INTRODUCTION
1. INTRODUCTION

Fulminant hepatic failure (FHF) is a rare, potentially devastating syndrome characterized by the abrupt collapse of liver function and hepatic encephalopathy. It is a serious and fatal disease which causes significant morbidity and mortality (Fernandez et al., 2003). It is a condition in which the rapid deterioration of liver function results in alteration in the mental status of a previously healthy individual. Fulminant hepatic failure is one of the leading causes of death in hospitalized children in India (Alam et al., 2009). The condition is particularly distressing as it occurs acutely, in previously healthy children and progresses rapidly inspite of all modern treatment. FHF, characterized by severe metabolic derangements, neurologic complications and, ultimately, multiorgan failure and in many cases by death, is seen to be a syndrome that may result from numerous causes.

Etiology: FHF can result from diverse etiological agents. Of these, hepatitis viruses, acetaminophen overdose and idiosyncratic drug reactions account for the bulk of cases, drugs, poisons, toxins and metabolic disorders being relatively less common causes (Gotthardt et al., 2007). Metabolic and vascular liver diseases, liver diseases unique in pregnancy and a number of miscellaneous liver diseases cause a small number of the remaining cases. Viral hepatitis is nearly the sole causative agent of FHF in the Indian subcontinent, the most important cause in Europe and the United States, and comes next only to acetaminophen hepatotoxicity as a cause of FHF in the United Kingdom (McCrudden et al., 2000, Kwo et al., 1995).

Sex & Age: Distribution of FHF is equal among males and females. Children and adults of all ages may develop FHF (Arora et al., 1996).

Incidence: FHF often affects young people and results in a very high mortality. Hepatitis E causes large-scale epidemics of hepatitis leading to FHF in the Indian subcontinent (Acharya et al., 1996), affecting hundreds of thousands of people, high mortality (Khan et al., 2006). In
the US the incidence of FHF is low with approximately 2000 cases occurring annually (Hoofnagle et al., 1996). Drug-related hepatotoxicity comprises more than 50% of ALF cases, including acetaminophen toxicity (42%) and idiosyncratic drug reactions (12%). Nearly 15% of cases remain of indeterminate etiology.

**Survival rate:** Despite aggressive treatment, many patients die from FHF. Prior to liver transplantation for FHF, the mortality rate was generally greater than 90% (Atillasoy & Berk 1995). However, with improved intensive care, the prognosis is much better now than in the past (Ostapowicz et al., 2002). The development of liver support systems provides some promise for this particular circumstance but has no impact on survival.

**Mortality and Morbidity** FHF is fatal for most affected children below 10 years and adults above 40 years of age. Several factors contribute to morbidity and mortality. The etiologic factor leading to hepatic failure and the development of complications plays an important role. In general, the best prognoses occur in the absence of complications. Cerebral edema, renal failure, adult respiratory distress syndrome, bleeding, and sepsis pose challenges that reduce the probability of survival (Shakil et al., 2000). Early recognition and hospitalization is the most important factor in reduction of mortality from FHF. In the past three decades, improved intensive care has increased mean survival from 15% to 50% in certain patient groups by providing metabolic support and management of specific, frequent, and potentially fatal complications (Ericzon et al., 2001).

**Pathogenesis:** The pathogenesis of FHF usually begins with exposure of a susceptible person to an agent capable of producing severe hepatic injury. Viral agents cause damage to hepatocytes either by direct cytotoxic effect or as a result of hyperimmune response (Seneviratne et al., 2006). Also hepatotoxic metabolites, which accumulate as a result of errors in metabolism or of taking drugs, cause injury to the hepatocytes resulting in accumulation of neurotoxic substances (Sturgill and Lambert, 1997).
Management: FHF remains a vexing and lethal clinical problem for liver specialists. Good intensive care is critical for patient survival. There are no specific therapies for FHF; medical management at the present time requires a multidisciplinary approach and must focus on anticipating, preventing, and rapidly identifying and treating complications that may affect every major organ system (Hoofnagle et al., 1996). Monitoring and early treatment of infections, hemodynamic abnormalities, and brain edema is critical to patient survival. Liver transplantation is a definitive therapeutic option for situations in which spontaneous recovery appears unlikely (Hadem et al., 2008). The diverse etiologies and difficulty in predicting which patients will recover spontaneously from those who will die without timely liver transplantation contribute to the complexity of this condition (Gotthardt et al., 2007). While intensive care is sufficient therapy in some patients (Group I), those with irreparable hepatic damage (Group III) can only survive if transplanted. In intermediate cases (Group II), the liver retains the potential to regenerate if the patient receives hepatic functional support (Atillasoy & Berk 1995). Liver transplantation has dramatically improved the chances of survival for patients with FHF, with current survival rates in the 55% to 75% range (Farmer et al., 2003). However the procedure is ridden with several issues that makes liver transplantation a less favorable alternative. The continuing challenge for the transplant team is to identify critical patients who would not survive without transplantation and allocate available donor organs to them. At the same time it is important to provide liver transplantation in a timely fashion to ensure the best chance of post-transplantation recovery. Factors that are valuable in assessing the likelihood of spontaneous recovery are features such as patient’s age, cause of FHF and dynamic features including severity of encephalopathy, prothrombin time, and serum bilirubin. However, the accuracy of these predictive indices decreases when they are applied to different populations, probably because of regional differences in etiology. Early prediction and timely availability of donor livers are essential
for a successful outcome. A donor shortage, however, continues to pose problems for hepatologists (Wiesner, 2005). Another impediment to successful revival of patients suffering from FHF is that liver transplantation needs to be individualized for each patient, because recovery depends on the cause of the hepatic failure. New therapeutic alternatives to liver transplantation are required. Effective liver support devices and hepatoprotective agents may greatly prolong survival to receive a donor liver, or alternatively to allow the native liver to regenerate (Lesnikov et al., 2004). A better understanding of mechanism of liver cell death and multiorgan failure, and the development of strategies to accelerate and maximize hepatic regeneration, may allow a more targeted approach to therapy. Encouraging research is being carried out in identifying innovative approaches to management and therapy. These include clinical application of cytoprotective and hepatotrophic drugs or antiviral medications and artificial hepatic support systems. None of these are of proven benefit, but many are promising as a means to support the patient with FHF until spontaneous recovery occurs or a suitable liver is available for transplantation.

A wide range of chemical agents and plant extracts have been analyzed for possible hepatoprotective effect. Most of these are synthetic and many are known to produce undesirable side effects (Stickel et al., 2000). Increasing attention is being given world wide on therapeutic effects of naturally occurring substances like vitamins, minerals, amino acids, small bioactive peptides commonly referred to as nutraceuticals. Taurine (2-aminoethanesulfonic acid), a non-protein sulfur containing amino acid, is the most abundant free amino acid and has been shown to play several essential roles in the human body. It is widely distributed in very high concentrations in brain, heart, liver, kidney, lens, and reproductive organs (Hayes, 1988). It is involved in various important biological and physiological functions, which include cell membrane stabilization, antioxidation,
detoxification, osmoregulation, neuromodulation and brain and retinal development (Kendler, 1989; Huxtable, 1992).

Fish is one of the best sources of taurine and for the same reason dietary fish can be a good nutritional supplement for ensuring adequate supply of taurine to the system (Gormley et al., 2007). Our studies on nutritional benefits of dietary fish pointed to such an effect that led us to a more detailed investigation into the protective effect of taurine in hepatotoxicity. The results and observations made in this study forms the topic of this thesis. Earlier studies demonstrated that pathology develops if the animal is depleted of taurine stores either through a taurine deficient diet or use of taurine transport antagonists (Gupta & Kim, 2003). There is considerable evidence concerning the pharmacological significance of taurine in maintaining the integrity of organism (Chesney, 1995). Taurine is reported to stabilize membranes, inhibit oxidative stress and Kupffer cell activation, phenomena associated with most types of liver (Timbrell et al., 1995). These effects may play an important role in taurine’s expected hepatoprotective effects.

Intraperitoneal (i.p.) intoxication of rats by D-galactosamine (D-GalN) produces a reproducible experimental model of FHF resembling the clinical condition. Numerous research studies carry reports of D-GalN injection producing metabolic and histopathological alterations which are similar to FHF condition (Feng et al., 2007; Takamura et al., 2007; Wu et al., 2009). They include rise in liver specific markers in blood, elevation of certain cytokines, prothrombin, bilirubin and extensively necrotic hepatic tissue (Hu et al., 1992). As a standard technique D-GalN was used in this work to induce FHF symptoms in albino rats, to study the hepatoprotective effect if any, of taurine in FHF case.
1.1 **Aim:** To successfully induce and maintain animal model of FHF by i.p. injection of D-GalN and study the protective effect of taurine treatment.

**Objectives:**

1. To study the hepatoprotective effects of taurine in experimentally induced FHF by assaying the levels of serum diagnostic marker enzymes, prothrombin time, and bilirubin.
2. To study the histopathological pattern to confirm the protective action of taurine against D-GalN-induced FHF in rats.
3. To determine the effect of taurine on protein and glycoprotein content of tissue and serum in the experimental model of FHF.
4. To study the effect of taurine on glucose metabolism in induced FHF.
5. To evaluate the effect of taurine on lipid metabolism in D-GalN-induced FHF in rats by determining the levels of various lipid components.
6. To study the effect of taurine on fatty acid profile in experimentally induced FHF in rats.
7. To study the anti-peroxidative effect of taurine on tissue antioxidant defense system in D-GalN-induced FHF in rats.
8. To determine the effect of taurine on mineral homeostasis and assess the membrane stabilizing action of taurine by assaying the activities of membrane bound ATPases.
9. To study the effect of taurine on mitochondrial function in experimentally induced FHF by determining the activities of TCA cycle enzymes and respiratory marker enzymes.