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Liver Toxicity and Role of Herbal Drugs as Hepatoprotective Agents: An Overview

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Abstract

The liver is a vital organ that plays a major role in the metabolism and excretion of xenobiotics from the body. Liver injury or liver dysfunction is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. Liver cell injury caused by various toxic chemicals (certain antibiotics, chemotherapeutic agents, carbon tetrachloride, thioacetamide, excessive alcohol consumption, and microbes are well-studied. The available synthetic drugs to treat liver disorders in this condition also cause further damage to the liver. Hence, Herbal drugs have become increasingly popular and their use is widespread. Herbal medicines have been used in the treatment of liver diseases for a long time so the maintenance of a healthy liver is essential for the overall well-being of an individual. Various herbal medicines are available in the market. The liver is the largest solid organ in the upper abdomen that aids in digestion and removes waste products and worn-out cells from the blood. Liver injury or liver dysfunction is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. Liver injury induced by toxins is more common nowadays. Herbal remedies are focused in the pharmaceutical industry to evolve a safe route for liver disorders. The present review is aimed at compiling data on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models using the modern scientific system.

1. Introduction

Many of the modern drugs are mainly based on synthetic chemical compounds however have been found to have harmful side effects on the human system. This has triggered off extensive research and development in the field of herbal medicine. There is a growing demand for herbal medicine in most of the developed and developing countries of the world today (Handa *et al.*, 1986). The predominant type of liver disease varies according to country and may be influenced by local factors. The causative factors of liver disorders include virus infection exposure to our consumption of certain chemicals. The substance that injures the liver cells in some people and results from serious harm to the liver caused by drugs and by the combination of drugs and other substances is an important health problem. Treatment options for common liver diseases such as cirrhosis, fatty liver, and chronic hepatitis are problematic. The effectiveness of treatment such as interferon colchicine, penicillamine, and corticosteroid are inconsistent at best, and the incidence of side effects is profound through the treatment is worse than the disease. Physicians and patients need effective therapeutic agents with low incidents of side effects. There are few effective therapeutic agents with a low incident of side effects. Few effective plants cure liver diseases so considerable interest has developed in the examination of these numerous plants remedies which are useful in liver diseases (Karandikar *et al.*, 1963; Thyagarajan *et al.*, 2002). The present review is aimed at compiling the data on promising herbal extracts from the plant that have been tested in the hepatotoxicity model using the modern scientific system.

The liver is considered to be one of the most vital organs that functions as a center of the metabolism of nutrients such as carbohydrates, proteins, and lipids and excretion of waste metabolites. Additionally, it is also handling the metabolism and excretion of drugs and other xenobiotics from the body thereby providing protection against foreign substances by detoxifying and eliminating them. Hepatotoxicity implies chemical-driven liver damage (Agarwal. 2001). Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic

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ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g. microcystins), and herbal remedies can also induce hepatotoxicity. Chemicals that causes liver injury are called hepatotoxins. Some of the inorganic compounds producing hepatotoxicity are arsenic, phosphorus, copper, and iron. The organic agents include certain naturally occurring plant toxins such as pyrrolizidine alkaloids, mycotoxins, and bacterial toxins. In addition, exposure to hepatotoxic compounds may be occupational, environmental, or domestic that could be accidental, homicidal, or suicidal ingestion (Sidana *et al.*, 2011). Hepatoprotective agents are those compounds, which mitigate the liver injury caused by hepatotoxic agents. Hepatoprotective effects of plant drugs and herbal formulations are studied against chemicals (alcohol, CCl_4, beta galactosamine, thioacetamide (TAA)) and drugs (Paracetamol (PCM), nimesulide, antitubercular drugs like isoniazid, rifampicin, etc.) induced hepatotoxicity in rats and mice as they virtually mimic any form of naturally occurring liver disease. In the absence of reliable liver protective drugs in allopathic medical practices, herbs play important role in the management of various liver disorders. However, in Ayurveda, many indigenous plants have been used as hepatoprotective agents. The Indian Traditional Medicine like Ayurveda, Siddha, and Unani are predominantly based on the use of plant materials. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy, and cost-effectiveness. The association of medicinal plants with other plants in their habitat also influences their medicinal values in some cases. One of the important and well-documented uses of plant products is their use as hepatoprotective agents. Hence, there is an ever-increasing need for a safe hepatoprotective agent (Lee *et al.*, 2000; Harshmohan. 2002). The liver is considered to be one of the most vital organs that functions as a center of the metabolism of nutrients such as carbohydrates, proteins, and lipids and excretion of waste metabolites. Additionally, it is also handling the metabolism and excretion of drugs and other xenobiotics from the body thereby providing protection against foreign substances by detoxifying and eliminating them. The bile secreted by the liver has, among other things, plays an important role in digestion. Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, carbon tetrachloride (CCl_4), TAA, etc., chronic alcohol consumption, and microbes are well-studied. Enhanced lipid peroxidation during the metabolism of ethanol may result in the development of hepatitis leading to cirrhosis. Since time immemorial, mankind has made use of plants in the treatment of various ailments. The Indian Traditional Medicine like Ayurveda, Siddha, and Unani are predominantly based on the use of plant materials. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy, and cost-effectiveness. 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 plant products is their use as hepatoprotective agents. Hence, there is an ever-increasing need for a safe hepatoprotective agent (Phaneendra *et al.*, 2011; Phaneendra *et al.*, 2011).

The liver is considered to be one of the most vital organs that functions as a center of the metabolism of nutrients such as carbohydrates, proteins, lipids, and excretion of waste metabolites. Additionally, it is also handling the metabolism and excretion of drugs and other xenobiotics from the body thereby providing protection against foreign substances by detoxifying and eliminating them. The bile secreted by the liver has, among other things, plays an important role in digestion. Hepatic disease (Liver disease) is a term that affects the cells, tissues, structures, or functions of the liver. The liver has a wide range of functions, including detoxification, protein synthesis, and production of biochemicals necessary for digestion and synthesis as well as the breakdown of small and complex molecules, many of which are necessary for normal vital functions. Herbal drugs are more widely used than allopathic drugs as hepatoprotective because they are inexpensive, have better cultural acceptability, have better compatibility, with the human body, and have minimal side effects. These herbal drugs have shown the ability to maintain the normal functional status of the liver with or without fewer side effects. The liver plays an astonishing array of vital functions in the maintenance, performance, and regulation of the homeostasis of the body. It is involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision, and reproduction. Therefore, the maintenance of a healthy liver is essential for the overall well-being of an individual. Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, CCl_4, TAA, etc., chronic alcohol consumption, and microbes is well-studied. Since The Indian Traditional Medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy, and cost-effectiveness. Several Indian medicinal plants have been extensively used in the Indian traditional system of medicine for the management of the liver disorder. The use of natural remedies for the treatment of liver diseases has a long history and medicinal plants and their derivatives are still used all over the world in one form or the other for this purpose. Scientific evaluation of plants has often shown that active principles in these are responsible for

therapeutic success. A large number of medicinal plants have been tested and found to contain active principles with curative properties against a variety of diseases. Liver protective plants contain a variety of chemical constituents like phenols, Coumarins, Lignans, essential oil, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids, and xanthenes (Ilyas *et al*, 2016; Tabeshpour *et al*, 2020; Shamsi-Baghbanan *et al*, 2014; Madrigal-Santillán *et al*, 2014; Al Eid and Al-Asmary. 2014; Rouf *et al*, 2021).

2. Hepatotoxicity Inducing Agents

2.1. Carbon tetrachloride (CCl_4) Induced Hepatotoxicity

Liver injury due to carbon tetrachloride in rats was first reported in 1936 and has been widely and successfully used by many investigators. Carbon tetrachloride is metabolized by cytochrome P-450 in the endoplasmic reticulum and mitochondria with the formation of CCl_3O-, a reactive oxidative free radical, which initiates lipid peroxidation. Administration of a single dose of CCl_4 to a rat produces centrilobular necrosis and fatty changes within 24 hrs. The poison reaches its maximum concentration in the liver within 3 hrs of use. Thereafter, the level falls and by 24 hrs there is no CCl_4 left in the liver. The development of necrosis is associated with leakage of hepatic enzymes into serum (Cameron *et al.*, 1936; Handa and Sharma. 1990; Shirwaiker *et al.*,1996; Zimmerman and Hayman. 1976; Agarwal and Mehendale. 1983; Dawkins. 1963).

2.2. Galactosamine Induced Hepatotoxicity

D-Galactosamine-induced liver damage has been extensively used as an experimental model. Galactosamine produces the diffuse type of liver injury simulating viral hepatitis. It presumably disrupts the synthesis of essential uridylate nucleotides resulting in organelle injury and ultimately cell death. Depletion of those nucleotides would impede the normal synthesis of RNA and consequently would produce a decline in protein synthesis. This mechanism of toxicity brings about an increase in cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductules or canalicular membrane of hepatocytes. Galactosamine decreases the bile flow and its content i.e. bile salts, cholic acid, and deoxycholic acid. Galactosamine reduces the number of viable hepatocytes as well as the rate of oxygen consumption (Saraswat *et al.*, 1996).

2.3. Thioacetamide Induced Hepatotoxicity

Thioacetamide (TAA) interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury. A metabolite of thioacetamide is responsible for hepatic injury. The TAA reduces the number of viable hepatocytes as well as the rate of oxygen consumption. It also decreases the volume of bile and its content i.e. bile salts, cholic acid, and deoxycholic acid (Saraswat *et al.*, 1996).

2.4. Alcohol Induced Hepatotoxicity

Among the organs, the liver is most susceptible to the toxic effects of ethanol. Alcohol consumption is known to cause fatty infiltration, hepatitis, and cirrhosis. Fat infiltration is a reversible phenomenon that occurs when alcohol replaces fatty acids in the mitochondria. Hepatitis and cirrhosis may occur because of enhanced lipid peroxidative reaction during the microsomal metabolism of ethanol. It is generally accepted that alcohol can induce *in vivo* changes in membrane lipid composition and fluidity, which may eventually affect cellular functions. Among the mechanisms responsible for the effects of alcohol, an increase in hepatic lipid peroxidation leads to alteration in membrane phospholipid composition. The effects of ethanol have been suggested to be a result of the enhanced generation of oxy free radicals during its oxidation in the liver. The peroxidation of membrane lipids results in loss of membrane structure and integrity. This results in elevated levels of ¡-glutamyl transpeptidase, a membrane-bound enzyme in serum. Ethanol inhibits glutathione peroxidase, decreases the activity of catalase, superoxide dismutase, along increases levels of glutathione in the liver. The decrease in the activity of antioxidant enzymes superoxide dismutase, glutathione peroxidase is speculated to be due to the damaging effects of free radicals produced following ethanol exposure or could be due to a direct effect of acetaldehyde, formed by oxidation of ethanol (Sandhir and Gill. 1999; Kapur *et al.*, 1994).

2.5. Paracetamol Induced Hepatotoxicity

Paracetamol (PCM), a widely used analgesic and antipyretic drug, produces acute liver damage in high doses. The PCM use causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm followed by the large excessive hepatic lesion. The covalent binding of N-acetyl-P-benzoquinone imine, an oxidative product of PCM to sulphydryl groups of protein, results in lipid peroxidative degradation of glutathione level and thereby, produces cell necrosis in the liver (Kapur *et al.*, 1994).

2.6. Nonsteroidal Antiinflammatory Drugs

Although individual analgesics rarely induce liver damage due to their widespread use, NSAIDS have emerged as a major group of drugs exhibiting hepatotoxicity. Both dose-dependent and idiosyncratic

reactions have been documented. Aspirin and phenylbutazone are associated with intrinsic hepatotoxicity and idiosyncratic reaction has been associated with ibuprofen, sulindac, phenylbutazone, piroxicam, diclofenac, and indomethacin (Padma *et al.*, 1998).

2.7. Glucocorticoids

Glucocorticoids are so named due to their effect on carbohydrate mechanisms. They promote glycogen storage in the liver. Enlarged liver is a rare side effect of long-term steroid use in children. The classical effect of prolonged use both in the adult and the pediatric population is steatosis. Herbal-based therapeutics for liver disorders have been in use in India for a long time and have been popularized the world over by leading pharmaceuticals. The present review is aimed at compiling data based on reported works on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models (Thyagarajan *et al.*, 2002).

3. Hepatoprotective Herbs

Herbal-based therapeutics for liver disorders have been in use in India for a long time and have been popularized the world over by leading pharmaceuticals. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver diseases. The limiting factors that contribute to this eventuality are (i) lack of standardization of the herbal drugs; (ii) lack of identification of active ingredient(s)/principles(s); (iii) lack of randomized controlled clinical trials (RCTs), and (iv) lack of toxicological evaluation. The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurvedic treatment, and extending to the Chinese, European and other systems of traditional medicines. The 21st century has seen a paradigm shift towards the therapeutic evaluation of herbal products in liver disease models by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence-based medicinal evaluation, standardization, and randomized placebo-controlled clinical trials to support clinical efficacy. A large number of plants and formulations have been claimed to have hepatoprotective activity. Nearly 160 phytoconstituents from 101 plants have been claimed to possess liver-protecting activity. In India, more than 87 plants are used in 33 patented and proprietary multi-ingredient plant formulations. Despite the tremendous advances made, no significant and safe hepatoprotective agents are available in modern therapeutics. Therefore, due importance has been given globally to develop plant-based hepatoprotective drugs effective against a variety of liver disorders. The present review is aimed at compiling data based on reported works on promising phytochemicals from medicinal plants that have been tested in hepatotoxicity models. Therefore, a large number of plants and formulations have been claimed to have hepatoprotective activity so the development of plant-based hepatoprotective drugs has been given importance in the global market. This review article has been presented to enumerate some indigenous plants that have hepatoprotective properties such as *Andrographic paniculata, Chamomile capitula, Silybum marianum, Coccinia grandis, Flacourtia indica, Wedelia calendulacea, Annona squamosa, Prostechea michuacana, Ficus carica, Lepidium sativum, Sargassum polycystum, Solanum nigrum, swertia chirata, Phyllanthus emblica, Curcuma longa, Picrorhiza kurroa, Azadirachta indica, Aegle marmelos, Cassia roxburghii, Orthosiphon stamineus, Jatropha curcas, Foeniculum vulgare, Trigonella foenum graecum, Eclipta alba, Garcinia mangostana* Linn is reviewed (Kumar. 2012).

3.1. *Annona squamosa*

The extracts of *Annona squamosa* (custard apple) (300 & 350 mg/kg BW) were used to study the hepatoprotective effect in isoniazid+rifampicin induced hepatotoxic animal model to explore its use for the treatment of hepatotoxicity in humans. There was a significant decrease in total bilirubin accompanied by a significant increase in the level of total protein and also a significant decrease in ALP, AST, alanine transaminase (ALT), and γ-GT in the treatment group as compared to the hepatotoxic group. In the histopathological study, the hepatotoxic group showed hepatocytic necrosis and inflammation in the centrilobular region with portal triaditis. The treatment group showed minimal inflammation with moderate portal triaditis and their lobular architecture was normal. It should be concluded that the extracts of *A. squamosa* were not able to revert completely hepatic injury induced by Isoniazid+rifampicin, but it could limit the effect of these drugs in the liver. The effect of extracts compared with standard drug silymarin (Saleem *et al.*, 2008). In another study, the protective effect was evaluated in diethylnitrosamine-induced hepatotoxicity. This study revealed that the extracts of *A. squamosa* exerted a hepatoprotective effect and the plant extract could be an effective remedial for chemical-induced hepatic damage (Raj *et al.*, 2009).

3.2. *Argemone mexicana*

The protective effects of the aqueous extracts of *Argemone mexicana* (Linn.) whole plant, against CCl_4 induced hepatic failure in male albino rats (Wistar

strain) was tested. For the acute and massive invasion of hepatopathy, CCl_4 (i.p. injection of CCl_4+Olive oil in 1:1 ratio; 2 ml/.kg) was used and the insidious intoxication was evidenced by significant turmoil of various biochemical parameters followed by significant weight loss in the toxic control group. The aqueous extracts (250 mg/kg and 150 mg/kg of body weight) for 7 days, elicited protective action since the elevated levels of marker enzymes (AST, ALT, ALP) of liver function were found to decrease progressively in a dose-dependent manner with net weight gain. In the aqueous extract 250 mg/ kg treated rat group all the market enzymes were analyzed to be decreasing significantly (AST, ALT, ALP) and the final body weight was also significantly increased when compared with the toxic control group. The serum total protein and the serum albumin were also approaching normal values. The results found in aqueous extract 250 mg/kg treated rats were quite promising and were comparable with a standard polyherbal drug Liv-52. The statistically processed results support the conclusion, that the aqueous extract of *A. mexicana* (Linn.) whole plant (250 mg/kg and 150 mg/kg) possesses dose-dependent, significant protective activity against CCl4 induced hepatotoxicity (Das *et al.*, 2009).

3.3. *Amorphophallus campanulatus* Roxb (Tubers)

Ethanolic and aqueous extract of *Amorphophallus campanulatus* tubers were evaluated against CCl_4 induced hepatic damage in rats. The extracts at a dose of 500 mg/kg were used orally once daily. The substantially elevated serum enzymatic levels were significantly restored towards normalization by the extracts. The biochemical observations were supplemented with histopathological examination of the rat liver section. The ethanol extract was found more potent hepatoprotective than aqueous extract (Sanjay *et al.*, 2009; Ahsan *et al.*, 2009).

3.4. *Andrographis paniculata*

Studies proved that *Andrographis paniculata* (Kalmegh) antihepatotoxic activity of the *A. paniculata* (acanthaceae) methanolic extract (equivalent to 100 mg/kg of andrographolide) and 761.33 mg/kg ip, of the andrographolide-free methanolic extract (equivalent to 861.33 mg/kg of the methanolic extract) of the plant, using CCl4-intoxicated rats. Biochemical parameters like serum transaminase, SGOT and SGPT, serum alkaline phosphatase (ALP), serum bilirubin, and hepatic triglycerides were estimated to assess liver function. The results suggest that andrographolide is the major active antihepatotoxic principle present in *A. paniculata.* Other species of *Andrographis* i.e. *Andrographis lineata nees* had also proved the hepatoprotective effect of *A. lineate* (Acanthaceae) extracts in CCl_4-induced liver injury in rats. Male Wistar rats with chronic liver damage, induced by subcutaneous injection of 50% v/v CCl_4 in liquid paraffin at a dose of 3 mL/kg on alternate days for 4 weeks, were treated with methanol and aqueous extracts of A. lineata orally at a dose of 845 mg/kg/day. The biochemical parameters such as serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase (SGPT), serum bilirubin, and ALP were estimated to assess the liver function. Histopathological examinations of liver tissue corroborated well with the biochemical changes. The activities of extracts were comparable to a standard drug. Andrographolide, the major antihepatotoxic component of the plant, exerted a pronounced protective effect in rats against hepatotoxicity induced by CCl_4, D-galactosamine, PCM, and ethanol. Andrographolide inhibited the CCl_4-induced increase in the activity of serum glutamate oxaloacetate transaminase, SGPT, ALP, bilirubin, and hepatic triglycerides. Oxidative damage through free radical generation is involved in the hepatotoxic effect of CCl_4 and PCM. The antioxidant property of Andrographolide is claimed to be one of the mechanisms of hepatoprotective effect. Adjuvant to hepatoprotective action drug is commonly have Antibacterial, Anti-inflammatory, Immunostimulatory, Antidiarrhoeal, Anti-human immunodeficiency virus (HIV), Antipyretic, Antimalarial & Antivenom activity, and used in urinary infections.

3.5. *Aerva lanata*

The study was conducted to test the hepatoprotective activity of hydroalcoholic extract of *Aerva lanata* against PCM-induced liver damage in rats. The hydroalcoholic extract of *A. lanata* (600 mg/kg) was used orally on the animals with hepatotoxicity induced by PCM (3 gm/kg). Silymarin (25 mg/kg) was given as a reference standard. All the test drugs were used orally by suspending in 0.5 % Carboxymethyl cellulose solution. The plant extract was effective in protecting the liver against the injury induced by PCM in rats. This was evident from a significant reduction in serum enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), ALP, and bilirubin. The hydroalcoholic extract of *A. lanata* possesses hepatoprotective activity against PCM-induced hepatotoxicity in rats (Manokaran *et al.*, 2008).

3.6. *Alocasia indica* Linn

Oral administration of hydroalcoholic extract of *A. indica* (250 and 500 mg/kg) effectively inhibited CCl_4 and PCM induced changes in the serum marker enzymes, cholesterol, serum protein, and albumin in a dose-dependent manner as compared to the drug silymarin-treated groups. Hepatic steatosis, fatty

infiltration, hydropic degeneration and necrosis observed in CCl_4 and PCM-treated groups were completely absent in histology of the liver sections of the animals treated with the extracts. The hydroalcoholic extract of leaves of an indica possesses significant potential as a hepatoprotective agent (Wahid *et al.*, 2008).

3.7. *Aegle marmelos*

Aegle marmelos (Bael, family: Rutaceae) leaves which are also called *Bilva* in ancient Sanskrit, were used as an herbal drug in the Indian System of medicine. The hepatoprotective effect of *A. marmelos* in alcohol-induced liver injury was evaluated on rats using essential marker biochemical parameters. The *Bael* leaves have an excellent hepatoprotective effect (Thyagarajan *et al.*, 2002; Singanan *et al.*, 2007).

3.8. *Apium graeolens* Linn

The hepatoprotective activity of the *Apium graeolens* Linn (Apiaceae) against CCl_4 induced hepatotoxicity in albino rats. The degree of protection was measured by using biochemical parameters like serum transaminases (SGOT and SGPT), ALP, total protein, and albumin. The methanolic extracts showed the most significant hepatoprotective activity comparable with the standard drug silymarin. Other extracts namely petroleum ether and acetone also exhibited a potent activity (Ahmed *et al.*, 2002).

3.9. *Azadirachta indica (Neem)*

Effect of *A. indica* leaf *(Meliaceae)* extract on serum enzyme levels (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acid phosphatase, and alkaline phosphatase) elevated by PCM in rats was studied to observe any possible hepatoprotective effect of this plant. It is stipulated that the extract-treated group was protected from hepatic cell damage caused by PCM induction. The findings were further confirmed by a histopathological study of the liver. The antihepatotoxic action of picroliv seems likely due to an alteration in the biotransformation of the toxic substances resulting in decreased formation of reactive metabolites (Chattopadhyay *et al.*, 1992).

3.10. *Baliospermum montanum*

Rats and primary cultures of rat hepatocytes were used as the *in vivo* and *in vitro* models to evaluate the hepatoprotective activity of sub-fractions from total methanol extract of *Baliospermum montanum*. The CCl_4 was selected as a hepatotoxin. Silymarin was the reference hepatoprotective agent. In the *in vivo* study, serum transaminases, ALP, total bilirubin, total cholesterol, albumin together with total protein and histopathological examination were the criteria for the evidence of liver injury. The CCl_4 caused alterations in all the biochemical parameters and centrilobular necrosis. Among the Ethyl methyl ketone and methanol sub-fractions tested (50,100 and 150 mg/kg), methanol sub-fraction (150 mg/kg) of the bio-active total methanol extract and silymarin (100 mg/kg) enhanced liver cell recovery by restoring all the altered biochemical parameters to normal. In the in vitro study, the release of transaminases, total protein together, and hepatocyte viability were the criteria. Primary cultures of hepatocytes were treated with carbon tetrachloride (l0 ul/ml) and various concentrations (100,500 and 1000jig/ml) of ethyl methyl ketone and methanol sub-tractions of total methane) extract and silymarin (100 ug/ml). The CCl_4 reduced hepatocyte viability and also altered the biochemical parameters, which were restored significantly by ethyl methyl ketone (1000 (mg/ml) and methanol (500 and 1000 ug/ml) subfractions. The *B. montanum* possesses the hepatoprotective activity against CCl_4 induced liver injury in both rats and primary cultures of rat's hepatocytes (Suresh and Mishra. 2009).

3.11. *Curcuma longa*

Curcuma longa or turmeric is a member of the Zingiberaceae family which is a perennial herb with short and thick rhizomes. Turmeric has been used extensively in traditional Chinese medicine and the Ayurvedic medical system. *C. longa* contains about 2% volatile oil, composed mainly of bturmerone, monoterpenes (Leung and Foster 1996), 5% curcuminoids, curcumin, minerals, carotene, and vitamin C. The active constituent of *C. longa* is Curcumin, which is the yellow pigment of turmeric. The hepatoprotective activity of the ethanol extract of *C. longa* was tested against PCM-induced liver damage in rats. At the dose of 600 mg/kg, PCM induced liver damage in rats as manifested by a statistically significant increase in serum ALT and AST and ALP. Pretreatment of rats with the ethanolic extract of *C. longa (100* mg/kg) before PCM dosing at 600 mg/kg statistically lowered the three serum liver enzyme activities. Moreover, treatment of rats with only the ethanolic extract of *C. longa* (100 mg/kg) had no effects on the liver enzymes. This current result suggests that ethanolic extract of *C. longa* has a potent hepatoprotective effect against PCM-induced liver damage in rats. Like silymarin, turmeric has been found to protect animal livers from a variety of hepatotoxic substances, including CCl_4, galactosamine, pentobarbitol, 1-chloro-2,4-dinitrobenzene, 4-hydroxy-nonenal, and PCM. Diarylhepatonoids including Curcumin are the active constituent of the plant which is responsible for hepatoprotective activity (Selvam *et al.*, 1995).

3.12. *Coccinia grandis*

Alcoholic extract of the fruits of *Coccinia grandis* was evaluated in CCl4 induced hepatotoxicity in rats and levels of AST, ALT, ALP, total proteins, total and direct bilirubin were evaluated. At a dose level of 250 mg/kg, the alcoholic extract significantly decreased the activities of serum enzymes (AST, ALT, and ALP) and bilirubin which were comparable to that of silymarin revealing its hepatoprotective effect (Srinivas and Shalini. 1991).

3.13. *Chamomilla recutita*

Hepatoprotective activity of aqueous ethanol extract of *Chamomilla recutita* capitula against PCM induced hepatic damage in albino rat has observed the effect of aqueous ethanol extract of *C. recutita* capitula on blood and liver glutathione Na^+-K^+-ATPase activity, serums marker enzyme, serums bilirubin glycogen, and thiobarbituric acid reactive substances against PCM induced damage in the rats have been studied to find out the possible mechanism of hepatoprotective. The extract of chamomile has a reversal effect on the levels of the above-mentioned parameter in PCM hepatotoxicity. The extract of *C. recutita* functions as a hepatoprotective agent and this hepatoprotective activity of chamomile may be due to normalization of impaired membrane function activity (Gupta and Misra. 2006).

3.14. *Casuarina equisetifolia*

The methanol extract of plant material of some plants like *Casuarina equisetifolia*, *Cajanus cajan*, *Glycosmis pentaphylla*, *Bixa orellana*, *Argemone mexicana*, *Physalis minima*, *Caesalpinia bonduc* belonging to the different families were studied for hepatoprotective activity against Swiss albino rats with liver damage induced by CC14. It was found that the methanol extract of *B. orellana*, *C. cajan*, *G. pentaphylla* and *C. equisetifolia* at a dose of 500 mg/kg body exhibited moderate protective effect by lowering the serum level of ALT, SGPT AST, SCOT, and cholesterol to a significant extent. The hepatoprotective activity was also supported by histopathological studies of liver tissue (Clawson. 1989).

3.15. Cichorium intybus

The effects of different concentrations of the hydroalcoholic extract of dried powdered leaves of *Cichorium intybus* L, on CCl_4 induced hepatotoxicity in vivo in rats and CCl_4 induced cytotoxicity in isolated rat hepatocytes were investigated. Rats received different concentrations of the extract by i.p. injection for 3 consecutive days before the injection of (3 ml/kg) CCl_4 (i.p.). Twenty-four h after CCl_4 injection the animals were sacrificed and the livers were dissected for biochemical and histopathological studies. The results showed that the *C. intybus* extract could protect the liver from CCl_4 induced damages with doses of 50 and 100 mg/kg, but concentrations higher than 200 mg/kg were less effective. For in vitro studies, the extract was added to the suspension of freshly isolated rat hepatocytes incubated in Krebs-Henseleit buffer under a gas flow of 95 % O_2 and 5 % CO_2, 20 minutes before the addition of l0 mM of CCl_4. The extract with a concentration of 60 to 600 ug/ml protected the cells against CCl_4 induced cytotoxicity, but concentrations of >1.5 mg/ml and higher increased the CCl_4 induced cytotoxicity. The Cichorium intybus extract itself was toxic towards isolated hepatocytes in concentrations above 3.6 mg/ml. The traditional beliefs on the hepatoprotective effect of the *C. intybus* extract, however, the concentrations were hepatotoxic (Jamshidzadeh *et al.*, 2006; Godgoli and Mishra. 1997). It is a popular Ayurvedic remedy for the treatment of liver diseases. It is commonly known as kasni and is part of polyherbal formulations used in the treatment of liver diseases. In mice, liver protection was observed at various doses of *C. intybus* but optimum protection was seen with a dose of 75 mg/kg given 30 minutes after CCl_4 intoxication. An alcoholic extract of the *C. intybus* was found to be effective against chlorpromazine-induced hepatic damage in adult albino rats. A bitter glucoside, Cichorin has been reported to be the active constituent of the herb (Vadivu *et al.*, 2008).

3.16. *Calotropis procera*

Hydro-ethanolic extract (70 %) of *Calotropis procera* flowers was prepared and tested for its hepatoprotective effect against PCM-induced hepatitis in rats. Alternation in the levels of biochemical markers of hepatic damage like SGPT, SCOT, and ALP, bilirubin, cholesterol, HDL, and tissue GSH was tested in both treated and untreated groups. The PCM (2 g/kg) has enhanced the SGPT, SGOT, ALP, bilirubin, and cholesterol levels and reduced the serum levels of HDL and tissue level of GSH. Treatment with hydro-ethanolic extract of *C. procera* flowers (200 mg/kg and 400 mg/kg) has brought back the altered levels of biochemical markers to the near-normal levels in a dose-dependent manner (Ramachandra *et al.*, 2007).

3.16. *Cassia roxburghii*

Seeds of *Cassia roxburghii* DC have been used in ethnomedicine for various liver disorders for its hepatoprotective activity. The methanolic extract of *C. roxburghii* reversed the toxicity produced by ethanol CCl_4 combination in a dose-dependent manner in rats. The extract at the doses of 250 mg/kg and 500 mg/kg are comparable to the effect produced by Liv-52®, a well-established plant-based hepatoprotective formulation against hepatotoxins (Arulkumaran *et al.*, 2009).

3.17. *Capparis deciduas*

Hepatoprotective effect of aqueous and methanolic extract of *Capparis decidua* stems were evaluated against CCl_4-induced liver damage in rats. Simultaneous oral administration of both extracts (200,400 mg/kg) with CCl_4 in paraffin oil (1:9 v/v) at a dose of 0.2 ml/kg for 10 days recovered the liver fatty changes induced by the hepatotoxic compound observed in the intoxicated control rats. Slight to mild changes in hepatocytes were observed in rats dosed by aqueous extract of *C. decidua* stems and a higher dose of methanolic extract, whereas the lower dose of the methanolic extract revealed more severe lesions than the higher dose. The results were compared with the hepatoprotective effect of the standard drug silymarin (Ali *et al*., 2010).

3.18. *Chamomile capitula*

The effect of ethanolic extract of *Chamomile recutita* capitula (400 mg/kg, P.O.) on blood and liver glutathione, Na^+ K^+- ATPase activity, serum marker enzymes, serum bilirubin, glycogen, and thiobarbituric acid reactive substances against PCM-induced liver damage in rats have been studied to find out the possible mechanism of hepatoprotection. It was observed that extract of *C. recutita* has reversal effects on the levels of the above-mentioned parameters in PCM hepatotoxicity (Gupta and Misra, 2006) suggesting its hepatoprotective and/or hepato-stimulant activity (Kalantari and Rastmanesh. 2008).

3.19. *Coptidis rhizoma* (Huanglian)

Berberine is an active compound in *Coptidis Rhizoma* (Huanglian) with multiple pharmacological activities including antimicrobial, antiviral, antiinflammatory, cholesterol-lowering, and anticancer effects. The hepatoprotective effects of berberine on serum and tissue superoxide dismutase (SOD) levels, the histology in CCl_4-induced liver injury. Sprague-Dawley rats aged seven weeks were injected intraperitoneally with 50% CCl4 in olive oil. Berberine was orally used before or after CCl_4 treatment in various groups. Twenty-four hours after CCl_4 injection, serum ALT and AST activities, serum and liver SOD activities were measured. Histological changes of the liver were examined with microscopy. The study shows that berberine possesses hepatoprotective effects (http://www.cmjournal.org/content).

3.20. *Careya arborea*

The methanol extract of *Careya arborea* bark, (myrtaceae) was tested for antioxidant and hepatoprotective activity in Ehrlich ascites carcinoma (EAC) tumor-bearing mice. Tumor control animals inoculated with EAC showed a significant alteration in the levels of antioxidant and hepatoprotective parameters. The extract treatment at 50, 100, and 200 mg/kg body weight doses given orally caused a significant reversal of these biochemical changes towards the normal in serum. Liver and kidney when compared to tumor control animals indicate the potent antioxidant and hepatoprotective nature of the standardized extract (Senthilkumar *et al*., 2008).

3.21. *Cassia fistula* (Amaltas)

Hepatoprotective activity of the n-heptane extract of *Cassia fistula* (Fabaceae) leaves was investigated by inducing hepatotoxicity with PCM in rats. The extract at a dose of 400 mg/kg body wt. exhibited orally, significant protective effect by lowering the serum levels of transaminases (SGOT and SGPT), bilirubin, and ALP. The effects produced were comparable to that of a standard hepatoprotective agent (Bhakta *et al*., 2001).

3.22. *Cleome viscose* Linn (Tickweed)

The hepatoprotective activity of the *Cleome viscose* Linn (Capparidaceae) extract was assessed in CCl_4 induced hepatotoxic rats. The test material was found effective as hepatoprotective, through in vivo and histopathological studies. The extract was found to be effective in shortening the thiopental induced sleep in mice poisoned with CCl_4. The hepatoprotective effect of ethanolic extract was comparable to that of silymarin, a standard hepatoprotective agent (Gupta and Dixit. 2009).

3.23. *Embelia ribes*

Embelia ribes commonly known as Vidanga has been reported to be useful in jaundice. It is a constituent of various formulations marketed for liver ailments. The protective effects of *E. ribes* on PCM-induced liver cell damage were studied using mice as experimental animals. The PCM was used orally in a dose of 500 mg/kg. Body wt. 48 hrs. Before administration of drugs. The mice treated with *E. ribes* extract (50, 100, 200 mg/100 gm/day) showed a dose-dependent fall of 41 % 47 %, and 66 % to respectively in the serum SGPT level as compared to the elevated levels in the mice receiving PCM only. Histopathology of liver mice revealed 67 %, 70 %, and 80 % normal liver respectively in the mice receiving the dose of E-ribs, the result suggests that extract of *E. ribes* possesses hepatoprotective activity against PCM induced acute hepatocellular damage in the mice (Nohid and Agarwal. 2003).

3.24. *Eclipta alba*

Eclipta alba (Bhringaraja), belonging to the family Composite is a perennial shrub that grows widely in moist tropical countries. It is used as an alternative, anthelmintic, expectorant, antipyretic, antiasthmatic,

tonic, deobstruent in hepatic and spleen enlargement, and significant anti-inflammatory activity. It has been reported to be useful in liver ailments and has been shown to possess hepatoprotective activity against CCl_4 induced liver cell damage in animals. The effect of *E. alba* extract was studied on PCM-induced hepatic damage in Mice. Treatment with ethanol extract of *E. alba* was found to protect the mice from hepatotoxic action of PCM as evidenced by a significant reduction in the elevated serum transaminase levels (Kumar. 2012).

3.25. *Foeniculum vulgare*

Fennel (*Foeniculum vulgare* Mill. Family Umbelliferae) is an annual, biennial, or perennial aromatic herb, depending on the variety, the leaves, stalks, and seeds (fruits) of the plant are edible. *F. vulgare* is an aromatic herb whose fruits are oblong, ellipsoid, or cylindrical, straight or slightly curved, and greenish or yellowish-brown in color. Volatile components of fennel seed extracts by chromatographic analysis include trans-anethole, fenchone, methylchavicol, limonene, α-pinene, camphene, β-pinene, β-myrcene, α-phellandrene, 3-carene, camphor, and cis anethole. The hepatoprotective activity of *F. vulgare* essential oil was studied using a CCl_4-induced liver fibrosis model in rats. The hepatotoxicity produced by chronic CCl_4 used was found to be inhibited by *F. vulgare* essential oil with evidence of decreased levels of serum aspartate aminotransferase, alanine aminotransferase, ALP, and bilirubin (Kumar. 2012).

3.26. *Flacourtia indica*

The extracts of the aerial parts of *Flacourtia indica*, were evaluated for hepatoprotective properties. In PCM-induced hepatic necrosis in rat models, all extracts were found to reduce AST, serum ALT, and serum ALP. The most significant reduction of the serum level of AST and ALT were exhibited by petroleum ether and ethyl acetate extracts at a single oral dose of 1.5g/kg of body weight with a reduction of 29.0% AST & 24.0% ALT level by petroleum ether extract, and 10.57% AST & 6.7% ALT level by ethyl acetate extract compared to PCM (3 g/kg of body weight) treated animals. Histopathological tests also showed good recovery of PCM-induced necrosis by petroleum ether and ethyl acetate extracts. On the other hand, the methanol extract did not show any remarkable effect on PCM-induced hepatic necrosis. The hepatoprotective effects exhibited by petroleum ether and ethyl acetate extract might be mediated through the inhibition of microsomal drug-metabolizing enzymes. But, in this study, the dose they have used is too high and it is not successful or rationale for human dose (Kagaku. 1985; Nazneen *et al.*, 2008).

3.27. *Fumaria indica (Hauskn)*

Fumaria indica (Fumariceae) were studied for their hepatoprotective activity against CCl_4, PCM, and rifampicin-induced hepatotoxicity in albino rats. The petroleum ether extract against CCl_4, total aqueous extract against PCM, and methanolic extract against rifampicin induced hepatotoxicities showed similar reductions in the elevated levels of some of the serum biochemical parameters like that of silymarin indicating its potential as a hepatoprotective agent (Rao and Mishra. 1997).

3.28. *Ficus carica*

Shade dried leaves of *Ficus carica* were extracted using petroleum ether and tested for antihepatotoxic activity on rats treated with 50 mg/ kg of rifampicin orally. The parameters assessed were serum levels of glutamic oxaloacetate transaminase, glutamic pyruvic transaminase, bilirubin, and histological changes in the liver. Liver weights and pentobarbitone sleeping time as a functional parameter were also monitored. There was a significant reversal of biochemical, histological, and functional changes induced by rifampicin treatment in rats by petroleum ether extract treatment, indicating promising hepatoprotective activity (Gond and Kadabadi. 2008). The methanolic extract of the leaves of *Ficus carica* was tested for hepatoprotective activity in CCl_4 induced liver-damaged rats. The extract at an oral dose of 500 mg/kg exhibited a significant protective effect reflected by lowering the serum levels of AST, ALT, total serum bilirubin, and malondialdehyde equivalent, an index of lipid peroxidation of the liver (Krishna *et al.*, 2007).

3.29. *Glychyrrhiza glabra*

Glychyrrhiza glabra is commonly known as licorice contains triterpene saponin, known as glycyrrhizin, which has potential hepatoprotective activity. It belongs to a group of compounds known as sulfated polysaccharides. Several studies carried out by Japanese researchers have shown glycyrrhizin to be antiviral and it has potential for therapeutic use in liver disease. Experimental hepatitis and cirrhosis studies on rats found that it can promote the regeneration of liver cells and at the same time inhibit fibrosis. Glycyrrhizin can alleviate histological disorder due to inflammation and restore the liver structure and function from the damage due to CCl_4. The effects include lowering the SGPT, reducing the degeneration and necrosis, and recovering the glycogen and RNA of liver cells. Effects of glycyrrhizin have been studied on free radical generation and lipid peroxidation in primary cultured rat hepatocytes. Favorable results have been reported in children suffering from cytomegalovirus after treating with glycyrrhizin (Numazaki *et al.*, 1994).

3.30. *Garcinia mangostana* Linn

Garcinia mangostana Linn. commonly known as " mangosteen", is a tropical evergreen tree and is an emerging category of novel functional foods sometimes called "super fruits" presumed to have a combination of appealing subjective characteristics, such as taste, fragrance, and visual qualities, nutrient richness, antioxidant strength and potential impact for lowering the risk of human diseases. The pericarps of *G. mangostana* have been widely used as a traditional medicine for the treatment of diarrhea, skin infection, and chronic wounds in South East Asia for many years. These are nature's most abundant sources of xanthones, which are the natural chemical substances possessing numerous bioactive properties that help to maintain intestinal health, neutralize free radicals, help and support joints and cartilage functions, and promote immune systems. These are extracted from the rind of mangosteen containing 95% xanthones also isoflavones, tannin, and flavonoids. Treatment of hepatocellular carcinomas (liver cancer) with chemotherapy has generally been disappointing and it is most desirable to have more effective new drugs. The investigators extracted and purified 6 xanthone compounds from the rinds (peel) of the fruit of *G. mangostana*, mangosteen fruit. The investigators tested this extract on 14 different human liver cancer cell lines. Several chemotherapeutic agents (drugs) were included in the study for comparison. The results showed that one of the xanthone derivatives which could be identified as garcinone E has the potent cytotoxic effect (kill cells) on all liver cancer cell lines as well (Kumar. 2012).

3.31. *Hygrophila auriculata*

Seeds of *Hygrophila auriculata* are used in Indian systems of medicine for the treatment of liver ailments. The antihepatotoxic effect of methanolic extracts of the seeds of these two plants was studied on rat liver damage induced by a single dose of PCM (3 g/kg p.o.) or TAA (l00 mg/kg, s.c.) by monitoring several liver function tests, viz serum transaminases (SGOT and SGPT), ALP, sorbitol dehydrogenase, glutamate dehydrogenase and bilirubin in serum. Furthermore, hepatic tissues were processed for assay of triglycerides and histopathological alterations simultaneously. A significant hepatoprotective activity of the methanolic extract of the seeds of both the plants was reported (Anubha and Hand. 1995).

3.32. *Juncus subulatus*

The volatile oil, ethyl acetate, n-butanol, and total alcoholic extracts of J. subulatus were tested for their hepatoprotective and antioxidant activity in female rats against ethanol-induced hepatic injury. Serum Liver enzymes (AST, ALT, and ALP), total protein, albumin, cholesterol, triglycerides, nitric oxide (NO), malondialdehyde (MDA), and total antioxidant capacity (TAC) were measured colorimetrically. The results showed that all extracts of *Juncus subulatus* exhibited hepatoprotective activity in the following order: volatile oil extract > ethyl acetate extract > n-butanol extract > total alcoholic extract (Abdel-razik *et al.*, 2009).

3.33. *Jatropha curcas*

Jatropha curcas Linn (Family: Euphorbiaceae), is an evergreen shrub, indigenous to America, but cultivated in most parts of India. This evergreen plant is common in waste places throughout India, especially on the Coromandel Coast and in Travancore; in the southern parts, it is cultivated chiefly for hedges in the Konkan, and also in Malay Peninsula. Leaves are regarded as antiphrastic, applied to scabies; rubefacient for paralysis, rheumatism; also applied to hard tumors. Leaves also show antileukemic activity. Compounds that have been isolated from *J. curcas* leaves include the flavonoids apigenin and its glycosides vitexin and isovitexin, the sterols stigmasterol, α-D-sitosterol, and its α-Dglucoside. Methanolic fraction of leaves of *J. curcas (MFJC)* was evaluated against hepatocellular carcinoma induced by Aflatoxin B1 (AFB1) (Kumar. 2012).

3.34. *Leucas ciliate*

Hepatoprotective activity of the ethanolic extract of *Leucas ciliata* leaves extract was tested by CCl_4 induced liver damage model in rats. The extract exhibited a significant dose-dependent antioxidant activity comparable with ascorbic acid. In hepatoprotective activity study, CCl_4 significantly increased the levels of SGPT, serum glutamate oxaloacetate transaminase (SGOT), ALP, and total bilirubin. Pretreatment of the rats with ethanolic extract of *L. ciliata* (100, 200, and 400mg/kg po) inhibited the increase in serum levels of SGPT, SGOT, ALP, and total bilirubin and the inhibition was comparable with silymarin (100mg/kg po). The present study revealed that L. ciliata leaves have significant hepatoprotective activity (Qureshi *et al.*, 2010).

3.35. *Lepidium sativum*

The role hepato-protective of Methanolic extract of *Lepidium sativum* at a dose of 200 and 400 mg/kg was investigated in CCl_4-induced liver damage in rats. Significant reductions in all biochemical parameters were found in groups treated with *L. sativum.* The severe fatty changes in the livers of rats caused by CCl_4 were insignificant in the *L. sativum* treated groups (Afaf *et al.*, 2008).

3.36. *Luffa echinata*

The different extracts of fruits of *Luffa echinata* Roxb (Cucurbitaceae) were tested for their hepatoprotective activity against CCU-induced hepatotoxicity in albino rats. The degree of protection was measured by using biochemical parameters like SGOT, SGPT, ALP, and total protein and total albumin. The petroleum ether, the methanolic extract showed significant activity compared with those of silymarin (Bahar *et al.*, 2001).

3.37. *Leucas aspera*

The effect of *Leucas aspera* leaves fresh juice against CCl_4 induced liver damage. The evaluation markers used were GOT, GPT, Alkaline phosphate, glucose, bilirubin, cholesterol, and total protein. These biochemical parameters were significantly changed due to a single dose of CCl_4, but the treatment of *Leucas aspera* leaves fresh juice significantly recovers all markers to normal levels. In this study, silymarin was used as a standard for comparison. The observation of markers, as well as Light and electron microscope photographs, supports the regeneration of liver parenchyma. This proves an overall promising effect against liver disorders (Pingale. 2010).

3.38. *Launaea intybacea*

Hepatoprotective activity of ethyl acetate extract of aerial parts of *Launaea intybacea* are evaluated in PCM induced hepatotoxicity in albino rats. Silymarin (200 mg/kg) was given as a reference standard. The ethyl acetate extract of aerial parts of *L. intybacea* have shown very significant hepatoprotection against PCM-induced hepatotoxicity in albino rats in reducing serum total bilirubin, SALP, SGPT, SCOT levels, and liver homogenates LPO, SOD, CAT, GPX, GST, and GSH levels (Takate *et al.*, 2010).

3.39. *Morinda citrifolia L. (Noni)*

The hepatoprotective effects of Noni juice (TNJ) (Rubiaceae) against CCl_4-induced chronic liver damage in female Sprague Dawley (SD) rats. Histopathological examination revealed that liver sections from the TNJ+ CCl_4 appeared similar to controls, whereas typical hepatic steatosis was observed in the placebo+CCl_4 group. Serum ALP, AST, ALT, total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) levels were increased in the placebo group compared with the TNJ group. In contrast, high-density lipoprotein (HDL) was increased in the TNJ group and decreased in the placebo group. Thus, TNJ juice appears to protect the liver from chronic exogenous CCl_4 exposures (Wang *et al.*, 2008).

3.40. *Orthosiphon stamineus*

Methanol extract of the (leaves of "*Orthosiphon stamineus*" was assessed in PCM-induced hepatotoxicity in rats. Alteration in the levels of biochemical markers of hepatic damage like SCOT, SGPT, ALP, and lipid peroxides was tested in both parasitical treated and untreated groups. The PCM (2 gm/kg) has enhanced the SGOT, SGPT, ALP, and lipid peroxides in the liver. Change in the levels of biochemical markers such as AST, ALT, ALP, and lipid peroxides were assayed in both PCM treated and control groups. Treatment of methanol extract of *O. stamineus* leaves (200 mg/kg.) has brought back the altered levels of biochemical markers to the near-normal levels in a dose-dependent manner (Maheshwari *et al.*, 2008).

3.40. *Phyllanthus amarus* (Bhuiamala)

Ethanolic extract of *Phyllanthus amarus* (Euphorbiaceae), at (0.3g /kg BW/0.2 ml/day was given to all groups except control groups (gp. I and gp. V), after 30 min of aflatoxin use. The entire study was carried out for 3 months and animals were sacrificed after 30 days till the completion of study. *P. amarus* extract was found to show hepatoprotective effect by lowering down the content of thiobarbituric acid reactive substances (TBARS) and enhancing the reduced glutathione level and the activities of antioxidant enzymes, glutathione peroxidase (GPx), glutathione transferase (GST), SOD, and catalase (CAT) (Naaz *et al.*, 2007).

3.41. *Piper longum*

Piper longum Linn. (Piperaceae) (Fruits and roots powder) is given with boiled milk in the Indian traditional system of medicine for the treatment of liver ailments and jaundice. However, the biochemical basis and mechanism of hepatoprotective action of *P. longum* milk extract are not scientifically studied. The hepatoprotective activity of *P. longum* milk extract, CCl_4 was used as a hepatotoxin at a dose of 0.5ml/kg p. o. with olive oil (1:1) thrice a week for 21 days to produce the chronic reversible type of liver necrosis. Following treatment with *P. longum* milk extract (200 mg/day p. o. for 21 days), a significant hepatoprotective effect was observed in CCl_4 induced hepatic damage as evident from a decreased level of serum enzymes, total bilirubin, and direct bilirubin. The hepatoprotective effect of *P. longum* is comparable to the standard drug silymarin (25 mg/kg/day p. o. for 21 days) (Patel and Shah. 2009).

3.42. *Pterocarpus santalinus*

The aqueous (45 mg/ml.) and ethanol (30 mg/ml) extracts of stem bark in 1 % gum tragacanth were administered orally for 14 days and hepatoprotective

activity was studied in CCl_4 induced hepatic damage model. The hepatoprotective activity was assessed using various biochemical parameters like serum bilirubin, protein ALT, aspartate transaminase, and ALP along with histopathological studies of the liver tissue. There was a significant increase in the serum levels of bilirubin ALT, aspartate transaminase and ALP with a decrease in total protein level in the CCl_4 treated animals, reflecting liver injury. Histological study of fatty lobules and cellular necrosis (Mankani *et al.*, 2005).

3.43. *Pterocarpus marsupium*

Hepatoprotective effects of the methanol and aqueous extracts of *P. marsupium* stem bark was evaluated by assay of liver function biochemical parameters (Total bilirubin, serum protein alanine aminotransaminase, aspartate aminotransaminase, and ALP activity and histopathological studies of the liver. In methanol extract-treated animals the toxic effects of CCl_4 were controlled significantly by restoration of levels of serum bilirubin protein, and enzyme, as compared to the normal and standard drug Silymarin, treated group histology of liver sections of the animals treated with extract showed the presence of the normal hepatic cords, absence of necrosis and fatty infiltration which further evidenced the hepatoprotective activity (Manjunatha. 2006).

3.44. *Polygala arvensis*

The suspensions of chloroform extract of leaves in 0.3 % Carboxymethyl cellulose (CMC) was tested for hepatoprotective activity in Wistar albino rats by inducing hepatic injury with D-galactosamine (400 mg/kg). The chloroform extract of Polygala arvensis at an oral dose of 200 mg/kg and 400 mg/kg exhibited a significant protective effect by normalizing the levels of AST, ALT, ALP, total bilirubin (TB), lactate dehydrogenase (LDH), total cholesterol (TC), triglycerides (TGL), albumin, total protein (TP) which were significantly increased in rats by treatment with 400 mg/kg i.p of D-galactosamine. Silymarin (25 mg/kg) is a known hepatoprotective drug used for comparison exhibited significant activity (Dhanabal *et al.*, 2006).

3.45. *Prostechea michuacana*

Methanol, hexane and chloroform extracts of *Prostechea michuacana* (PM) were studied against CCl_4-induced hepatic injury in albino rats. Pre-treatment with methanolic extract reduced biochemical markers of hepatic injury levels exhibited dose-dependent reduction in the *in vivo* peroxidation induced by CCl_4. Likewise, pretreatment with extracts of PM on PCM-induced hepatotoxicity and the possible mechanism involved in this protection were also investi-gated in rats after using the extracts of PM at 200, 400 and 600mg/kg. The degree of protection was measured by monitoring the blood biochemical profiles. The methanolic extract of orchid produced significant hepatoprotective effect as reflected by reduction in the increased activity of serum enzymes, and bilirubin. These results suggested that methanolic extract of PM could protect PCM lipid peroxidation thereby eliminating the deleterious effects of toxic metabolites of PCM. This hepatoprotective activity was comparable with silymarin. Hexane and chloroform extracts did not show any apparent effect. The findings indicated that the methanolic extract of PM can be a potential source of natural hepatoprotective agent (Rosa and Rosario, 2009).

3.46. *Phyllanthus emblica*

Ethanol extract of *Phyllanthus emblica* Linn. (Euphorbiaceous) (PE) induced rat hepatic injury. PE (0.5 and 1 mg/ml) increased the cell viability of rat primary cultured hepatocytes being treated with ethanol (96 µl/m) by increasing % MTT and decreasing the release of transaminase. Pretreatment of rats with PE at an oral dose of 25, 50, and 75 mg/kg or SL (silymarin, a reference hepatoprotective agent) at 5 mg/kg, 4 h before ethanol lowered the ethanol-induced levels of AST, ALT, and IL- 1beta. The 75 mg/kg PE dose gave the best result similar to SL. Treatment of rats with PE (75 mg/kg/day) or SL (5 mg/kg/day) for 7 days after 21 days with ethanol (4 g/kg/day, p.o.) enhanced liver cell recovery by bringing the levels of AST, ALT, IL-1beta back to normal.

3.47. *Picrorhiza kurroa* (Kutki)

Administration of picroliv, a standardized fraction of alcoholic extent of *Picrorhiza kurroa* (Scrophulariaceae) (3-12 mg/kg/day for two weeks) simultaneously with P. berghei infection showed significant protection against hepatic damage in Mastomys natalensis. The increased levels of SGOT, glutamate pyruvate transaminase (GPT), ALP, Lipoprotein-X (LP-X), and bilirubin in the infected animals were markedly reduced by different doses of picroliv. In the liver, picroliv decreased the levels of lipid peroxides and hydroperoxides and facilitated the recovery of SOD and glycogen.

3.48. *Plumbago zeylanica*

Petroleum ether extract of the root of *Plumbago zeylanica* was tested for hepatoprotective activity against PCM-induced liver damage to evaluate the hepatoprotective activity of the ethanolic extract. In serum total bilirubin, total protein, aspartate transaminase, ALT, ALP, lactate dehydrogenase, γ-Glutamyl transferase, Total Cholesterol, and serum

triglycerides were determined to assess the effect of the extract on the PCM induced hepatic damage. The study was also supported by histopathology of liver sections. The markers in the animals treated with PCM recorded elevated concentration indicating severe hepatic damage by PCM, whereas the blood samples from the animals treated with petroleum ether extract of roots showed a significant reduction in the serum markers indicating the effect of the plant extract in restoring the normal functional ability of the hepatocytes. The dosage of extract of plant roots used was 300 mg/kg body weight of rat. The present study reveals that the petroleum ether root extract of *P. zeylanica* could afford significant protection against PCM-induced hepatocellular injury (Kanchana *et al.*, 2011).

3.49. *Silybum marianum*

The protective effects of polyphenolic extracts of *Silybum marianum* on TAA-induced hepatotoxicity in rats were tested. The extracts were injected into the rats, at a dose of 25 mg/kg body weight together with TAA at a dose of 50 mg/kg body weight. A significant decrease in the activity of aminotransferases, ALP, and bilirubin were observed in the groups treated with extracts and TAA compared with the group that was treated only with TAA. The level of Na^+, K^+, and liver weight between different groups were not significantly altered. These findings suggested the hepatoprotective effect of *S. marianum* extracts on liver cells due to the presence of flavonoids and their antioxidant effects (Madani *et al.*, 2008).

3.50. *Swertia chirata*

Due to the effect of hepatotoxicants (like ethanol, drugs, chemicals, and others) serum AST, ALT, and ALP activities and bilirubin levels are increased, but liver glycogen and serum cholesterol levels are decreased. Histologically it produced hepatocytic necrosis, especially in the centrilobular region. Simultaneous treatments with *Swertia chirata* caused improvement at both biochemical and histopathological parameters. The drug also possesses digestive, hepatic (conditions of the liver), tonic, astringent, and appetizer properties and is used in cough, dropsy, and skin diseases. *S. Chirata* (Chirayata) Simultaneous treatments with *S. Chirata* (Gentianceae). (in different doses, viz. 20, 50, and 100 mg/kg body wt daily) and (CCl_4) caused improvement at both biochemical and histopathological parameters compared to that of (CCl_4) treatment alone but it was most effective when S. chirata was administered in a moderate dose (50 mg/kg body wt) (Karan *et al.*, 1999).

3.51. *Solanum nigrum*

In Ayurveda, the drug is known as kakamachi. Aromatic water extracted from the drug is widely prescribed by herbal vendors for liver disorders. Although the clinical show is scarce as far as hepatoprotective activity is concerned, some traditional practitioners have reported favorable results with powdered extract of the plant. The effects of *Solanum nigrum* extract (SNE) were evaluated on TAA-induced liver fibrosis in mice. Mice in the three TAA groups were treated daily with distilled water and SNE (0.2 or 1.0 g/kg) via gastrogavage throughout the experimental period. SNE reduced the hepatic hydroxyproline and α-smooth muscle-acting protein levels in TAA-treated mice. SNE inhibited TAA-induced collagen (α1) (I), transforming growth factor-β1(TGF-β1) and mRNA levels in the liver. Histological examination also confirmed that SNE reduced the degree of fibrosis caused by TAA treatment. Oral use of SNE significantly reduces TAA-induced hepatic fibrosis in mice, probably through the reduction of TGF-β1 secretion (Hsieh *et al.*, 2008). In another study, the protective effects of aqueous extract of SN (ASNE) against liver damage were evaluated in CCl_4-induced chronic hepatotoxicity in rats. The results showed that the treatment of ASNE significantly (Murthy *et al.*, 1993).

3.52. *Sargassum polycystum*

The protective effect of ethanol extract of *Sargassum polycystum* was evaluated in D-galactosamine-induced hepatitis in rats. Prior oral use of *S. polycystum* extract [125mg/kg body weight/day for 15 days] significantly attenuated the Dgalactosamine- induced increases in the levels of diagnostic marker enzymes (AST, ALT, and ALP) in plasma of rats. It has also exhibited antioxidant activity against D-galactosamine-induced hepatitis by inhibiting the activation of lipid peroxidation and by preserving the hepatic enzymatic and non-enzymatic antioxidant defense system at near normal. The antihepatotoxic potential of *S. polycystum* might be due to its antioxidant property and membrane-stabilizing action (Meena *et al.*, 2008).

3.53. *Spermacoce hispida*

Ethanolic extract of the *Spermacoce hispida* Linn (SHE) against carbon tetrachloride (CCl4) induced hepatotoxicity in rats. Liver functions were assessed by the determination of SGOT, SGPT, ALP, and bilirubin. Histopathological studies were carried out. The serum biochemical analysis results suggest that the use of the ethanolic extract of *S. hispida* Linn exhibited a significant protective effect from hepatic damage in CCl_4 induced hepatotoxicity model. Histopathological studies revealed that concurrent use of the extract with CCl_4 exhibited a protective effect on the liver, which further evidenced its hepatoprotective activity (Karthikeyan *et al.*, 2006).

3.54. *Tylophora indica*

The methanolic extract of *Tylophora indica* leaves was tested for hepatoprotective activity in CCl_4 induced hepatotoxicity in albino rats. The degree of protection was measured by estimating biochemical parameters like serum glutamate oxaloacetate transaminase, SGPT, total protein, and level of serum bilirubin (both total and direct). Hepatoprotective activity of methanolic extract at a dose of 200 mg/kg and 300 mg/kg body weight, i.p. was compared with Silymarin (25 mg/kg,i.p.) treated animals *T. indica* leaves (200 and 300 mg/kg) exhibited a significant reduction in serum hepatic enzymes when compared to rats treated with CCl_4 alone. Furthermore, histopathological studies were also done to support the study (Mohamed *et al.*, 2005; Mujeeb *et al.*, 2009).

3.55. *Thuja occidentalis*

Thuja occidentalis (Cupressaceae), also known as Arborvitae or white cedar has been used in folk medicine to treat bronchial catarrh, enuresis, cystitis, psoriasis, uterine carcinomas, amenorrhea, and rheumatism and is mainly used in homeopathy as a mother tincture. Extract of this plant has shown anti-oxidant, antiviral, anti-diarrhoeal activity. The hepatoprotective potential effect of ethanolic fraction of *T. occidentalis* has been assessed against CCl_4 induced liver damage in rats. A dose of EFTO 400 mg/kg p.o. exhibited significant protection from liver damage in acute and chronic CCl_4 induced liver damage models. Histopathological examination was carried out after the treatment to evaluate hepatoprotection. The fraction was found to possess good hepatoprotective properties (Dubey and Batra. 2008).

3.56. *Trigonella foenum graecum*

Fenugreek (*Trigonella foenum graecum*) is an annual herb that belongs to the family Leguminosae. The seeds of fenugreek are commonly used as a spice in food preparations due to their strong flavor and aroma. The seeds are reported to have restorative and nutritive properties. Fenugreek seeds have antioxidant activity and have been shown to produce beneficial effects such as neutralization of free radicals and enhancement of antioxidant apparatus. The protective effect of a polyphenolic extract of fenugreek seeds against ethanol-induced toxicity was investigated in human Chang liver cells. Ethanolic treatment suppressed the growth of Change liver cells and induced cytotoxicity, oxygen radical formation, and mitochondrial dysfunction. Incubation of FPEt along with EtOH significantly increased cell viability in a dose-dependent manner, causing a reduction in lactate dehydrogenase leakage and normalized GSH/GSSG ratio. The findings suggest that the polyphenolic compounds of fenugreek seeds on the other gastric and lung cancer cell lines are included in the screen. The investigators suggested that garcinone E may be potentially useful for the treatment of certain types of cancer (Kumar. 2012).

3.57. *Tephrosia purpurea*

In Ayurveda, the plant is known as sharpunkha. Alkali preparation of the drug is commonly used in the treatment of liver and spleen diseases. In animal models, it offered protective action against CCl_4 and D-galalactosamine poisoning. The roots, leaves, and seeds contain tephrosin, deguelin, and quercetin. The hepatoprotective constituent of the drug is still to be proved (Murthy *et al.*, 1993).

3.58. Vitex trifolia

Aqueous and ethanol extract of leaf of *Vitex trifolia* was tested for hepato-protective activity against CCl_4 induced liver damage. To assess the hepatoprotective activity of the extracts, various biochemical parameters viz. total bilirubin, total protein, ALT, aspartate transaminase, and ALP activities were determined. Results of the serum biochemical estimations revealed a significant reduction in total bilirubin and serum marker enzymes and an increase in total protein in the animals treated with ethanol and aqueous extracts. However significant rise in these serum enzymes and a decrease in total protein level was noticed in CCl_4 treated group indicating hepatic damage. The hepatoprotective activity is also supported by histological studies of liver tissue. Histology of the liver tissue treated with ethanol and aqueous extracts showed normal hepatic architecture with few fatty lobules. Hence the *V. trifolia* could afford significant protection against CCl_4 induced hepatocellular injury (Manjunath and Vidya. 2008).

3.59. Vitis Spcies (Grape Seeds)

Hepatoprotective effect of Grape Seed extract on hypercholesterolemia, where, Wistar rats fed a cholesterol-rich diet (hypercholesterolemic group-HCD) and to see the effect of GSE, another group fed on a cholesterol-rich diet enriched with 0.3% GSEW/W-PG) for 8 weeks. Serum lipid levels, serum antioxidant status, liver, and kidney function were analyzed in addition to histopathological examination of the liver. Furthermore, the liver function expressed as glutamic pyruvate transaminase (GPT) and Albumin serum levels, decreased significantly and reached to normal level in the case of oral use of GSE. Histological examination of liver sections confirmed the serum analysis where GSE had a protective effect on animals fed on HCD, the liver of these animals showed mild affection in the form of microvesicular vacuolation of hepatocytes in the peripheral zone of the hepatic lobule (<50%) in comparison to the fatty change observed as microvesicular and macrovesicular vacuolation in >50%

and <70% of the liver sections in HCD group (Abeer *et al.*, 2008).

3.60. *Wedelia calendulacea* (Bhanra)
The hepatoprotective activity of ethanolic extract of *Wedelia calendulacea* (Family: Asteraceae) was studied against CCl_4 induced acute hepatotoxicity in rats was studied by estimating serum enzyme activities of AST, ALT, ALP, protein, and bilirubin. The treatment with extract showed a dose-dependent reduction of CCl_4 induced elevated serum levels of enzyme activities with a parallel increase in total protein and bilirubin, indicating the extract could preserve the normal functional status of the liver. The treatment with ethanolic extract of *W. calendulacea* showed a dose-dependent reduction in CCl_4-induced elevated serum enzyme activities with a parallel increase in total proteins and bilirubin, indicating the extract could enhance the return of normal functional status of the liver comparable to normal rats. The weight of the organs such as liver, heart, lung, spleen, and kidney in CCl_4-induced hepatic damaged animals that received an ethanolic extract of *W. calendulacea* showed an increase over the CCl_4-treated control group (Murugaian *et al.*, 2008).

3.61. *Mamordica subangulata* and *naragamia alata*
The hepatoprotective activity of *Mamordica subangulata* (leaf) and *Naragamia alata* (whole plant) suspension was studied using PCM overdose induced liver damage in rats. The effect of the plant suspensions on bile flow was studied in anesthetized normal rats by surgical cannulation of the bile duct with polyethylene tubing. The drug was given intraduodenally after 1-hour bile collection. *M. subangulata* leaf suspension (500mg/kg, fresh weight; 50mg/kg, dry weight) protected rats from PCM-induced liver damage as judged from serum marker enzyme activities. It also stimulated bile flow in normal rats. *N. alata* was inactive in protecting rats from PCM-induced hepatotoxicity. A suspension of *M. subangulata* leaf (dry or fresh) can protect rats from PCM-induced hepatotoxicity (Asha.2001).

3.62. *Ixora coccinea* (Rubiaceae), *rhinacanthus nasuta* (Acanthaceae) and *spilanthes ciliata* (Asteraceae)
Roots of *Ixora coccinea* (Rubiaceae) and *Rhinacanthus nasuta* (Acanthaceae) and whole plants of *Spilanthes ciliata* (Asteraceae) are extensively used by tribal communities in South India to treat liver diseases. However, the veracity of these tribal claims has been investigated scientifically using the liver toxin, aflatoxin. This study reports on the protective effects of these three herbal ethanolic extracts on the aflatoxin Bi (AFBI)-intoxicated livers of albino male Wistar rats. It was concluded that the hepatoprotective effects of the three plant extracts observed in this study might result from their potent antioxidative properties (Moron *et al.*, 1979; Thabrew and Babaunmi. 1980).

4. Discussion

The popularity of herbal is increasing globally and at least one-quarter of patients with liver diseases use ethnobotanicals. More efforts need to be directed towards methodological scientific evaluation for their safety and efficacy by subjecting (o vigorous preclinical studies followed by clinical trial, to unravel the mysteries hidden in the plants. This approach will help explore the real therapeutic value of these natural pharmacotherapeutic agents and standardize the dosage regimen on evidence-based findings to become more than a fashionable trend. Many herbals are on the market to support health, relieve symptoms, and cure diseases. However, most of these products lack scientific pharmacological validation (Mohamed *et al.*, 2010). In experimental hepatotoxicity models in the laboratory or higher animals, several herbals exerted hepatoprotective/curative effects that warrant their clinical testing. Due to a lack of scientific-based pharmacological data, most herbal formulations cannot be recommended for the treatment of liver diseases. Despite the availability of more than 300 preparations for the treatment of jaundice and chronic liver diseases in Indian Systems of Medicine (using more than 87 Indian medicinal plants), only four terrestrial plants have been scientifically elucidated while adhering to the internationally accepted scientific protocols (Jain *et al.*, 2013).
The present study reveals plant extracts with hepatoprotective properties against toxic chemicals that cause liver injury, seeming to validate their use in folk medicine. These plants may offer new alternatives to the limited therapeutic options that exist at present in the treatment of liver diseases or their symptoms, and they should be considered for future studies. The liver plays an astonishing array of vital functions in the maintenance and performance of the body. Some of these major functions include carbohydrate, protein, and fat metabolism, detoxification, and secretion of bile. Therefore, the maintenance of a healthy liver is vital to overall health and well-being. Unfortunately, the liver is often abused by environmental toxins, poor eating habits, alcohol, and prescription and over-the-counter drug use, which can damage and weaken the liver and eventually *lead to* hepatitis, cirrhosis, and alcoholic liver disease. Conventional medicine is now pursuing the use of natural products such as herbs to provide the support that the liver needs daily. Many of these herbs have been evaluated in clinical studies and are currently

being investigated phytochemically to better understand their actions. The presented review suggests that biologically active molecules derived from herbal extracts may serve as suitable primary compounds for effective and targeted hepatoprotective drugs. The popularity of herbal remedies is increasing globally and at least one-quarter of patients with liver diseases use ethnobotanicals (Ali *et al*, 2019; Ali *et al*, 2018; Krepkova *et al*, 2021; Nair *et al*, 2015; Daoudi and Bnouham. 2020). More efforts need to be directed towards methodological scientific evaluation for their safety and efficacy by subjecting them to vigorous preclinical studies followed by clinical trials to unravel the mysteries hidden in the plants. This approach will help explore the real therapeutic value of these natural pharmacotherapeutic agents and standardize the dosage regimen on evidence-based findings to become more than a fashionable trend. Many herbals are on the market to support health, relieve symptoms, and cure diseases. However, most of these products lack scientific pharmacological validation. In experimental hepatotoxicity models in the laboratory or higher animals, several herbals exerted hepatoprotective/curative effects that warrant their clinical testing. Due to a lack of scientific-based pharmacological data, most herbal formulations cannot be recommended for the treatment of liver diseases (Bardhan *et al.*, 1985; Stickel and Schuppan. 2007; Karandikar *et al.*, 1963). Despite the availability of more than 300 preparations for the treatment of jaundice and chronic liver diseases in Indian Systems of Medicine (using more than 87 Indian medicinal plants,) only four terrestrial plants have been scientifically elucidated while adhering to the internationally accepted scientific protocols. In-depth studies have proved *Sylibum marianum* to be antioxidative, anti-lipid peroxidative, antifibrotic, antiinflammatory, immunomodulating, and liver regenerative. *Glycyrrhiza glabra* is hepatoprotective and capable of inducing endogenous interferon. *Picrorhiza kurroa* is proved to be antiinflammatory, hepatoprotective, and immunomodulatory. Extensive studies on *Phyllanthus amarus* have confirmed this plant preparation possessed antiviral against hepatitis B and C viruses, hepatoprotective and immunomodulating effects, besides anti-inflammatory properties (Thyagarajan *et al.*, 2002; Sidana *et al.*, 2011).

5. Conclusions

Chronic hepatic diseases stand as one of the foremost health troubles worldwide, with liver cirrhosis and drug-induced liver injury accounting ninth leading cause of death in western and developing countries. Therapies developed along the principles of western medicine are often limited in efficacy; carry the risk of adverse effects, and are often too costly, especially for the developing world. Therefore, treating liver diseases with plant-derived compounds which are accessible and do not require laborious pharmaceutical synthesis seems highly attractive. In this review article, an attempt has been made to compile the reported hepatoprotective plants from India and abroad and may be useful to the health professionals, scientists, and scholars working in the field of pharmacology, therapeutics, and pharmacognosy to develop evidence-based alternative medicine to cure different kinds of liver diseases in man and animals.

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References

1. Abdel-razik AF, Elshamya A-SI, Nassar, MI, El-Kousy SM, Hamdy H. Chemical constituents and hepatoprotective activity of *Juncus subulatus* Rev. Latinoamer. Quim. 2009; 37: 70-84.
2. Achuthan CR, Babu BH, Padikkala J. Antioxidant and Hepatoprotective effects of Rosa damascene. Pharmaceut Biol. 2003; 41: 357-361.
3. Afaf I, Abuelgasim, Nuha HS, Mohammed AH. Hepatoprotective effect of *Lepidium sativum* against carbon tetrachloride-induced damage in rats. Res J Animal Veterinary Sci. 2008; 3: 20-23.
4. Agarwal AK, Mehendale JK. Potentiation of carbon tetrachloride hepatotoxicity and lethality by chlordecone in female rats. *Toxicol*. 1983; 26:231-42.
5. Agarwal SS. Development of hepatoprotective formulations from plant sources. In: *Pharmacology and Therapeutics in the New Millennium*. Edited by Gupta SK, Narosa Publishing House, New Delhi, 2001, 357-358.
6. Ahmed B, Alam T, Varshney M, Khan SA. Hepatoprotective activity of two plants belonging to the Apiaceae and the Euphorbiaceae family. J Ethnopharmacol. 2002; 79: 313–316.
7. Ahsan R, Islam MK, Musaddik A, Haque E. Hepatoprotective Activity of Methanol Extract of Some Medicinal Plants Against Carbon Tetrachloride Induced Hepatotoxicity in Albino Rats. Global J Pharmacol. 2009; 3(3):116-122.
8. Ajay KG, Neelam M. Hepatoprotective activity of aqueous and ethanolic extract of Chamomile capitula in Paracetamol-intoxicated albino rats. Am J Pharmacol Toxicol. 2006; 1(1): 17-20.
9. Al Eid A, Al-Asmary SM. A Review of Hepatoprotective Plants Used in Saudi Traditional Medicine. Evid Based Complement Alternat Med. 2014; 2014: 890842.
10. Ali AS, Gameel AA, Mohamed AH, Hassan T. Hepatoprotective activity of *Capparis decidua* aqueous and

methanolic stems extracts against carbon tetrachloride induced liver histological damage in rats. J Pharmacol Toxicol. 2010; 6(1): 62-68.

11. Ali M, Khan T, Fatima K, Ali QA, Ovais M, Khalil AT, Ullah I, Raza A, Shinwari ZK, Idrees M. Selected hepatoprotective herbal medicines: Evidence from ethnomedicinal applications, animal models, and possible mechanism of actions. Phytother Res. 2018; 32(2): 199–215.
12. Ali SA, Sharief NH, Mohamed YS. Hepatoprotective Activity of Some Medicinal Plants in Sudan. Evid Based Complement Alternat Med. 2019; 2019: 2196315.
13. Aniya Y, Miyagi A, Nakandakari, Kamiya N, Imaizumi N, Ichiba T. Free radical scavenging action of the medicinal herb *Limonium wrightii* from the Okinawa islands. Phytomed. 2002; 9: 239-244.
14. Ansari RA, Tripathi SC, Patnaik GK, Dhawan BN. Antihepatotoxic properties of picroliv: an active fraction from rhizomes of *Picrorhiza kurrooa*. J Ethnopharmacol. 1991; 34(1): 61-8.
15. Anubha SS. Hepatoprotective activity of *Apium graveolens* and *Hygrophila auriculata* against Paracetamol and thioacetamide intoxication in rats. J Ethnopharmacol. 1995; 49(3):119-126.
16. Arulkumaran KS, Rajasekaran A, Ramasamy A, Jegadee-san M, Kavimani S, Somasundaram A. *Cassia rox-burghii* seeds protect liver against toxic effects of ethanol and carbontetrachloride in rats. Int J Pharm-Tech Res. 2009; 1(2): 273-246.
17. Asha VV. Preliminary studies on the hepatoprotective activity of *Mamordica subangulata* and *Naragamia alata*. Indian J Pharmacol. 33; 2001: 276-279.
18. Bahar A, Tanveer A, Shah AK. Hepatoprotective activity of *Luffa echinata* fruits. J Ethanopharmacol. 2001; 76:87-89.
19. Bardhan P, Sharma SK, Garg NK. In vitro effect of an ayurvedic liver remedy on hepatic enzymes in carbon tetrachloride treated rats. *Indian J Med Res*, 1985; 82:359-364.
20. Bhakta T, Banerjee S, Subhash C. M, Tapan K. Maity, Saha B.P, Pal M. Hepatoprotective activity of *Cassia fistula* leaf extract. Phytomed. 8; 2001: 220-24.
21. Budavari S. The Merck Index: An Encyclopedia of Chemicals, Drugs and Biological, 12th Edition, New York Merck & Co. Inc, Whitehouse Station, 1996: 1674.
22. Cameron GR, Thomas JC, Karunara the WAE. The pathogenesis of liver injury in carbon tetrachloride and thioacetamide poisioning. J Path Bact. 41; 1936: 41: 297
23. Chander R, Dwivedi Y, Rastogi R, Sharma SK, Garg NK, Kapoor NK, Dhawan BN Evaluation of hepatoprotective activity of picroliv from *Picrorhiza kurroa* in Mastomys natalensis infected with *Plasmodium berghei*. Int J Medicinal Res. 92; 1990: 34-7.
24. Chandra T, Sadique J, Soma Sundram S. Effect of *Eclipta alba* on inflammation and liver injury. Fitoterapia. 1987; 58(1): 23-32.
25. Chang-Chi H, Hsun-Lang F, Wen-Chuan L. Inhibitory effect of *Solanum nigrum* on thioacetamide-induced liver fibrosis in mice. J Ethnopharmacol. 2008; 119: 117–121.
26. Chaterjee TK. Medicinal Plants with Hepatoprotective Properties, Herbal Options, Books & Allied (P) Ltd, Calcutta, 2000:155.
27. Chattopadhyay RR, Sarkar SK, Ganguly S, Banerjee RN, Basu TK, Mukherjee A. Hepatoprotective activity of *Azadirachta indica* leaves on Paracetamol induced hepatic damage in rats. Indian J Exp Biol. 1992; 30(8): 738-40.
28. Chopra RN, Nayar SL, Chopra IC. In: Glossary of medicinal plants, SIR Publication, New Delhi, 1966: 104.
29. Clawson GA. Mechanisms of carbon tetrachloride hepatotoxicity. *Pathol Immunopathol Res*, 1989; 8(2): 104-12.
30. Daoudi NE, Bnouham M. Hepatoprotective Essential Oils: A Review. J Pharmacopuncture. 2020; 23(3): 124–141.
31. Das PK, Prasanna P, Somya RP, Ranjan S. Hepatoprotective activity of plant argemon mexicana against $CC1_4$ induced hepatotoxicityin rats. Int J Pharm Res develop. 2009; 8: 002-003.
32. Dawkins MJR. J. Path. Bact. Potentiation of Carbon Tetrachloride Toxicity by Dimethyl Sulphoxide, 1963; 85: 189.
33. Dhanabal SP, Syamala G, Satish KMN, Suresh B. Hepatoprotective activity of the Indian medicinal plant *Polygala arvensis* on d-galactosamine-induced hepatic injury in rats. Fitoterapia. 2006; 77(6): 472-474.
34. Dubey SK, Batra A. Hepatoprotective Activity from ethanolfraction of *Thuja occidentalis* Linn. Asian J Res Chem. 2008; 1(l): 32-35.
35. El-Wahab AEA, El-Adawi H, kassem HS. Towards Understanding the Hepatoprotective effect of Grape Seeds Extract on Cholesterol-Fed Rats. *Aust J Basic Appl Sci*,2008; 2: 412-417.
36. Godgoli C, Mishra SH. Antihepatotoxic activity of Cinchorium intybus. J Ethnopharmacol. 1997; 58: 131-134.
37. Gond NY, Kadabadi SS. Hepatoprotective Activity of *Ficus carica* Leaf Extract on Rifampicin-Induced Hepatic Damage in Rats. Indian J Phanna Sci. 2008; 70(3): 364-366.
38. Gupta AK, Chitme H, Dass SK, Misra N. Antioxidant activity of *Chamomile recutita* capitula methanolic extracts against CCl_4-induced liver injury in rats. J Pharmacol & Toxicol. 2006; 1(b): 101-107.
39. Gupta AK, Misra N. Hepatoprotective activity of aqueous ethanolic extract of *Chamomile capitula* in Paracetamol intoxicated albino rats. Am J Pharmacol Toxicol, 2006; 1(1): 17-20.
40. Gupta N.K, Dixit V.K. Evaluation of hepatoprotective activity of Cleome viscosa Linn. Extract. Indian J Pharmacol, 2009; 41: 36-40.
41. Handa SS, Sharma A, Chakraborti KK. Natural products and plants as liver protecting drugs. Fitoterapia. 1986; 57(5): 307-352.
42. Handa SS, Sharma A. Hepatoprotective activity of Andrographolide from *Andrographis paniculata* against carbon tetrachloride. Ind J Med Res. 1990; 92: 276-92.
43. Harshmohan. The liver, biliary tract and exocrine pancreas. In: *Text book of pathology*, 4th Ed, Jaypee Brothers Medical Publishers (P) Ltd. New Delhi. 2002; 22-4 and 569-630.
44. http://www.cmjournal.org/content/5/1/33
45. Hui-Mei L, Hsien-Chun T, Chau-Jong W, Jin-Jin L, Chia-Wen L, Fen-Pi C. Hepatoprotective effects of Solanum nigrum Linn extract against CCl_4-iduced oxidative damage in rats. Chemico Biological Interactions. 2008; 171: 283–293.
46. Ilyas U, Katare, D.P, Aeri, V, Naseef P.P. A Review on Hepatoprotective and Immunomodulatory Herbal Plants. Pharmacogn Rev. 2016; 10(19): 66-70.

47. Jain SK, Rajvaidy S, Desai P, Singh GK, Nagori BP. Herbal Extract as Hepatoprotective-A Review. J Pharmacog Phytochem. 2013; 2(3): 170-175.
48. Jamshidzadeh A, Khoshnoud MJ, Dehghani Z, Niknahad H. Hepatoprotective Activity of *Cichorium Intybus* L. Leaves Extract against Carbon Tetrachloride Induced Toxicity. Iran J Pharm Res. 2006; 5(1): 41-46.
49. Kalantari H, Rastmanesh M. Protective Property of *Cichorium Intybus* in CCl_4 Induced Liver Damage in mice. School of Pharmacy, Ahwaz University of Medical Sciences, Ahwaz, 2008, Iran.
50. Kanchana N, Sadiq MA. Hepatoprotective effect of *Plumbago zeylanica* on Paracetamol induced liver toxicity in rats. Int J Pharm Pharm Sci. 2011; 3: 151-154.
51. Kapoor LD, CRC Handbook of Ayurvedic Medicinal Plants, Boca Raton, CRC Press, 1990: 149-150.
52. Kapur V, Pillai KK, Hussain SZ, Balani DK. Hepatoprotective activity of Jigrine on liver damage caused by alcohol-carbon tetrachloride and Paracetamol in rats. Ind J Pharmacol. 1994; 26: 35-40.
53. Karan M, Vasisht K, Handa SS. Antihepatotoxic activity of *Swertia chirata* on Paracetamol and galactosamine induced hepatotoxicity in rats. Phytother Res. 1999; 13(2):95-101.
54. Karandikar SM, Joglekar GV, Chitale GK, Balwani JH. Protection by indigenous drugs against hepatotoxic effects of CCl_4 a long term study. Acta Pharmacologia et toxicologia. 1963; 20: 274-280.
55. Karthikeyan M, Wawdhane SS, Kannan M, Rajasekar S. Hepatoprotective activity of ethanolic extract of spermacoce hispida.linn against carbon tetrachloride (CCl_4) induced hepatotoxicity on albino wistar rats. Int J Pharm Res develop. 2006; 2: 45-52.
56. Kaviarasan S, Ramamurty N, Gunasekaran P, Varalakshmi E, Anuradha CV. Fenugreek (*Trigonella foenum graecum*) seed extract prevents ethanol-induced toxicity and apoptosis in chang liver cells. Alcohol Alcoholism. 2006; 41(3): 267–273.
57. Khosla P, Gupta DD, Nagpal RK. Effect of *Trigonella foenum* graecum (Fenugreek) on serum lipids in normal and diabetic rats. Inter J Pharmacol. 1995; 27: 89–93.
58. Kokate CK, Purohit AP, Gokhale SB. Pharmacognosy. 37th ed. Nirali Prakashan, 2006: 232, 233, 248, 249, 251.
59. Krepkova LV, Babenko AN, Saybel, OL, Lupanova IA, Kuzina OS, Job KM, Sherwin CM, Enioutina EY. Valuable Hepatoprotective Plants-How Can We Optimize Waste Free Uses of Such Highly Versatile Resources? Front Pharmacol. 2021; 12: 738504.
60. Krishna MG, Pallavi E, Ravi KB, Ramesh M, Venkatesh S. Hepatoprotective activity of *Ficus carica* (Linn) leaf extract against carbon tetrachloride-induced hepato-toxicity in rats. Daru. 2007; 15(3): 162-167.
61. Kumar A. A review on hepatoprotective herbal drugs. Int J Res Pharm Chem. 2012; 2(1): 92-102.
62. Lee MK, Yeo H, Kim J, and Kim YC. Protection of rat hepatocytes exposed to CCl4 in-vitro by cynandione A, a biacetophenone from *Cynanchum wilfordii*. J Pharm Pharmacol. 2000; 52(3): 341-5.
63. Madani H, Talebolhosseini M, Asgary S, Nader GH. Hepatoprotective activity of Silybum marianum and Ci-chorium intybus against thioacetamide in rat. Pak J Nutrition. 2008; 7(1): 172-176.
64. Madrigal-Santillán E, Madrigal-Bujaidar E, Álvarez-González I, Sumaya-Martínez, M.T, Gutiérrez-Salinas J, Bautista M, Morales-González A, González-Rubio M.G.-L, Leopoldo Aguilar-Faisal, J, Morales-González J.A. Review of natural products with hepato-protective effects. World J Gastroenterol. 2014; 20(40): 14787–14804.
65. Maheshwari C, Maryammal R, Venkatanarayanan R. Hepatoprotective activity of orthosiphon stamineus on liver damage caused by Paracetamol in Rats. Jordan J Biol Sci. 2008; 1(3):105-108.
66. Mama K, Nyunt N, Tin M. The protective effects of *Eclipta alba* on carbon tetrachloride Induced Acute Liver Damage. Toxicol & Appl Pharmacol. 1978; 45:723-728.
67. Manjunath BK, Vidya SM. Hepatoprotective Activity of *Vitex trifolia* against Carbon tetrachloride-induced Hepatic Damage. Ind J Pharma Sci. 2008; 70(2): 241-5.
68. Manjunatha BK. Hepatoprotective activity of *Pterocarpus santalinus* L.f, an endangered medicinal plant. Ind J Pharmacol. 2006; 38(1): 25-28.
69. Mankani KL, Krishna V, Manjunatha BK, Vidya SM, Jagadeesh Singh SD *et al*. Evaluation of hepatoprotective activity of stem bark of *Pterocarpus marsupium* Roxb. Ind J Pharmacol. 2005; 37(3):165-168.
70. Manokaran S, Jaswanth A, Sengottuvelu S, Nandhakumar J, Duraisamy R, Karthikeyan D, Mallegaswari R. Hepatoprotective activity of *Aerva lantana* Linn. Against Paracetamol induced Hepatotoxicity in Rats. Res J Pharm & Technol. 2008; 1(4): 398-400.
71. Meena B, Ezhilan RA, Rajesh R, Hussain KS, Ganesan B, Anandan R. Antihepatotoxic potential of *Sargassum polycystum* (Phaeophyceae) on antioxidant defense status in Dgalactosamine-induced hepatitis in rats. African J Biochem Res. 2008; 2(2): 51-55.
72. Mehra PN, Nanda SS. Pharmacognosy of Bhringaraja. Antihepatotoxic drug of Indian origin. Ind J Pharm. 1968; 30: 284.
73. Mohamed AF, Ali HAG, Hamamy MI, Abdel-Sattar E. Antioxident and hepatoprotective effect of Eucalyptus maculate. Med Sci Monit. 2005; 11(11):426-431.
74. Mohamed STS, Madhusudhana CC, Ramkanth S, Rajan VST, Mahesh KK, Gauthaman K. Hepatoprotective Herbs-A Review. Int J Res Pharm Sci. 2010; 1(1):l-5.
75. Mohammad N. Qureshi et alIn-vitro Antioxidant and In-vivo Hepatoprotective activity of Leucas ciliate leaves. Rec Nat Prod. 2010: 4, 124-130.
76. Moongkarndi P, Kosema N, Kaslungka S, Luanratana O, Pongpan N, Neungton N. Antiproliferation, anti-oxidation and induction of apoptosis by Garcinia mangostana (mangosteen) on SKBR3 human breast cancer cell line. J Ethanopharmacol. 2004; 90: 161–166.
77. Moron MS, Depierre JW, Mannervik B. Levels of glitathione, glutathione reductase adn glutathione S. trasnferase activities in rat lung and liver. Biochem Biophysics Acta. 1979; 582: 67-78.
78. Mujeeb M, Aeri V, Bagri P, Khan SA. Hepatoprotective activity of the methanolic extract of *Tylophora indica* (Burm. f.) Merill. leaves. Int J Green Pharms. 2009; 3(2):125-127.
79. Mukherjee S, Sur A, Maiti BR. Hepatoprotective effect of Swertia chirata on rat. Indian J Exp Biol. 1997; 35(4): 384-8.
80. Murugaian P, Ramamurthy V, Karmegam N. Hepatoprotective activity of *Wedelia calendulacea* L. aainst

acute hepatotoxicity in rats. Res J Agri Biol Sci. 2008, 4(6): 685- 687.
81. Naaz F, Javed S, Abdin M.Z. Hepatoprotective effect of ethanolic extract of *Phyllanthus amarus* Schum on aflatoxin B1-induced liver damage in mice. J Ethnopharmacol. 2007; 113: 503-509.
82. Nair DG, Weiskirchen R, Al-Musharafi SK. The use of marine-derived bioactive compounds as potential hepatoprotective agents. Acta Pharmacol Sin. 2015; 36(2): 158–170.
83. Nazneen M, Mazid MA, Kundu JK, Bachar SC, Begum F, Datta BK. Protective effects of Flacourtia indica aerial parts extracts against Paracetamol induced hepatotoxicity in rats. J Taibah Uni for Sci. 2009; 2: 1-6.
84. Niranjan A, Tewari SK, Alok L. Biological activities of *Kalmegh* (*Andrographis paniculata* Nees). *Indian J Nat Prod Resources*. 2010; 1(2):125-135.
85. Nohid T, Agarwal SS. Hepatoprotective activity of *Embelia ribes* against Paracetamol induced acute hepatocellular damage in mice. JK. Practitioner. 2003; 1091:43-44.
86. Numazaki, K, Umetsu M, Chiba S. Effect of glycyrrhizin in children with liver dysfunction associated with cytomegalovirus infection. Tohoku J Exp Med. 1994; 172(2): 147-53.
87. Özbek H, Ugras S, Bayram I, Uygan I, Erdogan E, Öztürk A, Huyut Z. Hepatoprotective effect of Foeniculum vulgare essential oil: A carbon-tetrachloride induced liver fibrosis model in rats. J Lab Anim Sci. 2004; 1: 3.
88. Özcan M, Akgül A, Baser KHC, Özok T, Tabanca N. Essential oil composition of sea fennel (*Crithmum maritimum*) from Turkey. Nahrung Food. 2001; 45(5): 353-6.
89. Padma VV, Suja V, Shyamala DCS, Prema. Hepatoprotective effect of Liv-52 on antitubercular drug induced hepatotoxicity in rats. Fitoterapia. 1998; 69(6): 520-22.
90. Patel JA, Shah US. Hepatoprotective activity of *Piper longum* traditional milk extract on carbon tetrachloride induced liver toxicity in Wistar rats. *Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas*, 2009; 8(2):121-128.
91. Pedraza-Chaverri J, Cárdenas-Rodríguez N, Orozco-Ibarra M, Perez-Rojas JM. Medicinal properties of mangos teen (*Garcinia mangostana*). J Food Toxicol. 2004; 3: 24-27.
92. Phaneendra P, Kumar MR, Bodhanapu S, Rahaman F. Tamizmani OMT. Hepatoprotective herbs: an overview. Int J Pharm Res develop. 2011; 3(3): 105-111.
93. Pramyothin P, Samosorn P, Poungshompoo S, Chaichantipyuth C. The protective effects of *Phyllanthus emblica* Linn. Extract on ethanol induced rat hepatic injury. J Ethnopharmacol. 2006; 107(3): 361-64.
94. Raj DS, Vennila JJ, Aiyavu C. Panneerselvam K. The hepatoprotective effect of alcoholic extract of Annona squamosa leaves on experimentally induced liver in-jury in Swiss albino mice. Int J Int Bio. 2009; 5(3):162-166.
95. Ramachandra SS, Absar AQ, Viswanath SAHM, Tushar P, Prakash T, Prabhu K *et al.* Hepato-protective activity of *Calotropis procera* flowers against Paracetamol-induced hepatic injury in rats. Fitoterapia. 2007; 78(7-8):451-454.
96. Rao K.S, Mishra S.H, Hepatoprotective activity of the whole plants of *Fumaria indica*. Ind J Pharm Sci. 59:1997: 165-70.
97. Rosa MP and Gutiérrez, Rosario VS. Hepatoprotective and inhibition of oxidative stress of *Prostechea michuacana*. Rec Nat Prod. 2009; 3(1): 46-51.
98. Rouf R, Ghosh P, Uzzaman M.R, Sarker D.K, Zahura F.T, Uddin SJ, Muhammad I. Hepatoprotective Plants from Bangladesh: A Biophytochemical Review and Future Prospect. Evid Based Complement Alternat Med. 2021; 2021: 1633231.
99. Saleem MTS, Christina AJM, Chidambaranathan N, Ravi V and Gauthaman K. Hepatoprotective activity of *Annona squamosa (*Linn) on experimental animal model. Int J Appl Res Nat Pro. 2008; 1(3):1-7.
100. Sandhir R, Gill KD. Hepatoprotective effects of Liv-52 on ethanol induced liver damage in rats. Ind. J Expt Biol. 1999; 37:762-66.
101. Sanjay J, Dixit VK, Malviya N, Ambawatia V. Antioxident and hepatoprotective activity of ethanolic and aqouaes extract of *Amorphophallus companulatus* Roxb. Acta Pol Pharma. 2009; 66(4):423-428.
102. Sanwa Kagaku Kenkyusha Co. Ltd.: Marmen Pharmaceutical Co. Ltd.-Japanese patent. Chem Abst. 102: 32261b, 1985.
103. Saraswat B, Visen PKS, Dayal R, Agarwal DP, Patnaik GK. Protective action of ursolic acid against chemical induced hepatotoxicity in rats. Ind J Pharmacol. 1996; 28: 232-39.
104. Saxena S, Sharma R, Rajore S, Batra A. Isolation and identification of flavonoid. Vitexin. from *Jatropha curcas* L. J Pl Sci Res. 2005; 21:116.
105. Selvam R, Subramanian L, Gayathri R, Angayarkanni N. The antioxidant activity of turmeric (*Curcuma longa*). *J Ethnopharmacol*, 1995; 47:59-67.
106. Senthilkumar N, Badami S, Dongre S.H, Bhojraj S. Antioxidant and hepatoprotective activity of the methanol extract of *Careya arborea* bark in Ehrlich ascites carcinoma-bearing mice. J Ethnopharmacol. 2008; 116: 1-6.
107. Shamsi-Baghbanan H, Sharifian A, Esmaeili S, Minaei B. Hepatoprotective Herbs, Avicenna Viewpoint. Iran. Red. Crescent Med J. 2014; 16(1): e12313.
108. Shirish S. Pingale Hatoprotection by fresh juice of *Leucas Aspera* leaves. *Der Pharmacia Sinica*. 2010; 1: 136-140.
109. Shirwaiker A, Sreenivasan KK, Krishnanand BR, Kumar AV. Chemical investigation and anti-hepatotoxic activity of the root bark of *Caparis spinosa*. Fitoterapia. 1996; 67(3): 200-4.
110. Sidana J, Deswal G, Nain P, Arora K. Liver toxicity and hepatoprotective herbs. Inter J Pharm Sci Rev Res. 2011, 9(1), 116-121.
111. Simándi B, Deák A, Rónyani E, Yanxiang G, Veress T, Lemberkovics È, Then M, Sass-Kiss Á, Vámos- Falusi Z. Supercritical carbon dioxide extraction and fractionation of Fennel oil. J Agric Food Chem. 1999; 47:1635-40.
112. Singanan V, Singanan M, Begum H. Hepatoprotective effect of bael leaves (aegle marmelos) in alcohol induced liver injury in albino rats. Inter J Sci Technol. 2007; 2: 83-92.
113. Somchit MN, Sulaiman MR, Noratunlina R, Ahmad Z. Hepatoprotective effects of *Curcuma longa* rhizomes in Paracetamol-induced liver damage in rats, Proceedings of the Regional Symposium on Environment and Natural Resources. 2002; 1: 698-702.

114. Sree Rama Murthy M, Srinivasan M. Hepatotprotective Effect of *Tephrosia pupurea* in experimental animals. Ind J Pharmacol. 1993; 25:34-36.
115. Srinivas L, Shalini VK. DNA damage by smoke: Protection by turmeric and other inhibitors of ROS. Free Radical Biol Med. 1991; 11:277-283.
116. Stickel F, Schuppan D. Herbal medicine in the treatment of liver diseases. Digestive & Liver Disease. 2007; 39: 293–304.
117. Sultana S, Perwaiz S, Iqbal M, Athar M. Crude extracts of hepatoprotective plants, *Solanum nigrum* and Ci-chorium intybus inhibit free radical-mediated DNA damage. J Ethnopharmacol. 1995; 45: 189-192.
118. Suresh KSV, Mishra SH. Hepato protective activity of *Baliospermum montanum* (Wild) Muell-ARg in rats treated with CCl_4: *In viva* and *in vitro* studies. PhCog Mag. 2009; 19(5): 196-202.
119. Tabassum N, Agarwal SS. Hepatoprotective activity of *Eclipta alba* hassk. against Paracetamol induced hepatocellular damage in mice. Exp Med. 2004; 11(4).
120. Tabeshpour J, Hosseinzadeh H, Hashemzaei, M, Karimi G. A review of the hepato-protective effects of hesperidin, a flavanon glycoside in *citrus* fruits, against natural and chemical toxicities. Daru. 2020; 28(1): 305–317.
121. Takate SB, Pokharkar RD, Chopade VV, Gite VN. Hepatoprotective activity of ethyl acetate extract of *Launaea intybacea* in Paracetamol inuced hepatotoxicity in Albino rat. Inter J Pharm Sci Rev Res. 2010; 1(2):72-74.
122. Thabrew MI, Babaunmi EA. Levels of microsomal drug metabolizing enzymes in animals which are highly susceptible to aflatoxin carcinogenicity: case of duck. Cancer Lett. 1980; 9(4): 333-8.
123. Thyagarajan SP, Jayaram S, Gopalakrishnan V, Hari R, Jeyakumar P, Sripathi MS. Herbal medicines for liver diseases in India. J Gastroenterol Hepatol. 2002; 17(3): 370-376.
124. Thyagarajan SP, Jayaram S, Gopalakrishnan V, Hari R, Jeyakumar P, Ms Sripathi *et al*. Herbal medicine for liver diseases. India J Gastroenterol Hepatol. 2002; 39: 293-304.
125. Tripathi KD. Essential of Medical Pharmacology. 6th ed. Jaypee brother's medical publishers, 2008.
126. Vadivu R, Krithika A, Biplab C, Dedeepya P, Shoeb N, Lakshmi KS. Evaluation of hepatoprotective activity of the fruits of *Coccinia grandis* Linn. Int J Health Res. 2008; 1(3): 163-168.
127. Wahid AM, Vijay R Salunkhe, Satish B Bhise. Hepatoprotective activity of hydroalcohalic extract o leaves of *Alcocasia indica* (Linn). Ind J Exper Biol. 2008; 47:816-821.
128. Wang M.Y, Anderson G, Nowicki D, Jensen J. Hepatic protection by noni fruit juice against CCl(4)-induced chronic liver damage in female SD rats. Plant Foods Hum Nut. 2008; 63: 141- 145.
129. Warrier PK, Nambiar VPK, Ramankutty C. Foeniculum vulgare, Indian Medical Plants, Chennai,1996: 492.
130. Zimmerman MD, Hayman J. Function and integrity of the liver, In: Clinical diagnosis and management by laboratory methods In: *Clinical diagnosis and management by laboratory methods*, 17th Ed. 1976; 217-50.