LITERATURE REVIEW:

Singh and Handa, 1995 reported that *Apium graveolens* L. grows wild at the base of the North Western Himalayas and outlying hills in Punjab and in Western India. The seeds are used in India to treat bronchitis, asthma, liver and spleen diseases. Its hepatoprotective effect was tested against paracetamol and thioacetamide induced liver injury in rats. The results obtained after oral administration of the methanolic extract of the seeds of *A. graveolens* suggest that this plant has hepatoprotective action which may be due to its role as a membrane stabilizer.

Suja et al. 2004 reported the effect of the methanol extract of *Helminthostachys zeylanica* (L.)Hook rhizomes on carbon tetrachloride (CCl4) induced liver damage in wistar rats. The results showed that significant hepatoprotective effect was obtained against CCl4 induced liver damage, by oral administration of *H. zeylanica* methanol extract as evident from decreased levels of serum enzymes and an almost normal architecture of the liver, in the treated groups, compared to the controls. Thus, the study provides a scientific rationale for the traditional use of this plant in the management of liver diseases.

Olaleye et al., 2006 discovered the hepatoprotective activity of the leaf extract of *Alchornea cordifolia* (Schum and Thonn), a Nigerian plant on acetaminophen induced toxicity in vivo has been reported. The antioxidative properties revealed total phenolic content of 0.22 mg/ml and reducing power of 0.062 mg/ml as compared to vitamin E with a reducing power of 0.042 mg/ml. The authors concluded that the hepatoprotective activity of this plant on acetaminopheninduced liver damage is connected to its antioxidative properties.

Dahiru et al. 2005 reported the protective effect of the ethanol extract of the leaves of *Ziziphus mauritiana* Lam., on CCl4 induced liver damage. Pretreatment of rats with 200 and 300 mg/kg body weight of *Z. mauritiana* leaf extract protected rats against CCl4 liver injury by significantly lowering aspartate aminotransaminase, alanine aminotransaminase, alkaline phosphatase, total bilirubin, and lipid peroxide levels compared to control.

Al-Qarawi et al., 2003 reported the fruit pulp of *Adansonia digitata* (Linn.), commonly known as baobab is an important human nutrition source in East, Central and West Africa (Beckier, 1983; Szolnoki, 1985). The aqueous extract of *A. digitata* pulp was tested for hepatoprotective activity against liver injury by CCl4 in rats. The aqueous extract exhibited significant hepatoprotective activity and consumption of the fruit may play an important part in human resistance to liver damage in areas where the plant is consumed. The mechanism of liver
protection may be due to the presence of triterpenoids, β-sitosterol, β-amyrin palmitate and ursolic acid in the fruit pulp of A. digitata

Bishayee et al. 1995 reported the hepatoprotective effect of aqueous extracts of fresh tuber roots of Daucus carota L. on CCl4- induced acute liver damage. The increased serum enzyme levels by CCl4 induction were lowered due to pretreatment with the extract. The extract also decreased the elevated serum bilirubin and urea content due to CCl4 administration. Results of this study revealed that Daucus carota could afford a significant protective action in the alleviation of CCl4 induced hepatocellular injury.

Jafri et al., 1999 studied the leaf extract of Cassia occidentalis L. a weed of the family Caesalpinaceae is found throughout India and is an important ingredient of several polyherbal formulations marketed for liver diseases. The hepatoprotective activity of aqueous-ethanolic extract (50%, v/v) of leaves was studied on rat liver damage induced by paracetamol and ethyl alcohol by monitoring serum transaminase, alkaline phosphatase, serum cholesterol, serum total lipids and histological alterations.

Opoku et al., 2007 demonstrated that Rhoicissus tridentata (L.F) Wild and Drum, a South African medicinal plant is commonly used for the treatment of ailments like epilepsy, kidney and bladder complaints. The aqueous extract of the roots were shown to possess significant hepatoprotective effect against CCl4 induced acute liver injury in rats. The variables investigated were the enzymes alanine aminotransferase, aspartate aminotransferase and glucose-6- phosphate (G-6-Pase). CCl4 intoxication resulted in significant increases in all the variables investigated except G-6-Pase which was significantly decreased. The administration of R. tridentate extracts after CCl4 intoxication resulted in significant decreases in all the variables investigated except G-6-Pase which was significantly increased.

Ahsan et al. 2009, investigated that the methanol extracts of Bixa orellana, Cajanus cajan, Glycosmis pentaphylla and Casuarina equisetifolia were all shown to possess significant hepatoprotective activity. The four plant extracts at a dose of 500 mg/kg body weight exhibited moderate protective effect by lowering the serum levels of alanine aminotransferase (ALT) or serum glutamate pyruvate transaminase (SGPT), aspartate aminotrans-ferase (AST) or serum glutamate oxaloacetate transaminse (SGOT), and cholesterol to a significant extent against liver damage induced by CCl4. It was possible to list 107 species of medicinal plants studied, that have shown hepatoprotective activity.
Yoshikawa et al., 2003 discovered new skeletal flavonoids, anastatins A and B, were isolated from the methanol extract of *Anastatica hierochuntica* L. Anastatins A and B were found to show hepatoprotective effects on D-galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes and their activities were stronger than those of related flavonoids and commercial silybin - a known hepatoprotective compound.

Farombi, 2000, examined the protective mechanisms of kolaviron, a biflavonoid fraction from *Garcinia kola* (Heckel) seeds in rats treated with CCl4. When administered at a dose of 1.2 g kg-1, three times a week for two weeks, it significantly depressed the activities of microsomal aniline hydroxylase, aminopyrine N-demethylase, ethoxyresorufin O-demethylase and p-nitroanisole Odemethylase. Kolaviron (200 mg kg-1), administered for 14 days consecutively, inhibited the CCl4 mediated decrease in the activities of these enzymes by 60, 65, 55 and 63% respectively. Kolaviron exerted its protective action by acting as an in vivo natural antioxidant and by enhancement of drug-detoxifying enzymes.

Visen et al., 1991 reported Picroliv, an iridoid glycoside isolated from *Picrorhiza kurrooa* demonstrated dose-dependent protective activity on isolated hepatocytes against paracetamol-induced hepatic damage in rats. It also restored the normal values of enzymes (glutamic oxaloacetic transaminase, glutamic-pyruvic transaminase, and alkaline phosphatase) both in the isolated hepatocyte suspension as well as in the serum.

Oh et al., 2004 stated that hepatoprotective activity-guided fractionation of the methanol extract of *Equisetum arvense* L. resulted in the isolation of two phenolic petrosins and four flavonoids. Among these compounds, onitin and luteolin demonstrated hepatoprotective activities on tacrine-induced cytotoxicity in human liver-derived Hep G2 cells, displaying EC (50) values of 85.8 +/- 9.3 microM and 20.2 +/- 1.4 microM, respectively. Silybin used as a positive control, showed the EC (50) value of 69.0 +/- 3.3 microM. Both compounds also showed superoxide scavenging effects which indicates good antioxidant activity. These results support the use of *E. arvense* in the treatment of hepatitis in oriental traditional medicine.

Oliveira et al., 2005 isolated two triterpenes α- and β-amyrin isolated from *Protium heptaphyllum* (Aubl.) March. were tested against acetaminophen-induced liver injury in mice. Liver injury was analysed by quantifying the serum enzyme activities and by histopathological observation. Pretreatment with α- and β-amyrin attenuated the acetaminophen-induced acute increase in serum alanine aminotransferase and aspartate aminotransferase activities, replenished
the depleted hepatic glutathione, and considerably reduced the histopathological alterations. These findings demonstrated the hepatoprotective potential of α- and β-amyrin against toxic liver injury and suggest that the diminution in oxidative stress and toxic metabolite formation as likely mechanisms involved in its hepatoprotection.

Mankani et. al., 2005 reported that Methanol extract of the stem bark of P. marsupium possesses significant hepatoprotective activity. In methanol extract-treated animals, the toxic effect of CCl4 was controlled significantly by restoration of the levels of serum bilirubin, protein and enzymes as compared to the normal and the standard drug silymarin-treated groups. Histology of the liver sections of the animals treated with the extracts showed the presence of normal hepatic cords, absence of necrosis and fatty infiltration, which further evidenced the hepatoprotective activity.

Singanan et al., 2007 demonstrated that Aegle marmelos leaves (Bael, family of Rutaceae) which is also called as Bilva in ancient Sanskrit, was used as herbal drug in the Indian System of medicine. The hepatoprotective effect of Aegle marmelos in alcohol-induced liver injury was evaluated rats using essential marker biochemical parameters. The results indicated that, the Bael leaves have excellent hepato-protective effect. Similar findings were also reported by other workers.

Rosa and Rosario, 2009 reported that Methanol, hexane and chloroform extracts of Prostechea michuacana (PM) were studied against CCl4-induced hepatic injury in albino rats. Pre-treatment with methanolic extract reduced biochemical markers of hepatic injury levels demonstrated dose-dependent reduction in the in vivo peroxidation induced by CCl4. Likewise, pretreatment with extracts of PM on paracetamol-induced hepatotoxicity and the possible mechanism involved in this protection were also investi-gated in rats after administering 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 paracetamol-induced lipid peroxidation thereby eliminating the deleterious effects of toxic metabolites of paracetamol. 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.
**Pramyothin et al., 2006** discovered that the ethanolic extract of *Phyllanthus amarus* (Euphorbiaceae), at (0.3g kg^{-1} BW 0.2 ml^{-1} day^{-1}) was given to all groups except control groups (gp. I and gp. V), after 30 min of aflatoxin administration. The entire study was carried out for 3 months and animals were sacrificed after an interval of 30 days till the completion of study. *Phyllanthus 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-S transferase (GST), superoxide dismutase (SOD) and catalase (CAT).

**Chattopadhyay et al., in 1992** studied the effect of *A. indica* leaf (Meliaceae) extract on serum enzyme levels (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acid phosphatase and alkaline phosphatase) elevated by paracetamol in rats was studied with a view 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 paracetamol induction. The findings were further confirmed by histopathological study of 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.

**Arulkumaran et al., in 2009** studied hepatoprotective activity of the n-heptane s extract of *Cassia fistula* (Fabaceae) leaves was investigated by inducing hepatotoxicity with paracetamol in rats. The extract at a dose of 400 mg/kg body wt. exhibited orally, significant protective effect by lowering the serum levels of transaminase (SGOT and SGPT), bilirubin and alkaline phosphatase (ALP). The effects produced were comparable to that of a standard hepatoprotective agent.

**Chaterjee TK 2000,** stated that 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 indicating the potent antioxidant and hepatoprotective nature of the standardized extract.

**Somchit et al., 2002** reported that Curcuma longa or turmeric is a member of Zingiberaceae family which is a perennial herb with short and thick rhizomes, has been used extensively in traditional Chinese medicine and Ayurvedic medical system. Curcuma longa contains
approximately 2% volatile oil, composed mainly of α- and β-turmerone, monoterpenes (Leung and Foster 1996), 5% curcuminoids, mainly curcumin, minerals, carotene and vitamin C.

The active constituent of Curcuma longa is Curcumin, which is the yellow pigment of turmeric. The hepatoprotective activity of the ethanol extract of Curcuma longa was investigated against paracetamol-induced liver damage in rats. At the dose of 600 mg/kg, paracetamol induced liver damage in rats as manifested by statistically significant increase in serum alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) and alkaline phosphatase (ALP). Pretreatment of rats with the ethanolic extract of Curcuma longa (100 mg/kg) prior to paracetamol dosing at 600 mg/kg statistically lowered the three serum liver enzyme activities. Moreover, treatment of rats with only the ethanolic extract of Curcuma longa (100 mg/kg) had no effects on the liver enzymes. This current result suggests that ethanolic extract of Curcuma longa has potent hepatoprotective effect against paracetamol-induced liver damage in rats.

Meena et al., in 2008 studied the protective effect of ethanol extract of Sargassum polycystum was evaluated in D-galactosamine-induced hepatitis in rats. Prior oral administration of S. polycystum extract [125mg/kg bodyweight/day for 15 days] significantly attenuated (P<0.05) the D-galactosamine-induced increases in the levels of diagnostic marker enzymes (AST, ALT and ALP) in plasma of rats. It has also demonstrated 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 possibly due to its antioxidant property and membrane stabilizing action.

Abeer E.et al 2008 stated the 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 cholesterol-rich diet enriched with 0.3% GSE/W-PG) for 8 weeks. Serum lipid levels, serum antioxidant status, liver and kidney function were analysed 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 case of oral administration 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.
Shirish, 2010, stated the effect of Leucas aspera leaves fresh juice against carbon tetrachloride (CCl4) 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 single dose of CCl4, 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 overall promising effect against liver disorders.

Kanchana et al., 2011 investigated petroleum ether extract of root of Plumbago zeylanica for hepatoprotective activity against paracetamol induced liver damage to evaluate the hepatoprotective activity of ethanolic extract. In serum total bilirubin, total protein, aspartate transaminase, alanine transaminase, alkaline phosphatase, lactate dehydrogenase, \( \gamma \)-Glutamyl transferase, Total Cholesterol and serum triglycerides were determined to assess the effect of the extract on the paracetamol induced hepatic damage. The study was also supported by histopathology of liver sections. Results of this study revealed that the markers in the animals treated with paracetamol recorded elevated concentration indicating severe hepatic damage by paracetamol, whereas the blood samples from the animals treated with petroleum ether extract of roots showed 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 bodyweight of rat. The present study reveals that the petroleum ether root extract of Plumbago zeylanica could afford a significant protection against paracetamol-induced hepatocellular injury.

Wang et al., 2008 demonstrated that the hepatoprotective effects of Noni juice (NJ) (Rubiaceae) against CCl(4)-induced chronic liver damage in female Sprague Dawley (SD) rats. Histopathological examination revealed that liver sections from the NJ + CCl(4) appeared similar to controls, whereas typical hepatic steatosis was observedmin the placebo + CCl(4) group. Serum alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (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 NJ group. In contrast, high-density lipoprotein (HDL) was increased in the NJ group and decreased in the placebo group. Thus, NJ juice appears to protect hepatocytes.
Abdel-razik a. f. et al., 2009 discovered that the volatile oil, ethyl acetate, n-butanol and total alcoholic extracts of J. subulatus were evaluated 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.

Mohammad et al., 2010 reported hepatoprotective activity of the ethanolic extract of Leucas ciliata leaves extract by carbon tetrachloride (CCl4) induced liver damage model in rats. The extract demonstrated a significant dose dependent antioxidant activity comparable with ascorbic acid. In hepatoprotective activity study, CCl4 significantly increased the levels of serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), alkaline phosphatase (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.

Bhakta et al., in 2001 stated that Berberine is an active compound in Coptidis Rhizoma (Huanglian) with multiple pharmacological activities including antimicrobial, antiviral, anti inflammatory, cholesterol-lowering and anticancer effects. The hepatoprotective effects of berberine on serum and tissue superoxide dismutase (SOD) levels, the histology in tetrachloride (CCl4)-induced liver injury. Sprague-Dawley rats aged seven weeks were injected intraperitoneally with 50% CCl4 in olive oil. Berberine was orally administered before or after CCl4 treatment in various groups. Twenty-four hours after CCl4 injection, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, serum and liver superoxide dismutase (SOD) activities were measured. Histological changes of liver were examined with microscopy. The present study demonstrates that berberine possesses hepatoprotective effects.

Ahmed B. et al. 2002 revealed in their study that 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 on a daily basis. 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.