5. SUMMARY AND CONCLUSION

The protective effect of chitosan and glucosamine against ibuprofen-induced gastric ulcer was studied. Administration of ibuprofen had brought about the ulcerated mucosal lesions in the experimental rats. It is evident by the increased acidity, number of lesions and decreased peptic activity. The gross pathological and histopathological observations also confirmed the mucosal tissue damage.

Pre-oral treatment with chitosan and glucosamine significantly decreased the ibuprofen induced gastric lesions and acidity and brought back the peptic activity to the normal level. This shows the cytoprotective effect of these compounds. Chitosan and glucosamine might be neutralized the increased acid secreted by the stomach due to ibuprofen irritant.

The levels of antioxidant enzymes, antiperoxidative enzymes, reduced glutathione, lipid peroxidation and membrane bound ATPases were also altered by the ibuprofen intake. Chitosan and glucosamine pre-treatment maintained these levels to near normalcy. The results of the present study indicate that the pre-oral administration of chitosan and glucosamine maintain near to the normal status the activities of the mucosal antioxidant enzymes and the level of GSH, which protect mucosa against oxidative damage by decreasing the lipid peroxidation and strengthening the mucosal barrier, and which are the first line of defense against exogenous and endogenous ulcerogenic agents. Pre-treatment with chitosan and glucosamine significantly maintained the activities of membrane bound ATPases by the counteraction of ibuprofen-induced free radicals by the free radical scavenging property of chitosan and glucosamine.

Administration of ibuprofen deteriorated protein and glycoprotein levels due to the corrosion of gastric mucosa, resulting in the disruption and disintegration of gastric mucosal cells. This was reflected in the electrophoretic pattern also. Oral pre-treatment with chitosan and glucosamine maintained these levels. This may be because; the incorporation of glucosamine units into mucosal glycoprotein might have resulted in strengthening of the mucosal barrier.

Histopathological study showed that ibuprofen induction was characterized by severe cell necrosis, which is normalized by the administration of chitosan and glucosamine showing their cytoprotectivity. The level of sodium was decreased and potassium, calcium, magnesium and zinc were increased due to ibuprofen administration. The accumulation of intracellular calcium levels also play an important role in the DNA fragmentation and ulcer induced by ibuprofen. Increased peroxidation may be the cause of increment in the magnesium level. Chitosan and glucosamine pre-treatment maintained the levels of these minerals to the normal level. Changes in the amino acid levels bought about by the ibuprofen induced cell damage were also restored to normal level by the pre-oral aministration of chitosan and glucosamine.

Observations in this study indicate that the oral pre-treatment of chitosan and glucosamine can prevent ibuprofen-induced peptic ulcer in rats. The overall antiulcerogenic activity of chitosan and glucosamine is probably related to the ability to neutralize the hydrochloric acid secreted into the stomach, and to the maintenance of GSH level by decreasing lipid peroxidation and to the capability to strengthen the mucosal barrier by increasing mucosal glycoprotein synthesis and the free radical scavenging property. On comparison, glucosamine was found to have better antiulcerogenic property than chitosan.

The protective effect of chitosan and glucosamine against antitubercular drugs-induced hepatotoxicity was also studied. Administration of isoniazid and rifampicin, most widely used antitubercular drugs, caused severe toxicity to liver. It increased the levels of diagnostic marker enzymes in the serum. Enhanced susceptibility of hepatocytes cell membrane to the isoniazid and rifampicin-induced peroxidative damage might have resulted in increased release of these diagnostic marker enzymes into the systemic circulation. In cases of liver damage with hepatocellular lesions and parenchymal cell necrosis, these marker enzymes are released from the damaged tissues into the blood stream. As a result the levels of liver ALT and AST were decreased in the antitubercular drugs-induced rats. Co-administration of chitosan and glucosamine maintained the levels of diagnostic marker enzymes in the serum and liver near normalcy.

They probably did so by preventing the antitubercular drugs induced necrotic damage by the membrane stabilizing action normalizing the protein metabolism.

Histopathological investigations showed severe vacuolation and degeneration of hepatocytes in the three zones of lobules. Membrane disintegration with intense vacuolation accompanied with cytoplasmic rarefication resulting in loss of polyhedral structure in the liver of rat treated with antitubercular drugs. Treatment with chitosan and glucosamine caused reversal of such pathology with no evidence of necrotic areas.

The oral administration of antitubercular drugs led to periportal infiltration of inflammatory cells, disruption of lobular architecture, and liver cell necrosis and causes severe disturbance of RNA and protein metabolism. Accumulation of metabolites of antitubercular drugs may also contribute to the disturbance in protein metabolism. The eletrophoretic pattern of hepatotoxic rats was also found disturbed especially in albumin fraction. Drug induced hepatotoxicity is associated with failure to maintain serum albumin level whereas serum globulins, particularly γ-globulin, which is formed in the reticuloendothelial system are increased. In hepatotoxic condition, due to the failure of the liver to convert amino acids and ammonia to urea, a significant decrease in urea was observed. The inhibition of protein synthesis in isoniazid and rifampicin-administered rats disturbed the glycoprotein synthesis. Thus, the glycoprotein conjugates (hexose, hexosamine and sialic acid) were found decreased in hepatoxic animals. Alterations in all these factors were maintained to near normal level by chitosan and glucosamine co-administration. Since, chitosan and glucosamine were N-acetyl sugars they induced glycocylation, which helped glycoprotein synthesis. These muco-compounds can decrease the accumulation of reactive metabolites of isoniazid and rifampicin and balance protein metabolism.

Administration of isoniazid and rifampicin was characterized by increased lipid peroxidation and decreased levels of glutathione-dependent antioxidant enzymes, reduced glutathione and antiperoxidative enzymes. Co-administration of chitosan and glucosamine along with antitubercular drugs brought back the

levels of these enzymes, lipid peroxidation and reduced glutathione to normal status. The antioxidant property of chitosan and glucosamine prevented the formation of free radicals and they inhibited some of the deleterious actions of reactive oxygen species that damage lipids, DNA and proteins

The antitubercular drugs-induced hepatitis is characterized by the fatty accumulation in the liver, which develops either due to excessive supply of lipids to the liver or interference with lipid deposition. The levels of total cholesterol and LDL-cholesterol were increased whereas HDL-cholesterol was decreased in antitubercular drugs induced animals. Increased cholesterol levels in the liver might due to increased uptake of LDL from the blood by the tissues. The abnormal cholesterol deposition is favored by the dangerous tendency of cholesterol to passive exchange between the plasma lipoproteins and the cell membranes. Animals co-administerd with chitosan and glucosamine maintained the levels of total, HDL and LDL cholesterol levels to the near normal level. The alterations in triglycerides, free fatty acids and phospholipids in the hepatotoxic rats were also normalized by chitosan and glucosamine co-administration. This may be due to their ability to inhibit the lipid accumulation in the liver tissue by the antilipidemic property and membrane stabilizing effect.

Chitosan and glucosamine co-administration rectified the deviations, caused by the anititubercular drugs administration,in the levels of membrane bound ATPases, hepatic thiols, minerals and fatty acid components.

From all the results obtained in the present study, it can be concluded that co-administration of chitosan and glucosamine can effectively prevent the isoniazid and rifampicin induced hepatotoxicity in rats. Comparatively, chitosan was found to have better results than glucosamine in alleviating the hepatic disorders.