SUMMARY & CONCLUSIONS
Fulminant hepatic failure (FHF) is a challenging syndrome in clinical medicine. Though it is not a very common disease, it is fatal and can affect even normally healthy people. Exact causes of the disease are not clearly known. But viral hepatitis and drug induced liver injury account for the majority of cases. Hepatitis E is a commonly encountered problem in the Indian sub continent affecting hundreds of thousands of people and resulting in high mortality. FHF is associated with clinical features like jaundice, shrunken liver, easy bruising, low levels of serum proteins, fatigue, multi-organ failure etc and metabolic derangements like hypoglycemia, hyperlipidemia, hyponatremia, defective protein synthesis, reduced energy production, decreased rate of urea production etc. These disturbances are predominantly attributed to oxidative stress, membrane destabilization and osmotic imbalances. The options available for patients suffering from this problem are minimal, liver transplantation being the main one. But due to cost, difficulties and inconveniences involved this procedure doesn’t find favor among patients and care-givers. Use of cytoprotective and hepatoprotective drugs is considered a more acceptable alternative as a strategy to enhance liver regeneration. Isolated studies have suggested taurine, as a promising compound for this purpose. The present study was designed to investigate the hepatoprotective effect of this simple yet promising sulphur containing β-amino acid on experimentally induced FHF by feeding experiments using albino rats. D-GalN is known to induce FHF in rats. The protective effect of taurine, if any was studied in detail with induced FHF. The study shows that taurine supplementation can effectively retard or prevent all metabolic and structural aberrations associated with FHF. All relevant parameters were studied for this purpose. The conclusion was that consumption of foods rich in taurine like fish can be beneficial and supplementation of taurine in diet can help regenerate the damaged liver of patients suffering from this problem. Adult male Wistar strain albino rats, weighing 100-120g were selected for the
study. The animals were divided into four groups of six rats each. For each set of analyses feeding trials with taurine were conducted at different times using four separate sets of albino rats. The quantity of taurine was decided after preliminary experiments using 25, 50, 75, 100, 150 and 200mg of taurine/kg body weight.

1. Group I was taken as the control fed on commercial feed.
2. Group II was fed on commercial feed with added taurine (100mg/kg body weight) to see if taurine by itself caused any undesirable changes.
3. Group III was fed on commercial feed alone. After 30 days feeding, rats were given i.p. injection of D-GalN (500mg/100g body weight/day for 2 days) for the induction of FHF to see the effects of induced-FHF.
4. Group IV was fed on commercial feed with added taurine and after 30 days they were given i.p. injection of D-GalN to see whether unlike in Group III the added taurine could prevent or lessen the adverse effects of D-GalN. All relevant biochemical, enzymic and histopathological parameters were also studied for this purpose.

**Biochemical, enzymic and histopathological parameters studied:**

- The effect of taurine on the liver parenchyma was studied by assaying the levels of **diagnostic marker enzymes like ALT, AST, LDH, arginase etc.**

- Prothrombin is a clotting factor synthesized by liver in whose absence or deficiency, clotting time or prothrombin time is prolonged. To study the effect of taurine on liver function, **prothrombin time** was measured.

- Liver is a site of bilirubin formation and urea cycle; to test taurine’s effect on liver function, **serum bilirubin content and blood urea** were determined.

- The effect of taurine on **protein and glycoprotein content** of tissue and serum were studied.
• The effect of taurine on glucose metabolism with respect to important metabolic pathways viz. glycolysis, gluconeogenesis and glycogenolysis were also followed systematically.

• To evaluate the effect of taurine on lipid metabolism in induced FHF, levels of various lipid components and fatty acid profile were determined.

• In liver damage including human FHF and FHF induced by D-GalN, there is enhanced oxidative stress and significant decrease of antioxidant defense. Therefore the anti-peroxidative effect and membrane stabilization action of taurine were studied.

• Among the organelles, mitochondrial membrane damage causes the maximum harm to the cell. To study the effect of taurine on mitochondrial function the activities of TCA cycle enzymes, respiratory marker enzymes, mitochondrial antioxidant defense system and membrane bound ATPases were assayed.

• To confirm the protective action of taurine against D-GalN-induced FHF in rats the histopathological pattern was studied.

The hepatic damage induced by D-GalN is believed to be primarily due to the reactive oxygen species produced by activated hepatic macrophages. Defective protein synthesis also contributes to liver injury. In the present study D-GalN administration caused severe damage to the liver parenchyma, as evidenced by the rise in the liver specific enzymes in serum. Prothrombin time was prolonged. The contents of serum bilirubin and blood urea were markedly elevated. Due to defective protein and glycoprotein synthesis significant decrease occurred in the liver and serum content of protein and glycoprotein components. D-GalN caused metabolic disturbances chief among them were the changes that occurred in glucose and lipid metabolism. Hypoglycemia was a marked feature with other changes like reduced glycolysis, and gluconeogenesis contributing to the liver injury. Changes in lipid metabolism
included accumulation of fat, elevation of lipid parameters and unfavorable changes in the fatty acid profile. Also defective protein synthesis caused impairment in lipid bilayers formation that made cell and organelle membranes susceptible to oxidative stress. The antiperoxidative enzymes and reduced glutathione were markedly reduced and lipid peroxides were significantly elevated by D-GalN. Being the site of respiration, oxidative phosphorylation and generation of ATP, D-GalN-induced loss of mitochondrial membrane function resulted in inhibition of enzymes of TCA and ATP synthesis. Mitochondria are both source and easy targets of oxidative stress. Significant reductions were observed in antioxidant defense parameters and membrane transporters as a consequence of D-GalN toxicity in this study. Na⁺ K⁺ ATPase in the cell membrane and mitochondrial membrane play an important role in maintaining cell homeostasis. In the current study, loss of activity of Na⁺ K⁺ ATPase pump and also Ca²⁺ and Mg²⁺ dependent pumps due to membrane destabilization resulted in significant and cell death-inducing alterations in mineral (Ca²⁺, Na⁺, K⁺ and Mg²⁺) balance. D-GalN intoxication also caused extensive hepatocyte necrosis and inflammation as evidenced by histopathology. The extensive hepatocyte parenchymal damage and membrane destabilization by D-GalN caused liver specific enzymes to spill into the blood stream as supported by their enhanced activity in serum.

In the present study prior administration of taurine prevented the rise in the levels of liver specific enzymes in serum, which indicate that the histopathological alterations and the parenchymal damage induced by D-GalN in the hepatocytes were opposed by taurine. Histopathological analysis shows that taurine has prevented the parenchymal damage to liver tissue that was caused by D-GalN. Also the blood levels of urea, serum bilirubin and prothrombin time returned to normal which are indications of normal liver function. In the present study taurine administration in D-GalN-intoxicated rats alleviated the D-GalN-induced decreases in protein and glycoprotein content. Taurine helped to regain glucose
homeostasis by affecting and modulating changes in metabolic pathways of glycolysis, gluconeogenesis and glycogenolysis. Hypoglycemia was corrected by reducing glycogenolysis and enhancing gluconeogenesis and as a consequence glycolysis was restored. Taurine supplementation has helped to restore the lipid content to normal as indicated by the changes in levels of the parameters measured in liver and serum. One of the serious aberrations seen in D-GalN intoxication was loss of membrane integrity that made cell and organelle membranes susceptible to attack by ROS. Taurine prevented the loss of membrane function and ameliorated oxidative stress. Lipid bilayers were stabilized by taurine that contributed to preserving the structure and function of several membrane bound proteins like the Na$^+$ K$^+$ ATPase pump and also Ca$^{2+}$ and Mg$^{2+}$ dependent pumps. Mineral homeostasis was restored that was unfavorably affected in D-GalN toxicity. Mitochondria are the powerhouses of the cell and they have a major role to play in enhancing cell death by either necrosis or apoptosis. Proper mitochondrial function is essential for the survival of the cell, they being the site of TCA cycle, respiration, Ca$^{2+}$ sequestration and apoptosis. Taurine enhances the activity of TCA cycle enzymes and oxidative phosphorylation that restores the energy levels (ATP) in the cell. Calcium concentration is under strict control in the cells and mitochondria play a key role in eliminating calcium from inside of a cell. In D-GalN toxicity, oxidative damage to the membranes causes calcium to flood the cell triggering apoptosis and necrosis. Taurine plays an important role in stabilizing the membranes and prevents accumulation of excess calcium in cells.

Taurine is involved in a number of crucial physiological processes. Earlier studies demonstrate that pathology develops if the animal is depleted of taurine stores either through a taurine deficient diet or use of taurine transport antagonists. There is considerable scientific evidence concerning the pharmacological significance of taurine in maintaining the integrity
of organism, and this study further proves the therapeutic nature of taurine. These findings have considerable clinical significance and warrant further detailed investigation.

Earlier this century, Thomas A. Edison predicted "the doctor of the future will give no medicine, but will interest his patients in the care of the human frame, in diet, and in the cause and prevention of disease." In the years ahead, physicians and patients alike should embrace Edison's prediction and look to natural sources for healing and wellbeing.
REDUCES MITOCHONDRIAL DAMAGE
Protects mitochondrial membrane
Restores respiratory enzyme activity
Protects mitochondrial membrane bound ATPases
Restores mineral homeostasis especially Ca^2+

HEPATOCYTE PROTECTION
Hepatocyte membrane stabilization
Preserves activity of membrane bound ATPases
Restores mineral homeostasis
Protects liver parenchyma from necrosis

PROTEINS AND GLYCOPROTEINS
Restores galactosamine induced loss of protein and glycoprotein components of hepatocytes

OXIDATIVE STRESS
Strengthens antioxidant defences
Preserves antioxidant molecules like GSH
Enhances activities of antiperoxidative enzymes

LIPID METABOLISM
Prevents lipid accumulation
Reduces lipolyses
Lowers excess free fatty acids release that triggers apoptosis
Preserve integrity of membrane bilayers
Restores phospholipid and PUFA content

GLUCOSE METABOLISM
Counteracts the hypoglycemic condition induced by galactosamine
Influences all pathways of glucose metabolism

SCHEMATIC DIAGRAM SHOWING PROBABLE MECHANISM OF ACTION OF TAURINE IN ATTENUATING GALACTOSAMINE-INDUCED HEPATIC FAILURE