leads. Medicinal Research Reviews, 2008; 28(5): 746 -772.

44. Sharma, A., Chakraborti, K.K., and Handa, S.S., Antihepatotoxic activity of some Indian herbal formulation as compared to silymarin, Fitoterapia., 1991; 62: 229.
45. Asha, V.V., Pushpangadan, P., Preliminary evaluation of antihepatotoxic activity of Phyllanthus maderaspatensis, P. kozhikodianus and Solanum indicum. Fitoterapia, 1998.
46. Subramoniam, A., Evans, D.A., Rajasekharan, S., Pushpangadan, P., Hepatoprotective activity of *Trichopus zeylanicus* extract against paracetamol induced hepatic damage in rats. Indian J Exp Biol. 1998; 36: 385-9.
47. Asha, V.V., Ethnobotany, pharmacognosy and ethnopharmacology of hepatoprotective agents employed by the folk practitioners and tribal physicians of South lndia. Ph.D. Thesis, University of Kerala. (1996).
48. Kumar, R.J., David, G.L., and Krupadanam, M., Phenolic constituents from the pods of Bauhinia vahlii., Fitoterapia., 1990; 61: 456- 460.
49. Shukla, B., Visen, P.K.S., Patnaik, G.K., Tripathi, S.C., Srimal, R.C., Dayal, R., Dobhal, P.C., Hepatoprotective activity in the rat of ursolic acid isolated from Eucalyptus hybrid. Phytotheraphy Res., 1992; 6: 74-9.
50. Saraswat, B., Visen, P.K.S., Dayal, R., Agarwal, D.P., Patnaik, G.K., Protective action of ursolic acid against chemical-induced hepatotoxicity in rats. Indian J Pharmacol, 1996; 28: 232-9.
51. Wagner, H., Hikino, H., and Farnsworth, N.R., Economic and medicinal plant Research, vol. 2, Academic press, London. 1998; 39: 22.
52. Lim, H., Kim, M.K., Lim, Y., Cho, Y.H., and Lee, C.H., Inhibition of cell-cycle progression in HeLa cells by HY52, a novel cyclin-dependent kinase inhibitor 9+isolated from Bauhinia forficata. Cancer Letters, 2006; 233(1): 89-97.
53. Olukoya, D.K., Idugbmi, T., Antibacterial activity of some medicinal plants from Nigeria, J.Ethnopharmacol., 1993; 39: 69-72.
54. Handa, S.S., Sharma, A., Chakraborti, K.K., Natural products and plants as liver protecting drugs., Fitoterapia., 1986; 57: 307-51.
55. Balandrin, M.F., Klocke, J.A., Wurtele, E.S., Bollinger, W.H., Natural Plant Chemicals: Sources of industrial and medicinal materials. Science, 1985; 288: 1154-6.
56. Doreswamy, R., Sharma, D., Plant drugs for liver disorders management. Indian Drugs, 1995; 32: 139-44.
57. Medicinal plants in India, Indian J Med Res., 2004; 120: 9.
58. Daonian Zhoua B, Jinlan Ruana, Yaling Caia, Zhaemoi Xionga, Weifua, Anhua Weia, anti-antioxidant And Hepatoprotective Activity of Ethanol Extract of Arachniodes Exilis (Hance) Ching, Journal of Ethanopharmacology, 2010; 129: 232–237.
59. Jayashree P. Kamat A, Krutin K. Boloor A, Thomas P.A. Devasagayam A, S.R. Venkatachalam Bantioxidant Properties of *Asparagus Racemosus* against Damage Induced By G-Radiation in Rat Liver Mitochondria, Journal of Ethnopharmacology, 2000; 71: 425–435.
60. Hussain Zeashan A, G. Amresh A, Satyawan Singh B, Chandana Venkateswara Rao A, Hepatoprotective Activity Of *Amaranthus Spinosus* In Experimental Animals, Food And Chemical Toxicology, 2008; 46: 3417–3421.
61. B.K. Chandan, A.K. Saxena, Sangeeta Shukla, Neelam Sharma, D.K. Gupta, K.A. Suri, Jyotsna Suri, M. Bhadauria, B. Singh, Hepatoprotective Potential of *Aloe Barbadensis* Mill. Against Carbon Tetrachloride Induced Hepatotoxicity, Journal of Ethnopharmacology, 2007; 111: 560–566.
62. Nurmuhammat Amata, Halmuratupura, Biljanabla˘Zekovi´ Cb, In Vivo Hepatoprotective Activity of the Aqueous Extract of *Artemisia Absinthium* L. Against Chemically An Immunologically Induced Liver Injuries In Mice, Journal Ofethnopharmacology, 2010; Xxx: Xxx–Xxx.
63. R. R. Chattopadhyay, M. Bandyopadhyay, Possible Mechanism Of Hepatoprotective Activity Of *Azadirachta Indica* Leaf Extract Against Paracetamol-Induced Hepatic Damage In Rats: Part III, Indian J Pharmacol, June 2005; 37: 184-185.
64. Manokaran S, Jaswanth A, Sengottuvelu S , Nandhakumar J, Duraisamy R, Karthikeyan D And Mallegaswari R, hepatoprotective activity of *Aerva Lanata* Linn. against paracetamol induced hepatotoxicity in rats, Research J. Pharm. And Tech., Oct.-Dec. 2008; 1(4).
65. Yu-Tang Tung, Jyh-Horng Wu, Chi-Chang Huang, Hsiang-Chi Peng, Ya-Ling Chen, Suh-Ching Yang, Shang-Tzen Chang, protective effect of *Acacia Confusa* Bark extract and its active compound gallic acid against carbon tetrachloride-induced chronic liver injury in rats, Food and Chemical Toxicology, 2009; 03-21.
66. Wahid A Mulla, Vijay R Salunkhe & Satish B Bhise, Hepatoprotective activity of hydroalcoholic extract of leaves of *Alocasia Indica* (Linn.), Indian Journal Of Experimental Biology, October 2009; 47: 816-821.
67. P. Jayasekhar, P.V. Mohanan*, K. Rathinam, Hepatoprotective Activity Of Ethyl Acetate Extract Of *Acacia Catechu*, Indian Journal Of Pharmacology, 1997; 29: 426-428.
68. Md. Rajib Ahsan, Km Monirul Islam, Israt Jahan Bulbul, Md. Ashik Musaddik, Ekramul Haque, Hepatoprotective Activity Of Methanol Extract Of Some Medicinal Plants Against Carbon Tetrachloride-Induced Hepatotoxicity In Rats, European Journal Of Scientific Research, 2009; 37(2): 302-310.
69. Pradeep KS: Hepatoprotective activity of *Ardisia solanacea* in carbon tetrachloride induced

hepatotoxic albino rats. Asian Journal of Research in Pharmaceutical Sciences, 2013; 3(2): 79-82.
70. Mukul KG and Dasgupta S: Role of plant metabolites in toxic liver injury. Asian Pacific Journal of Clinical Nutrition, 2002; 11(1): 48–50.
71. Patience OO, Festus BC, Philip FU, Nneka RN, Ijeoma EA and Nkemakonam CO: Phytochemical analysis, hepatoprotective and antioxidant activity of *Alchornea cordifolia* methanol leaf extract on carbon tetrachloride-induced hepatic damage in rats. Asian Pacific Journal of Tropical Medicine, 2012: 289-293.
72. Bahar A, Tanveer A, Manoj V and Shah AK: Hepatoprotective activity of two plants belonging to the Apiaceae and the Euphorbiaceae family. Journal of Ethnopharmacology, 2002; 79: 313–316.
73. Hewawasam RP, Jayatilaka KAPW, Parthirana C and Mudduwa LKB: Protective effect of *Asteracantha longifolia* extract in mouse liver injury induced by carbon tetrachloride and paracetamol. Journal of Pharmacy and Pharmacology, 2003; 55(10): 1413-1418.
74. Arthika S, Shanthammal Y, Sheryl Igal N, Elankini P, Ganesan R, Gaidhani SN and Pramod Reddy G: Hepatoprotective Activity of the Ethanoilc Extract of *Azima tetracantha* against Paracetamol-Induced Hepatotoxicity in Wistar Albino Rats. Journal of Advances in Pharmacy and Healthcare Research, 2011; 1(2): 14-21.
75. Simon RP, Patel Hitesh V and Kiran K: Hepatoprotective activity of some plants extract against paracetamol induced hepatotoxicity in rats. Journal of Herbal Medicine and Toxicology, 2010; 4(2): 101-106.
76. Manokaran S, Jaswanth A, Sengottuvelu S, Nandhakumar J, Duraisamy R, Karthikeyan D and Mallegaswari R: Hepatoprotective Activity of *Aerva lanata* Linn. Against Paracetamol Induced Hepatotoxicity in Rats. Research Journal of Pharmacy and Technology, 2008; 1(4): 398-400.
77. Asif L, Bolay B, Mousumi Das, Debmalya M, Sudipta K, Samit B and Amalesh Samanta: Hepatoprotective activity of ethanolic extract of *Aerva sanguinolenta* (Amaranthaceae) against paracetamol induced liver toxicity on Wistar Rats. NSHM Journal of Pharmacy and Healthcare Management, 2012; 03: 57-65.
78. Fasalu Rahiman OM, Rupesh Kumar M, Tamizh Mani T, Mohamed Niyas K, Satya Kumar B, Phaneendra P and Surendra B: Hepatoprotective Activity of "*Asparagus Racemosus* Root" On Liver Damage Caused By Paracetamol in Rats. Indian Journal of Novel Drug delivery, 2011; 3(2): 112-117.
79. Shirode DS, Jain BB, Mahendra kumar CB and Setty SR: Hepatoprotective and antioxidant effects of *Albizzia lebbeck* against thioacetamide induced hepatotoxicity in rats. Journal of Chemical and Pharmaceutical sciences, 2012; 5: 199-204.
80. Venkatesh P, Dinakar A and Senthilkumar N: Screening of hepatoprotective and antioxidant activity of alcoholic and aqueous extracts of *Boerhaavia diffusa* and *anisochilus carnosus.* International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 5(2): 208-211.
81. Ramnik Singh, Harwinder Singh Rao, Hepatoprotective Effect Of The Pulp/Seed Of *Aegle Marmelos Correa Ex Roxb* Against Carbontetrachloride Induced Liver Damage In Rats, International Journal Of Green Pharmacy, Oct-17 2010; 232-234.
82. Handa SS, Hepatoprotective activity of andrographolide from *Andrographis paniculata* against carbontetrachloride, Indian J Med Res., 1990; 92: 276-83.
83. K.S. Rawat A S. Mehrotra A, S.C. Tripathi B, U. Shome, Hepatoprotective Activity Of *Boerhaavia Diffusa* L. Roots - A Popular Indian Ethnomedicine, Journal Of Ethnopharmacology, 1997; 56: 61- 66.
84. Abidemi J. Akindele, Kenneth O. Ezenwanebe, Chidozie C. Anunobi, Olufunmilayo O. Adeyemi, Hepatoprotective And In Vivo Antioxidant Effects of *Byrsocarpus Coccineus Schum. and Thonn.* (Connaraceae), Journal of Ethnopharmacology, 2010; 129: 46–52.
85. Rajib A, Monirul Islam KM, Musaddik A and Haque E: Hepatoprotective activity of methanol extract of some medicinal plants against carbon tetrachloride induced hepatotoxicity in albino rats. Global Journal of Pharmacology, 2009; 3(3): 116-122.
86. Murugesh, Kanda Samy Y, Veerendra CM, Charan Bhim M and Tapan Kumar: Hepatoprotective and antioxidant role of *Berberis tinctorial* Lesch leaves on paracetamol-induced hepatic damage in rats. Iranian Journal of Pharmacology and Therapeutics, 2006; 4(1).
87. Duraiswamy B, Satish kumar MN, Gupta S, Rawat M, Om Porwal and Murugan R: Hepatoprotective activity of *Betula utilis* bark on D-galactosamine induced hepatic insult. World Journal of Pharmacy and Pharmaceutical Sciences, 2012; 1(1): 456-471.
88. Raju Ratan Wadekar, Radhika Sachin Supale, Kunal Mahesh Tewari, Kalpana S.Patil, Sunil Satyappa Jalalpure, Screening of Roots of *Baliospermum Montanum* For Hepatoprotective Activity Against Paracetamol Induced Liver Damage In Albino Rats, International Journal Of Green Pharmacy, July 2010; 220-223.
89. Be-Jen Wang,, Chu-Ting Liu, Chin-Yin Tseng, Chien-Ping Wu, Zer-Ran Yu, Hepatoprotective And Antioxidant Effects Of *Bupleurum Kaoi Liu* (Chao Et Chuang) Extract And Its Fractions Fractionated Using Supercritical CO2 On Ccl4-Induced Liver Damage, Food And Chemical Toxicology, 2004; 42: 609–617.
90. Naseem N. Qureshi A, Bhanudansh S. Kuchekar B, Nadeem A. Logade A, Majid A. Haleem A, Antioxidant And Hepatoprotective Activity of

Cordia Macleodii Leaves, Saudi Pharmaceutical Journal, 23 May 2009; 17: 299– 302.
91. T. Bhakta A, Pulok K. Mukherjee B, Kakali Mukherjee A, S. Banerjee A, Subhash C. Mandal A, Tapan K. Maity A, M. Pal A, B.P. Saha A, Evaluation of Hepatoprotective Activity *of Cassia Fistula* Leaf Extract, Journal Of Ethnopharmacology, 1999; 66: 277–282.
92. N. Gopal A, S. Sengottuvelu B, Hepatoprotective Activity of *Clerodendrum Inerme* against CCL4 Induced Hepatic Injury In Rats, Fitoterapia, 2008; 79: 24–26.
93. M.A. Jafri A,*, M. Jalis Subhani A, Kalim Javed A, Surender Singh B, Hepatoprotective Activity Of Leaves Of *Cassia Occidentalis* Against Paracetamol And Ethyl Alcohol Intoxication In Rats, Journal Of Ethnopharmacology, 1999; 66: 355–361.
94. Bahar Ahmed, Tanveer Alam, Manoj Varshney, Shah Alam Khan, hepatoprotective activity of two plants belonging to the apiaceae and the euphorbiaceae family, journal of ethnopharmacology, 2002; 79: 313–316.
95. J.C. S´Anchez-Salgado, R.R. Ortiz-Andrade, F. Aguirre-Crespo, J. Vergara-Galicia, I. Le´On-Rivera, S. Montes, R. Villalobos-Molina, S. Estrada-Soto, Hypoglycemic, Vasorelaxant and Hepatoprotective Effects of *Cochlospermum Vitifolium* (Willd.) Sprengel: A Potential Agent for the treatment of metabolic syndrome, Journal of Ethnopharmacology, 2007; 109: 400–405.
96. Muniyappan Dhanasekarana, Savarimuthu Ignacimuthua, Paulagastianb, Potential Hepatoprotective Activity Of Ononitol Monohydrate Isolated From *Cassia Tora L*.on Carbontetrachloride Induced Hepatotoxicity In Wistar Rats, Phytomedicine, 2009; 16: 891–895.
97. A.H. Gilani A, Q. Jabeen A, M.N. Ghayur A, K.H. Janbaz B, M.S. Akhtar C, Studies On The Antihypertensive, Antispasmodic, Bronchodilator And Hepatoprotective Activities Of The *Carum Copticum* Seed Extract, Journal Of Ethnopharmacology, 2005; 98: 127–135.
98. Ajay Kumar Gupta and 2Neelam Misra, hepatoprotective activity of aqueous ethanolic extract of *Chamomile Capitula* in paracetamol intoxicated albino rats, American Journal of Pharmacology and Toxicology, 2006; 1(1): 17-20.
99. S. Ramachandra Setty A, Absar Ahmed Quereshi A, A.H.M. Viswanath Swamy B,Tushar Patil A, T. Prakash A, K. Prabhu A, A. Veeran Gouda A, Hepatoprotective activity of *Calotropis procera* flowers against paracetamol-induced hepatic injury in rats, Fitoterapia, 2007; 78: 451–454.
100. Nasrin Aghel*a*, Iran Rashidi*b* And Amir Mombeini*a*, hepatoprotective activity of *Capparis Spinosa* Root Bark *against* CCl4 *induced hepatic damage in mice*, Iranian Journal Of Pharmaceutical Research, 2007; 6(4): 285-29.
101. Nishant Kumar Gupta, Vinod Kumar Dixit, Evaluation Of Hepatoprotective Activity Of *Eome viscose Linn*. Extract., Indian Journal Of Pharmacology, Feb 2009; 41: 36-40.
102. Rajib A, Monirul Islam KM, Musaddik A and Haque E: Hepatoprotective activity of methanol extract of some medicinal plants against carbon tetrachloride induced hepatotoxicity in albino rats. Global Journal of Pharmacology, 2009; 3(3): 116-122.
103. Mohammed HH: Protective effect of *Coriandrum sativum* plant of hepatotoxicity and nephrotoxicity induced by carbon tetrachloride in male albino rats. The 6th Arab and 3rd International Annual Scientific Conference on: Development of Higher Specific Education Programs in Egypt and the Arab World in the Light of Knowledge Era Requirements; 2011: April 13-14.
104. Karunakar HE and Arun BJ: Hepatoprotective effect of *Carissa carandas* Linn root extract against carbon tetrachloride and paracetamol induced hepatic oxidative stress. Indian Journal of Experimental Biology, 2009; 47(8): 660-667.
105. Akram E, Pejman M, Maryam B, Jalal Z: Hepatoprotective activity of Cinnamon ethanolic extract against CCl4-induced liver injury in rats. EXCLI Journal, 2012; 11: 495-507.
106. Adeneye AA, Olagunju JA, Banju AAF, Abdul SF, Sanusi OA, Sanni OO, Osarodion BA and Shoniki OE: The aqueous seed extract of *Carica papaya* Linn. Prevents carbon tetrachloride induced hepatotoxicity in rats. International Journal of Applied Research in Natural Products, 2009; 2(2): 19-32.
107. Aghel N, Rashidi I and Mombeini A: Hepatoprotective activity of *Capparis spinosa* Root bark against carbon tetrachloride induced hepatic damage in mice. Iranian Journal of pharmaceutical research, 2007; 6(4): 285-290.
108. Sumaira S, Muhammad RK and Rahmat AK: Hepatoprotective effects of methanol extract of *Carissa opaca* leaves on carbon tetrachloride-induced damage in rats. BMC Complementary and alternative Medicine, 2011; 11: 48.
109. Arun KS and Eswar KK: Hepatoprotective Activity of Aqueous Fruit Extract of *Coccinia indica* against Paracetamol Induced Hepatotoxicity in rats. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2013; 4(1): 179-182.
110. Karunakar HE and Arun BJ: Hepatoprotective effect of *Carissa carandas* Linn root extract against carbon tetrachloride and paracetamol induced hepatic oxidative stress. Indian Journal of Experimental Biology, 2009; 47(8): 660-667.
111. Samaresh D, Susmita D, Nayak SS and Subas CD: Hepatoprotective activity of *Cyperus articulatus Linn*.against paracetamol induced hepatotoxicity in rats. Journal of Chemical and Pharmaceutical Research, 2013; 5(1): 314-319.
112. Nirmal KB, Neeraj K and Mishra SH: Protective effect of stem bark of *Ceiba pentandra Linn.*

Against paracetamol-induced hepatotoxicity in rats. Pharmacognosy Research. 2010; 2(1): 28-30.
113. Pradeep D, Tanaji N, Mahendra Singh R, Anil M and Nithin J: Hepatoprotective activity of *Calotropis gigantea* Root bark experimental liver damage induced by D-galactosamine in rats. International Journal of Pharmaceutical Sciences and Nanotechnology, 2008; 1(3): 281-286.
114. Ganesan R, Venkatanarasimhan M, Sharad P, Pramod reddy G, Anandan T and Masilamani G: Hepatoprotective effect of *Coldenia procumbens* linn against D-galactosamine induced acute liver damage in rats. International Journal of Integrative sciences, Innovation and Technology, 2013; 2(2): 9-11.
115. Yoko A, Tomoyuki K, Chika M, Manami M, Chiho I, Shizula K and Toshio I: Free radical scavenging and hepatoprotective actions of the medicinal herb, *Crassocephalum crepidiodes* from the Okinawa Islands. Biological and Pharma Bulletin, 2005; 28(1): 19-23.
116. Kuppan Nithianantham, Murugesan Shyamala, Yeng Chen, Lachimanan Yoga Latha, Subramanion L. Jothy, Sreenivasan Sasidharan, Hepatoprotective potential of *Clitoria ternatea* leaf extract against paracetamol induced damage in mice, Molecules, 2011; 16: 10134-10145.
117. Anup Srivastava, T. Shivanandappa, Hepatoprotective Effect Of The Root Extract Of *Decalepis Hamiltonii* Against Carbon Tetrachloride-Induced Oxidative Stress In Rats, Food Chemistry, 2010; 118: 411–417.
118. Jameel A, Sunil N, Vipul D, Anuja P, Sagar K, Subodh Pal, Subhash M and Shashikant P: Hepatoprotective activity of methanol extract of aerial parts of *Delonix regia*. Phytopharmacology, 2011; 1(5): 118-122.
119. Shrinivas B and Suresh RN: Hepatoprotective Activity of Methanolic Extract of *Dipteracanthus patulus* (JACQ) NEES: possible involvement of antioxidant and membrane stabilization property. International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(2): 685-690.
120. Pallab KH, Moulisha B, Sanjib B, Tarun KK and Ashoke KG: Hepatoprotective Activity of *Dregea volubilis* Fruit against Paracetamol-Induced Liver Damage in Rats. Indian Journal of Pharmaceutical Education and Research, 2012; 46(1): 17-22.
121. Jayadevaiah KV, Ishwar Bhat K, Joshi AB, Vijayakumar MMJ and Pinkey R: Hepatoprotective activity of *Desmodium oojeinense* (ROXB) H. Ohashi against paracetamol induced hepatotoxicity. Asian Journal of Pharmaceutical and Health Sciences, 2012; 2(2): 312-315.
122. Fei Yana,1, Qiao-Yanzhanga,1, Leijiaoa, Tinghana, Hongzhanga, Lu-Pingqina, Rahman Khalid, Synergistic Hepatoprotective effect of Schisandrae Lignans With Astragalus Polysaccharides On Chronic Liver Injury In Rats, Phytomedicine, 2009; 16: 805–813.
123. Hyuncheol Oh, Do-Hoon Kim, Jung-Hee Cho, Youn-Chul Kimc, Hepatoprotective and Free Radical Scavenging Activities Of Phenolic Petrosins and Flavonoids isolated from Equisetum Arvense, Journal Of Ethnopharmacology, 2004; 95: 421–424.
124. Nahid Tabassum, Shyam S. Agrawal, hepatoprotective activity of *Emebelia ribes* against paracetamol induced acute hepatocellular damage in mice, Experimental Medicine, 2000; 10: 43-44.
125. V. Jaishree, Shrishailappa Badami, Antioxidant and hepatoprotective effect of Swertiamarin from Enicostemma Axillare against D-Galactosamine Induced Acute Liver Damage in Rats, Journal of Ethnopharmacology, 2010; 130: 103–106.
126. N. Anusuya, K. Raju, S. Manian, Hepatoprotective and Toxicological Assessment of an Ethnomedicinal Plant *Euphorbia fusiformis* Buch.-Ham. Ex D. Don, Journal Of Ethnopharmacology, 2010; 127: 463–467.
127. Anshu Rathia, Arvind Kumar Srivastava, Annie Shirwaikarc, Ajay Kumar Singh Rawata, Shanta Mehrotrad, Hepatoprotective Potential of *Fumaria indica pugsley* whole plant extracts, fractions and an isolated alkaloid protopine, phytomedicine, 2008; 15: 470–477.
128. Krishna Mohan G, Pallavi E, Ravi Kumar B, Ramesh M and Venkatesh S: Hepatoprotective activity of *Ficus carica* Linn. leaf extract against carbon tetrachloride-induced hepatotoxicity in rats. DARU, 2007; 15(3): 162-166.
129. M.G.Rajesh, M.S.Latha, Protective Activityof *Glycyrrhiza Glabra* Linn. On Carbantetrachloride-Induced Peroxidative Damage, Indian Journal Pharmacol, October 2004; 38: 284-287.
130. Didem Deliorman Orhana, Mustafa Aslana, Go¨Knur Aktayb, Ender Ergunc, Erdem Yesiladaa, Fatma Erguna, Evaluation Of Hepatoprotective Effect Of *Gentiana Olivieri* Herbs on subacute Administration And Isolation Of Active Principle, Life Sciences, 2003; 72: 2273–2283.
131. K. Ashok Shenoy, S.N.Somayaji, K.L.Bairy, Hepatoprotective Effects Of *Ginko biloba* Against Carbontetrachloride, Induced Hepatic Injury In Rats, Indian Journal Of Pharmacology, 2001; 33: 260-266.
132. Akram J, Fatema F, Zohreh S and Hossein N: Hepatoprotective activity of *Gundelia tourenfortii.* Journal of Ethanopharmacology, 2005; 101(1-3): 233-237.
133. P. Shanmugasundaram, S. Venkataraman, Hepatoprotective And Antioxidant Effects of *Hygrophila Auriculata* (K. Schum) Heine Acanthaceae Root Extract, Journal of Ethnopharmacology, 2006; 104: 124–128.
134. Bouang, Xiaoquanban, Jingshenghe, Hongzeng, Pengzhang, Youweiwang, Hepatoprotective and antioxidant effects of the methanolic Extract from *Halenia Elliptica*, Journal Ofethnopharmacology, 2010; Xxx: Xxx–Xxx.
135. Ning W, Peibo Li, Yonggang W, Wei P, Zhong W, Suiyi T, Shaoling L, Xiao S and WeiWei Su:

Hepatoprotective effect of *Hypericum japonicum* extract and its fractions. Journal of Ethnopharmacology, 2008; 116(1): 1-6.
136. Gayathiri S, Vetriselvan S, Shankar Jothi, Ishwin S, Hemah Devi, Shereenjeet Kaur and Yaashini A: Hepatoprotective activity of aqueous extract of *Hippophae rhamnoides L.* in carbon tetrachloride induced hepatotoxicity in albino wistar rats. International Journal of Biological & Pharmaceutical Research, 2012; 3(4): 531-537.
137. Ayman F. Abdel-Razika*, Abdel-Samid I. Elshamya, Mahmoud I. Nassara, Salah M. El-Kousyb, Hanaa Hamdyc, Chemical Constituents And Hepatoprotective Activity Of *Juncus Subulatus*, 2009; 70-84.
138. N.P. Yadav, V.K. Dixit, Hepatoprotective Activity of Leaves of *Kalanchoe Pinnata* Pers, Journal of Ethnopharmacology, 2003; 86: 197–202.
139. Hemamalini K, Preethi B, Anurag Bhargav and Uma V: Hepatoprotective activity of *Kigelia africana* and *Anogeissus accuminata* against paracetamol induced hepatotoxicity in rats. International Journal of Pharmaceutical and Biomedical Research, 2012; 3(3): 152-156.
140. Bahar Ahmed, Tanveer Alam, Shah A. Khan, Hepatoprotective Activity Of *Luffa Echinata* Fruits, Journal of Ethnopharmacology, 2001; 76: 187–189.
141. Yihang Wu A, B, Leixiang Yang B, Fang Wang C, Xiumei Wu D, Changxin Zhou B, Shuyun Shi B, Jianxia Mo B, Yu Zhao B, Hepatoprotective And Antioxidative Effects Of Total Phenolics From *Laggera Pterodonta* on chemical-induced injury in primary cultured neonatal rat hepatocytes, Food and Chemical Toxicology, 2007; 45: 1349–1355.
142. Ki Hyun Kim, A Young Ho Kimb And Kang Ro Leea,*, Isolation Of Quinic Acid Derivatives And Flavonoids From The Aerial Parts Of *Lactuca indica* L.And Their Hepatoprotective Activity In Vitro, Bioorganic & Medicinal Chemistry Letters, 2007; 17: 6739–6743.
143. Takate SB, Pokharkar RD, Chopade VV and Gite VN: Hepato-Protective activity of the aqueous extract of *launaea intybacea* (*Jacq) Beauv* against carbon tetrachloride-induced hepatic injury in Albino Rats. Journal of Pharmaceutical Science and Technology, 2010; 2(7): 247-251.
144. Kotoky J, Dasgupta B and Sarma GK: Protective properties of *Leucas lavendulaefolia* extracts against D-galactosamine induced hepatotoxicity in rats. Fitoterapia, 2008; 79(4): 290-292.
145. Avijeet Jain, Manish Soni, Lokesh Deb, Anurekha Jain, A.P. Roult, V. B. Gupta, K.L. Krishna Antioxidant And Hepatoprotective Activity of Ethanolic And Aqueous Extracts of *Momordica Dioica* Roxb. Leaves, Journal of Ethnopharmacology, 2008; 115: 61–66.
146. Hwa-Kyung Lim, Hack-Seang Kim, Hong-Serck Choi, Seikwan Oh, Jongwon Choi, Hepatoprotective Effects of Bergenin, A Major Constituent of *Mallotus Japonicus*, on Carbon Tetrachloride-Intoxicated Rats, Journal of Ethnopharmacology, 2000; 72: 469–474.
147. Hogade MG, Patil KS, Wadkar GH, Mathapati SS and Dhumal PB: Hepatoprotective activity of *Morus alba* (Linn.) leaves extract against carbon tetrachloride induced hepatotoxicity in rats. African Journal of Pharmacy and Pharmacology, 2010; 4(10): 731-734.
148. Rekha R, Hemalatha S, Akasakalai K, Madhu Krishna CH, Bavan S, Vittal and Meenakshi Sundaram R: Hepatoprotective activity of *Mimosa pudica* leaves against Carbon tetrachloride induced toxicity. Journal of Natural Products, 2009; 2: 116-122.
149. Pramod kumar, Devala rao G, lakshmayya and Ramachandra settee S: Hepatoprotective effect of ethanol extract of tubers of *Momordica tuberosa* cogn. In thioacetamide induced hepatic damage. Pharmacologyonline, 2008; 3: 181-189.
150. Bo Huang, Xiaoquan Ban, Jingsheng He, Jing Tong, Jun Tian, Youwei Wang, Hepatoprotective And Antioxidant Activity Of Ethanolic Extracts Of Edible Lotus (*Nelumbo Nucifera Gaertn.)* Leaves, Food Chemistry, 2010; 120: 873–878.
151. Usha Rani K, Amirtham D and Nataraja TS: Hepatoprotective activity of *Nilgirianthus ciliatus* (Nees) bremek in paracetamol induced toxicity in Wister albino rats. African Journal of Internal Medicine, 2013; 1(4): 026-030.
152. Shamshun N and Mamta Kumari: Ameliorating effect of *Nigella sativa* oil in thioacetamide-induced liver cirrhosis in albino rats. Indian journal of Pharmaceutical education and Research, 2013; 47(2): 135-139.
153. Delhi, 1997: 45-7 J.H.Chin, A.H.Hussin And S.Ismai, Anti-Hepatotoxicity Effect of *Orthosiphon Stamineus Benth* Against Acetaminophen-Induced Liver Injury In Rats By Enhancing Hepatic GST Activity, Pharmacognosy Research, March-April 2009; 1: 53-58.
154. R.R. Chattopadhyay, S.K. Sarkar, S. Ganguly, C. Medda, T.K. Basu, Hepatoprotective Activity Of *Oclmum Sanctum* Leaf Extract Against Paracetamol Induced Hepatic Damage In Rats, *Indian Journal Of Pharmacology, 1992; 24: 163-165*.
155. Suresh Kumar SV, Sujatha C, Syamala J, Nagasudha B and Mishra SH: Hepatoprotective effect of root extract of *Operculina turpethum* Linn. Against paracetamol-induced hepatotoxicity in rats. Indian Journal of Pharmaceutical Sciences, 2006; 68: 32-5.
156. Pandian S, Badami S and Shankar M: Hepatoprotective Activity of Methanolic Extract of *Oldenlandia herbacea* Against D – Galactosamine Induced Rats. International Journal of Applied Research in Natural Products, 2008; 6(1): 16-19.
157. R. Harish, T. Shivanandappa, Antioxidant Activity and Hepatoprotective Potential of *Phyllanthus Niruri*, Food Chemistry, 2006; 95: 180–185.
158. Hisashi Matsuda A, Kiyofumi Ninomiya A,B, Toshio Morikawa A,B, Daisuke Yasuda A, Itadaki

Yamaguchi A,Masayuki Yoshikawa A,*, Hepatoprotective Amide Constituents From The Fruit Of *Piper Chaba* : Structural Requirements, Mode Of Action, And New Amides, Bioorganic & Medicinal Chemistry, 2009; 17: 7313–7323.

159. Hyeung Sik Lee, Hyo Chan Ahn, Sae Kwang Ku, Hypolipidemic Effect Of Water Extracts Of *Picrorrhiza Rhizoma* In PX-407 Induced Hyperlipemic ICR Mouse Model With Hepatoprotective Effects: A Prevention Study, Journal Of Ethnopharmacology, 2006; 105: 380–386.
160. Jagruti A. PATEL & Urvi S. SHAH, hepatoprotective activity of *Piper Longum* Traditional Milk extract on carbon tetrachloride induced liver toxicity in wistar rats, 2009; 8: 121-129.
161. S. C. Tripathi, G, K. Patnaik And B. N. Dhawan, Hepatoprotective Activity Of Picroliv Against Alcohol-Carbon Tetachloride Induced Damage In Rat, Indian Journal Of Pharmacology, 1991; 23: 143-148.
162. Guntupalli M. Mohana Rao, Chandana V. Rao, Palpu Pushpangadan, Annie Shirwaikar, Hepatoprotective Effects Of Rubiadin, A Major Constituent Of *Rubia Cordifolia* Linn., Journal Of Ethnopharmacology, 2006; 103: 484–490.
163. M. *V. Natu. Suraj Agarwal. S. L. Agarwal And S. Agarwal,* Protective Effect Of *Ricinus communis* Leaves In Experimental Liver Injury. Indian Journal Of Pharmacology, *1977; 9(4)*: 265-268.
164. Amani, S. Awaad, A D. J. Maitlandb And G. A. Solimanc, Hepatoprotective Activity Of *Schouwia Thebica* Webb, Bioorganic & Medicinal Chemistry Letters, 2006; 16: 4624–4628.
165. H. Madani, M. Talebolhosseini, S. Asgary and G. H. Naderi, Hepatoprotective activity of *Silybum marianum* And *Clchorium Intybus* against Thioacetamide In Rats, Pakistan Journal of Nutrition, 2008; 7(1): 172-176.
166. T. K. Praveen, S.D. Harmaraj, Jitendra Bajaj, S. P. Dhanabai, S.Manimaran, M.J.Nanjan, Rema Razdan, Hepatoprotective activity of petroleum ether, diethyl ether and methanol extract of *Scoparia Dulcis* L. Against CCL4-Induced Acute Liver Injury In Mice, Indian Journal Of Pharmacology, June 2009; 41: 110-114.
167. Nwachukwu DC, Okwuosa CN, Chukwu PU, Nkiru AN and Udeani T: Hepatoprotective Activity of Methanol Extract of the Seeds of *Sesamum Indicum* in Carbon Tetrachloride Induced Hepatoxicity in Rats. Indian Journal of Novel Drug delivery, 2011; 3(1): 36-42.
168. Reddipalli Hemalatha, Anti-Hepatotoxic and Anti-Oxidant Defense Potential of *Tridax Procumbens*, International Journal of Green Pharmacy, July 2010; 164-169.
169. Vipul Gujrati, Nilesh Patel, Venkat N.Rao, K.Nandakumar, T.S. Gouda, Md.Shalam, S.M.Shanta Kumar, Hepatoprotective Activity Vof Alcoholic And Aqueous Extracts Of Leaves *Of Tylophora Indica*(Linn.) In Rats, Indian Journal Of Pharmacology, Feb-2007; 39: 43-47.
170. El-Banna H, Soliman M and Al-wabel N: Hepatoprotective Effects of Thymus and *Salvia* Essential oils on Paracetamol-Induced Toxicity in Rats. Journal of Physiology and Pharm acology Advances, 2013; 3(2): 41-47.
171. Pimple BP, Kadam PV, Badgujar NS, Bafna AR and Patil MJ: Protective effect of *Tamarindus indica Linn*. against paracetamol-induced hepatotoxicity in rats. Indian Journal of Pharmaceutical Sciences, 2007; 69: 827-831.
172. Didem Deliorman Orhan, Nil¨Ufer Orhan, Ender Ergun, Fatma Ergun, Hepatoprotective Effect Of *Vitis Vinifera* L. Leaves On Carbontetrachloride-Induced Acute Liver Damage In Rats, Journal of Ethnopharmacology, 2007; 112: 145–151.
173. B. K. Manjunatha And S.M. Vidya, Hepatoprotective activity of *Vitex Trifolia* against CCl4 induced hepatic damage, Indian Journal Of Pharmaceutical Sciences, April 2008; 70(2): 241-245.
174. Geegi PG, Anitha P, Anthoni Samy A and Kanimozhi R: Hepatoprotective activity of *Vanilla planifolia* against paracetamol induced hepatotoxicity in albino rats. International Journal of Institutional Pharmacy and Life Sciences, 2011; 1(3): 70-74.
175. B.K. Chandan, A.K. Saxena, Sangeeta Shukla, N. Sharma, D.K. Gupta, K. Singh, Jyotsna Suri, M. Bhadauria, G.N. Qazi, Hepatoprotective Activity of *Woodfordia Fruticosa* Kurz Flowers against Carbontetrachloride induced Hepatotoxicity, Journal Of Ethnopharmacology, 2008; 119: 218–224.
176. Pallab KH, Malaya Gupta, Upal KM, Chandi CK and Laxmanan M: Hepatoprotective effect of *Wedelia calendulaceae* against thioacetamide induced liver damage in rats. Pharmacologyonline, 2007; 3: 414-421.
177. Lalit singh, Ranawat, Jigar Bhatt, Jagruti Paetl, Hepatoprotective activity of Ethanolic Extracts of Bark of *Zanthoxylum Armatum* In Ccl4 Induced Hepatic Damage In Rats, Journal of Ethnopharmacology, 2010; 127: 777–780.
178. Parameshwar P, Reddy YN and Aruna Devi M: Hepatoprotective and antioxidant activities of *Ziziphus rotundifolia* (Linn.) against carbon tetrachloride-induced hepatic damage in rats. International journal of pharmaceutical sciences and nanotechnology, 2012; 5(3): 1775-1779.
179. Prasanna Kumar S, Basheeruddin Asdaq SM, Prem Kumar N, Asad M and Khajuria DK: Protective Effect Of *Zizyphus Jujuba* Fruit Extract Against Paracetamol And Thioacetamide Induced Hepatic Damage In Rats. The Internet Journal of Pharmacology, 2009; 7(1): DOI: 10.5580/2991.