REVIEW OF LITERATURE:

1. **Naseem NQ et al., (2009)** investigated the antioxidant & hepatoprotective activity in ethanolic extract of *Cordia Macleodii* leaves. The extract demonstrated a significant dose dependent antioxidant activity comparable with ascorbic acid by in vitro methods viz. 1,1-diphenyl-2-picryl hydroxyl (DPPH) radical scavenging method, nitric oxide (NO) radical scavenging method, iron chelation method and reducing power method. CCl4 produced a significant increase in levels of serum glutamate pyruvate transaminase (GPT), serum glutamate oxaloacetate transaminase (GOT), Alkaline Phosphatase (ALP) and total bilirubin by liver damage. Pretreatment of the rats with ethanolic extract of C. macleodii inhibited the increase in levels of GPT, GOT, ALP and total bilirubin and the inhibition was comparable with Silymarin.

2. **Chandan BK et al., (2007)** studied hepatoprotective activity by oral administration of various extracts of dried flowers of *Woodfordia fruticosa Kurz* against carbon tetrachloride induced hepatotoxicity using biochemical markers, hexobarbitone sleep time, bromosulphalein (BSP) clearance test and effect on bile flow and bile solids. The restoration of microsomal aniline hydroxylase and amidopyrine-N-demethylase activities indicated the improvement in functional status of endoplasmic reticulum. Restoration of lipid peroxidation and glutathione contents suggests the antioxidant property of WF Extracts. The recovery in bromosulphalein clearance and stimulation of bile flow suggested the improved excretory and secretory capacity of hepatocytes. aqueous extract of Woodfordia fruticosa significantly restores physiological integrity of hepatocytes. WF4 did not show any sign of toxicity up to oral dose of 2 g/kg in mice.

3. **Pramyothin P et al., (2005)** investigated the Hepatoprotective activity of *Thunbergia laurifolia(TL) Linn* Aqueous extract in rats treated with ethanol using In vitro and in vivo studies. In the in vitro study, MTT reduction assay and release of transaminases (ALT and AST) were the criteria for cell viability. Primary cultures of rat hepatocyte (24 h culturing) were treated with ethanol and various concentrations of TLE or SL (Siliyamarine) for 2 h. Ethanol decreased MTT (%) nearly by half. Both TLE and SL increased MTT reduction and brought MTT (%)
to normal. Ethanol induced release of ALT and AST was also reduced by TLE and SL in dose dependeant manner. In the in vivo study, oral administration of ethanol for 14 days leads to liver damage with evidence of increase in serum transaminases, serum triglyceride (STg) together with hepatic triglyceride (HTg) and histopathological examination. Authors investigated that oral administration of TLE & SL for 7 days after ethanol enhanced liver cell recovery by bringing HTg, ALT and/or AST back to normal. These results suggest that TLE and SL possess the hepatoprotective activity against ethanol induced liver injury in both primary cultures of rat hepatocyte and rats.

4. **Huang B et al., (2009)**, studied leaves ethanolic extracts of edible Lotus (Nelumbo nucifera Gaertn.) were subjected screening out to antioxidant & hepatoprotective activity in CCl₄, induced heaptotoxicity. The results showed the hepatoprotective activity of lotus leaf extract (LLE) at doses of 300 and 500 mg/kg and in vivo antioxidant activity at 100 mg/kg that was comparable with that of a standard treatment comprising 100 mg/kg of silymarin, a known hepatoprotective drug. The main flavonoids and phenolic compounds of LLE were analysed by HPLC-DAD-ESI/MS methods. Six of the compounds detected were tentatively characterized, one as catechin glycoside and five as flavonoid glycoside derivatives: miricitrin-3-O-glucoside, hyperin, isoquercitrin, quercetin-3-O-rhamnoside and astragalin.

5. **Sundaram R et al., (2011)** investigated the hepatoprotective and in vitro antioxidant activity of Lumnitzera racemosa (L.racemosa) leaf extract. This was tested in rats by carbon tetrachloride ( 9 days ,po) induced hepatotoxic rats using oral administration of Lumnitzera racemosa (L.racemosa) leaf extract in dose dependence manner using siliyamarine as standard hepatoprotective agent. Lumnitzera racemosa (L.racemosa) leaf extract treated animals showed significantly reduction in SGPT, SGOT, ALP, Bilirubuin, LDH ,Sugar levels. Hepatroprotective effect of Lumnitzera racemosa (L.racemosa) leaf extract might be due to presence of phenolic compound,terpenoids,alkaloids & in vitro antioxidant property.
6. **Tandon VR et al.,(2008)** studied Hepatoprotective (HP) activity of *Vitex Negundo* (VN) leaf ethanolic extract was investigated against hepatotoxicity (HT) produced by administering a combination of three anti-tubercular drugs isoniazid (INH)-7.5 mg/kg, rifampin (RMP)-10 mg/kg and pyrazinamide (PZA)-35 mg/kg for 35 days by oral route in rats. *V. negundo* leaf extract in one of our previous study also has been recorded to produce reduction of oxidative stress by reducing lipid peroxidation in ethanol induced oxidative stress model, which may be due to its various antioxidant constituents like iridoid glycosides, flavonoids, vitamin C, and carotene. In conclusion *V. negundo* leaf ethanol extract possesses hepatoprotective activity against anti-tubercular drugs induced HT at dose of 250 mg/kg and high 500 mg/kg doses. The investigation for an efficient hepatoprotective drug from the natural resource is an urgent necessity to ameliorate hepatotoxicity induced by anti-tubercular drugs, our finding may have some clinical relevance.

7. **Sreelatha S et al.,(2008)** evaluated the Protective effects of *Coriandrum Sativum* extracts on carbon tetrachloride-induced hepatotoxicity in rats. Oxidative damage is implicated in the pathogenesis of various liver injuries. CCl4 injection induced oxidative stress by a significant rise in serum marker enzymes and thiobarbituric acid reactive substances (TBARS) along with the reduction of antioxidant enzymes. In serum, the activities of enzymes like ALP, ACP and protein and bilirubin were evaluated. Pretreatment of rats with different doses of plant extract (100 and 200 mg/kg) significantly lowered SGOT, SGPT and TBARS levels against CCl4 treated rats. Hepatic enzymes like SOD, CAT, GPx were significantly increased by treatment with plant extract, against CCl4 treated rats. Histopathological examinations showed extensive liver injuries, characterized by extensive hepatocellular degeneration/necrosis, inflammatory cell infiltration, congestion, and sinusoidal dilatation. Oral administration of the leaf extract at a dose of 200 mg/kg body weight significantly reduced the toxic effects of CCl4. The activity of leaf extract at the dose of 200 mg/kg was comparable to the standard drug, silymarin.
8. **Kyung JL et al., (2008)** elucidated protective effects of the saponins isolated from the root of Platycodi Radix (Changkil saponins: CKS) on carbon tetrachloride (CCl4)-induced hepatotoxicities in mice. Pretreatment with CKS prior to the administration of CCl4 significantly prevented the increase in serum alanine aminotransferase and aspartate aminotransferase activities and hepatic lipid peroxidation formation. In addition, CKS prevented CCl4-induced apoptosis and necrosis, as indicated by a liver histopathologic study and DNA laddering. CKS markedly decreased CCl4-induced Fas/FasL protein expression levels and in turn attenuated CCl4-induced caspase-3, -8 activities in mouse livers were tested by ELISA & Western Blotting. Additionally, CKS protected the CCl4-induced depletion of hepatic glutathione levels. The effect of CKS on CYP2E1, the major isozyme involved in CCl4 bioactivation, was investigated. Treatment with CKS resulted in a significant decrease in the CYP2E1-dependent hydroxylation of aniline. In addition, CKS exhibited antioxidant effects on FeCl2-ascorbate induced lipid peroxidation in liver homogenates, and on superoxide radical scavenging activity.

9. **Yang YS et al.,(2008)** investigated the ability of Pycnogenol (PYC) as an antioxidant to protect against CCl4-induced oxidative stress and hepatotoxicity in rats. Animals received a 14-day repeated intraperitoneal (i.p.) dose of distilled water and then a single oral dose of CCl4 at 1.25 ml/kg & CCl4 & PYC 10 and CCl4&PYC 20 groups received a 14-day repeated i.p. dose of PYC 10 and 20 mg/kg, respectively, and then a single oral dose of CCl4 at 1.25 ml/kg. Hepatotoxicity was assessed 24 h after the CCl4 treatment by measurement of serum aminotransferase (AST) and alanine aminotransferase (ALT) activities, hepatic malondialdehyde (MDA) and glutathione (GSH) concentrations, and catalase, superoxide dismutase (SOD), and glutathione-S-transferase (GST) activities. PYC treatment prior to the administration of CCl4 significantly prevented the CCl4-induced hepatotoxicity, including the elevation of serum AST and ALT activities and histopathological hepatic lesions, in a dose-dependent manner. Moreover, MDA and GSH levels and catalase, SOD, and GST activities in hepatic tissues were not affected by administration of CCl4, indicating that the
pretreatment of PYC efficiently protects against CCl4-induced oxidative damage in rats.

10. **Quan J et al., (2009)** evaluated the hepatoprotective effect of Boschniakia rossica extract (BRE), rich in phenylpropanoid glycoside and iridoid glucoside, on CCl4-induced liver damage. CCl4 challenge not only elevated the serum marker enzyme activities and reduced albumin(ALB)level but also Increased liver oxidative stress, as evidenced by elevated lipid hydroperoxide(LOOH) and malondialdehyde(MDA)concentrations, combined with Suppressed potential of hepatic anti oxidative Defense system including superoxide ismutase(SOD),glutathione peroxidase(GPx)activities and reduced glutathione(GSH)content. Furthermore, serum tumor necrosis factor-a (TNF-a), hepatic nitrite level, inducible nitric oxide synthase(iNOS) and cyclo oxygenase-2(COX-2)protein contents were elevated while cytochromeP4502E1(CYP2E1) expression and function were inhibited.

11. **Yue J et al.,( 2009)** evaluated protective effects of thiopronin against isoniazid-induced hepatotoxicity in rats. Isoniazid is a widely used drug for the treatment of tuberculosis, but hepatotoxicity is a major concern during treatment. Thiopronin contains an SH-group and is generally considered an antioxidant. Rats were injected daily with isoniazid (100 mg/kg, i.p.) for 21 days with or without thiopronin co-administration (60 mg/kg, i.p.) from day 11 to day 21. The influence of thiopronin on isoniazid-induced DNA oxidative damage was analyzed in precision-cut rat liver slices by HPLC–MS/MS. Thiopronin prevented isoniazid-induced hepatotoxicity, indicated by both diagnostic indicators of liver damage (alanine aminotransferase and aspartate aminotransferase) and histopathological analysis. In vivo, thiopronin significantly inhibited isoniazid-induced CYP2E1 activity as assessed by both chlorzoxazone hydroxylase and aniline hydroxylase Thiopronin concentration-dependently inhibited CYP2E1-dependent aniline hydroxylation, and the Dixon plots suggest that thiopronin is a competitive inhibitor of CYP2E1. Thiopronin markedly attenuated isoniazid-induced inhibition of the detoxification system through cytosolic glutathione S-transferases (GSTs), including muGST and alpha GST. Thiopronin may reduce
free radical generation via inhibition of hepatic CYP2E1 and increase the removal of free radicals directly or through the induction of cytosolic GSTs.

12. Shen C et al., (2006) investigated Gel entrapment culture of rat hepatocytes in hollow fibers as a potential in vitro model for studies on isoniazid induced hepatotoxicity. After exposure to isoniazid (0.11 mM and 1.1 mM) for 24–96 h, gel entrapped hepatocytes were more severely damaged than hepatocyte monolayers according to the assays on methyl thiazolyl tetrazolium (MTT) reduction, intracellular glutathione (GSH) content, reactive oxygen species (ROS) levels, and albumin secretion. Furthermore, CYP 2E1 activity detected by 4-nitrocatechol (4-NC) formation maintained at least 7 days in gel entrapped hepatocytes but decreased to an undetectable level within 2 days in hepatocyte monolayer. And the addition of CYP 2E1 inhibitor, diethyl-dithiocarbamate (DDC), significantly reduced isoniazid-induced GSH depletion in gel entrapped hepatocytes. In addition, the protective effects of N-acetylcysteine (NAC), GSH, liquorice extract and glycyrrhizic acid (GA), a purified compound from liquorice extract, against isoniazid hepatotoxicity were clearly observed in gel entrapped hepatocytes at 72 h incubation. Overall, gel entrapped hepatocytes were more susceptible to isoniazid-induced hepatotoxicity than hepatocyte monolayers by a possible mechanism that higher CYP 2E1 activity in gel entrapped hepatocytes could enhance isoniazid toxicity. This indicates that gel entrapped hepatocytes in hollow fibers could be a more effective model than hepatocyte monolayer for hepatotoxicity research in vitro.

13. Upadhyay G et al., (2007) elucidate the role of drug/toxicant-metabolizing enzymes in rifampicin- and pyrogallol-induced hepatotoxicity and the effect of silymarin, a herbal antioxidant, on rifampicin- and pyrogallol-induced alterations in mouse liver. Male Swiss albino mice were treated intraperitoneally with and without rifampicin (20 mg/kg) and/or pyrogallol (40 mg/kg) for 4 weeks. Animals were treated with silymarin (40 mg/kg), 2 h prior to rifampicin and/or pyrogallol. The differential expression and catalytic activity of cytochrome P-450 (CYP) 1A1, CYP1A2 and CYP2E1, the activity of glutathione-S transferase, glutathione peroxidase and glutathione reductase, and lipid peroxidation were
measured in the liver of control and treated groups. CYP1A1 expression and catalytic activity were not altered following individual or combinational treatment. A significant augmentation in the expression and activity of CYP1A2 and CYP2E1 was observed following pyrogallol and rifampicin+pyrogallol treatment; however, rifampicin exhibited a significant induction of CYP2E1 only. Attenuation of glutathione-S-transferase, glutathione reductase and glutathione peroxidase activities and augmentation of lipid peroxidation were observed following rifampicin and/or pyrogallol treatment and a cumulative effect was seen when the two drugs were administered in combination. Silymarin restored the rifampicin- and/or pyrogallol-induced alterations in the expression and activity of CYP1A2 and CYP2E1, the activity of glutathione-S-transferase, glutathione reductase, and glutathione peroxidase, and lipid peroxidation.

14. **Harish R et al., (2006)** investigated the antioxidant & hepatoprotective activity of Phyllanthus niruri. Methanolic and aqueous extract of leaves and fruits of P. niruri showed inhibition of membrane lipid peroxidation (LPO), scavenging of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical and inhibition of reactive oxygen species (ROS) in vitro. Antioxidant activities of the extracts were also demonstrable in vivo by the inhibition of the carbon tetrachloride (CCl4) – induced formation of lipid peroxides in the liver of rats by pretreatment with the extracts. CCl4 – induced hepatotoxicity in rats, as judged by the raised serum enzymes, glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT), was prevented by pretreatment with the extracts, demonstrating the hepatoprotective action of P. niruri.

15. **Sathiyaraj K et al., (2010)** evaluated the effective concentration of aqueous extract of Aegle Marmelos leaves on male reproductive system of albino rats for antifertility activity. Animals were administered the aqueous leaf extract daily at 250mg/kg body wt., and 350mg/kg body wt., respectively for a period of 45days. Significant decreases in the weights of testis, epididymes and seminal vesicle were observed. A dose related reduction in the testicular sperm count, epididymal sperm count and motility and abnormal sperm count were observed. The results
showed that *Aegle Marmelos* has effects on male rat reproduction, affecting the sexual behavior and epididymal sperm concentration.

16. **Gangadharan G et al.,(2007)** investigated the changes in the total muscarinic and muscarinic M1 receptor ([3H]QNB) binding and gene expression in the cerebral cortex of streptozotocin (STZ) induced diabetic, insulin and aqueous extract of *Aegle Marmelose* leaf treated diabetic rats. The results showed that there is decrease in total muscarinic and muscarinic M1 receptors during diabetes which is up regulated by insulin and Aegle marmelose leaf extract treatment. This has clinical significance in therapeutic management of diabetes.

17. **Arul V et al.,(2002)** studied effect of the alcoholic extract of the leaves of Aegle marmelos Corr. on guinea pig isolated ileum and tracheal chain. As this plant is used traditionally to treat asthma and related afflictions. These effects were investigated using the isolated organ bath method. alcoholic extracts elicited the antagonistic effect against histamine and also relaxed the histamine-induced contractions, it can be concluded that relaxations induced by A. marmelos in both guinea pig ileum and tracheal chain were due to the depression of H1- receptors. Since we observed a complete relaxation of the guinea pig ileum and tracheal chain produced by the extract, we investigated its antagonistic effect against histamine.

18. **Narender T et al.,(2006)** investigated Antihyperglycemic and antidyslipidemic activity in sucrose challenged streptozotocin induced diabetic rats (STZ-S) model at the dose of 100 mg/kg body weight. From the leaves of A. marmelos an alkaloidal-amide, Aegeline 2, was isolated and found to have antihyperglycemic activity as evidenced by lowering the blood glucose levels.

19. **Upadhya S et al.,(2004)** studied hypoglycemic and antioxidant activity of aegle marmelos in alloxan induced diabetic rats. There was a decrease in blood glucose at the end of 4 weeks in treated animals compared with diabetic rats. There was an increase in erythrocyte GSH and a decrease in MDA in treated animals. Owing to hypoglycemic and antioxidant properties, AML may be useful in the longterm management of diabetes.
20. **Arul Vet al., (2005)** studied serial extracts of the leaves of *Aegle marmelos* Corr. for anti-inflammatory property. The analgesic and antipyretic properties were also evaluated. The most of the extracts derived from the plant *Aegle marmelos* caused a significant inhibition of the carrageenan-induced paw oedema and cotton-pellet granuloma in rats. The extracts also produced marked analgesic activity by reduction the early and late phases of paw licking in mice. A significant reduction in hyperpyrexia in rats was also produced by the most of the extracts. This study was established anti-inflammatory, antinociceptive and antipyretic activities of the leaves of *Aegle marmelos*.

21. **Maheshwari VL et al., (2009)** studied on ethnolic extract of dried fruit pulp of *Aegle Marmelos* against various intestinal pathogens i.e. *Shigella boydii*, *S. sonnei* & *S. Flexneri* and proposed that certain phytochemicals including Phenols, Tannins and Flavonoids were effective against all. It was also confirmed by *Kaur et al., (2009)* by getting treat *E. Coli* with Aegle Marmelos fruit extract.

22. **Rani P et al., (2005)** studied the 54 plant extracts (methanol and aqueous) for their activity against muti-drug resistant *Salmonella typhi*. The methanol extracts of *Aegle marmelos*, *Salmalia malabarica*, *Punica granatum*, *Myristica fragrans*, *Holarrhena antidysenterica*, *Terminelia arjuna* and Triphala showed strong antimicrobial activity.

23. **Rana BK., (1997)** evaluated anti fungal activity of essential oils isolated from the leaves of Bael using spore germination assay. The oil exhibited variable efficacy against different fungal isolates and 100% inhibition of spore germination of all the fungi tested was observed at 500ppm. They proposed that essential oil from bael leaves may interfere with the Ca$^{2+}$-dipicolonic acid metabolism pathway and possibly inhibit the spore formation.

24. **Costa LV et al., (2005),** evaluated the anticancer potential of folk medicine used in Bangladeshi and used extracts of *Aegle marmelos* for cytotoxic action using brine shrimp lethality assay; sea urchin eggs assay, and MTT assay using tumor cell lines. The extract of *Aegle marmelos* was found to exhibited toxicity on all used assays.
25. **Jagetia GC. et al., (2005)** reported the anticancer effect of hydroalcoholic extract of bael leaves in the animal model of Ehrlich ascites carcinoma and proposed that induction of apoptosis may be due the presence of skimmianine in extract.

26. **Jagetia GC et al.,(2005)** investigated the Radioprotective effect of Aegle marmelos extract by exposing to different doses of gamma-radiation in mice and found that oral administration of extract resulted in an increase in radiation tolerance by 1.6 Gy. Also studied effects of plant extract on the peripheral blood and small intestine of Swiss albino mice. They exposed the animals to gamma radiation and data were collected against radiation-induced changes in the peripheral blood, spleen colony forming units, and intestinal mucosa, reported that Aegle marmelos extract significantly reduces the deleterious effect of radiation in intestine and bone marrow of mouse.

27. **Panda S, and Kar A. (2006)**, isolated, Scopoletin (7-hydroxy-6-methoxy coumarin) from Aegle marmelos leaves and evaluate for its potential to regulate hyperthyroidism. It was observed that scopoletin (at 1.00 mg / kg, p.o. for 7 days) to levo-thyroxine treated animals, decreased serum thyroid hormones level. It was also proved that the scopoletin have superior therapeutic activity than the standard antithyroid drug, propylthiouracil.

28. **Goel RK** (1997) reported that oral; administration of pyranocoumarin isolated from the seeds of Aegle marmelos Correa, showed significant protection against pylorus-ligated and aspirin-induced gastric ulcers in rats and cold restraint stress-induced gastric ulcers in rats and guinea pigs.

29. **Dhuley JN; (2007)**, reported that pretreatment of rats with unripe bael fruit extract produce a significant inhibition of absolute ethanol induced gastric mucosal damage.

30. **Rajadurai M et al., (2005)** studied Pretreatment with Bael leaf extract at 100 mg/kg and 200 mg/kg doses for 35 days have shown significant improvement on the activities of marker enzymes, decrement of lipid peroxides, plasma lipids and lipoproteins in isoproterenol-treated rats, suggesting its antihyperlipidaemic effect.

31. **Vijaya C et al, (2009)** Ethanolic extract of Bael leaves also inhibited the elevation of serum cholesterol and triglycerides level in triton WR 1339 treated hyperlipidaemic rat. This extract als potentiates glucose utilization. The higher
level of fatty acid and their metabolites such as acyl carnitine and long chain acyl CoA usually interfere with NA+/K+ ATPase activity level.

32. Prince P et al., (2005) evaluated the preventive effects of an aqueous *Aegle marmelos* leaf extract (AMLEt) in isoprenaline (isoproterenol)- induced myocardial infarction in rats. Pretreatment with AMLEt decreased the activity of creatine kinase (CK) and lactate dehydrogenase (LDH) in serum and increased them in the heart, also AMLEt pretreatment increased the activity of Na+K+ ATPase and decreased the activity of Ca2+ATPase in the heart and aorta simultaneously and the levels of cholesterol and triglycerides decreased whereas phospholipids increased in heart and aorta of AMLEt-pretreated rats. All the deranged biochemical parameters were restored with 200 mg kg-1 AMLEt.

33. Mishra P et al., (1991) studied development of resistance to existing antimalarial drugs has led to complications in treating this dreadful disease Thus, identification of novel molecules to treat this multidrug resistant malaria is vital. The alcoholic extracts of the Bael seeds and leaves have been tested *in vivo* and *in vitro* for antimalarial activity against the NK65 strain of *Plasmodium berghei*. The seeds have shown schizontocidal activity in both the system, whereas, the leaves have shown activity only in the in-vitro system.