Chapter 1:

INTRODUCTION
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Liver is the main organ responsible for the major metabolic and secretory functions in the body and hence appears to be a sensitive target site for substances modulating biotransformation (Gram and Gillette, 1971). It is involved in the detoxification from the exogenous and endogenous challenges like xenobiotics, drugs, viral infections and chronic alcoholism. The duration and intensity of the pharmacological response to drugs is influenced by their metabolic rate, hence substances capable of modifying drug metabolism would be able to alter the outcome of drug therapy (Testa and Jenner, 1981). If during all such exposures to the above mentioned challenges, the natural protective mechanisms of the liver are overpowered, the result is liver injury.

Liver disease is a major cause of morbidity and mortality. The occurrence of drug-induced hepatotoxicity (Shah and Anand, 2003) is due to indiscriminate consumption of alcohol, NSAIDS, antitubercular, anticancer and anticonvulsant drugs. It exhibits clinically as jaundice, cirrhosis, hepatitis, steatosis, fibrosis, liver cancer and ultimately to hepatic failure (Lewis, 2003).

Drug-induced liver injury (DILI) is a major health problem that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies. DILI accounts for more than 50% of acute liver failure including hepatotoxicity caused by overdose of acetaminophen. Because of the significant patient morbidity and mortality associated with DILI (Zimmerman, 1999), the U.S. Food and Drug Administration (USFDA) has removed several drugs from the market, including bromfenac (Hunter et al., 1999), ebrotidine (Anonymous, 1998), and troglitazone (Kohlroser et al., 2000). Other hepatotoxic drugs such as risperidone, trovafloxacin and
nefazodone etc (Thames, 2004; Lasser et al., 2002) have been assigned as “black box” warnings. DILI is the most common cause for the withdrawal of drugs from the pharmaceutical market (Temple and Himmel, 2002).

A number of reports indicate that overdose of paracetamol (PCM) produces hepatic necrosis in humans and experimental animals (Hinson et al., 1981). PCM is metabolized by two non-toxic pathways: sulphation and glucuronidation, and one oxidative and potentially toxic pathway, and is oxidized into a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI) (Dahlin et al., 1984). Carbon tetrachloride (CCl₄), another hepatotoxicant, requires metabolic activation by cytochrome P450 to form potentially reactive and toxic metabolites (Gonzalez, 1988; Guengerich, 1994). These reactive metabolites are known to initiate lipid peroxidation (Sipes et al., 1974), and release of inflammatory mediators leading to various impairments in the liver, including centrilobular necrosis, fatty infiltration and decreased activities of microsomal enzymes that catalyse the oxidation of drugs (Badger et al., 1996; Edwards et al., 1993).

Alcoholic liver disease (ALD) continues to be an important health problem now a days. Chronic liver damage is a widespread pathology, characterized by a progressive evolution from steatosis to chronic hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma (Cederbaum, 2001). Progress in the understanding of the pathogenesis of alcoholic liver disease was achieved when it was discovered that alcohol affects the liver through not only nutritional disturbances but also its direct toxicity, and it is because of its predominant metabolism in the liver associated with oxidation-reduction (redox) changes and oxidative stress. The clinical course and ultimate outcome of alcoholic liver disease are dismal. In a prospective survey of 280 patients with alcoholic liver injury,
Chedid et al. (1991) found that, within 48 months of follow-up, 30% of those with a fatty liver, more than half of those with cirrhosis, and two-thirds of those with cirrhosis plus alcoholic hepatitis died.

A number of studies have shown that antioxidants, including the plant extracts protect against ethanol-induced hepatotoxicity by inhibiting lipid peroxidation and enhancing antioxidant enzyme activity (Naik et al., 2004; Rajagopal et al., 2003). The DILI or ALD is due to enhanced production of toxic reactive metabolites. Moreover, it is reported to produce oxidative stress: reactive oxygen species (ROS) and reactive nitrogen species (RNS) which induce oxidative cell damage through lipid peroxidation reaction and depletion of antioxidants: glutathione and superoxide dismutase and catalase. Furthermore, free radicals cause inflammatory liver injury by augmenting the activation of Kupffer cells and thereby releasing cytokines which consequently increase the expression of inducible nitric oxide (iNOS) (Zima and Kalousova, 2005). Moreover, oxidative stress is noted to induce mitochondrial dysfunction through mitochondrial permeability transition pore (MPTP) and adenosine triphosphate (ATP) depletion (Kessova and Cederbaum, 2007). The inflammatory mediators activate hepatic stellate cells which consequently increase the expression of TGF-β, collagen and elastin resulting in cirrhosis of liver (Jeong et al., 2005). These all intervening reactions, ultimately lead to hepatic damage through certain necrotic, apoptotic and fibrotic cascades.

In spite of phenomenal growth of modern medicine, few synthetic drugs are available for the treatment of hepatic disorders (Setty et al., 2007). The treatments available for the cure from liver diseases are Modern medications and Traditional medications.
The modern medications include anti-inflammatory; immunomodulatory (Kamath and Kim, 2007; Worman, 1997); corticosteroid, antiviral drugs (Toniutto et al., 2008), S-adenosyl-L-methionine (Wang et al., 2006), α-Lipoic acid (Packer et al., 1995), dipeptide caspase inhibitor (Ueno, et al., 2009), ursodeoxycholic acid (UDCA), a hydrophilic bile acid, with putative immunomodulatory capacities (Miyaguchi and Mori, 2005; Rolandi et al., 1991), and prednisone in combination with azathioprine is also preferred for treating liver diseases (Ishibashi et al., 2007). The current modern therapeutic strategies are not efficient enough for the complete removal of liver hazard, without provoking adverse drug reactions. While a curative agent has not yet been found in modern medicine, the current usage of corticosteroids and immunosuppressive agents only brings about symptomatic relief (Handa et al., 1986). Furthermore, their usage is associated with risk of relapses and danger of side effects. In spite of tremendous strides in modern medicine, there are hardly any drugs that stimulate liver function, and offer protection to the liver from damage or help regeneration of hepatic cell (Chaterjee, 2000). Hence, the ultimate treatment of severe liver damage is surgical liver transplantation.

The traditional medications include antioxidant therapy like rutin, quercetine, tocopherol, myricetin etc (Ohta et al., 2006; Duthie et al., 1997); use of several plant drugs like silymarin alone and in-combination as multi-ingredi ents herbal formulations (Handa et al., 1986).

The indigenous system of medicine in India has a long tradition of treating liver disorders with plant drugs (De et al., 1993). Indian System of Medicine (ISM) has recommended more than eighty seven hepatoprotective plants (Batey et al., 2005) and many of them are used clinically. There are several herbs/herbal formulations claimed to
possess beneficial activity in treating hepatic disorders. Recently, the use of herbal natural product has gained interest among the world population. Many of the herbs have been developed into herbal supplement which are claimed to assist in healthy lifestyle (Fakurazi et al., 2008).

The traditional therapies claims include symptomatic relief, cure with no side effects, marked efficacy and cost effectiveness. These claims are however, not backed by well documented scientific data.

Conventional, as well as traditional medications, used in the treatment of liver diseases are often inadequate and can have serious adverse effects. There is, thus, an unmet need for alternative drugs for the treatment of liver disease, to replace the currently used drugs of doubtful efficacy and safety (Ahmed and Khater, 2001).