

SUMMARY AND CONCLUSION

In the present study all the flavonoids, viz; Silymarin, Chrysin and Quercetin were found to be safe upto 5000 mg/kg, b.w. and showed significant hepatoprotective activity. These flavonoids delayed the development of liver damage induced by CCl₄ vapour via, necrosis, fibrosis to cirrhosis in experimental animals. Silymarin and Quercetin showed significant hepatoprotective activity throughout the course of study, whereas Chrysin has lesser activity. The combination of Quercetin and Chrysin also showed significant hepatoprotective activity, and this hepatoprotection was comparable to Silymarin.

In CCl₄ treated group there was significant increase in free and decrease in total activity of lysosomal enzymes (B-Glu, NAC and acid phosphatase). There was significant increase in the levels of AST, ALT, ALP, Bilirubin and decrease in protein content. The total/ free ratio was decreased through out the treatment period.

Silymarin (250mg/kg), Quercetin (250 and 500mg/kg) and combination of Quercetin 250mg/kg and Chrysin 250mg/kg significantly decreased free and increased total activity of lysosomal enzymes (B-Glu, NAC and acid phosphatase) at the end of 2, 6 and 12 weeks study. Also there was significant decrease in the levels of AST, ALT, bilirubin and increase in protein content throughout the treatment period. The total/ free ratio was also increased.

Furthermore, histopathological studies support the fact that CCl₄ vapours induced necrosis, fibrosis and cirrhosis at 2nd, 6th and 12th weeks respectively. Silymarin, Quercetin and Chrysin were able to maintain normal architecture of liver till 2nd week. At the 6th week study Silymarin (250mg/kg), Quercetin (500 mg/kg) and Quercetin + Chrysin (250 mg/kg) maintained normal architecture of liver whereas, the

other test groups showed loss of normal architecture and development of mild to moderate necrosis due to CCl₄. At the end of 12 weeks study, all the treatment groups showed development of necrosis, but prevented the development of cirrhosis.

The ratio of total/free activity of lysosomal enzymes has been interpreted as an expression indicating the stability of lysosomal membrane. A decreased value suggests decreased stability and/or an increased vulnerability of lysosomal membrane (fragility) resulting in leakage of the lysosomal enzymes and consequently leading to cell injury. The total/free ratio of the lysosomal enzymes was decreased throughout the treatment period with CCl₄ which contributes to lysosomal membrane instability.

In the present study, the Silymarin, Quercetin and Chrysin increased the stability and/or decreased vulnerability of lysosomal membrane and prevented leakage of lysosomal enzymes. One of the possible mechanisms may be due to the antioxidant property of these flavonoids. There are several reports that the antioxidants prevent the free radical formation and liver damage. The flavonoids used in the study have been reported for their antioxidant activity in the order Quercetin>Silymarin>Chrysin.

There are reports that exogenous GH-treatment showed development and regeneration hepatic cells in CCl₄ induced hepatic injury in GH-deficient rats. Liver regeneration is a fundamental mechanism by which the liver responds to injury. This process is regulated by endogenous growth factors and cytokines, and it involves proliferation of all mature cells that exists within the intact organ. The growth promoting effects of GH can be direct in selected target tissues, such as liver.

GH plays a critical role in liver regeneration, although whether it acts directly or indirectly remains to be determined. GH improves bioenergetics and decreases

catecholamines in post infarct rat hearts. It is also reported that adrenaline administration in immature cockerels lowered the levels of plasma GH. Moreover, there is report suggesting paracetamol induced hepatocellular damage is associated with increased circulating catecholamines.

The mechanism of adrenaline action on the structure and function of the lysosomal- vacuolar cell apparatus were shown to produce a labializing effect on lysosomal membranes, increasing free activity of lysosomal enzymes and osmotic sensitivity of lysosomes in liver.

Quercetin has been reported to inhibit catecholamines secretion from cultured bovine adrenal chromaffin cells. In the present work, Quercetin in combination with Chrysin showed significant increase in GH and decreases in catecholamine (adrenaline, noradrenalin) levels in plasma, whereas Silymarin and Chrysin failed to modulate the hormonal levels.

In the present study the hepatoprotective activity of Quercetin is by its strong antioxidant potential and its ability to prevent the leakage of lysosomal enzymes and increased stability of lysosomal membrane may be due to increase in GH and decrease in catecholamine levels. Silymarin and Chrysin prevented the leakage of lysosomal enzymes and increased stability of lysosomal membrane only due to their antioxidant activity as these two flavonoids (Silymarin and Chrysin) did not modulated the catecholamine levels.

In conclusion, apart from antioxidant activity, increase in GH and decrease in catecholamines levels recorded by Quercetin and its combinations (Quercetin + Chrysin) play an important role in hepatoprotective activity, whereas Silymarin and

Chrysin only their antioxidant potential offered hepatoprotection in CCl₄ induced hepatic damage in rodents.