PRECLINICAL INVESTIGATION OF SOME HERBAL DRUGS FOR
HEPATOPROTECTIVE ACTIVITY

INTRODUCTION:

Liver is an important organ actively involved in many metabolic functions and is the frequent target for a number of toxicants (Meyer et al., 2001). Hepatic damage is associated with distortion of these metabolic functions (Wolf, 1999). Liver disease is still a worldwide health problem. Unfortunately, conventional or synthetic drugs used in the treatment of liver diseases are inadequate and sometimes can have serious side effects (Guntupalli et al., 2006).

Liver is considered to be one of the most vital organs that functions as a centre of metabolism of nutrients such as carbohydrates, proteins and lipids and excretion of waste metabolites. Additionally, it is also handling the metabolism and excretion of drugs and other xenobiotics from the body thereby providing protection against foreign substances by detoxifying and eliminating them. The bile secreted by the liver has, among other things, plays an important role in digestion. Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, carbon tetrachloride, thioacetamide etc., chronic alcohol consumption and microbes is well-studied. Enhanced lipid peroxidation during metabolism of ethanol may result in development of hepatitis leading to cirrhosis.

Alcohol affects the liver both nutritional disturbances and damaging cells, leads to alcoholic liver disease (ALD): fatty liver, alcoholic hepatitis and cirrhosis (Bouneva et al., 2003).

These potential damage elicits by complex mechanisms involving metabolite of ethanol that has direct cytotoxicity and ability to form protein adduct with several protein of hepatocytes (Zimmerman, 1999), the increase in reduced form of nicotinamide adenine dinucleotide (NADH) causing fat accumulation (Zimmerman, 1999), free radicals inducing oxidative stress leading to peroxidation and inflammatory response (Jarvelainen, 2000), and ethanol-induced elevation of endotoxin pass to the liver. Endotoxin stimulated Kupffer cells to produce free radicals and pro-inflammatory cytokines such as TNF- alpha and IL-1, the two important mediators of inflammation and celldeath (Hoek and Pastorino, 2002).

Because of its unique metabolism and relationship to the gastrointestinal tract, the liver is an important target of the toxicity of drugs, xenobiotics, and oxidative stress. In cholestatic disease, endogenously generated bile acids produce hepatocellular apoptosis by stimulating Fas
translocation from the cytoplasm to the plasma membrane where self-aggregation occurs to trigger apoptosis.

Kupffer cell activation and neutrophil infiltration extend toxic injury. Kupffer cells release reactive oxygen species (ROS), cytokines, and chemokines, which induce neutrophil extravasation and activation. The liver expresses many cytochrome P450 isoforms, including ethanol-induced CYP2E1. CYP2E1 generates ROS, activates many toxicologically important substrates, and may be the central pathway by which ethanol causes oxidative stress. In acetaminophen toxicity, nitric oxide (NO) scavenges superoxide to produce peroxynitrite, which then causes protein nitration and tissue injury. In inducible nitric oxide synthase (iNOS) knockout mice, nitration is prevented, but unscavenged superoxide production then causes toxic lipid peroxidation to occur instead. Microvesicular steatosis, nonalcoholic steatohepatitis (NASH), and cytolytic hepatitis involve mitochondrial dysfunction, including impairment of mitochondrial fatty acid b-oxidation, inhibition of mitochondrial respiration, and damage to mitochondrial DNA. Induction of the mitochondrial permeability transition (MPT) is another mechanism causing mitochondrial failure, which can lead to necrosis from ATP depletion or caspase-dependent apoptosis if ATP depletion does not occur fully. Because of such diverse mechanisms, hepatotoxicity remains a major reason for drug withdrawal from pharmaceutical development and clinical use (Hartmut et al., 2002).