OBJECTIVES
OBJECTIVES AND SCOPE OF THE PRESENT STUDY

Mitochondria are important organelles involved in TCA cycle and oxidative phosphorylation. Membrane integrity is essential for the synthesis of ATP by oxidative phosphorylation. Various agents and pathological conditions produce mitochondrial dysfunction which can cause loss of cell function and cell death. Liver is a prominent site for drug metabolism and mitochondria are the initial target organelles within the hepatocyte. In this study, the effect of four hepatotoxins (i.e., CCl4, TAA, ethionine and galactosamine) on mitochondrial function was studied using rat as an experimental model.

CCl4, TAA, ethionine and galactosamine differ in the mechanism by which they bring about hepatic failure. CCl4 and TAA require to be converted to toxic metabolites within the liver while galactosamine and ethionine cause toxicity by inducing metabolic deficit.

CCl4, a notorious hepatotoxin is very effective against adult liver fluke, Fasicola hepatica but because of its toxicity its use as an antihelminthic or anaesthetic is discouraged. It is also a widely used solvent in plastic and dry cleaning industry and is a classic model of hepatotoxicity. Thioacetamide is known to retard fruit spoilage and is also widely used to induce cirrhosis and necrosis of the liver. Galactosamine induced liver injury is known to resemble human viral hepatitis in its morphological and functional features (Keppler et al, 1968). Ethionine, an ethyl analog of methionine is a known alkylating hepatocarcinogen and produces a variety of physiological and pathological effects in liver and pancreas of animals.

In this study it was observed that all these hepatotoxins induce toxicity by the initiation of lipid peroxidation. Malondialdehyde (MDA), a secondary product of lipid peroxidation was measured by TBARS, which is an index of membrane damage. As vitamin E (biological antioxidant) was shown to prevent lipid peroxidation both in vitro and in vivo, it was employed to prevent the toxicity induced by these hepatotoxins. Colchicine which was shown earlier to reverse the experimental and clinical cirrhosis, was used to prevent the CCl4 induced liver damage. Recent studies in our laboratory have shown that the administration of the aqueous extract of P.fraternus along with alcohol prevented most of the alcohol induced liver damages. In this study the ability of P.fraternus in protecting against CCl4 induced liver toxicity was also examined.

Objectives of the study :

1) To study the effect of hepatotoxins on the rate of transfer of electrons through different segments of the electron transport chain. Lipid peroxidation and
phospholipid composition, were also studied to relate the effect of hepatotoxins to the membrane integrity and finally the ability of the system to make ATP.

2) Cytochrome oxidase from control and CCl₄ administered rats was purified to study the kinetic properties and the subunit composition of the enzyme compared to controls.

3) The most important is to find a mechanism to prevent the toxicity that is induced by these hepatotoxins, which has an applied value. For this study, vitamin E, colchicine or an aqueous extract of P.fraternus was administered independently along with these hepatotoxins.