5. SUMMARY

Cisplatin is currently being used in cancer chemotherapy. However, as its nephrotoxicity represents a life-threatening complication and is a major dose-limiting factor in its widespread use as an antitumor agent. Since, cisplatin nephrotoxicity parallels its antitumor activity, various attempts have been made to increase its clinical usefulness by reducing its cytotoxicity.

Glutathione ester got effectively transported into cells and converted intracellularly into glutathione. Glutathione is a sulphur containing nucleophile that modulates cisplatin induced renal toxicity without reducing its antitumor activity. Cisplatin induced nephrotoxicity and changes in the nephrotoxicological parameters were found to be effectively modulated by glutathione ester through the utilisation of exogenous glutathione.

Glutathione ester participates in numerous cellular functions including protection of cells from free radical damage, detoxification of xenobiotics and rehabilitating lysosomal and transaminase enzyme levels in cisplatin induced renal damage.

Cisplatin induced alterations in the activities of antioxidant enzymes and in the concentrations of cellular non-enzymic antioxidants were found to be effectively protected by glutathione ester administration which clearly indicates the rehabilitating role of glutathione ester by replenishing the cellular antioxidant pool.
Administration of glutathione ester effectively delivers glutathione into cells which helps in maintaining the non-protein sulphydryl stores, leading to the formation of diminished levels of free oxygen radicals and maintains the cellular reparative functions in cisplatin induced lipid peroxidation.

Administration of glutathione ester effectively modulated the alterations in glutathione metabolising enzymes, glycolytic and gluconeogenic enzymes along with the TCA cycle enzymes to near normal levels. This could demonstrate the protective efficacy of glutathione ester in maintaining the mitochondrial membrane integrity and also the possible regeneration of renal proximal tubules. This may even signify the prevention of lipid peroxidation that could reflect the cytoprotective effect of glutathione ester.

Inhibition of ATPase activity by cisplatin is considered to be one of the possible mechanisms of cisplatin induced nephrotoxicity. Administration of glutathione ester clearly indicates its special role in maintaining renal function and membrane structure against cisplatin induced alterations seen in membrane bound ATPases.

The exogenous administration of glutathione ester along with cisplatin was found to be very effective in minimizing the accumulation of platinum and also in restoring the levels of minerals from disturbances observed in cisplatin treated rats.

The use of urinary markers for nephrotoxicity traced the acute and chronic effects of cisplatin therapy on renal tubular cells. Enzymes appearing
in urine originate owing to leakage from damaged cells or remain in the urine owing to inadequate reabsorption by the proximal tubules. Administration of glutathione ester along with cisplatin seems to protect the renal tubules and that prevents the increased excretion of urinary enzymes in cisplatin treated rats.

The histopathological examination of kidney and liver further confirms the modulating efficacy of glutathione ester against cisplatin induced nephrotoxicity with reference to the biochemical parameters studied (Plates I & II).

Studies on the intra renal immunohistochemical localisation of heat-shock protein 90 (HSP90) in kidney (Plate III) clearly depicts the cytoplasmic positivity for HSP90 in the tubular epithelium. This demonstrates a significant impairment in renal function due to the administration of cisplatin and that was found to be normalised later upon glutathione ester administration (Plate III).

From this study, it may be suggested in general that glutathione ester may be used as an effective protective agent against cisplatin induced nephrotoxicity. Glutathione ester can be co-administered along with cisplatin in the treatment of solid tumors to minimize or to nullify the nephrotoxic side effect of cisplatin. However, further studies are needed to confirm its modulating efficacy against cisplatin induced nephrotoxicity in the chemotherapy of neoplastic diseases.