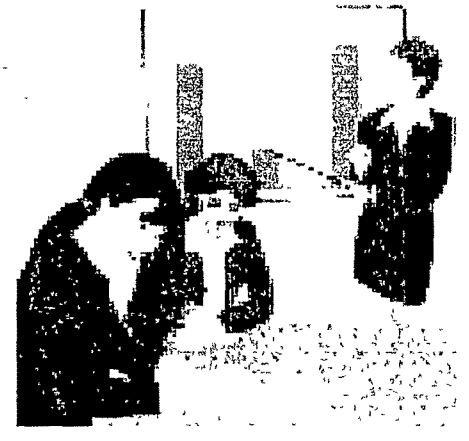
CHAPTER 4



RESULTS

4.1 *IN VITRO* STUDIES

The methanolic extract of formulations, DHC-1, Activit, Pepticare and Normacid exhibited different levels of antioxidant activity in the models studied.

4.1.1 DPPH ASSAY

DHC-1 showed a concentration dependent antiradical activity by inhibiting DPPH radical with an IC_{50} value of 0.428 mg/ml. The % inhibitions at the concentrations of 0.1 and 0.2 mg/ml of the methanolic extract of the drug were 10.25% and 23.85%, respectively. The % inhibitions at the concentrations of 0.4 (62.15%, $p<0.01$), 0.6 (73.20%, $p<0.001$), 0.8 (87.43%, $p<0.001$) and 1.0 mg/ml (92.77%, $p<0.001$) were significant as compared to the control (Fig 4.1).

Methanolic extract of Activit at the concentrations of 0.1 and 0.2 mg/ml, exhibited % inhibitions of 6.53% and 11.12%, respectively. The % inhibitions at the concentrations of 0.4 (27.63%, $p<0.05$), 0.6 (58.98%, $p<0.01$), 0.8 (62.33%, $p<0.01$) and 1.0 mg/ml (78.42%, $p<0.001$) of DPPH radical were significant as compared to the control. The IC_{50} value was found to be 0.626 mg/ml (Fig 4.2).

It was observed that 0.1, 0.2 and 0.4 mg/ml of methanolic extract of Pepticare produced an inhibition of DPPH radical by about 4.15%, 8.14%, and 16.45%, respectively. The % inhibitions at the concentrations of 0.6 (31.79%, $p<0.05$), 0.8 (51.55%, $p<0.01$) and 1.0 (67.35%, $p<0.001$) were significant as compared to the control. The IC_{50} value of methanolic extract of Pepticare was 0.799 mg/ml (Fig 4.3).

The methanolic extract of Normacid at the concentrations of 0.5 and 1.0 mg/ml produced % inhibitions of 8.94% and 15.56% of DPPH radical, respectively. 2.0 (36.88%, $p<0.05$), 3.0 (66.36%, $p<0.001$) and 4.0 mg/ml (89.14%, $p<0.001$) of methanolic extract of Normacid produced significant % inhibitions of DPPH radical as compared to the control. The IC_{50} value of Normacid was 2.380 mg/ml (Fig 4.4).

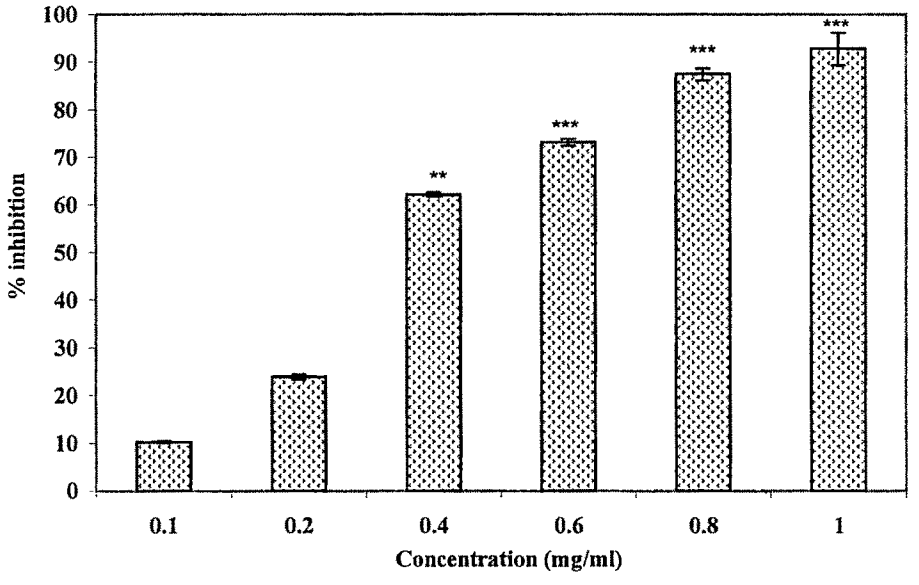
The IC_{50} of Pyrogallol was 0.010 mg/ml.

Fig. 4.1. Scavenger effect of methanolic extract of DHC-1 (0.1, 0.2, 0.4, 0.6, 0.8 and 1.0 mg/ml) on the stable DPPH radical.

Fig. 4.2. Scavenger effect of methanolic extract of Activit (0.1, 0.2, 0.4, 0.6, 0.8 and 1.0 mg/ml) on the stable DPPH radical.

Results were expressed as percentage inhibition of absorbance at 516 nm with respect to control. Each value represents the mean ± SEM of three experiments.

Fig. 4.1.


100
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% inhibition
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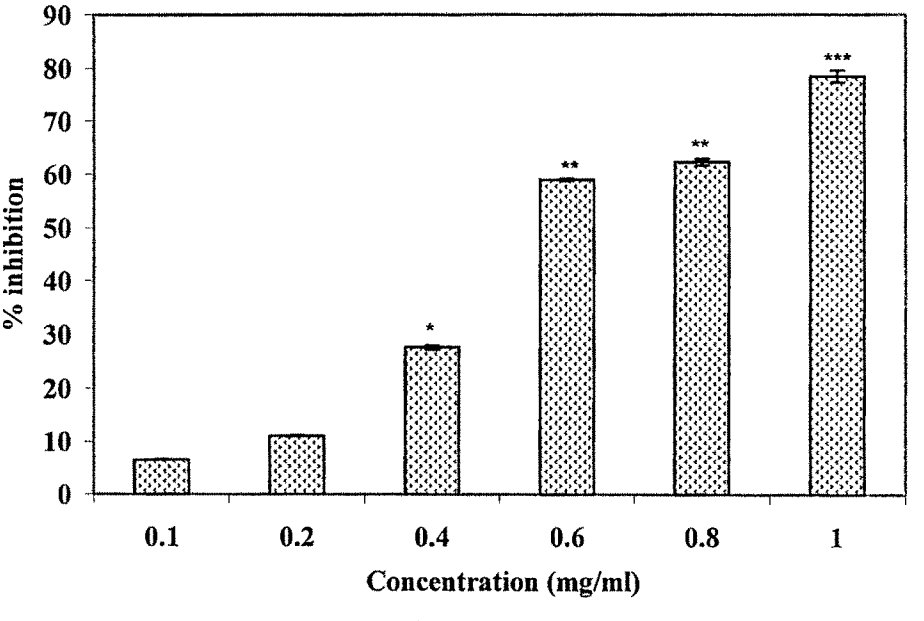
1
Concentration (mg/ml)

Fig. 4.2.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% inhibition
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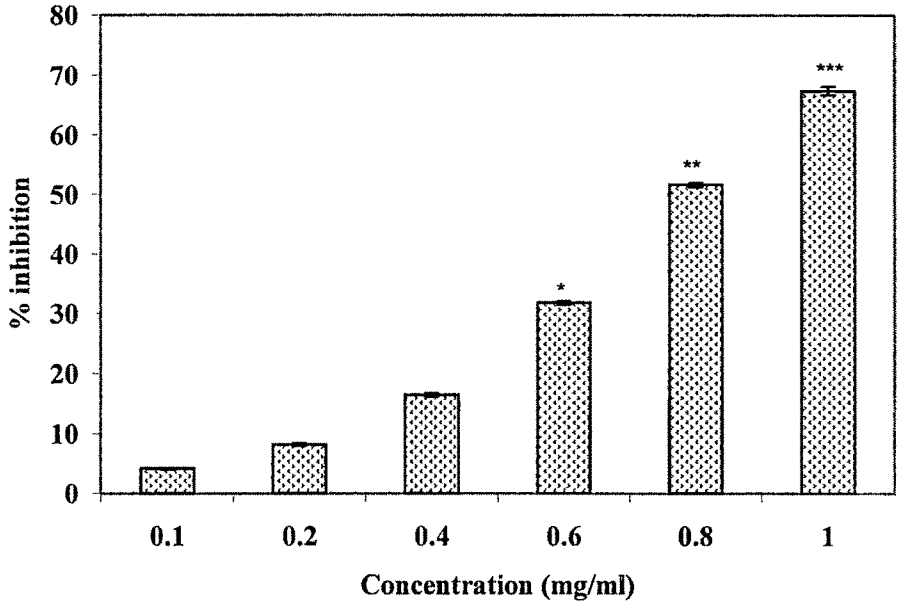
1
Concentration (mg/ml)

Fig. 4.3. Scavenger effect of methanolic extract of Pepticare (0.1, 0.2, 0.4, 0.6, 0.8 and 1.0 mg/ml) on the stable DPPH radical.

Fig. 4.4. Scavenger effect of methanolic extract of Normacid (0.5, 1.0, 2.0, 3.0 and 4.0 mg/ml) on the stable DPPH radical.

Results were expressed as percentage inhibition of absorbance at 516 nm with respect to control. Each value represents the mean ± SEM of three experiments.

Fig. 4.3.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% inhibition
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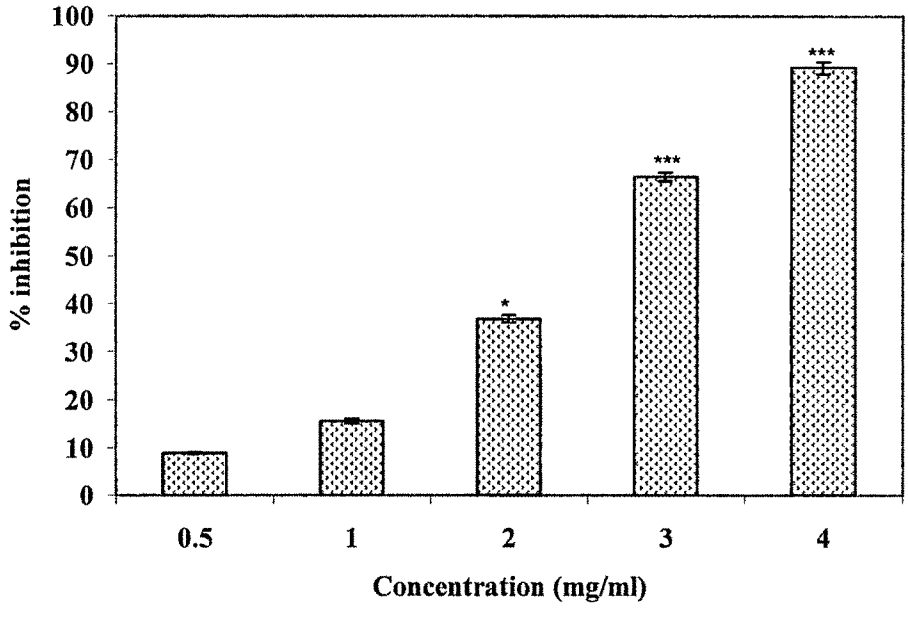
1
Concentration (mg/ml)

Fig. 4.4.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% inhibition
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0.5
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4
Concentration (mg/ml)

4.1.2 ASSAY FOR SUPEROXIDE RADICAL SCAVENGING ACTIVITY

DHC-1 showed a concentration dependent inhibition of superoxide radical with an IC_{50} value of 0.607 mg/ml. The % inhibitions at various concentrations of methanolic extract of the drug, namely 0.1, 0.2, 0.4, 0.6, 0.8 and 1.0 mg/ml were 8.22%, 14.79%, 31.63%, 50.22%, 67.48% and 75.45%, respectively as compared to the control. The % inhibitions produced at the concentrations of 0.4 ($p<0.05$), 0.6 ($p<0.01$), 0.8 ($p<0.001$) and 1.0 mg/ml ($p<0.001$) were significant as compared to the control (Fig. 4.5.).

Methanolic extract of Activit at the concentrations of 0.1, 0.2, 0.4, 0.6, 0.8 and 1.0 mg/ml exhibited % inhibitions of 3.86%, 7.94%, 21.61%, 34.70%, 48.24% and 62.11% of superoxide anion. The % inhibitions produced at the concentrations of 0.6 ($p<0.05$), 0.8 ($p<0.05$) and 1.0 mg/ml ($p<0.01$) were significant as compared to the control The IC_{50} value was 0.825 mg/ml (Fig. 4.6.).

It was observed that 0.25, 0.50, 0.75, 1.0, 1.25 and 1.50 mg/ml of methanolic extract of Pepticare produced an inhibition of superoxide production by about 11.97%, 26.31%, 32.89%, 40.38%, 53.96% and 66.09% with an IC_{50} value of 1.151 mg/ml. The % inhibitions produced at the concentrations of 0.50 ($p<0.05$), 0.75 ($p<0.05$), 1.0 ($p<0.05$), 1.25 ($p<0.01$) and 1.50 mg/ml ($p<0.001$) were significant as compared to the control (Fig. 4.7).

The inhibition of generation of superoxide radical was 6.21%, 10.76%, 22.19%, 37.28%, 46.22% and 61.08%, respectively when treated with 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 mg/ml of Normacid. The % inhibitions produced at the concentrations of 3.0 ($p<0.05$), 4.0 ($p<0.05$) and 5.0 mg/ml ($p<0.01$) were significant as compared to the control The IC_{50} value of Normacid was 4.170 mg/ml (Fig. 4.8).

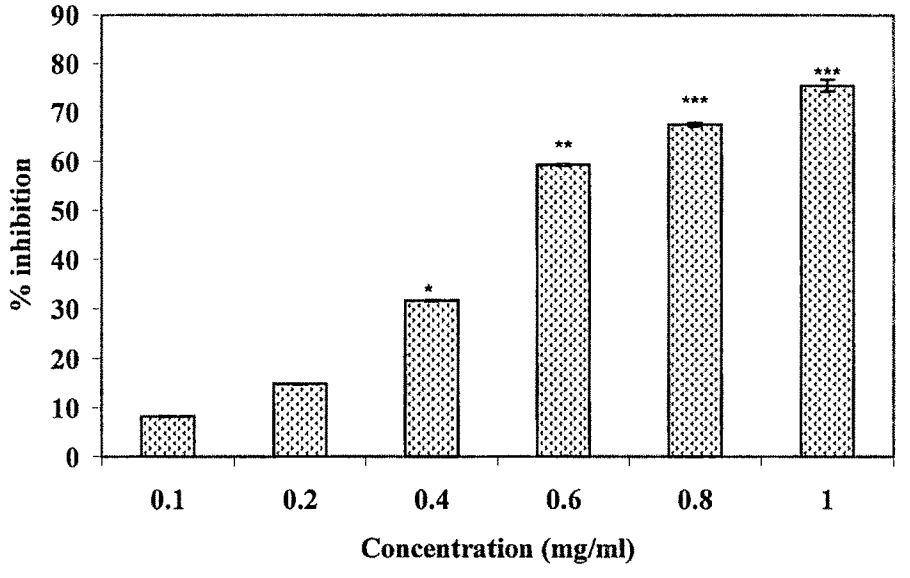
IC_{50} of ascorbic acid was 0.025 mg/ml.

Fig. 4.5. Scavenger effect of methanolic extract of DHC-1 (0.1, 0.2, 0.4, 0.6, 0.8 and 1.0 mg/ml) on superoxide production generated in riboflavin-light-NBT system.

Fig. 4.6. Scavenger effect of methanolic extract of Activit (0.1, 0.2, 0.4, 0.6, 0.8 and 1.0 mg/ml) on superoxide production generated in riboflavin-light-NBT system.

Results were expressed as percentage inhibition of absorbance at 290 nm with respect to control. Each value represents the mean ± SEM of three experiments.

Fig. 4.5.


90
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70
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40
30
20
10
0
% inhibition
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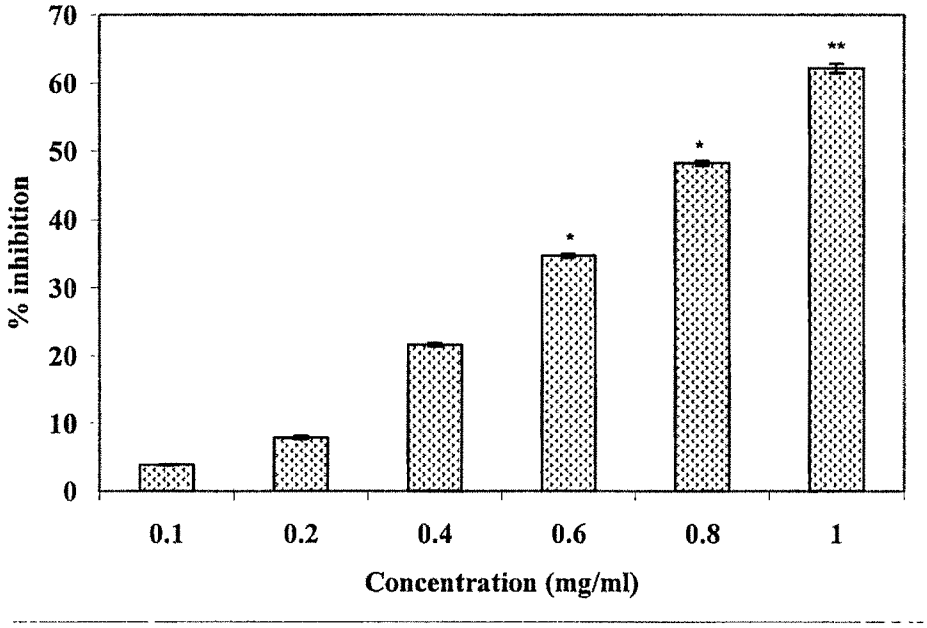
0.1
0.2
0.4
0.6
0.8
1
Concentration (mg/ml)

Fig. 4.6.


70
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% inhibition
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0.1
0.2
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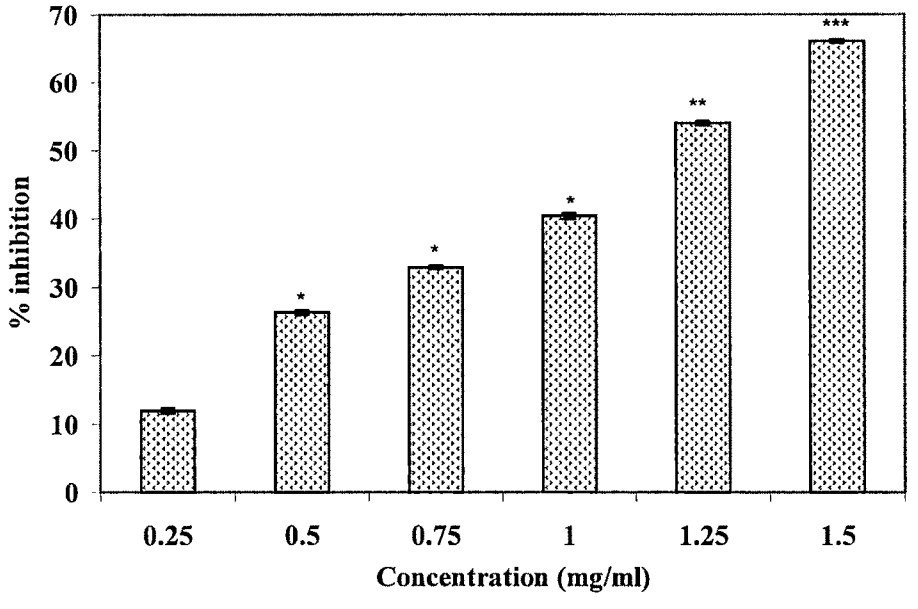
0.6
0.8
1
Concentration (mg/ml)

Fig. 4.7. Scavenger effect of methanolic extract of Pepticare (0.25, 0.50, 0.75, 1.0, 1.25 and 1.50 mg/ml) on superoxide production generated in riboflavin-light-NBT system.

Fig. 4.8. Scavenger effect of methanolic extract of Normacid (0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 mg/ml) on superoxide production generated in riboflavin-light-NBT system.

Results were expressed as percentage inhibition of absorbance at 290 nm with respect to control. Each value represents the mean ± SEM of three experiments.

Fig. 4.7.


70
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% inhibition
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0.25
0.5
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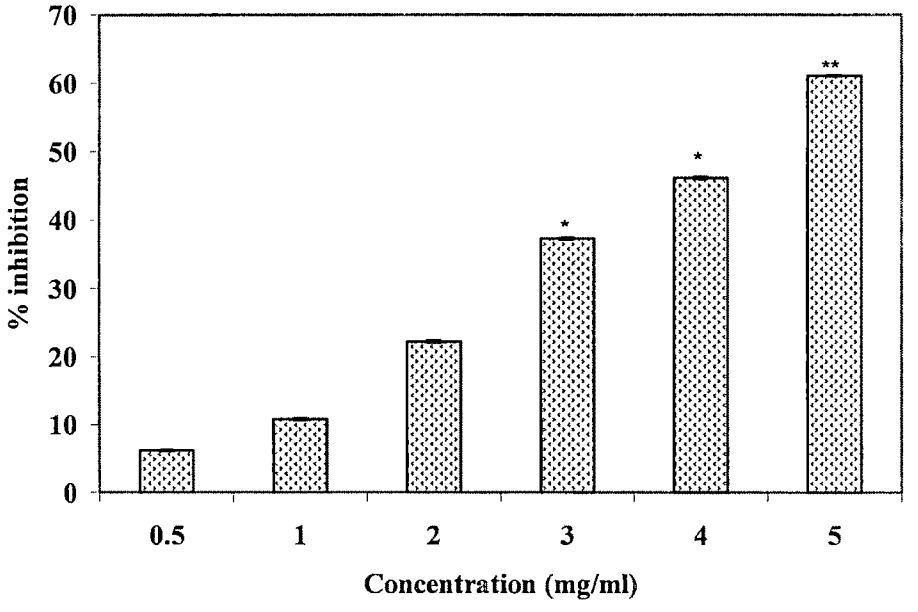
1
1.25
1.5
Concentration (mg/ml)

Fig. 4.8.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% inhibition
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0.5
1
2
3
4
5
Concentration (mg/ml)

SET 1:

PYLORUS-LIGATION

INDUCED ULCER MODEL

4.2 *IN VIVO* STUDIES

4.2.1 PYLORUS LIGATION-INDUCED ULCER METHOD

4.2.1.1 GASTRIC PARAMETERS

4.2.1.1.1 Effect of drugs on ulcer index

In the stomach of normal control rats (Group 1) no ulcers were observed. However, it was observed that in the pylorus-ligated control group (Group 2) the ulcer index was significantly ($p<0.001$) increased as compared to normal control group. In the rats of this group, maximum number of ulcers were of the ulcer score 4 and 5. A number of perforated ulcers (score 25) were also observed (Fig. 4.9 and Fig. 4.17).

Administration of DHC-1 in pylorus-ligated rats, produced a significant ($p<0.001$) reduction in ulcer index at all the four doses (125, 250, 500 and 1000 mg/kg) as compared to the pylorus-ligated control group. The percentage reductions in ulcer index were 42.19%, 77.63%, 87.87% and 95.42% in groups 3, 4, 5 and 6, respectively. All the ulcers in DHC-1 treated groups were of score 1 and 2 and no perforated ulcers were observed (Fig. 4.9 and Fig. 4.18).

Administration of Activit (125 mg/kg and 250 mg/kg) in pylorus-ligated rats did not produce a significant decrease in ulcer index as compared to the pylorus-ligated control (Group 2); the percentage reduction being only 1.08% and 11.05%, respectively. A significant reduction in ulcer index was observed at the doses of 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) with percentage reductions of 30.13% and 42.53%. The ulcers in groups 5 and 6 were of score 1, 2, 3, and 4 but no perforated ulcers (score 25) were observed (Fig. 4.11 and Fig. 4.19).

Administration of Pepticare (125, 250, 500 and 1000 mg/kg) followed by pylorus-ligation produced a decrease in ulcer index at all the four doses as compared to the control group (Group 2); the percentage reductions being 16.77%, 48.46%, 70.46% and 92.24%, respectively. Significant reduction ($p<0.001$) in ulcer index was observed at the doses of 250 mg/kg, 500 mg/kg and 1000 mg/kg. The ulcers of rats of groups 4, 5

and 6 were of score 1, 2, 3 and 4 and no perforated ulcers were observed (Fig. 4.13 and Fig. 4.20).

Administration of Normacid followed by pylorus-ligation did not reduce the ulcer index significantly at the doses of 125 mg/kg (6.74%) and 250 mg/kg (16.17%) but at the higher doses namely, 500 mg/kg (66.31%) and 1000 mg/kg (80.59%), it produced a significant ($p<0.001$) reduction in ulcer index as compared to pylorus-ligated control. The ulcers of groups 5 and 6 were of score 1 and 2 and no perforated ulcers were observed (Fig. 4.15 and Fig. 4.16).

4.2.1.1.2 Effect of drugs on total acidity of gastric fluid

The total acidity of gastric fluid secreted in the rats of pylorus-ligated control group (Group 2) was significantly ($p<0.001$) increased as compared to the normal control group (Group 1).

Administration of DHC-1 followed by pylorus-ligation significantly ($p<0.001$) decreased the total acidity of gastric fluid at all the four doses, namely 125, 250, 500 and 1000 mg/kg as compared to pylorus-ligated control (Fig. 4.9).

Administration of Activit followed by pylorus-ligation did not affect the total acidity of gastric fluid at the lower doses, namely 125 mg/kg and 250 mg/kg but significantly ($p<0.01$) reduced it at the higher doses of 500 mg/kg and 1000 mg/kg as compared to pylorus-ligated control (Fig. 4.11).

Administration of Pepticare followed by pylorus-ligation, significantly lowered the total acidity at all the four dose levels, namely, 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to pylorus-ligated control (Fig. 4.13).

Administration of Normacid followed by pylorus-ligation significantly lowered the total acidity at all the four doses, namely, 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) when compared to the pylorus-ligated control (Fig. 4.15).

4.2.1.1.3 Effect of drugs on volume of gastric fluid

In the rats of pylorus-ligated control group (Group 2) the volume of gastric fluid secreted was significantly ($p<0.001$) increased as compared to the normal control group (Group 1).

Administration of DHC-1 followed by pylorus-ligation did not alter the volume of gastric fluid at the dose of 125 mg/kg but significantly reduced the volume of gastric fluid at the doses of 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to the pylorus-ligated control (Fig. 4.10).

Administration of Activit, at all the four doses (125, 250, 500 and 1000 mg/kg) significantly ($p<0.001$) reduced the volume of gastric fluid as compared to the pylorus-ligated control group (Fig. 4.12).

Administration of Pepticare in pylorus-ligated rats did not significantly alter the gastric content at the doses of 125 and 250 mg/kg, but reduced the volume at the doses of 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) as compared to the pylorus-ligated control group (Fig 4.14).

Administration of Normacid (125, 250, 500 and 1000 mg/kg) followed by pylorus-ligation did not significantly reduce the volume of gastric fluid as compared to the pylorus-ligated control group (Fig. 4.16).

4.1.1.1.4 Effect of drugs on pH of gastric fluid

The pH of gastric fluid secreted in the rats of pylorus-ligated control group (Group 2) was significantly ($p<0.001$) reduced as compared to the normal control group (Group 1).

Administration of DHC-1 followed by pylorus-ligation raised the pH of gastric fluid in pylorus-ligated rats at the doses of 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) but did not produce a significant rise in pH at the lower dose of 125 mg/kg as compared to the pylorus-ligated control group (Fig. 4.10).

Administration of Activit (125 mg/kg) followed by pylorus-ligation did not significantly alter the pH of gastric fluid. However, at the higher doses of 250 mg/kg, 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$)

increased the pH of the gastric content as compared to the pylorus-ligated control (Fig. 4.12).

Administration of Pepticare followed by pylorus-ligation increased the pH of gastric fluid in pylorus-ligated rats at the dose levels of 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) when compared to pylorus-ligated control, whereas it did not produce any significant change at the lower dose of 125 mg/kg (Fig. 4.14).

Administration of Normacid at the lower dose levels of 125 mg/kg and 250 mg/kg followed by pylorus-ligation did not affect the pH of gastric juice but significantly ($p<0.001$) increased the pH at the higher doses of 500 mg/kg and 1000 mg/kg as compared to the pylorus-ligated control group (Fig. 4.16).

Fig. 4.9. Effect of DHC-1 on the ulcer index and total acidity of gastric fluid of pylorus-ligated rats.

Fig. 4.10. Effect of DHC-1 on the volume and pH of gastric fluid of pylorus-ligated rats.

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: DHC-1 (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: DHC-1 (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: DHC-1 (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with group 1.

Groups 3, 4, 5 and 6 were compared with group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.9.

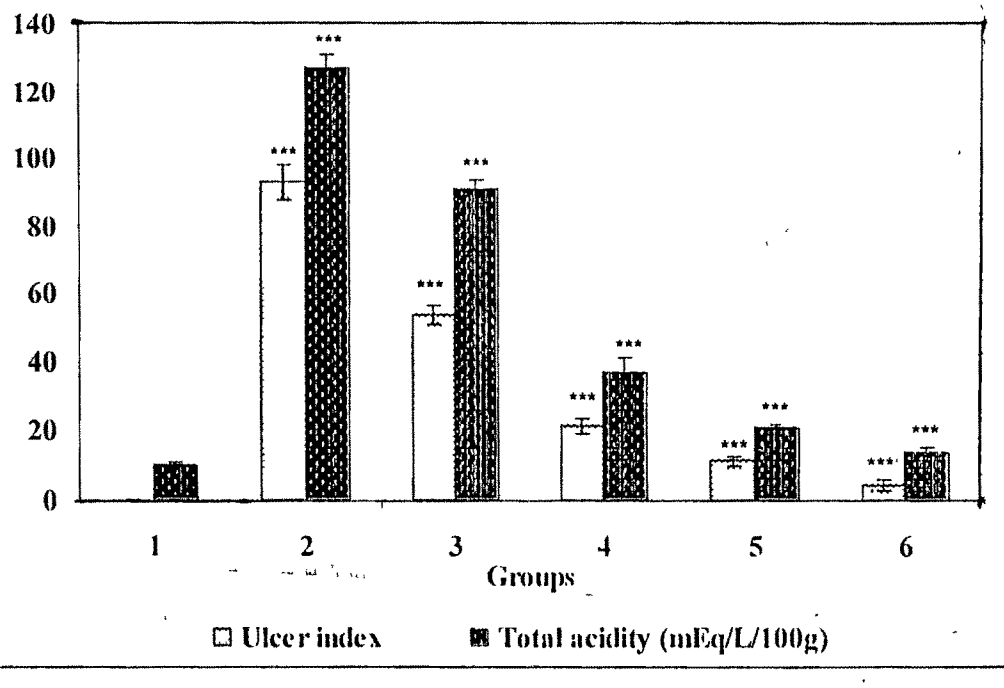


Fig. 4.10.

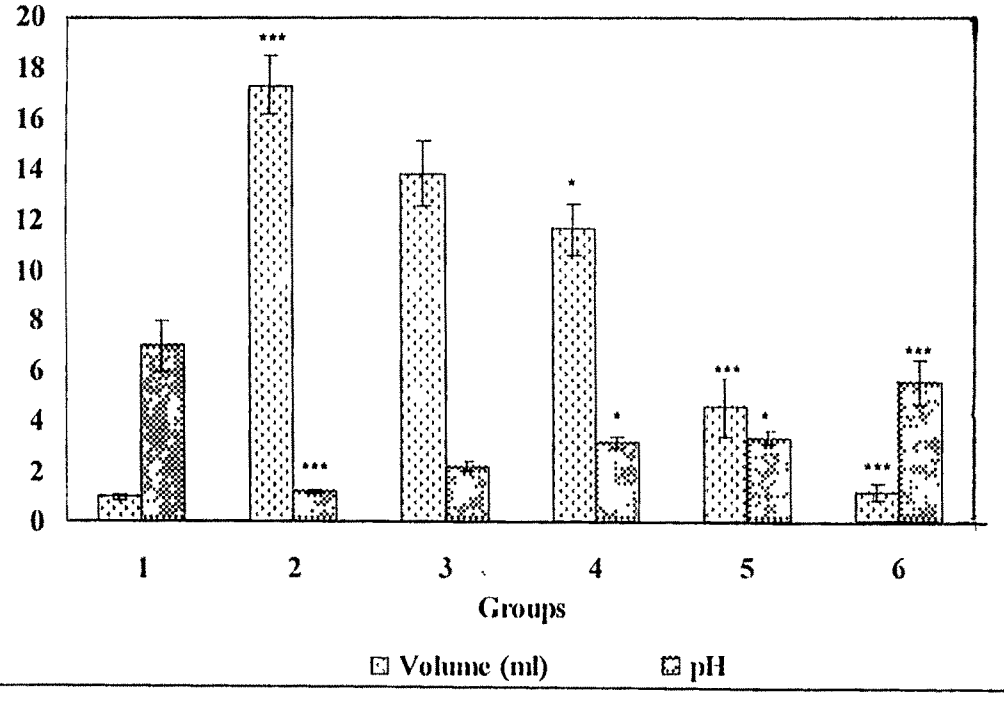


Fig. 4.11. Effect of Activit on the ulcer index and total acidity of gastric fluid of pylorus-ligated rats.

Fig. 4.12. Effect of Activit on the volume and pH of gastric fluid of pylorus-ligated rats.

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: Activit (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: Activit (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5. Activit (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: Activit (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with group 1.

Groups 3, 4, 5 and 6 were compared with group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.11.

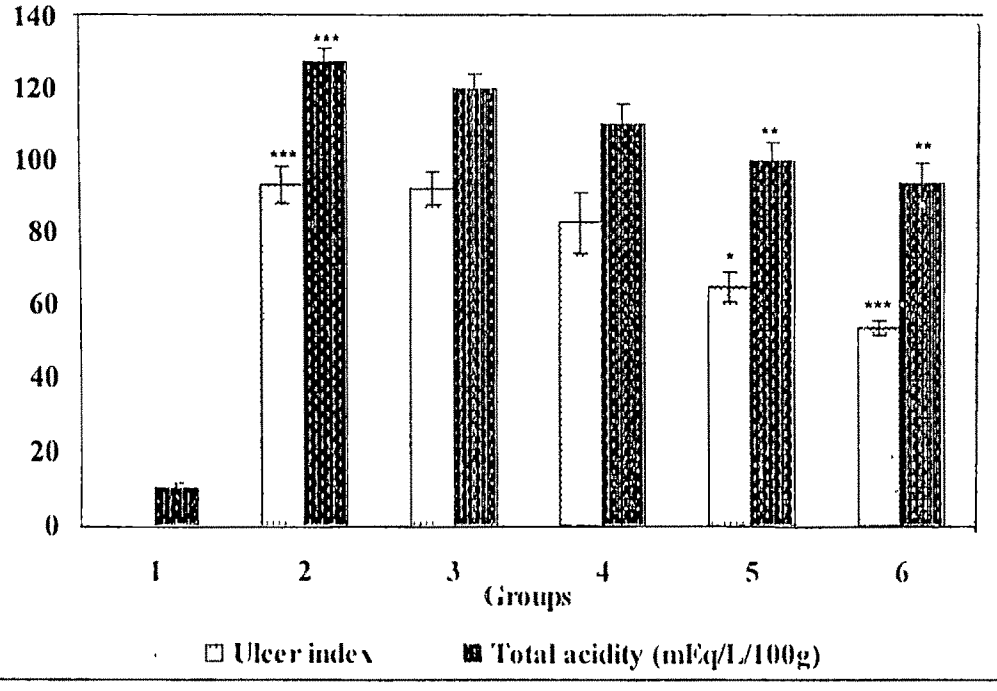


Fig. 4.12.

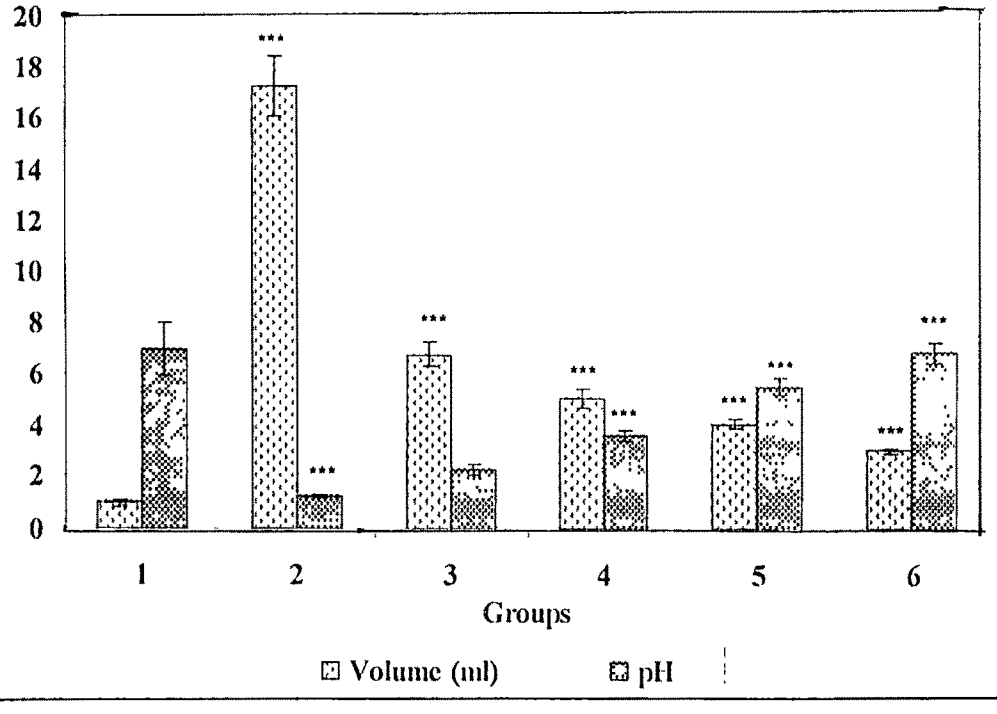


Fig. 4.13. Effect of Pepticare on the ulcer index and total acidity of gastric fluid of pylorus-ligated rats.

Fig. 4.14. Effect of Pepticare on the volume and pH of gastric fluid of pylorus-ligated rats.

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: Pepticare (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: Pepticare (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: Pepticare (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: Pepticare (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with group 1.

Groups 3, 4, 5 and 6 were compared with group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.13.

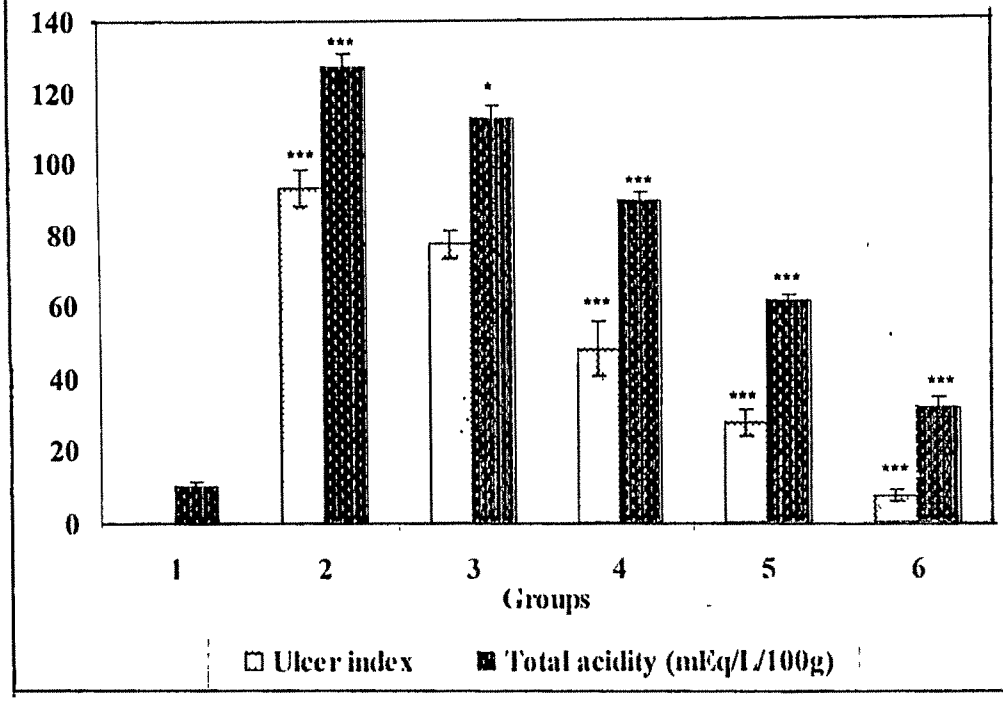


Fig. 4.14.

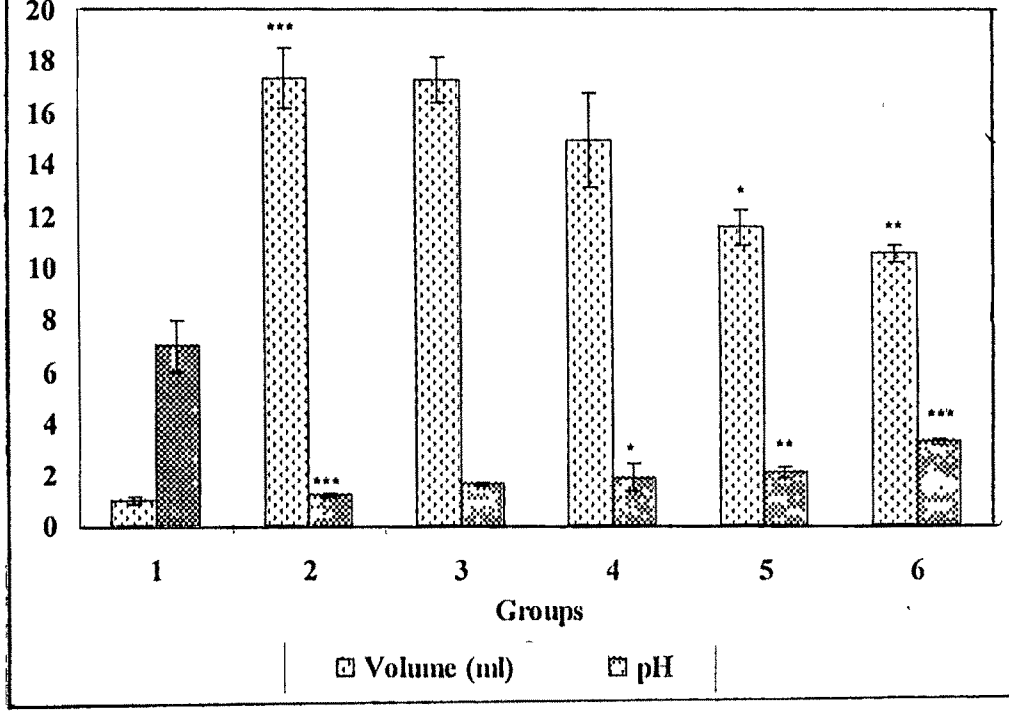


Fig. 4.15. Effect of Normacid on the ulcer index and total acidity of gastric fluid of pylorus-ligated rats.

Fig. 4.16. Effect of Normacid on the volume and pH of gastric fluid of pylorus-ligated rats.

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: Normacid (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: Normacid (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: Normacid (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: Normacid (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with group 1.

Groups 3, 4, 5 and 6 were compared with group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.15.

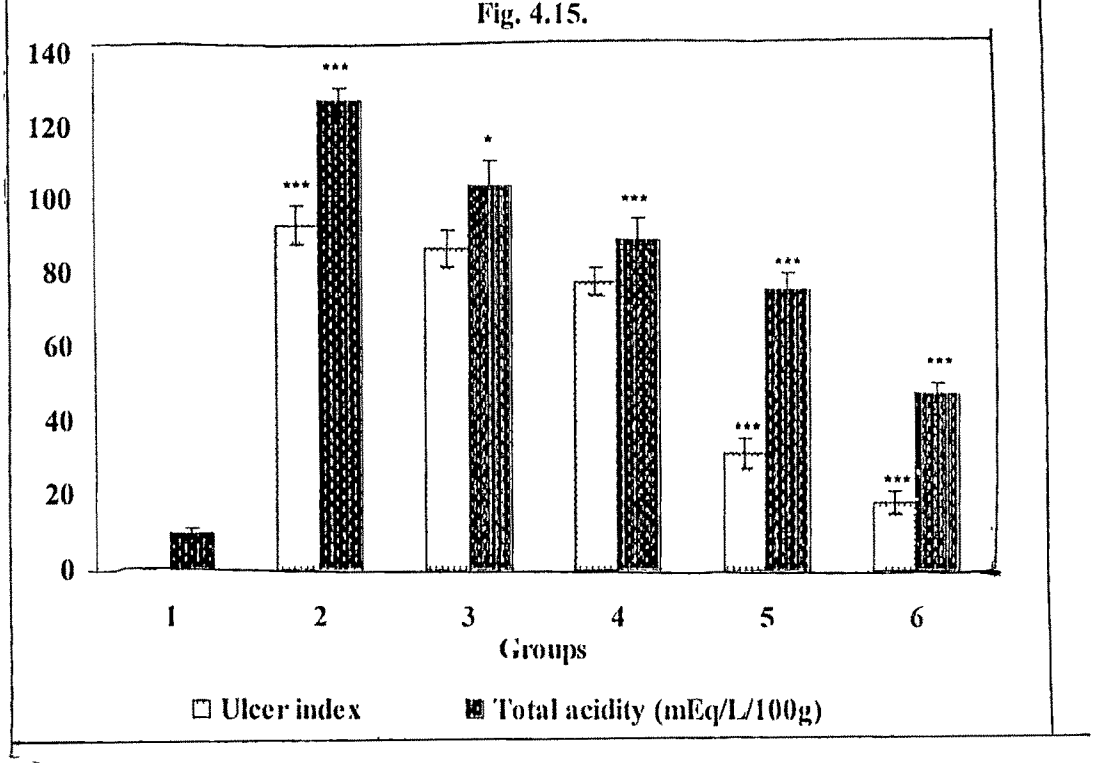


Fig. 4.16.

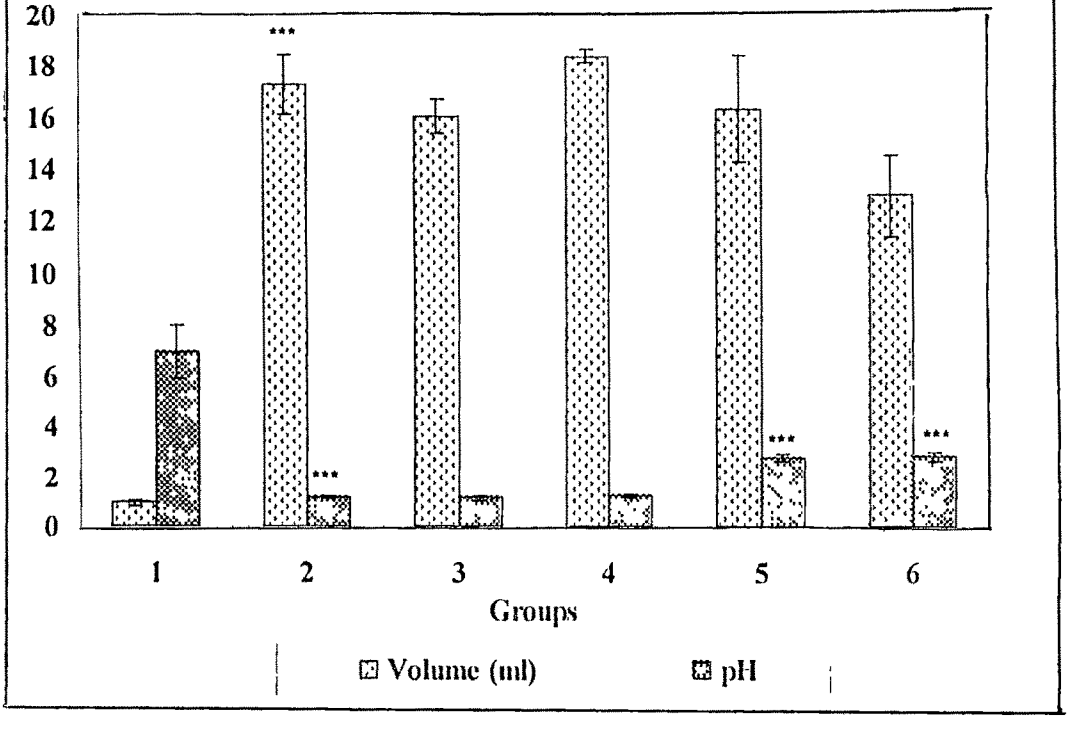


Fig. 4.17. Photomicrographs showing effect of DHC-1 on the stomach of pylorus ligated rats.

1. **Normal control**
2. **Pylorus ligated control**
3. **DHC-1 (125 mg/kg, p.o.)**
4. **DHC-1 (250 mg/kg, p.o.)**
5. **DHC-1 (500 mg/kg, p.o.)**
6. **DHC-1 (1000 mg/kg, p.o.)**

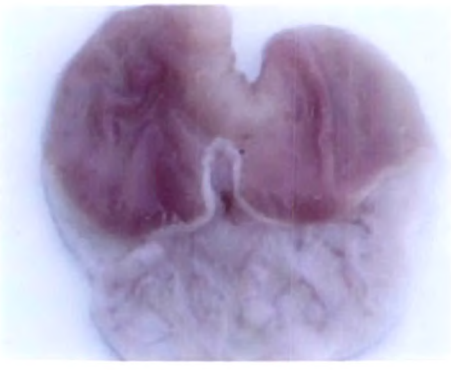


Fig. 4.17 (A)

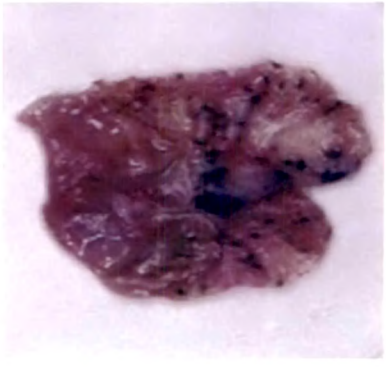


Fig. 4.17 (B)

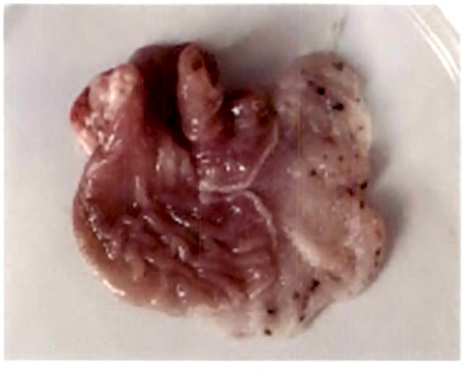


Fig. 4.17 (C)

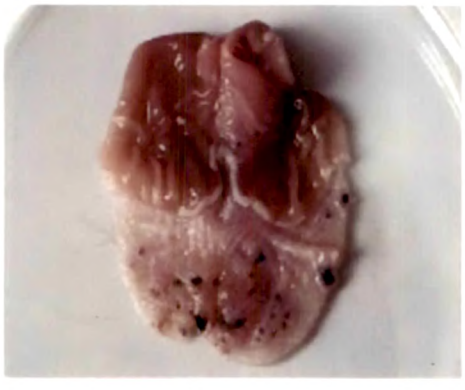


Fig. 4.17 (D)

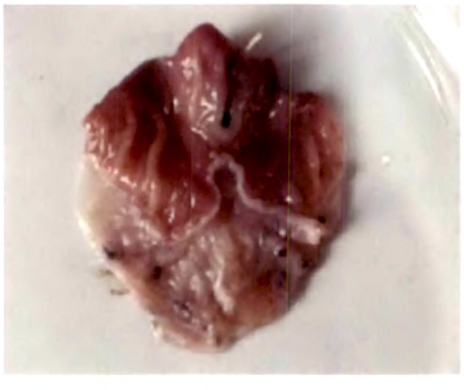


Fig. 4.17 (E)

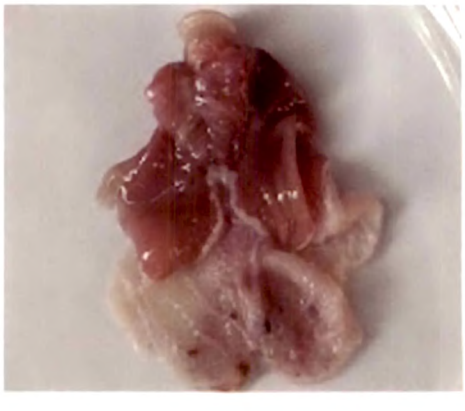


Fig. 4.17 (F)

Fig. 4.18. Photomicrographs showing effect of Activit on the stomach of pylorus ligated rats.

A. Activit (125 mg/kg, p.o.)

B. Activit (250 mg/kg, p.o.)

C. Activit (500 mg/kg, p.o.)

D. Activit (1000 mg/kg, p.o.)

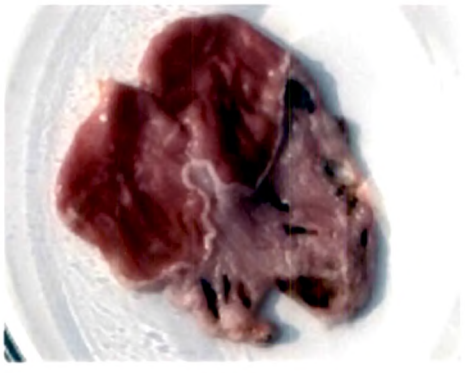


Fig 4 18 (A)

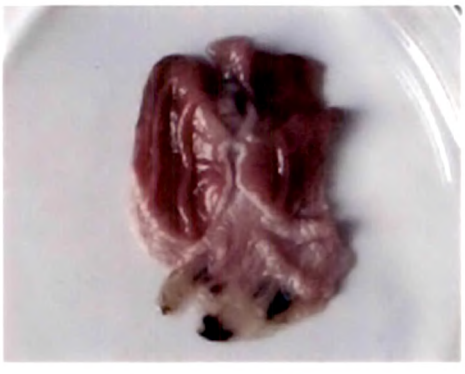


Fig 4 18 (B)

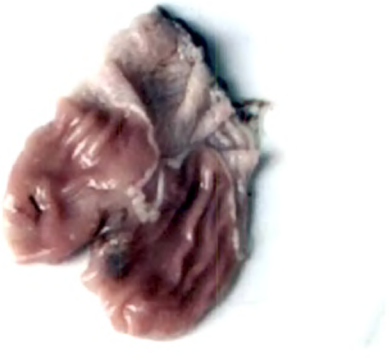


Fig 4 18 (C)

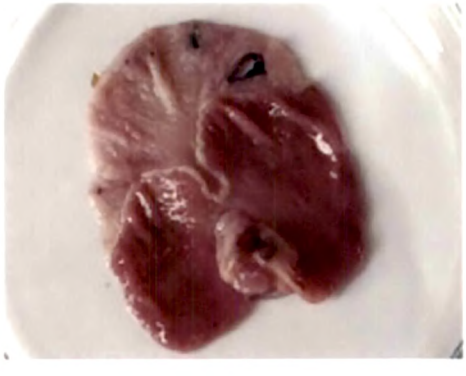


Fig 4 18 (D)

Fig. 4.19. Photomicrographs showing effect of Pepticare on the stomach of pylorus ligated rats.

A. Pepticare (125 mg/kg, p.o.)

B. Pepticare (250 mg/kg, p.o.)

C. Pepticare (500 mg/kg, p.o.)

D. Pepticare (1000 mg/kg, p.o.)

Fig. 4.19 (A)

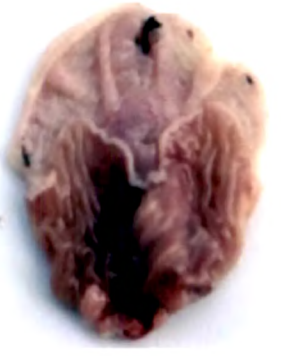


Fig. 4.19 (B)

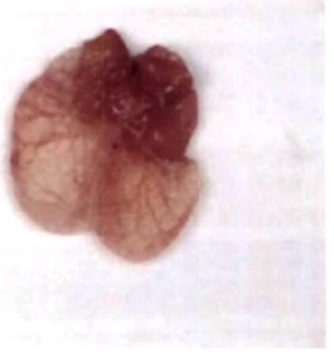


Fig. 4.19 (C)

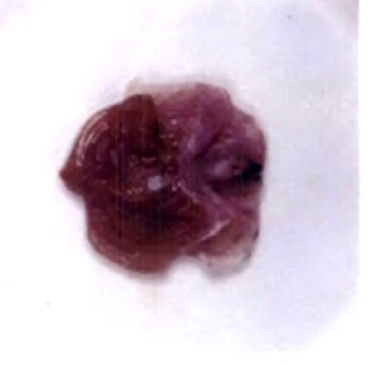


Fig. 4.19 (D)

Fig. 4.20. Photomicrographs showing effect of Normacid on the stomach of pylorus ligated rats.

A. Normacid (125 mg/kg, p.o.)

B. Normacid (250 mg/kg, p.o.)

C. Normacid (500 mg/kg, p.o.)

D. Normacid (1000 mg/kg, p.o.)

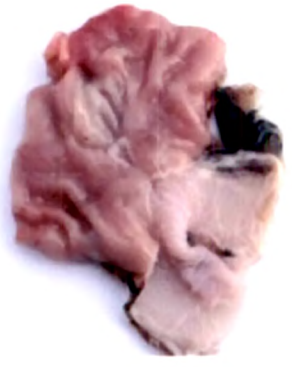


Fig 4.20 (A)

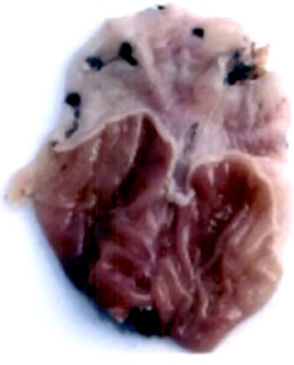


Fig 4.20 (B)

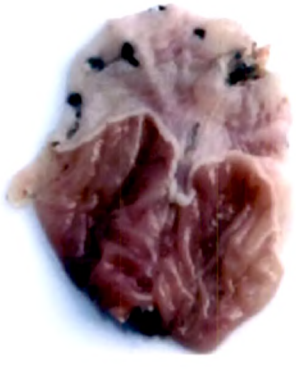


Fig 4.20 (C)

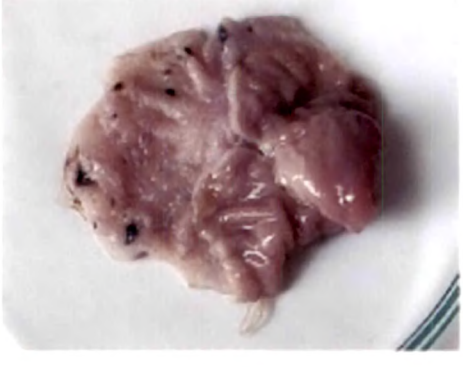


Fig 4.20 (D)

4.2.1.2 TISSUE PARAMETERS

4.2.1.2.1 Effect on lipid peroxidation

Pylorus-ligation (Group 2) significantly ($p<0.001$) increased lipid peroxidation in stomach of rats as compared to the normal control group (Group 1).

Administration of DHC-1 (250 mg/kg, 500 mg/kg and 1000 mg/kg) followed by pylorus-ligation brought about a significant ($p<0.001$) reduction in lipid peroxidation as compared to pylorus-ligated control; but could not affect the same at the lower dose of 125 mg/kg (Table 4.1).

Administration of Activit followed by pylorus-ligation did not reduce the MDA content at the dose of 125 mg/kg but decreased the MDA content significantly at the dose levels of 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to pylorus-ligated control (Table 4.2).

The extent of lipid peroxidation was not reduced by 125 mg/kg of Pepticare, but treatment with higher doses, namely 250, 500 and 1000 mg/kg lowered the MDA levels significantly ($p<0.001$) as compared to the pylorus-ligated control group (Table 4.3).

Administration of Normacid (125, 250, 500 and 1000 mg/kg) followed by pylorus-ligation significantly ($p<0.001$) lowered the MDA content in stomach as compared to the pylorus-ligated control group (Table 4.4).

4.2.1.2.2 Effect on endogenous antioxidants

4.2.1.2.2.1 Effect on Superoxide dismutase

Pylorus-ligation (Group 2) significantly ($p<0.001$) reduced the SOD levels as compared to normal control group (Group 1).

Administration of DHC-1, Activit, Pepticare and Normacid followed by pylorus-ligation did not affect the levels of SOD at the doses of 125, 250 and 500 mg/kg but at the dose of 1000 mg/kg they significantly ($p<0.001$) increased the SOD levels as compared to the pylorus-ligated control group (Tables 4.1, 4.2, 4.3 and 4.4).

4.2.1.2.2.2 Effect on Catalase

The catalase activity pylorus-ligated control group (Group 2) was significantly ($p<0.01$) reduced as compared to normal control group

Administration of DHC-1, Activit, Pepticare and Normacid (125, 250 and 500 mg/kg) followed by pylorus-ligation did not produce any significant effect on catalase levels as compared to the pylorus-ligated control group; but at the higher doses of 1000 mg/kg, DHC-1 ($p<0.05$), Activit ($p<0.05$), Pepticare ($p<0.05$) and Normacid ($p<0.01$) increased the catalase levels significantly (Tables 4.1, 4.2, 4.3 and 4.4).

4.2.1.2.2.3 Effect on Reduced glutathione

A significant ($p<0.001$) reduction in reduced glutathione concentration was observed in pylorus-ligated rats (Group 2) as compared to normal control group (Group 1).

Administration of DHC-1 followed by pylorus-ligation significantly increased the GSH content at all the four doses, namely 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to pylorus-ligated control group (Table 4.1).

Administration of Activit followed by pylorus-ligation increased the GSH content significantly at all the four doses, namely 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to pylorus-ligated control (Table 4.2).

Administration of Pepticare and Normacid, at the dose of 125 mg/kg followed by pylorus-ligation did not produce any significant effect on the level of GSH in stomach of rats but significantly ($p<0.001$) increased GSH concentration at the doses of 250, 500 and 1000 mg/kg as compared to pylorus-ligated control (Tables 4.3 and 4.4).

Table 4.1: Effect of DHC-1 on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the stomach of pylorus-ligated rats.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.45 ± 0.24	3.31 ± 0.14	5.64 ± 0.32	8.27 ± 0.22
Group 2	10.09 ± 0.44***	0.58 ± 0.14***	2.37 ± 0.26***	5.93 ± 0.60*
Group 3	9.13 ± 0.63NS	1.25 ± 0.32*	2.49 ± 0.2 NS	5.99 ± 0.71 NS
Group 4	4.75 ± 0.41***	1.88 ± 1.04**	2.63 ± 0.93 NS	6.25 ± 0.85NS
Group 5	3.99 ± 0.13***	2.49 ± 0.43***	3.03 ± 1.08NS	7.09 ± 1.15NS
Group 6	2.23 ± 0.17***	3.53 ± 0.36***	4.95 ± 1.35***	8.25 ± 1.10*
F value	74.675	28.426	26.073	6.494
P value	<0.0001	<0.0001	<0.0001	0.0013

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: DHC-1 (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: DHC-1 (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: DHC-1 (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with group 1.

Groups 3, 4, 5 and 6 were compared with group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.2: Effect of Activit on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the stomach of pylorus-ligated rats.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.45 ± 0.24	3.31 ± 0.14	5.64 ± 0.32	8.27 ± 0.22
Group 2	10.09± 0.44***	0.58 ± 0.14***	2.37 ± 0.26***	5.93 ± 0.60***
Group 3	9.66 ± 0.55NS	1.58 ± 0.30*	2.29 ± 0.12NS	5.97 ± 0.15NS
Group 4	7.30 ± 0.42**	2.35 ± 0.22***	2.30 ± 0.13NS	6.03 ± 0.26 NS
Group 5	5.84 ± 0.38***	2.63 ± 0.25***	3.13 ± 0.09NS	6.51 ± 0.29 NS
Group 6	4.90 ± 0.36***	3.07 ± 0.19***	4.40 ± 0.32***	7.46± 0.21*
F value	42.061	22.436	36.541	8.792
P value	<0.0001	<0.0001	<0.0001	0.0002

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: Activit (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: Activit (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: Activit (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: Activit (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.3: Effect of Pepticare on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the stomach of pylorus-ligated rats.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.45 ± 0.24	3.31 ± 0.14	5.64 ± 0.32	8.27 ± 0.22
Group 2	10.09± 0.44***	0.58 ± 0.14***	2.37 ± 0.26***	5.93 ± 0.60*
Group 3	9.12 ± 0.60NS	1.51 ± 0.24NS	2.42 ± 0.45NS	5.96 ± 0.64NS
Group 4	5.87 ± 0.35***	2.71 ± 0.58***	2.78 ± 0.37NS	6.49 ± 0.43NS
Group 5	4.17 ± 0.39***	2.92 ± 0.30***	3.30 ± 0.18NS	7.37 ± 0.19NS
Group 6	3.59 ± 0.57***	3.53 ± 0.36***	5.07 ± 0.17***	8.28 ± 0.19*
F value	42.169	14.813	26.073	6.494
P value	<0.0001	<0.0001	<0.0001	0.0002

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: Pepticare (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: Pepticare (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: Pepticare (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: Pepticare (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.4: Effect of Normacid on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the stomach of pylorus-ligated rats.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.45 ± 0.24	3.31 ± 0.14	5.64 ± 0.32	8.27 ± 0.22
Group 2	10.09 ± 0.44***	0.58 ± 0.14***	2.37 ± 0.26***	5.93 ± 0.60**
Group 3	5.38 ± 0.48***	1.43 ± 0.18NS	2.34 ± 0.26NS	5.73 ± 0.38 NS
Group 4	4.00 ± 0.17***	2.44 ± 0.19***	2.73 ± 0.10NS	6.52 ± 0.36 NS
Group 5	3.35 ± 0.43***	3.36 ± 0.20***	3.17 ± 0.08NS	6.93 ± 0.15 NS
Group 6	2.89 ± 0.15***	4.45 ± 0.34***	4.55 ± 0.20***	8.23 ± 0.14**
F value	61.058	45.725	36.698	9.991
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: Normacid (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: Normacid (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: Normacid (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: Normacid (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

4.2.1.2.3 Effect on membrane bound enzymes

4.2.1.2.3.1 Effect on Sodium Potassium ATPase

In the stomach of pylorus-ligated rats (Group 2) the activity of Na^+K^+ATPase enzyme was significantly ($p<0.001$) reduced as compared to the normal control group.

Administration of DHC-1 and Activit, at the doses of 250, 500 and 1000 mg/kg followed by pylorus-ligation, significantly ($p<0.001$) increased the activity of Na^+K^+ATPase enzyme as compared to the pylorus-ligated control but did not affect the levels at 125 mg/kg (Tables 4.5 and 4.6).

Administration of Pepticare and Normacid, at the doses of 125, 250 and 500 mg/kg followed by pylorus-ligation, did not significantly increase the activity of Na^+K^+ATPase enzyme as compared to the pylorus-ligated control group. Only the higher dose of these drugs, i.e. 1000 mg/kg produced a significant ($p<0.001$) rise in the activity of Na^+K^+ATPase enzyme (Tables 4.7 and 4.8).

4.2.1.2.3.2 Effect on Calcium ATPase

Pylorus-ligation (Group 2) led to a significant ($p<0.001$) decrease in the Ca^{2+}ATPase activity when compared with normal control group (Group 1).

Administration of DHC-1 followed by pylorus-ligation significantly increased the Ca^{2+}ATPase activity at all the doses namely, 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to pylorus-ligated control (Table 4.5).

Administration of Activit (125 mg/kg and 250 mg/kg) followed by pylorus-ligation did not significantly increase the activity of Ca^{2+}ATPase enzyme as compared to the pylorus-ligated control group. Only the higher doses of this drug, i.e. 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) produced a significant rise in the activity of Ca^{2+}ATPase enzyme (Table 4.6).

Administration of Pepticare followed by pylorus-ligation also significantly increased the Ca^{2+}ATPase activity at all the doses namely, 125

mg/kg ($p<0.01$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to pylorus-ligated control (Table 4.7).

Administration of Normacid in pylorus-ligated rats increased the Ca^{2+}ATPase activity significantly at all the four doses, namely 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to pylorus-ligated control group (Table 4.8).

4.2.1.2.3.3 Effect on Magnesium ATPase

In the stomach of pylorus-ligated rats (Group 2) there was a significant ($p<0.001$) reduction in the Mg^{2+}ATPase activity as compared to normal control group (Group 1).

Administration of DHC-1 (125, 250, 500 and 1000 mg/kg) followed by pylorus-ligation produced a significant ($p<0.001$) increase in the activity of Mg^{2+}ATPase as compared to pylorus-ligated control group (Table 4.5).

Administration of Activit at the dose of 125 mg/kg followed by pylorus-ligation did not produce a significant change in the level of Mg^{2+}ATPase enzyme, but a significant ($p<0.001$) rise in activity of Mg^{2+}ATPase enzyme was observed at the higher doses of 250 mg/kg, 500 mg/kg and 1000 mg/kg as compared to pylorus-ligated rats (Table 4.6).

Administration of Pepticare followed by pylorus ligation produced a significant ($p<0.001$) increase in the activity of Mg^{2+}ATPase at all the four doses namely, 125, 250, 500 and 1000 mg/kg as compared to the pylorus-ligated rats (Table 4.7).

Administration of Normacid also significantly increased the Mg^{2+}ATPase activity at all the doses namely, 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to pylorus-ligated control group (Table 4.8).

Table 4.5: Effect of DHC-1 on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the stomach of pylorus ligated rats.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.29 ± 0.18	3.65 ± 0.30	3.52 ± 0.20
Group 2	1.49 ± 0.10***	1.62 ± 0.17***	1.54 ± 0.13***
Group 3	2.17 ± 0.08NS	1.98 ± 0.24*	2.78 ± 0.27***
Group 4	3.61 ± 0.07***	2.73 ± 0.12**	3.13 ± 0.24***
Group 5	4.63 ± 0.08***	2.83 ± 0.17***	3.43 ± 0.17***
Group 6	6.70 ± 0.10***	3.80 ± 0.32***	3.56 ± 0.15***
F value	70.96	18.774	27.149
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: DHC-1 (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: DHC-1 (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: DHC-1 (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.6: Effect of Activit on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the stomach of pylorus ligated rats.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.29 ± 0.18	3.65 ± 0.30	3.52 ± 0.20
Group 2	1.49 ± 0.10***	1.62 ± 0.17***	1.54 ± 0.13***
Group 3	2.18 ± 0.13 NS	2.12 ± 0.14 NS	2.02 ± 0.14 NS
Group 4	2.80 ± 0.17***	2.61 ± 0.36 NS	2.50 ± 0.15***
Group 5	3.06 ± 0.13***	2.91 ± 0.13**	3.14 ± 0.06***
Group 6	4.26 ± 0.20***	3.33 ± 0.13***	3.31 ± 0.06***
F value	79.436	11.444	34.538
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: Activit (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: Activit (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: Activit (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: Activit (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.7: Effect of Pepticare on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the stomach of pylorus ligated rats.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.29 ± 0.18	3.65 ± 0.30	3.52 ± 0.20
Group 2	1.49 ± 0.10***	1.62 ± 0.17***	1.54 ± 0.13***
Group 3	1.50 ± 0.05NS	2.79 ± 0.12**	2.63 ± 0.14***
Group 4	1.92 ± 0.17NS	2.88 ± 0.11***	2.93 ± 0.14***
Group 5	2.46 ± 0.39NS	2.99 ± 0.10***	3.30 ± 0.10***
Group 6	3.69 ± 0.40***	3.30 ± 0.13***	3.62 ± 0.17***
F value	34.338	16.909	27.149
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: Pepticare (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: Pepticare (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: Pepticare (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: Pepticare (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.8: Effect of Normacid on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the stomach of pylorus ligated rats.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.29 ± 0.18	3.65 ± 0.30	3.52 ± 0.20
Group 2	1.49 ± 0.10***	1.62 ± 0.17***	1.54 ± 0.13***
Group 3	1.53 ± 0.10 NS	2.59 ± 0.23*	2.42 ± 0.18*
Group 4	2.06 ± 0.12 NS	2.65 ± 0.15*	2.75 ± 0.17***
Group 5	2.50 ± 0.40 NS	3.06 ± 0.10***	3.17 ± 0.17***
Group 6	3.64 ± 0.29***	3.56 ± 0.05***	3.52 ± 0.07***
F value	42.265	16.318	22.819
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Pylorus ligated control

Group 3: Normacid (125 mg/kg, p.o.) followed by pylorus-ligation

Group 4: Normacid (250 mg/kg, p.o.) followed by pylorus-ligation

Group 5: Normacid (500 mg/kg, p.o.) followed by pylorus-ligation

Group 6: Normacid (1000 mg/kg, p.o.) followed by pylorus-ligation

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

SET 2:

ETHANOL-INDUCED

ULCER MODEL

4.2.2 ETHANOL-INDUCED ULCER METHOD

4.2.2.1 GASTRIC PARAMETERS

4.2.2.1.1 Effect of drugs on ulcer index

No ulcers were found in the stomach of rats of group 1 (Normal control). Administration of ethanol (96%, 5ml/kg, p.o.) produced significant ($p<0.001$) ulcers in rats (Group 2) as compared to the normal control group (Group 1) (Fig. 4.21 and Fig. 4.25).

Administration of DHC-1 (125, 250, 500 and 1000 mg/kg) in ethanol treated rats resulted in a significant ($p<0.001$) reduction in ulcer index, the percentage reduction being 74.66%, 82.05%, 90.33% and 98.45% in groups 3, 4, 5 and 6, respectively (Fig. 4.21 and Fig. 4.25).

Administration of Activit followed by ethanol treatment also significantly ($p<0.001$) reduced the ulcer index at all the four doses when compared with ethanol control group. The percentage reductions in ulcer index at the doses of 125 mg/kg, 250 mg/kg, 500 mg/kg and 1000 mg/kg were 83.00%, 91.85%, 94.76% and 99.48%, respectively (Fig. 4.22 and Fig. 4.26).

Administration of Pepticare followed by ethanol treatment also significantly ($p<0.001$) lowered the ulcer index at all the four dose levels with percentage reductions of 72.57%, 85.93%, 94.31% and 98.44% in groups 3, 4, 5 and 6, respectively as compared to ethanol control group (Fig. 4.23 and Fig. 4.27).

Administration of Normacid followed by ethanol treatment significantly ($p<0.001$) decreased the ulcer index at the doses of 125, 250, 500 and 1000 mg/kg. The percentage reductions in ulcer index were 70.41%, 80.27%, 86.95% and 98.00%, respectively in the four groups as compared to the ethanol control group (Fig. 4.24 and Fig. 4.28).

Fig. 4.21. Effect of DHC-1 on the ulcer index of ethanol-treated rats.

Fig. 4.22. Effect of Activit on the ulcer index of ethanol-treated rats.

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: DHC-1/Activit (125 mg/kg, p.o.) followed by ethanol treatment

Group 4: DHC-1/Activit (250 mg/kg, p.o.) followed by ethanol treatment

Group 5: DHC-1/Activit (500 mg/kg, p.o.) followed by ethanol treatment

Group 6: DHC-1/Activit (1000 mg/kg, p.o.) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.21.

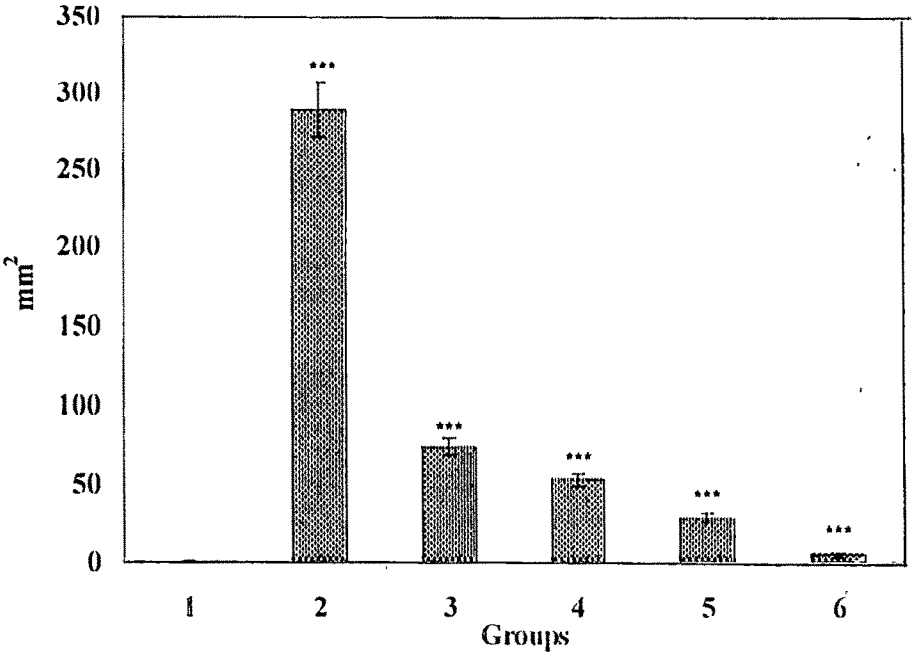


Fig. 4.22.

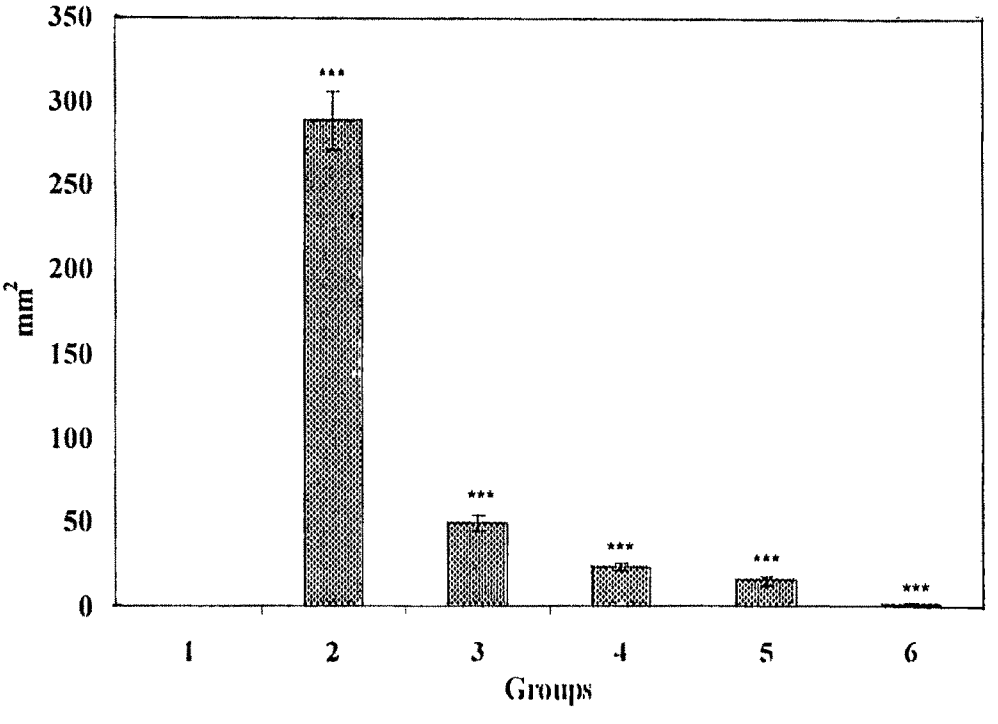


Fig. 4.23. Effect of Pepticare on the ulcer index of ethanol-treated rats.

Fig. 4.24. Effect of Normacid on the ulcer index of ethanol-treated rats.

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: Pepticare/Normacid (125 mg/kg) followed by ethanol treatment

Group 4: Pepticare/Normacid (250 mg/kg) followed by ethanol treatment

Group 5: Pepticare/Normacid (500 mg/kg) followed by ethanol treatment

Group 6: Pepticare/Normacid (1000 mg/kg) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.23.

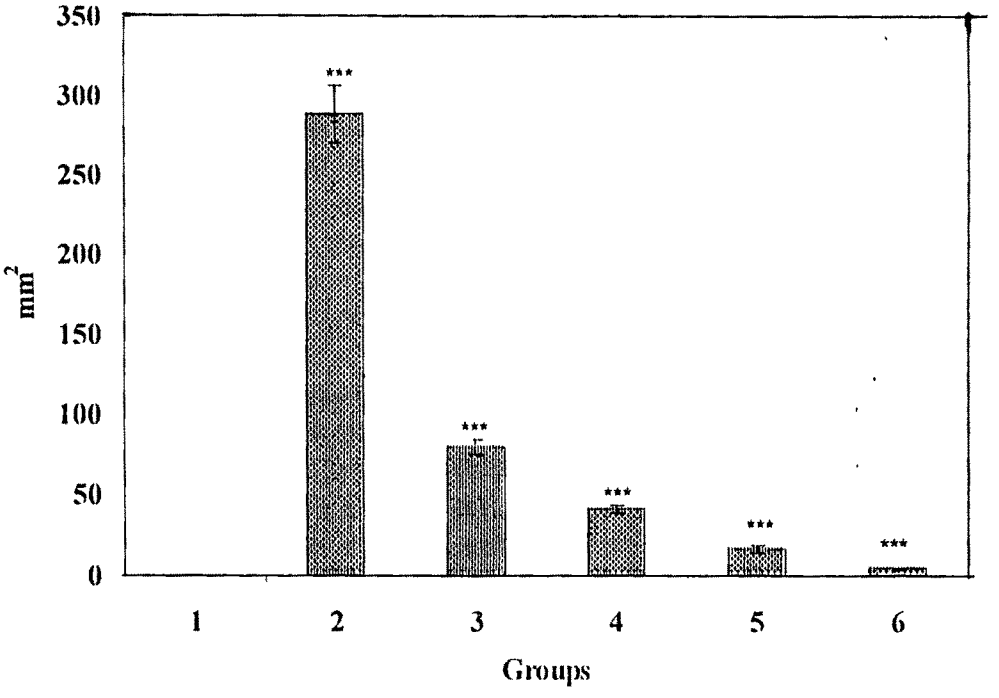


Fig. 4.24.

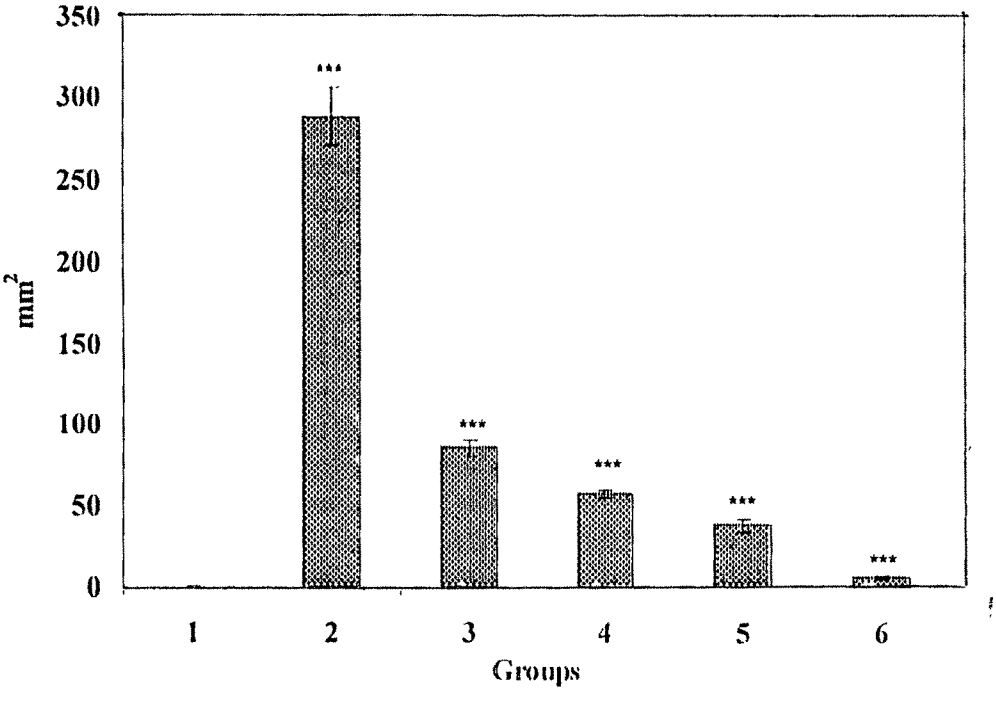


Fig. 4.25. Photomicrographs showing effect of DHC-1 on the stomach of ethanol treated rats.

A. Normal control

B. Ethanol control (96%, 5ml/kg, p.o.)

C. DHC-1 (125 mg/kg, p.o.)

D. DHC-1 (250 mg/kg, p.o.)

E. DHC-1 (500 mg/kg, p.o.)

F. DHC-1 (1000 mg/kg, p.o.)

Fig. 4.25 (A)

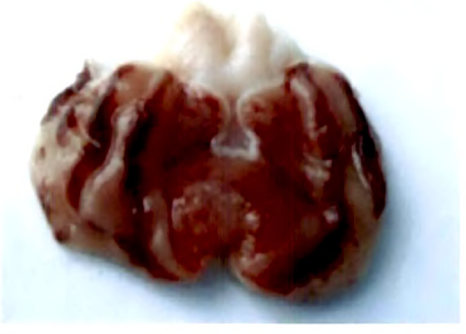


Fig. 4.25 (B)

Fig. 4.25 (C)

Fig. 4.25 (D)

Fig. 4.25 (E)

Fig. 4.25 (F)

Fig. 4.26. Photomicrographs showing effect of Activit on the stomach of ethanol treated rats.

A. Activit (125 mg/kg, p.o.)

B. Activit (250 mg/kg, p.o.)

C. Activit (500 mg/kg, p.o.)

D. Activit (1000 mg/kg, p.o.)

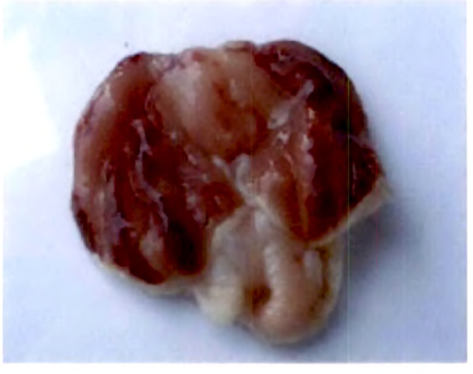


Fig 4 26 (A)

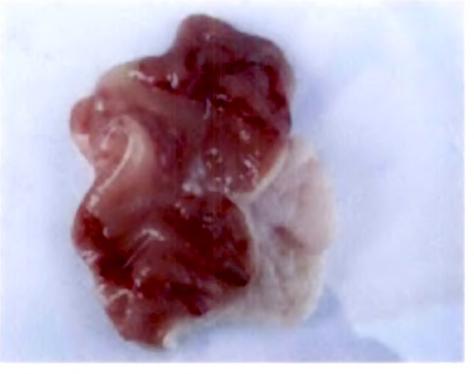


Fig 4 26 (B)

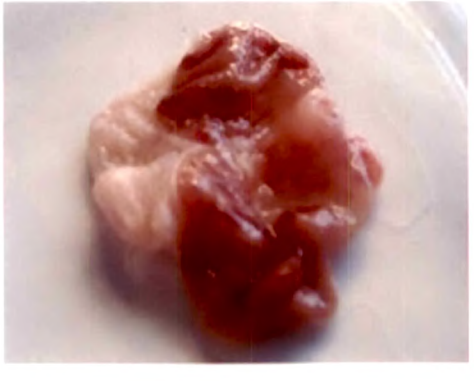


Fig 4 26 (C)

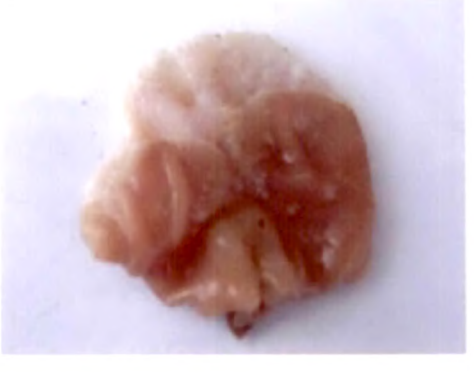


Fig 4 26 (D)

Fig. 4.27. Photomicrographs showing effect of Pepticare on the stomach of ethanol treated rats.

A. Pepticare (125 mg/kg, p.o.)

B. Pepticare (250 mg/kg, p.o.)

C. Pepticare (500 mg/kg, p.o.)

D. Pepticare (1000 mg/kg, p.o.)

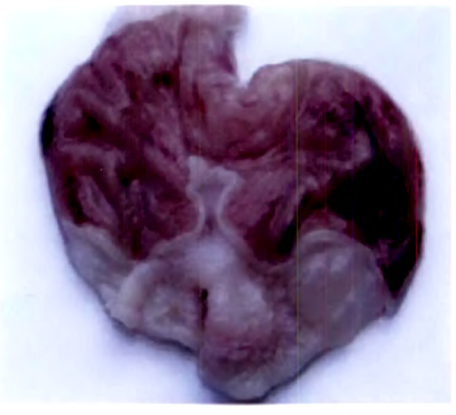


Fig 4.27 (A)

Fig 4.27 (B)

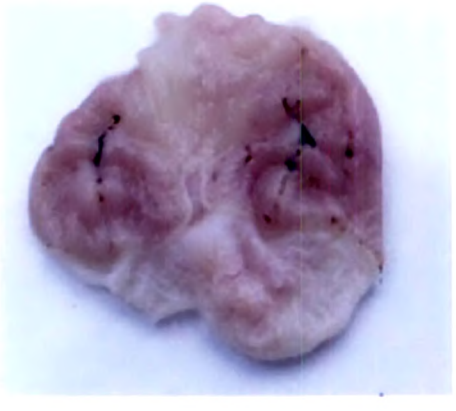


Fig 4.27 (C)

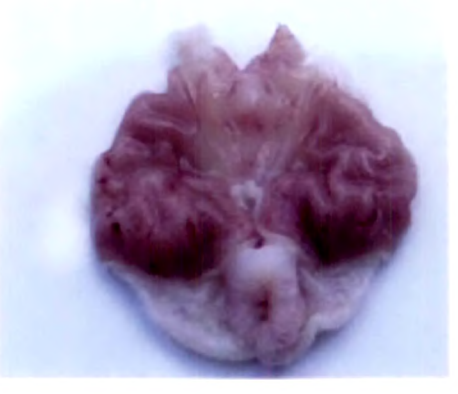


Fig 4.27 (D)

Fig. 4.28. Photomicrographs showing effect of Normacid on the stomach of ethanol treated rats.

A. Normacid (125 mg/kg, p.o.)

B. Normacid (250 mg/kg, p.o.)

C. Normacid (500 mg/kg, p.o.)

D. Normacid (1000 mg/kg, p.o.)

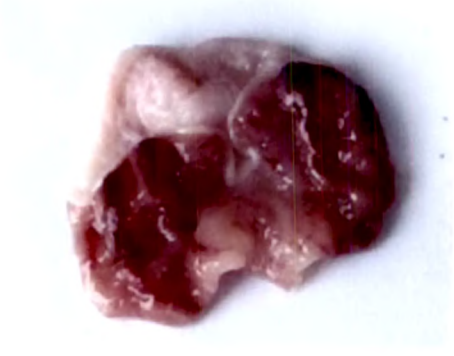


Fig 4.28 (A)

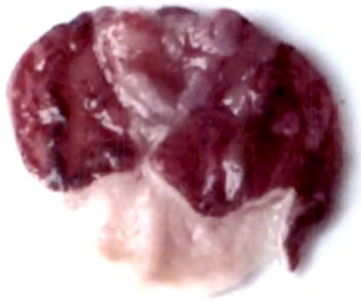


Fig 4.28 (B)

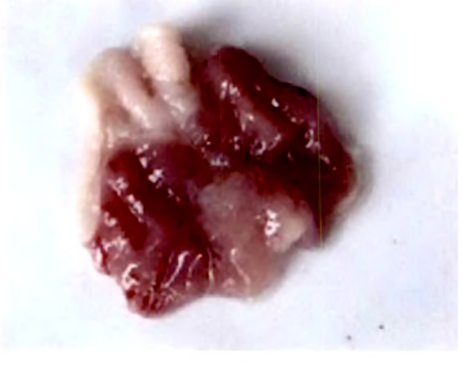


Fig 4.28 (C)

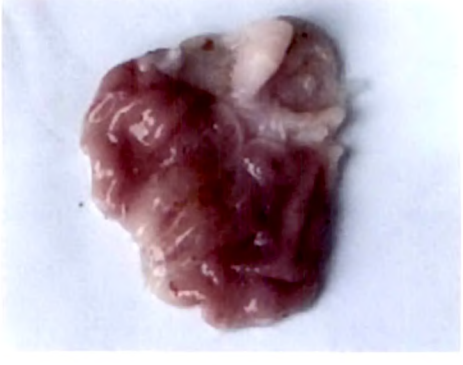


Fig 4.28 (D)

4.2.2.2 TISSUE PARAMETERS

4.2.2.2.1 Effect on lipid peroxidation

Ethanol treatment (Group 2) to rats led to a significant ($p<0.001$) increase in lipid peroxidation or MDA content as compared to the normal control (Group 1).

Administration of DHC-1 (125, 250, 500 and 1000 mg/kg) followed by ethanol treatment significantly ($p<0.001$) lowered the MDA content in stomach as compared to the ethanol control group (Table 4.9).

Administration of Activit at the doses of 125 mg/kg and 250 mg/kg followed by ethanol treatment did not produce any significant lowering of MDA content; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$) reduced the MDA content when compared with ethanol control group (Table 4.10).

Administration of Pepticare (125 mg/kg) followed by ethanol treatment did not alter the MDA level as compared to ethanol control group, but produced a significant decrease in lipid peroxidation at the doses of 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to ethanol treated rats (Table 4.11).

Administration of Normacid at the doses of 125 mg/kg and 250 mg/kg followed by ethanol treatment did not produce any significant change in the levels of MDA; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$) reduced the MDA content as compared to ethanol control group (Table 4.12).

4.2.2.2.2 Effect on endogenous antioxidants

4.2.2.2.2.1 Effect on Superoxide dismutase

Ethanol treatment (Group 2) reduced the SOD activity significantly ($p<0.001$) in stomach of rats as compared to normal control group.

Administration of DHC-1 at all the four doses (125, 250, 500 and 1000 mg/kg) followed by ethanol treatment significantly ($p<0.001$) increased the SOD content in stomach as compared to the ethanol control group (Table 4.9).

Administration of Activit (125 mg/kg) followed by ethanol treatment did not produce any significant rise in SOD level; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly increased the SOD levels in stomach when compared with ethanol control group (Table 4.10).

Administration of Pepticare (125 mg/kg) followed by ethanol treatment did not alter the SOD level as compared to ethanol control group, but produced a significant increase in level of SOD at the doses of 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to ethanol treated rats (Table 4.11).

Administration of Normacid at the doses of 125 mg/kg and 250 mg/kg followed by ethanol treatment did not produce any significant change in the levels of SOD; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased the SOD activity as compared to ethanol control group (Table 4.12).

4.2.2.2.2.2 Effect on Catalase

The catalase activity in ethanol treated control group (Group 2) was significantly ($p<0.001$) reduced as compared to normal control (Group 1).

Administration of DHC-1, Activit and Pepticare, at the dose of 125 mg/kg followed by ethanol treatment did not alter the catalase activity as compared to ethanol control group, but produced a significant increase at the doses of 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to ethanol treated rats (Tables 4.9, 4.10 and 4.11).

Administration of Normacid (125 mg/kg and 250 mg/kg) followed by ethanol treatment did not produce any significant change in the levels of catalase; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$) increased the catalase activity as compared to ethanol control group (Table 4.12).

4.2.2.2.2.3 Effect on Reduced glutathione

A significant ($p<0.001$) reduction in reduced glutathione concentration was observed in ethanol treated rats (Group 2) as compared to normal control (Group 1).

Administration of DHC-1 (125 mg/kg and 250 mg/kg) followed by ethanol treatment did not produce any significant increase in GSH content; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased the GSH content as compared to ethanol control group (Table 4.9).

Administration of Activit (125 mg/kg) followed by ethanol treatment did not result in any significant rise in GSH content of stomach; but at the higher doses, namely 250, 500 and 1000 mg/kg it significantly ($p<0.001$) increased the GSH levels as compared to ethanol control group (Table 4.10).

Administration of Pepticare (125 mg/kg) followed by ethanol treatment did not alter the concentration of GSH as compared to ethanol control group, but produced a significant increase at the doses of 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to ethanol treated rats (Table 4.11).

Administration of Normacid (125 mg/kg) followed by ethanol treatment did not produce any significant rise in GSH content of stomach; but at the higher doses, namely 250, 500 and 1000 mg/kg it significantly ($p<0.001$) increased the GSH levels when compared with ethanol control group (Table 4.12).

Table 4.9: Effect of DHC-1 on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the stomach of ethanol-treated rats.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.45 ± 0.24	3.31 ± 0.13	5.64 ± 0.32	8.27 ± 0.22
Group 2	6.75 ± 0.72***	0.79 ± 0.17***	2.23 ± 0.14***	5.12 ± 0.21***
Group 3	2.20 ± 0.13***	0.98 ± 3.03NS	3.68 ± 0.04***	5.95 ± 1.17NS
Group 4	1.86 ± 0.03***	1.28 ± 3.78NS	5.58 ± 0.54***	6.03 ± 0.83*
Group 5	1.69 ± 0.08***	2.26 ± 4.10**	6.38 ± 0.79***	6.68 ± 1.55***
Group 6	1.43 ± 0.08***	4.65 ± 6.25***	8.05 ± 1.25***	7.68 ± 1.13***
F value	34.562	20.584	140.94	30.168
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: DHC-1 (125 mg/kg, p.o.) followed by ethanol treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by ethanol treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by ethanol treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.10: Effect of Activit on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the stomach of ethanol-treated rats.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.45 ± 0.24	3.31 ± 0.13	5.64 ± 0.32	8.27 ± 0.22
Group 2	6.75 ± 0.72***	0.79 ± 0.17***	2.23 ± 0.14***	5.12 ± 0.21***
Group 3	6.46 ± 0.26NS	0.91 ± 0.10 NS	2.29 ± 0.15 NS	5.13 ± 0.15 NS
Group 4	5.90 ± 0.12NS	2.20 ± 0.15***	3.16 ± 0.23*	5.98 ± 0.13*
Group 5	4.16 ± 0.17***	2.77 ± 0.18***	3.84 ± 0.14***	6.81 ± 0.16***
Group 6	3.96 ± 0.16***	3.14 ± 0.15***	4.98 ± 0.15***	7.43 ± 0.18***
F value	17.128	53.734	49.095	50.473
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: Activit (125 mg/kg, p.o.) followed by ethanol treatment

Group 4: Activit (250 mg/kg, p.o.) followed by ethanol treatment

Group 5: Activit (500 mg/kg, p.o.) followed by ethanol treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS - Non Significant

Table 4.11: Effect of Pepticare on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the stomach of ethanol-treated rats.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.45 ± 0.24	3.31 ± 0.13	5.64 ± 0.32	8.27 ± 0.22
Group 2	6.75 ± 0.72***	0.79 ± 0.17***	2.23 ± 0.14***	5.12 ± 0.21***
Group 3	5.93 ± 0.33NS	1.13 ± 0.16NS	2.64 ± 0.14NS	5.45 ± 0.19NS
Group 4	4.52 ± 0.27**	2.87 ± 0.40**	3.70 ± 0.17**	6.21 ± 0.25*
Group 5	3.58 ± 0.28***	3.35 ± 0.45***	4.27 ± 0.36***	6.96 ± 0.29***
Group 6	3.24 ± 0.13***	4.56 ± 0.58***	5.37 ± 0.19***	7.80 ± 0.20***
F value	14.659	20.584	34.032	30.168
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: Pepticare (125 mg/kg, p.o.) followed by ethanol treatment

Group 4: Pepticare (250 mg/kg, p.o.) followed by ethanol treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by ethanol treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.12: Effect of Normacid on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the stomach of ethanol-treated rats.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.45 ± 0.24	3.31 ± 0.13	5.64 ± 0.32	8.27 ± 0.22
Group 2	6.75 ± 0.72***	0.79 ± 0.17***	2.23 ± 0.14***	5.12 ± 0.21***
Group 3	6.40 ± 0.44NS	1.14 ± 0.08 NS	2.24 ± 0.12 NS	5.02 ± 0.17 NS
Group 4	5.79 ± 0.22 NS	2.72 ± 0.18***	3.13 ± 0.25 NS	5.72 ± 0.27 NS
Group 5	3.97 ± 0.29***	3.21 ± 0.08***	3.47 ± 0.13**	6.94 ± 0.08***
Group 6	3.97 ± 0.08***	3.96 ± 0.32***	4.32 ± 0.16***	7.23 ± 0.13***
F value	13.524	49.985	42.458	45.802
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: Normacid (125 mg/kg, p.o.) followed by ethanol treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by ethanol treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by ethanol treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

4.2.2.2.3 Effect on membrane bound enzymes

4.2.2.2.3.1 Effect on Sodium Potassium ATPase

In the stomach of ethanol-treated rats (Group 2) the activity of Na^+K^+ATPase enzyme was significantly ($p<0.001$) reduced as compared to the normal control (Group 1).

Administration of DHC-1 at all the four doses (125, 250, 500 and 1000 mg/kg) followed by ethanol treatment significantly ($p<0.001$) increased the activity of Na^+K^+ATPase in stomach as compared to the ethanol control group (Table 4.13).

Administration of Activit and Pepticare, at the doses of 125 mg/kg and 250 mg/kg followed by ethanol treatment did not produce any significant increase in Na^+K^+ATPase; but at the higher doses, namely 500 mg/kg (Group 5) and 1000 mg/kg (Group 6) they significantly ($p<0.001$) increased the level of Na^+K^+ATPase enzyme as compared to ethanol control group (Table 4.14 and 4.15).

Administration of Normacid (125 mg/kg) followed by ethanol treatment did not produce any significant rise in the level of Na^+K^+ATPase, but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly increased the Na^+K^+ATPase levels when compared with ethanol control group (Table 4.16).

4.2.2.2.3.2 Effect on Calcium ATPase

Ethanol treatment (Group 2) led to a significant ($p<0.001$) decrease in the Ca^{2+}ATPase activity when compared with the control group (Group 1).

Administration of DHC-1 followed by ethanol treatment significantly ($p<0.001$) enhanced the Ca^{2+}ATPase activity at all the four doses of 125, 250, 500 and 1000 mg/kg as compared to ethanol control group (Table 4.13).

Administration of Activit, at the highest dose i.e. 1000 mg/kg followed by ethanol treatment, increased Ca^{2+}ATPase activity significantly ($p<0.01$) as compared to ethanol control group, but did not affect the same at the lower doses of 125, 250 and 500 mg/kg (Table 4.14).

Administration of Pepticare followed by ethanol treatment did not alter the levels of Ca^{2+}ATPase enzyme at the doses of 125, 250 and 500 mg/kg, but at the highest dose of 1000 mg/kg it significantly ($p<0.001$) increased the Ca^{2+}ATPase activity when compared with ethanol control group (Table 4.15).

Administration of Normacid at the doses of 125 mg/kg and 250 mg/kg followed by ethanol treatment did not produce any significant increase in Ca^{2+}ATPase; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) it significantly increased the level of Ca^{2+}ATPase enzyme as compared to ethanol control group (Table 4.16).

4.2.2.2.3.3 Effect on Magnesium ATPase

In the stomach of ethanol-treated rats (Group 2) a significant ($p<0.001$) decrease in the Mg^{2+}ATPase activity was observed as compared to the control group (Group 1).

Administration of DHC-1 followed by ethanol treatment produced a significant ($p<0.001$) increase in the activity of Mg^{2+}ATPase at the doses of 125, 250, 500 and 1000 mg/kg as compared to ethanol control group (Table 4.13).

Administration of Activit, Pepticare and Normacid followed by ethanol treatment produced a significant rise in activity of Mg^{2+}ATPase enzyme at the doses of 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to ethanol-treated rats, but produced no significant effect at the lower dose of 125 mg/kg (Tables 4.14, 4.15 and 4.16).

Table 4.13: Effect of DHC-1 on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the stomach of ethanol-treated rats.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.29 ± 0.18	3.65 ± 0.30	3.52 ± 0.20
Group 2	2.03 ± 0.11***	1.50 ± 0.21***	1.49 ± 0.13***
Group 3	8.45 ± 0.53***	3.00 ± 0.11***	2.75 ± 0.17***
Group 4	9.80 ± 0.83***	3.17 ± 0.18***	3.28 ± 0.15***
Group 5	10.93 ± 0.59***	3.23 ± 0.27***	3.20 ± 0.29***
Group 6	11.23 ± 0.64***	3.30 ± 0.22***	3.56 ± 0.25**
F value	756.39	15.373	54.396
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: DHC-1 (125 mg/kg, p.o.) followed by ethanol treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by ethanol treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by ethanol treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.14: Effect of Activit on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the stomach of ethanol-treated rats.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.29 ± 0.18	3.65 ± 0.30	3.52 ± 0.20
Group 2	2.03 ± 0.11***	1.50 ± 0.21***	1.49 ± 0.13***
Group 3	2.05 ± 0.06 NS	1.43 ± 0.15 NS	1.78 ± 0.15 NS
Group 4	2.34 ± 0.13 NS	1.79 ± 0.20 NS	2.33 ± 0.09**
Group 5	4.18 ± 0.17***	1.86 ± 0.13 NS	3.06 ± 0.11***
Group 6	5.27 ± 0.03***	2.78 ± 0.18**	3.22 ± 0.11***
F value	155.14	18.813	37.081
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: Activit (125 mg/kg, p.o.) followed by ethanol treatment

Group 4: Activit (250 mg/kg, p.o.) followed by ethanol treatment

Group 5: Activit (500 mg/kg, p.o.) followed by ethanol treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.15: Effect of Pepticare on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the stomach of ethanol-treated rats.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.29 ± 0.18	3.65 ± 0.30	3.52 ± 0.20
Group 2	2.03 ± 0.11***	1.50 ± 0.21***	1.49 ± 0.13***
Group 3	2.13 ± 0.06NS	1.54 ± 0.12NS	1.73 ± 0.12NS
Group 4	2.38 ± 0.11NS	1.76 ± 0.14NS	2.52 ± 0.15**
Group 5	4.33 ± 0.22***	1.90 ± 0.09NS	3.28 ± 0.13***
Group 6	5.49 ± 0.08***	2.87 ± 0.05***	3.46 ± 0.17***
F value	142.04	25.666	34.955
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: Pepticare (125 mg/kg, p.o.) followed by ethanol treatment

Group 4: Pepticare (250 mg/kg, p.o.) followed by ethanol treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by ethanol treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.16: Effect of Normacid on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the stomach of ethanol-treated rats.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.29 ± 0.18	3.65 ± 0.30	3.52 ± 0.20
Group 2	2.03 ± 0.11***	1.50 ± 0.21***	1.49 ± 0.13***
Group 3	2.13 ± 0.05 NS	1.75 ± 0.09 NS	1.91 ± 0.11 NS
Group 4	2.57 ± 0.08*	2.18 ± 0.08 NS	2.39 ± 0.09**
Group 5	4.21 ± 0.10***	2.46 ± 0.17*	3.04 ± 0.11***
Group 6	5.12 ± 0.11***	3.01 ± 0.08***	3.23 ± 0.12***
F value	174.16	21.341	37.669
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Ethanol control (96%, 5ml/kg, p.o.)

Group 3: Normacid (125 mg/kg, p.o.) followed by ethanol treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by ethanol treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by ethanol treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by ethanol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

SET 3:

ISOPROTERENOL-INDUCED MYOCARDIAL INFARCTION

4.2.3 ISOPROTERENOL-INDUCED MYOCARDIAL INFARCTION

4.2.3.1 SERUM PARAMETERS

4.2.3.1.1 Effect of drugs on creatine kinase

Isoproterenol (25 mg/kg, s.c. twice at an interval of 24 hrs) produced a significant ($p<0.001$) increase in the activity of creatine kinase in serum of rats (Group 2) as compared to control group (Group 1).

Administration of DHC-1 (125 mg/kg) followed by isoproterenol treatment did not produce any significant reduction in the level of serum creatine kinase; but at the higher doses, namely 250, 500 and 1000 mg/kg it significantly ($p<0.001$) decreased these levels when compared with isoproterenol-treated control group (Fig. 4.29).

Administration of Activit followed by isoproterenol treatment significantly decreased the levels of creatine kinase at all the doses namely, 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.01$) as compared to isoproterenol control (Fig. 4.31).

Administration of Pepticare at the doses of 125 mg/kg and 250 mg/kg followed by isoproterenol treatment did not produce any significant decrease in creatine kinase; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.01$) decreased the level of creatine kinase enzyme as compared to isoproterenol-treated control group (Fig. 4.33).

Administration of Normacid (125 mg/kg) followed by isoproterenol treatment did not produce any significant reduction in the level of serum creatine kinase; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly decreased these levels as compared to isoproterenol-treated control group (Fig. 4.35).

4.2.3.1.2 Effect of drugs on Lactate dehydrogenase (LDH)

Treatment with isoproterenol (Group 2) led to a significant ($p<0.001$) increase in LDH level as compared to control group (Group 1).

Administration of DHC-1 and Activit, at the doses of 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg

($p<0.001$) followed by isoproterenol treatment resulted in a significant lowering of the LDH level as compared to isoproterenol-treated control group (Fig. 4.29 and Fig. 4.31).

Administration of Pepticare (125 mg/kg) followed by isoproterenol treatment did not produce any significant change in the level of serum LDH; but at the higher doses of 250, 500 and 1000 mg/kg it significantly ($p<0.001$) decreased these levels as compared to isoproterenol-treated control group (Fig. 4.33).

Administration of Normacid followed by isoproterenol treatment also significantly reduced the levels of LDH at all the doses namely, 125 mg/kg ($p<0.01$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to isoproterenol-treated control group (Fig. 4.35).

4.2.3.1.3 Effect of drugs on uric acid

Isoproterenol treatment (Group 2) led to a significant ($p<0.001$) increase in uric acid content as compared to control group (Group 1).

Administration of DHC-1 (125 mg/kg) followed by isoproterenol treatment did not produce any significant change in the level of serum uric acid; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) it significantly decreased these levels as compared to isoproterenol-treated control group (Fig. 4.30).

Administration of Activit at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not produce any significant reduction in uric acid levels; but at the higher doses, namely 500 and 1000 mg/kg it significantly ($p<0.05$) decreased the level of uric acid as compared to isoproterenol-treated control group (Fig. 4.32).

Administration of Pepticare (125 mg/kg) followed by isoproterenol treatment did not produce any significant change in the level of uric acid; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly decreased these levels when compared with isoproterenol-treated control group (Fig. 4.34).

Administration of Normacid (125, 250, 500 and 1000 mg/kg) followed by isoproterenol treatment produced a significant ($p<0.001$)

decrease in the level of LDH as compared to isoproterenol control (Fig. 4.36).

4.2.3.1.4 Effect of drugs on SGOT

In rats of group 2, isoproterenol treatment led to a significant ($p<0.001$) increase in level of SGOT as compared to the control group (Group 1).

Administration of DHC-1 (125 mg/kg) followed by isoproterenol treatment did not produce any significant change in the level of SGOT; but at the higher doses, namely 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly decreased these levels as compared to isoproterenol-treated control group (Fig. 4.30).

Administration of Activit followed by isoproterenol treatment also significantly reduced the levels of SGOT at all the doses namely, 125 mg/kg ($p<0.01$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to isoproterenol control group (Fig. 4.32).

Administration of Pepticare (125 mg/kg) followed by isoproterenol treatment did not produce any significant change in the level of SGOT; but at the higher doses, namely 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly decreased these levels as compared to isoproterenol-treated control group (Fig. 4.34).

Administration of Normacid at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not produce any significant reduction in SGOT levels; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) it significantly decreased the level of SGOT as compared to isoproterenol control (Fig. 4.36).

Fig. 4.29. Effect of DHC-1 on the serum levels of creatine kinase (CK) and Lactate dehydrogenase (LDH) in isoproterenol-induced myocardial infarction in rats.

Fig. 4.30. Effect of DHC-1 on the serum levels of uric acid and GOT in isoproterenol-induced myocardial infarction in rats.

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: DHC-1 (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$, $^{***}p<0.001$; NS = Non Significant

Fig. 4.29.

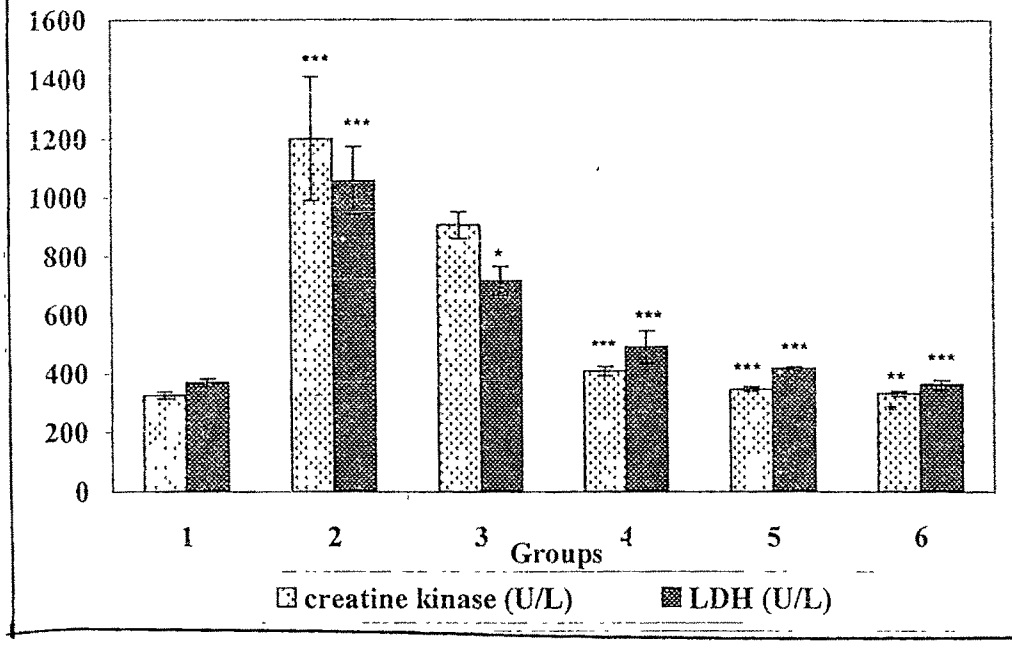


Fig. 4.30.

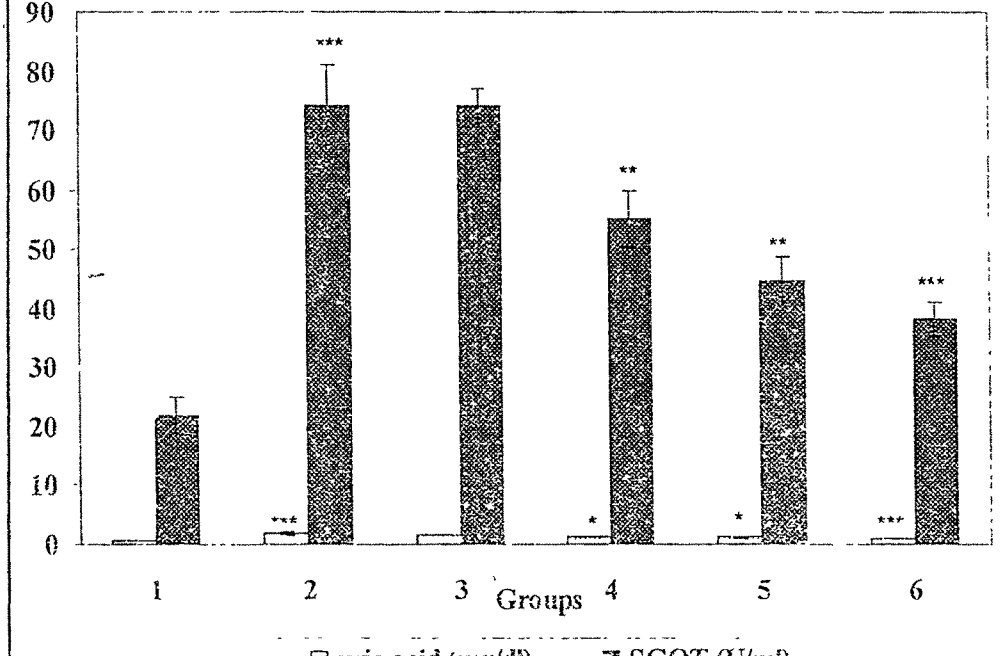


Fig. 4.31. Effect of Activit on the serum levels of creatine kinase (CK) and Lactate dehydrogenase (LDH) in isoproterenol-induced myocardial infarction in rats.

Fig. 4.32. Effect of Activit on the serum levels of uric acid and GOT in isoproterenol-induced myocardial infarction in rats.

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: Activit (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: Activit (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: Activit (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.31.

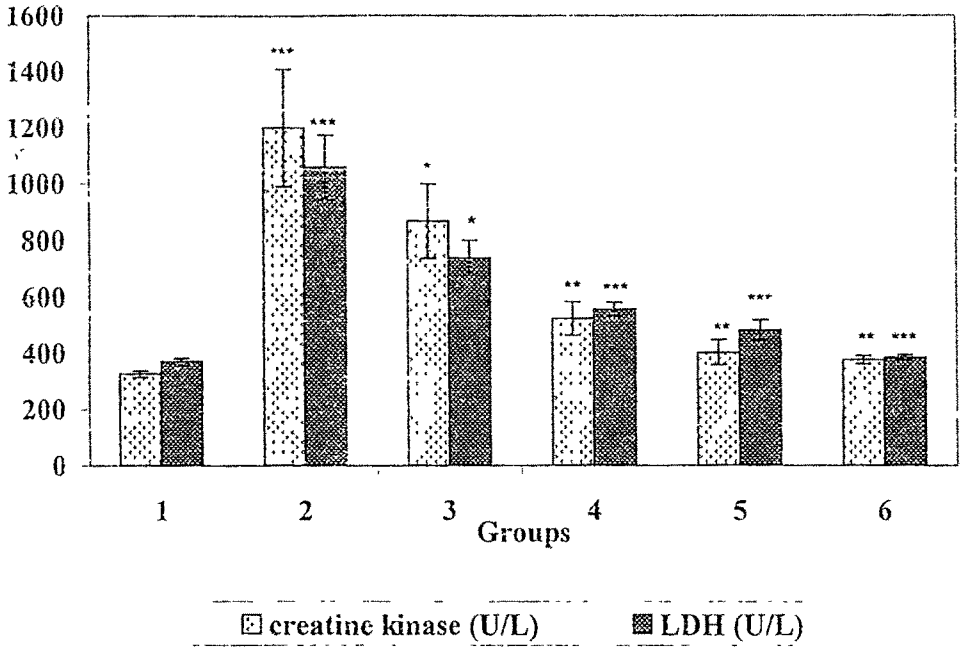


Fig. 4.32.

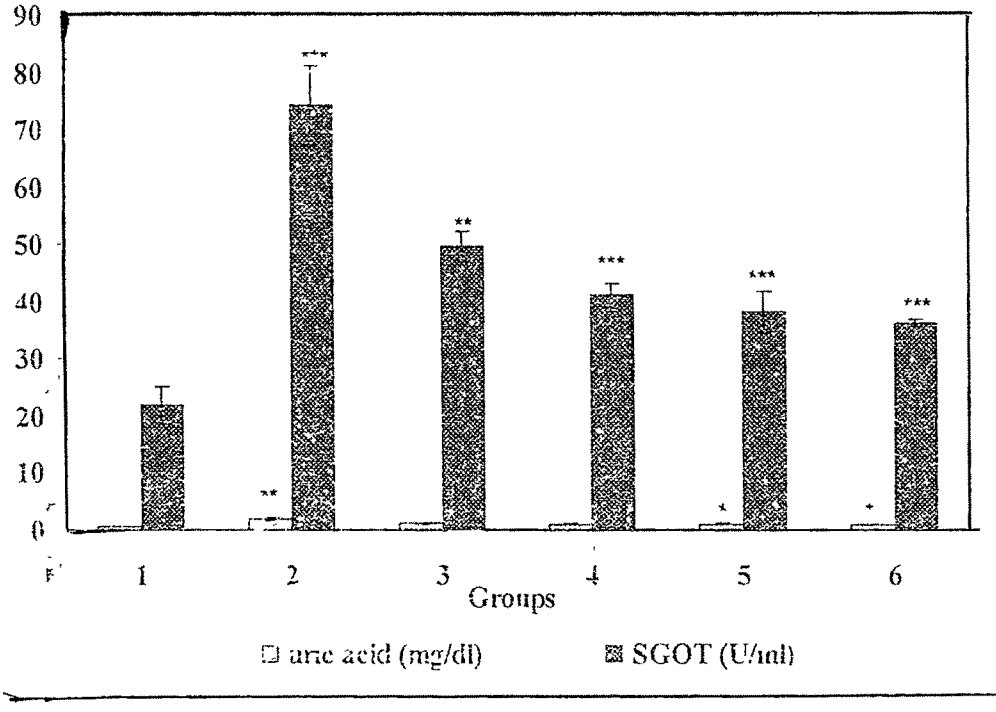


Fig. 4.33. Effect of Pepticare on the serum levels of creatine kinase (CK) and Lactate dehydrogenase (LDH) in isoproterenol-induced myocardial infarction in rats.

Fig. 4.34. Effect of Pepticare on the serum levels of uric acid and GOT in isoproterenol-induced myocardial infarction in rats.

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: Pepticare (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: Pepticare (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.33.

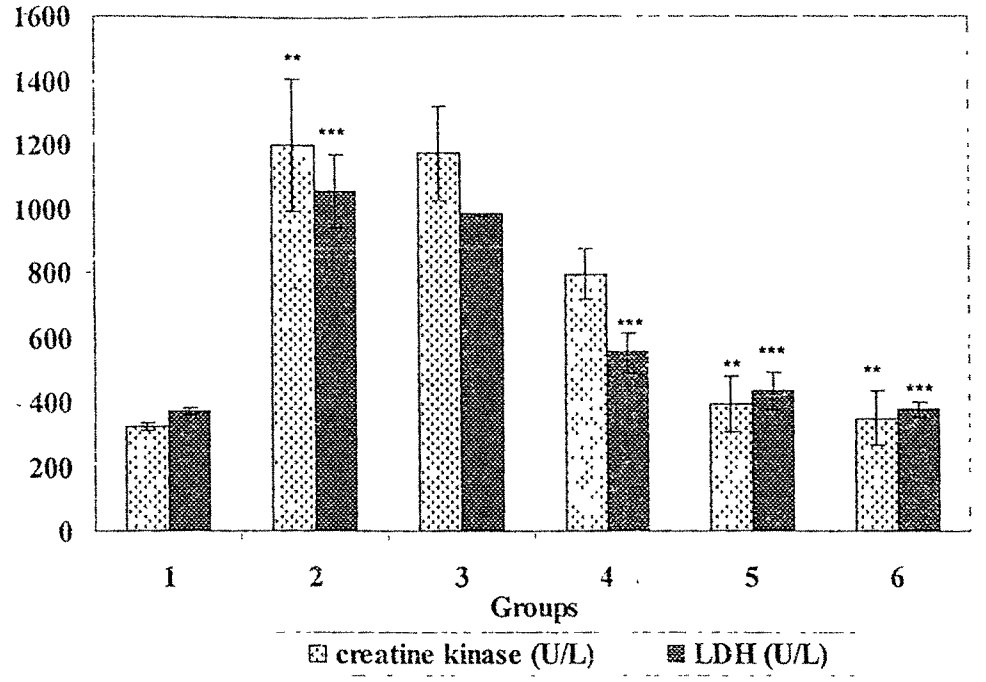


Fig. 4.34.

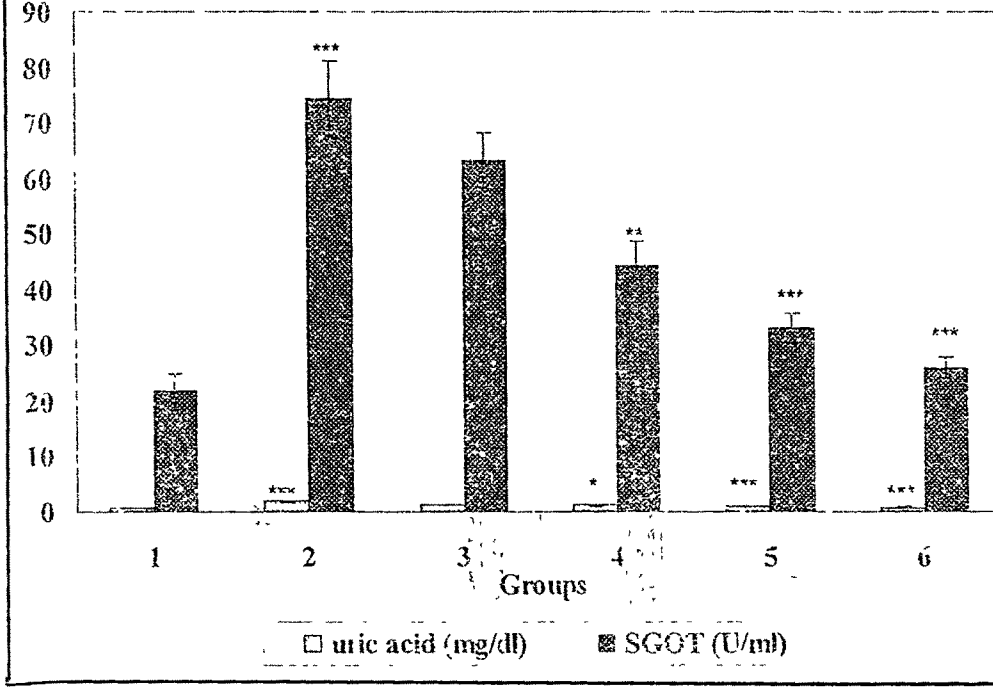


Fig. 4.35. Effect of Normacid on the serum levels of creatine kinase (CK) and Lactate dehydrogenase (LDH) in isoproterenol-induced myocardial infarction in rats.

Fig. 4.36. Effect of Normacid on the serum levels of uric acid and GOT in isoproterenol-induced myocardial infarction in rats.

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: Normacid (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.35.

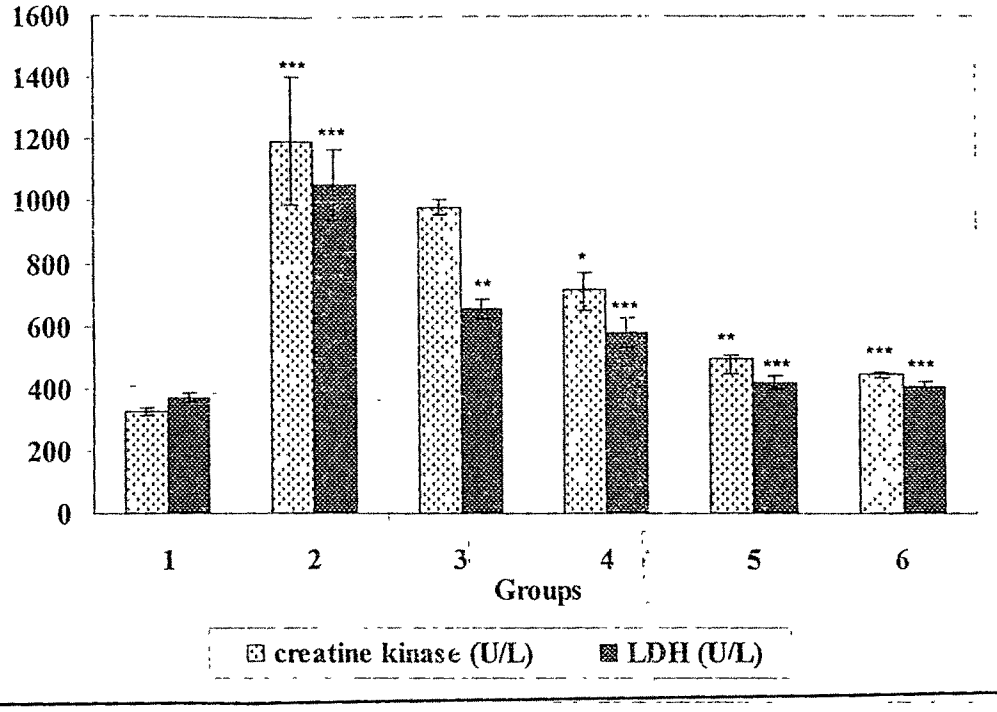
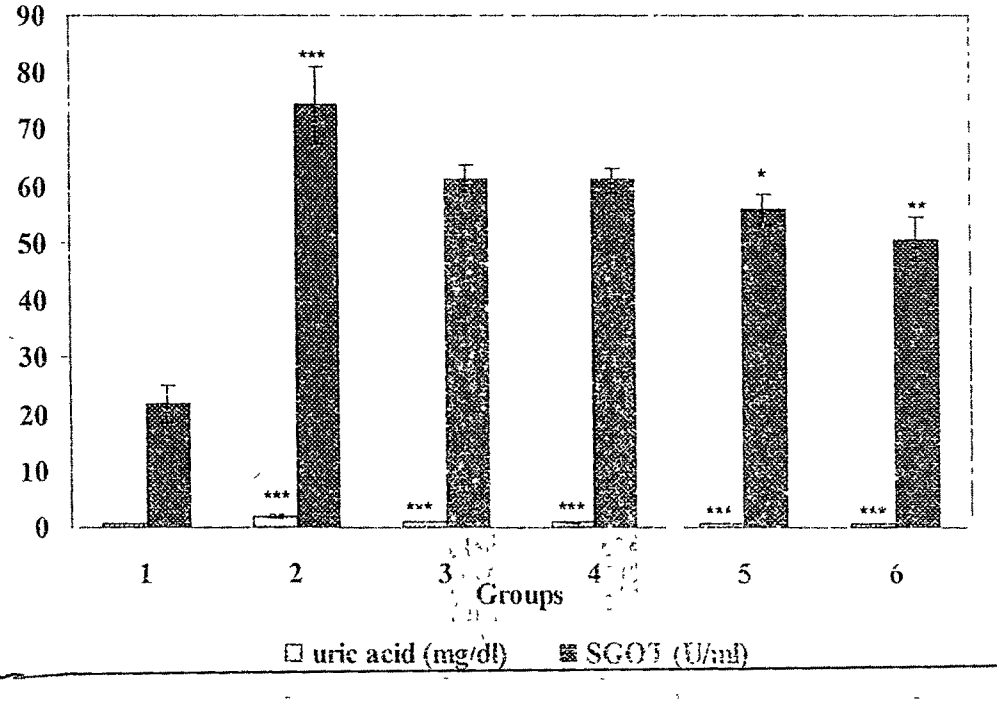


Fig. 4.36.



4.2.3.2 TISSUE PARAMETERS

4.2.3.2.1 Effect on lipid peroxidation

Isoproterenol treatment (Group 2) to rats led to a significant ($p<0.001$) increase in lipid peroxidation or MDA content in heart of rats as compared to the control group (Group 1).

Administration of DHC-1 followed by isoproterenol treatment significantly reduced the levels of MDA at all the doses namely, 125 mg/kg ($p<0.01$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to isoproterenol control group (Table 4.17).

Administration of Activit followed by isoproterenol treatment produced a significant ($p<0.001$) decrease in the MDA content at all the four doses namely, 125 mg/kg, 250 mg/kg, 500 mg/kg and 1000 mg/kg as compared to isoproterenol control (Table 4.18).

Administration of Pepticare (125 mg/kg) followed by isoproterenol treatment did not produce any significant change in the level of lipid peroxidation (MDA content); but at the higher doses, namely 250, 500 and 1000 mg/kg it significantly ($p<0.001$) decreased these levels when compared with isoproterenol control (Table 4.19).

Administration of Normacid (125 mg/kg) followed by isoproterenol treatment did not produce any significant change in the level of MDA; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly decreased these levels as compared to isoproterenol control (Table 4.20).

4.2.3.2.2 Effect on endogenous antioxidants

4.2.3.2.2.1 Effect on Superoxide dismutase

Isoproterenol treatment (Group 2) reduced the SOD activity significantly ($p<0.01$) in heart of rats as compared to control group 1.

Administration of DHC-1 and Pepticare, at the doses of 125, 250 and 500 mg/kg followed by isoproterenol treatment did not affect the SOD content in heart as compared to the isoproterenol control group. At the

higher dose i.e. 1000 mg/kg, the drugs led to a significant ($p<0.01$) rise in SOD content as compared to isoproterenol control (Tables 4.17 and 4.19).

Similarly, administration of Activit and Normacid, followed by isoproterenol treatment also did not affect the SOD levels at the lower doses, namely 125 mg/kg, 250 mg/kg and 500 mg/kg; but resulted in a significant ($p<0.05$) rise in SOD at the dose of 1000 mg/kg as compared to isoproterenol control (Tables 4.18 and 4.20).

4.2.3.2.2.2 Effect on Catalase

The catalase activity in isoproterenol treated control group (Group 2) was significantly ($p<0.001$) reduced as compared to control group (Group 1).

Administration of DHC-1 (125 mg/kg) followed by isoproterenol treatment did not produce any significant change in the level of catalase enzyme; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly increased these levels as compared to isoproterenol control (Table 4.17).

Administration of Activit and Pepticare at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not produce any change in level of catalase; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) they significantly increased the level of catalase enzyme as compared to isoproterenol control (Tables 4.18 and 4.19).

Administration of Normacid (125 and 250 mg/kg) followed by isoproterenol treatment did not produce any significant change in catalase activity; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$) increased the level of catalase enzyme as compared to isoproterenol control (Table 4.20).

4.2.3.2.1.3 Effect on Reduced glutathione

A significant ($p<0.001$) reduction in reduced glutathione concentration was observed in isoproterenol treated rats (Group 2) as compared to control group (Group 1).

Administration of DHC-1 and Pepticare, at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not produce any significant

increase in GSH content; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) they significantly increased the GSH content as compared to isoproterenol control (Tables 4.17 and 4.19).

Administration of Activit (125 mg/kg) followed by isoproterenol treatment did not alter the concentration of GSH in heart as compared to isoproterenol-treated control group, but produced a significant increase at the doses of 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) as compared to isoproterenol treated rats (Group 2) (Table 4.18).

Administration of Normacid at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not produce any significant change in GSH content of heart; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$) increased the level of GSH as compared to isoproterenol control (Table 4.20).

Table 4.17: Effect of DHC-1 on the levels of lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the heart of rats in isoproterenol-induced myocardial infarction.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.43 ± 0.15	3.27 ± 0.55	2.77 ± 0.31	4.61 ± 0.05
Group 2	7.15 ± 0.54***	0.61 ± 0.09***	1.69 ± 0.08**	1.87 ± 0.14***
Group 3	4.92 ± 0.40**	0.98 ± 0.13 NS	1.86 ± 0.06 NS	2.06 ± 0.15 NS
Group 4	4.18 ± 0.36***	1.87 ± 0.16 NS	2.01 ± 0.08 NS	2.60 ± 0.18*
Group 5	3.57 ± 0.29***	2.72 ± 0.17**	2.21 ± 0.06 NS	3.68 ± 0.18***
Group 6	3.49 ± 0.34***	3.69 ± 0.30***	2.63 ± 0.08**	4.27 ± 0.15***
F value	15.502	19.879	9.071	62.217
P value	<0.0001	<0.0001	0.0009	<0.0001

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: DHC-1 (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.18: Effect of Activit on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the heart of rats in isoproterenol-induced myocardial infarction.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.43 ± 0.15	3.27 ± 0.55	2.77 ± 0.31	4.61 ± 0.05
Group 2	7.15 ± 0.54**	0.61 ± 0.09***	1.69 ± 0.08*	1.87 ± 0.14***
Group 3	4.46 ± 0.53***	1.97 ± 0.20 NS	1.87 ± 0.12 NS	2.07 ± 0.08 NS
Group 4	3.66 ± 0.73***	4.65 ± 0.69*	2.04 ± 0.37 NS	2.61 ± 0.18 NS
Group 5	3.25 ± 0.43***	6.03 ± 1.23**	2.29 ± 0.04 NS	3.10 ± 0.09**
Group 6	2.24 ± 0.40***	7.33 ± 0.62***	2.84 ± 0.18*	3.83 ± 0.34***
F value	20.951	13.942	4.598	35.707
P value	<0.0001	<0.0001	0.0142	<0.0001

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: Activit (125 mg/kg, p.o) followed by isoproterenol treatment

Group 4: Activit (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: Activit (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.19: Effect of Pepticare on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the heart of rats in isoproterenol-induced myocardial infarction.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.43 ± 0.15	3.27 ± 0.55	2.77 ± 0.31	4.61 ± 0.05
Group 2	7.15 ± 0.54***	0.61 ± 0.09***	1.69 ± 0.08**	1.87 ± 0.14***
Group 3	5.88 ± 0.42NS	0.83 ± 0.20NS	1.78 ± 0.07NS	2.15 ± 0.10NS
Group 4	4.19 ± 0.53***	1.50 ± 0.18NS	1.95 ± 0.11NS	2.49 ± 0.15NS
Group 5	3.99 ± 0.07***	2.46 ± 0.14**	2.12 ± 0.05NS	3.04 ± 0.04**
Group 6	3.02 ± 0.06***	3.47 ± 0.16***	2.72 ± 0.19**	3.91 ± 0.29***
F value	19.211	21.150	8.270	50.050
P value	<0.0001	<0.0001	0.0014	<0.0001

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: Pepticare (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: Pepticare (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.20: Effect of Normacid on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the heart of rats in isoproterenol-induced myocardial infarction.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	3.43 ± 0.15	3.27 ± 0.55	2.77 ± 0.31	4.61 ± 0.05
Group 2	7.15 ± 0.54***	0.61 ± 0.09***	1.69 ± 0.08**	1.87 ± 0.14***
Group 3	6.72 ± 0.30NS	0.90 ± 0.03NS	1.75 ± 0.05 NS	2.05 ± 0.09 NS
Group 4	5.87 ± 0.11*	1.52 ± 0.13NS	1.94 ± 0.13 NS	2.26 ± 0.06 NS
Group 5	4.93 ± 0.09***	2.91 ± 0.07***	2.29 ± 0.06 NS	3.11 ± 0.08***
Group 6	4.55 ± 0.11***	3.03 ± 0.10***	2.64 ± 0.16*	3.95 ± 0.15***
F value	27.040	24.028	8.495	125.17
P value	<0.0001	<0.0001	0.0012	<0.0001

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: Normacid (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

4.2.3.2.3 Effect on membrane bound enzymes

4.2.3.2.3.1 Effect on Sodium Potassium ATPase

In the heart of isoproterenol-treated rats (Group 2) the activity of Na^+K^+ATPase enzyme was significantly ($p<0.001$) reduced as compared to the control group 1.

Administration of DHC-1 at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not affect the Na^+K^+ATPase levels; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$) increased the levels of Na^+K^+ATPase as compared to isoproterenol control (Table 4.21).

Similarly, administration of Activit, at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not produce any significant increase in Na^+K^+ATPase levels; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.01$) increased the levels of Na^+K^+ATPase as compared to isoproterenol-treated control group (Table 4.22).

Administration of Pepticare (125 mg/kg) followed by isoproterenol treatment did not produce any significant rise in the level of Na^+K^+ATPase of heart; but at the higher doses of 250, 500 and 1000 mg/kg it significantly ($p<0.01$) increased the Na^+K^+ATPase levels as compared to isoproterenol control (Table 4.23).

Administration of Normacid (125 mg/kg) followed by isoproterenol treatment did not produce any significant rise in the level of Na^+K^+ATPase; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased the Na^+K^+ATPase levels as compared to isoproterenol-treated control group (Table 4.24).

4.2.3.2.3.2 Effect on Calcium ATPase

Treatment with isoproterenol (Group 2) resulted in a significant ($p<0.05$) decrease in the Ca^{2+}ATPase activity as compared to the control group (Group 1).

Administration of DHC-1, Activit and Pepticare, at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not produce any

significant increase in Ca^{2+}ATPase levels; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) they significantly increased the levels of Ca^{2+}ATPase as compared to isoproterenol-treated control group (Tables 4.21, 4.22 and 4.23).

Similarly, administration of Normacid at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not produce any significant change in the levels of Ca^{2+}ATPase levels; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) it significantly increased the levels of Ca^{2+}ATPase as compared to isoproterenol control (Table 4.24).

4.2.3.2.3.3 Effect on Magnesium ATPase

In the heart of isoproterenol-treated rats (Group 2), the decrease in the Mg^{2+}ATPase activity was not significant as compared to the control group (Group 1).

Administration of DHC-1 followed by isoproterenol treatment did not produce any significant increase in the activity of Mg^{2+}ATPase at any of the four doses (125, 250, 500 and 1000 mg/kg) as compared to isoproterenol control (Table 4.21).

Administration of Activit (125 mg/kg) followed by isoproterenol treatment did not produce any significant rise in the level of Mg^{2+}ATPase of heart; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased the Mg^{2+}ATPase levels when compared with isoproterenol-treated control group (Table 4.22).

Administration of Pepticare and Normacid, at the doses of 125 and 250 mg/kg followed by isoproterenol treatment did not produce any significant change in the levels of Mg^{2+}ATPase levels; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) they significantly increased the levels of Mg^{2+}ATPase as compared to isoproterenol control (Tables 4.23 and 4.24).

Table 4.21: Effect of DHC-1 on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the heart of rats in isoproterenol-induced myocardial infarction.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.03 ± 0.30	2.76 ± 0.16	2.39 ± 0.06
Group 2	2.46 ± 0.21***	2.03 ± 0.20*	1.99 ± 0.15NS
Group 3	2.67 ± 0.16 NS	2.31 ± 0.10NS	1.97 ± 0.12 NS
Group 4	3.33 ± 0.07 NS	2.32 ± 0.05 NS	2.18 ± 0.08 NS
Group 5	4.12 ± 0.08***	2.98 ± 0.16**	2.40 ± 0.14 NS
Group 6	4.36 ± 0.22***	3.14 ± 0.08***	2.58 ± 0.20 NS
F value	28.022	10.497	3.516
P value	<0.0001	0.0005	0.0345

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: DHC-1 (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.22: Effect of Activit on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the heart of rats in isoproterenol-induced myocardial infarction.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.03 ± 0.30	2.76 ± 0.16	2.39 ± 0.06
Group 2	2.46 ± 0.21***	2.03 ± 0.20*	1.99 ± 0.15NS
Group 3	2.60 ± 0.20 NS	2.44 ± 0.16 NS	2.84 ± 0.24 NS
Group 4	3.26 ± 0.05 NS	2.57 ± 0.08 NS	3.12 ± 0.09*
Group 5	3.78 ± 0.04**	2.86 ± 0.03**	3.28 ± 0.12**
Group 6	3.80 ± 0.10**	3.13 ± 0.09***	3.63 ± 0.34***
F value	28.309	7.972	9.906
P value	<0.0001	0.0016	0.0006

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: Activit (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: Activit (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: Activit (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.23: Effect of Pepticare on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the heart of rats in isoproterenol-induced myocardial infarction.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.03 ± 0.30	2.76 ± 0.16	2.39 ± 0.06
Group 2	2.46 ± 0.21***	2.03 ± 0.20*	1.99 ± 0.15NS
Group 3	3.06 ± 0.18NS	2.43 ± 0.27NS	2.09 ± 0.12NS
Group 4	3.81 ± 0.11**	2.53 ± 0.12NS	2.30 ± 0.09NS
Group 5	4.02 ± 0.01**	2.73 ± 0.09**	3.01 ± 0.33*
Group 6	4.18 ± 0.33**	3.25 ± 0.27***	3.17 ± 0.20**
F value	16.959	8.220	7.155
P value	<0.0001	0.1197	0.0026

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: Pepticare (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: Pepticare (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.24: Effect of Normacid on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the heart of rats in isoproterenol-induced myocardial infarction.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	5.03 ± 0.30	2.76 ± 0.16	2.39 ± 0.06
Group 2	2.46 ± 0.21***	2.03 ± 0.20*	1.99 ± 0.15NS
Group 3	3.09 ± 0.23 NS	2.24 ± 0.16 NS	2.09 ± 0.09 NS
Group 4	3.67 ± 0.13*	2.49 ± 0.07 NS	2.37 ± 0.04 NS
Group 5	3.91 ± 0.19**	2.72 ± 0.09*	2.83 ± 0.34*
Group 6	4.44 ± 0.28***	2.95 ± 0.11**	3.20 ± 0.11**
F value	15.906	6.071	7.922
P value	<0.0001	0.0050	0.0017

Group 1: Normal control

Group 2: Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

Group 3: Normacid (125 mg/kg, p.o.) followed by isoproterenol treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by isoproterenol treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by isoproterenol treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by isoproterenol treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

4.2.3.3 HISTOPATHOLOGY

Fig 4.37(A) depicted the normal architecture of heart in rats of control group (group 1) on histological examination. The figure reflects the organized arrangement, well-defined boundaries and distinct bundles of myocardial fibres.

A massive necrosis of heart muscle fibres alongwith focal loss and marked fragmentation was observed in isoproterenol-administered group (Group 2). Disorganized arrangement with no well-defined boundaries or distinct bundles of myocardial fibres were observed. Nuclei were scattered, some were lost and some were pyknotic in nature [Fig. 4.37(B)].

Administration of DHC-1 exhibited decreased degree of necrosis with less fragmentation of fibres and well-defined boundaries or distinct bundles of myocardial fibres with increasing doses [Fig. 4.37(C)-4.37(F)].

The degree of myocardial damage in Activit treated group (125 mg/kg) was similar to isoproterenol control group in regard to morphological changes showing occasional loss and fragmentation of muscle fibres with disorganized arrangement [Fig 4.38(A)]. With increasing doses of Activit (250, 500 and 1000 mg/kg) there was lesser loss of myofibre. Bundles of myocardial fibres with more or less distinct boundaries were present [Fig 4.38(B) – Fig. 4.38 (D)].

Necrosis of heart muscle fibres alongwith focal loss and marked fragmentation similar to isoproterenol-administered group was observed in Pepticare treated groups (125 and 250 mg/kg). Disorganized arrangement with no well-defined boundaries or distinct bundles of myocardial fibres were observed. Nuclei were scattered and were pyknotic in nature [Fig. 4.39(A) and Fig. 4.39 (B)]. The degree of necrosis was reduced by the higher doses of Pepticare namely, 500 mg/kg [Fig. 4.39(C)] and 1000 mg/kg [Fig. 4.39(D)]. Nuclei were not lost and were not pyknotic in nature.

Pretreatment with Normacid (125, 250 and 500 mg/kg) also exhibited ill-defined boundaries of myocardial fibres but no pyknotic nuclei [Fig. 4.40(A)-4.40(C)]. Pretreatment with Normacid at the highest dose of 1000 mg/kg (Fig. 4.40 (D)] showed well-defined bundles of myocardial fibres with distinct normal nuclei.

Fig. 4.37. Photomicrographs showing effect of DHC-1 on the heart of isoproterenol-treated rats.

(Magnification 40 X)

A. Normal control

B. Isoproterenol control (25 mg/kg, s.c. twice at an interval of 24 hrs)

C. DHC-1 (125 mg/kg, p.o.)

D. DHC-1 (250 mg/kg, p.o.)

E. DHC-1 (500 mg/kg, p.o.)

F. DHC-1 (1000 mg/kg, p.o.)

Bundles of myocardial fibres

Boundaries of muscle fibres

Pyknotic nuclei

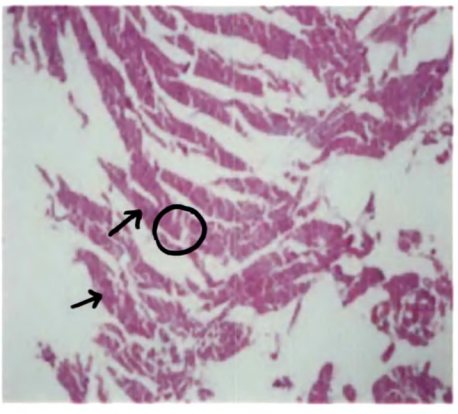


Fig. 4.37 (A)

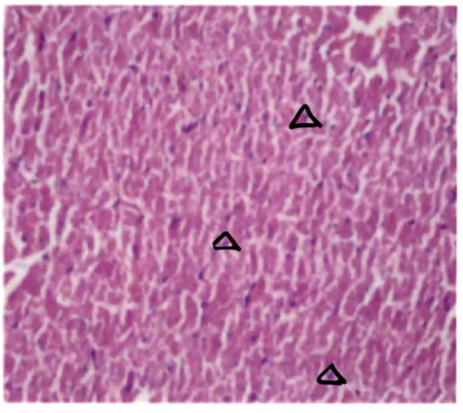


Fig. 4.37 (B)

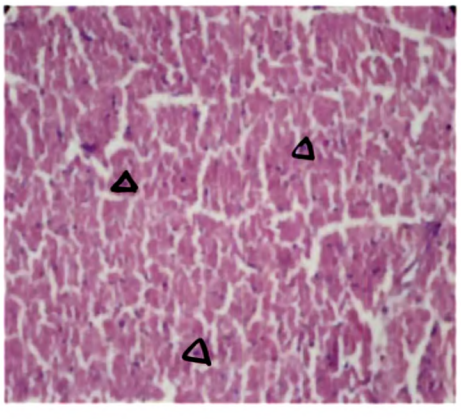


Fig. 4.37 (C)

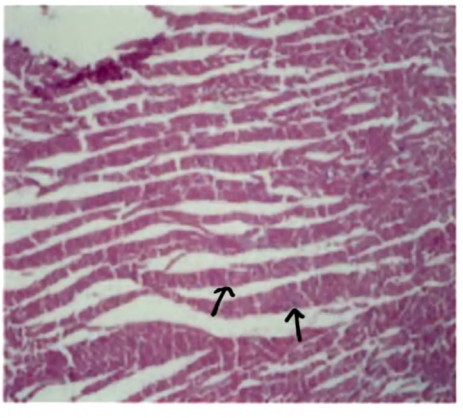


Fig. 4.37 (D)

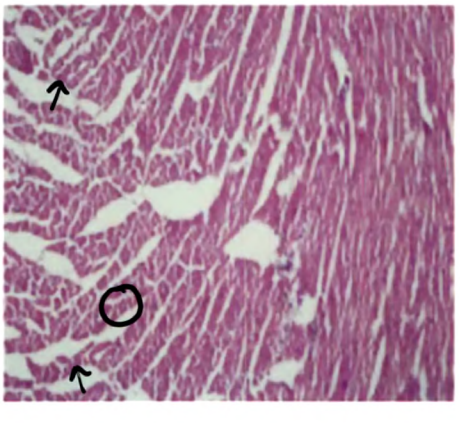


Fig. 4.37 (E)

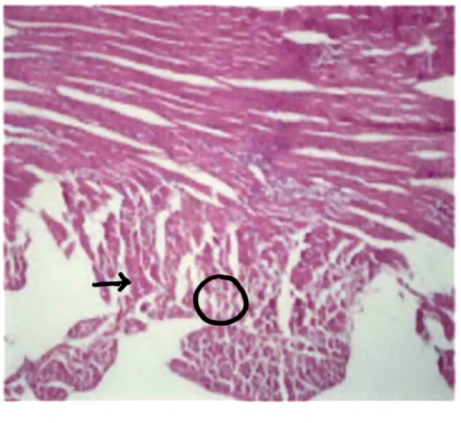


Fig. 4.37 (F)

Fig. 4.38. Photomicrographs showing effect of Activit on the heart of isoproterenol-treated rats.

(Magnification 40 X)

A. Activit (125 mg/kg, p.o.)

B. Activit (250 mg/kg, p.o.)

C. Activit (500 mg/kg, p.o.)

D. Activit (1000 mg/kg, p.o.)

○ **Bundles of myocardial fibres**

→ **Boundaries of muscle fibres**

△ **Pyknotic nuclei**

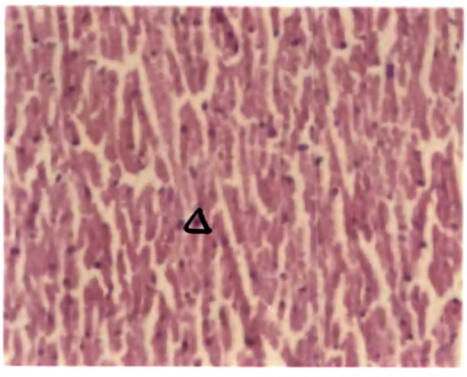


Fig. 4.38 (A)

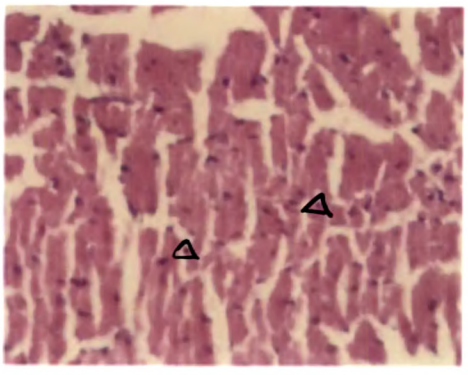


Fig. 4.38 (B)

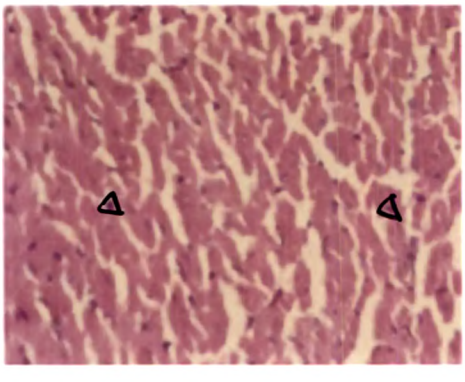


Fig. 4.38 (C)

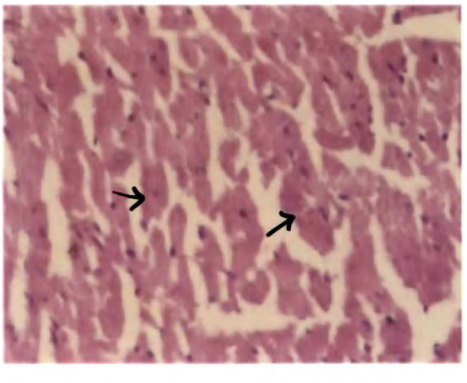


Fig. 4.38 (D)

Fig. 4.39. Photomicrographs showing effect of Pepticare on the heart of isoproterenol-treated rats.

(Magnification 40 X)

A. Pepticare (125 mg/kg, p.o.)

B. Pepticare (250 mg/kg, p.o.)

C. Pepticare (500 mg/kg, p.o.)

D. Pepticare (1000 mg/kg, p.o.)

○ **Bundles of myocardial fibres**

→ **Boundaries of muscle fibres**

△ **Pyknotic nuclei**

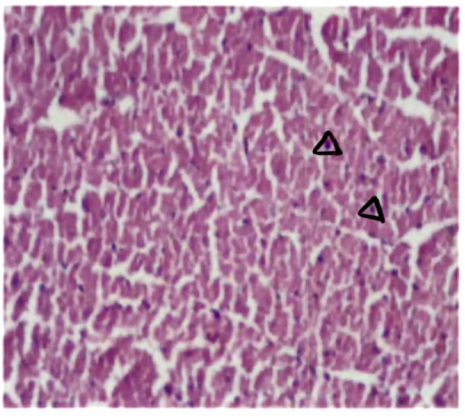


Fig. 4.39 (A)

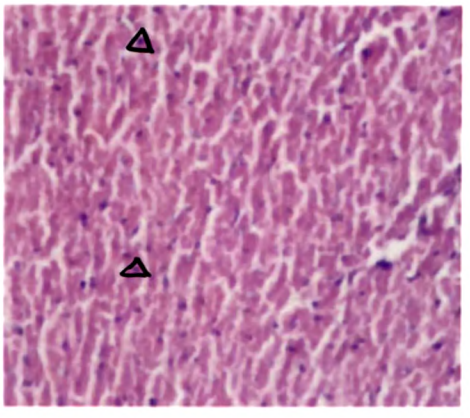


Fig. 4.39 (B)

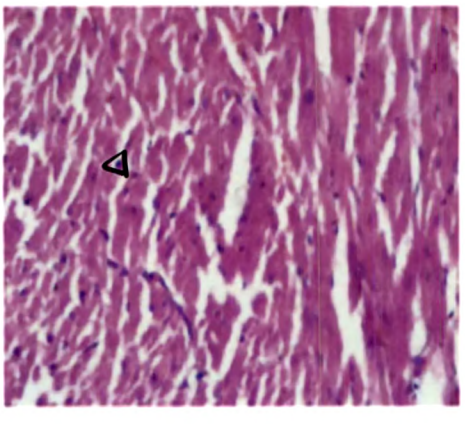


Fig. 4.39 (C)

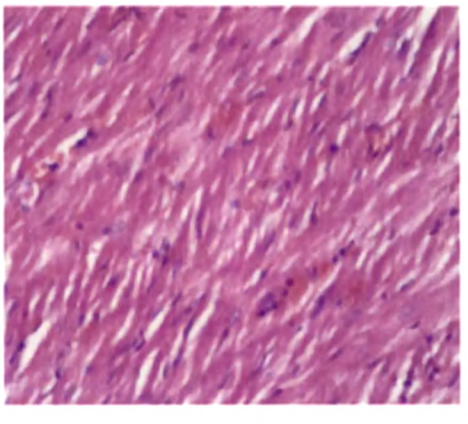


Fig. 4.39 (D)

Fig. 4.40. Photomicrographs showing effect of Normacid on the heart of isoproterenol-treated rats.

(Magnification 40 X)

A. Normacid (125 mg/kg, p.o.)

B. Normacid (250 mg/kg, p.o.)

C. Normacid (500 mg/kg, p.o.)

D. Normacid (1000 mg/kg, p.o.)

○ **Bundles of myocardial fibres**

→ **Boundaries of muscle fibres**

△ **Pyknotic nuclei**

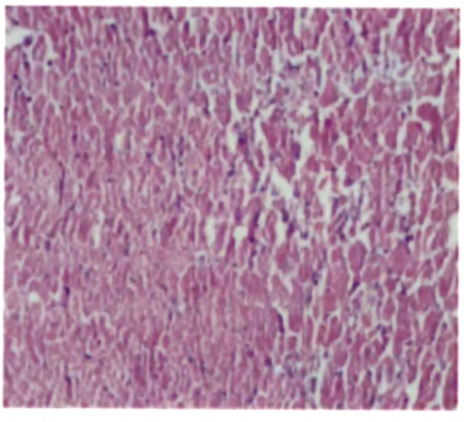


Fig. 4.40 (A)

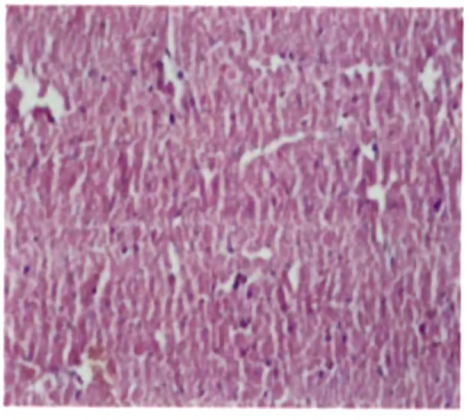


Fig. 4.40 (B)

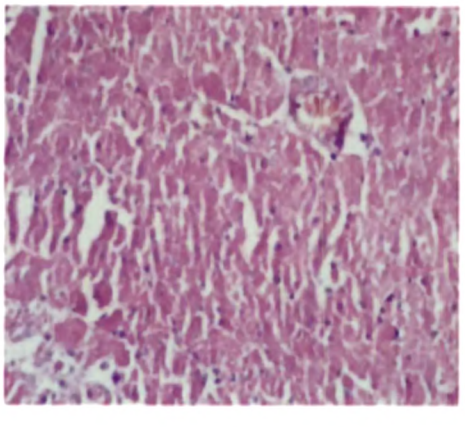


Fig. 4.40 (C)

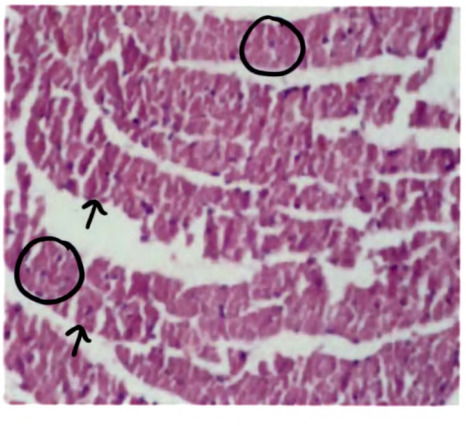


Fig. 4.40 (D)

SET 4:

CISPLATIN-INDUCED

NEPHROTOXICITY MODEL

4.2.4 CISPLATIN-INDUCED NEPHROTOXICITY (ACUTE MODEL)

4.2.4.1 SERUM PARAMETERS

4.2.4.1.1 Effect of drugs on creatinine

Treatment with a single dose of cisplatin (3mg/kg, i.p.) resulted in a significant ($p<0.001$) increase in the serum concentration of creatinine in rats (Group 2) as compared to control group (Group 1).

Administration of DHC-1, Activit, Pepticare and Normacid followed by cisplatin treatment did not produce a significant decrease in the level of serum creatinine at any of the four doses (125, 250, 500 and 1000 mg/kg) as compared to cisplatin control (Fig. 4.41, Fig. 4.43, Fig 4.45 and Fig 4.47).

4.2.4.1.2 Effect of drugs on uric acid

Cisplatin treatment (Group 2) resulted in a significant ($p<0.01$) increase in the serum concentration of uric acid as compared to control group (Group 1).

Administration of DHC-1 at the doses of 125 and 250 mg/kg followed by cisplatin treatment did not produce any significant change in the levels of serum uric acid; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) it significantly decreased the levels of uric acid as compared to cisplatin control (Fig. 4.41).

Administration of Activit, Pepticare and Normacid at all the four doses (125, 250, 500 and 1000 mg/kg) followed by cisplatin treatment did not produce any significant reduction in the level of serum uric acid as compared to cisplatin control (Fig. 4.43, Fig. 4.45 and Fig. 4.47).

4.2.4.1.3 Effect of drugs on urea

Cisplatin treatment (Group 2) resulted in a significant ($p<0.001$) increase in the serum concentration of urea as compared to control group (Group 1).

Administration of DHC-1 (125, 250, 500 and 1000 mg/kg) followed by cisplatin treatment did not significantly alter the levels of serum urea as compared to the cisplatin control group (Fig. 4.42).

Administration of Activit at the doses of 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) followed by cisplatin treatment produced a significant reduction in the level of serum urea as compared to cisplatin control (Fig. 4.44).

Administration of Pepticare at the doses of 125 and 250 mg/kg followed by cisplatin treatment did not produce any significant change in the levels of serum urea; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly decreased the levels of urea as compared to cisplatin control (Fig. 4.46).

Administration of Normacid (125 and 250 mg/kg) followed by cisplatin treatment did not produce any significant change in the levels of serum urea; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.01$) decreased the levels of urea as compared to cisplatin control (Fig. 4.48).

4.2.4.1.4 Effect of drugs on blood urea nitrogen (BUN)

Cisplatin treatment (Group 2) resulted in a significant ($p<0.001$) increase in the serum concentration of blood urea nitrogen as compared to control group (Group 1).

Administration of DHC-1 followed by cisplatin treatment did not produce a significant effect on the levels of serum BUN at the doses of 125, 250 and 500 mg/kg as compared to the cisplatin control group; but produced a significant ($p<0.01$) decrease at the dose of 1000 mg/kg (Fig. 4.42).

Administration of Activit (125, 250 and 500 mg/kg) followed by cisplatin treatment did not produce any significant change in the level of serum BUN; but at the higher dose of 1000 mg/kg it significantly ($p<0.05$) decreased the BUN levels as compared to cisplatin control (Fig. 4.44).

Administration of Pepticare at the doses of 125 and 250 mg/kg followed by cisplatin treatment did not produce any significant change in the levels of serum BUN; but at the higher doses of 500 and 1000 mg/kg it

significantly ($p<0.001$) decreased the levels of BUN as compared to cisplatin control group (Fig. 4.46).

Administration of Normacid (125 and 250 mg/kg) followed by cisplatin treatment did not produce any significant change in the levels of serum BUN; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly decreased the levels of BUN as compared to cisplatin control (Fig. 4.48).

Fig. 4.41. Effect of DHC-1 on the serum levels of creatinine and uric acid in cisplatin-induced nephrotoxicity (acute model) in rats.

Fig. 4.42. Effect of DHC-1 on the serum levels of urea and BUN in cisplatin-induced nephrotoxicity (acute model) in rats.

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: DHC-1 (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: DHC-1 (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.41.

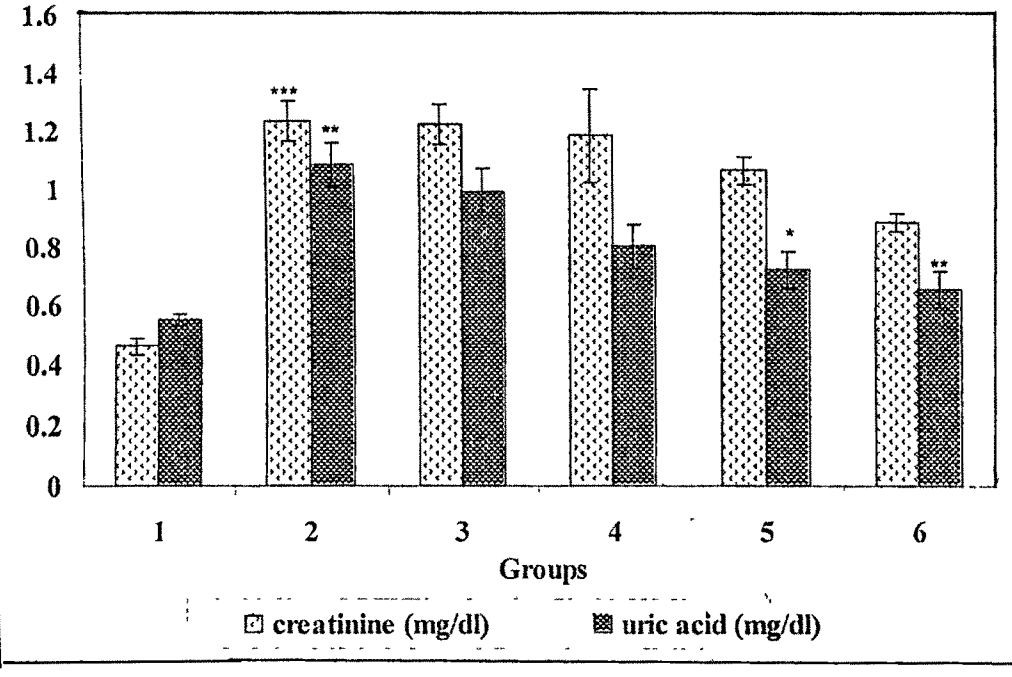


Fig. 4.42.

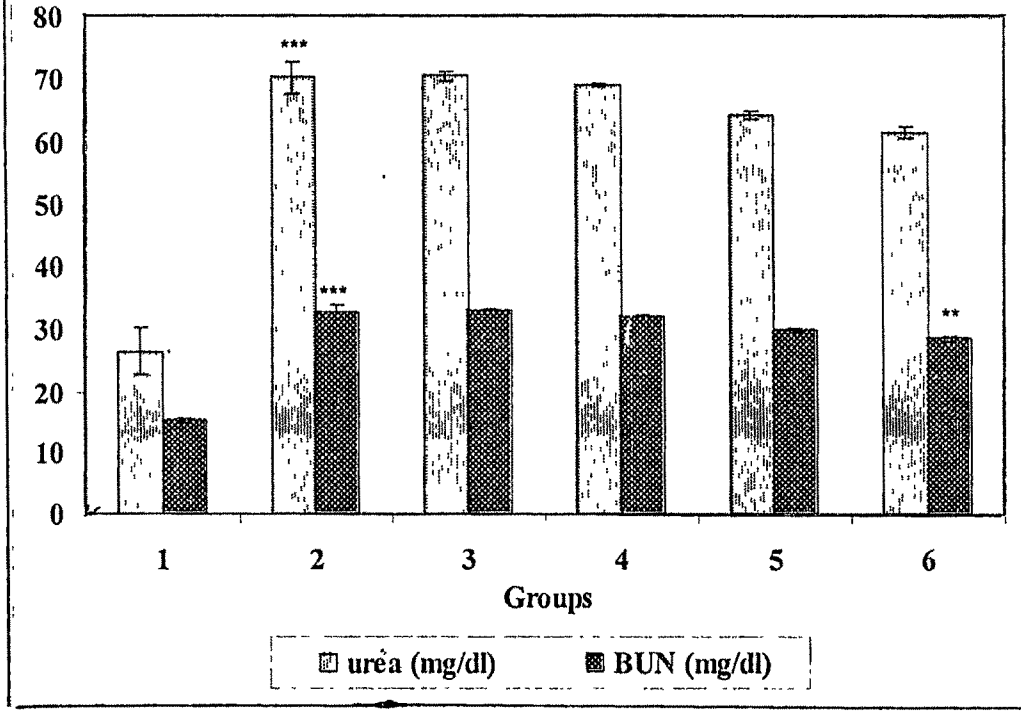


Fig. 4.43. Effect of Activit on the serum levels of creatinine and uric acid in cisplatin-induced nephrotoxicity (acute model) in rats.

Fig. 4.44. Effect of Activit on the serum levels of urea and BUN in cisplatin-induced nephrotoxicity (acute model) in rats.

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: Activit (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Activit (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Activit (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.
Group 2 was compared with Group 1.
Groups 3, 4, 5 and 6 were compared with Group 2.
$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.43.

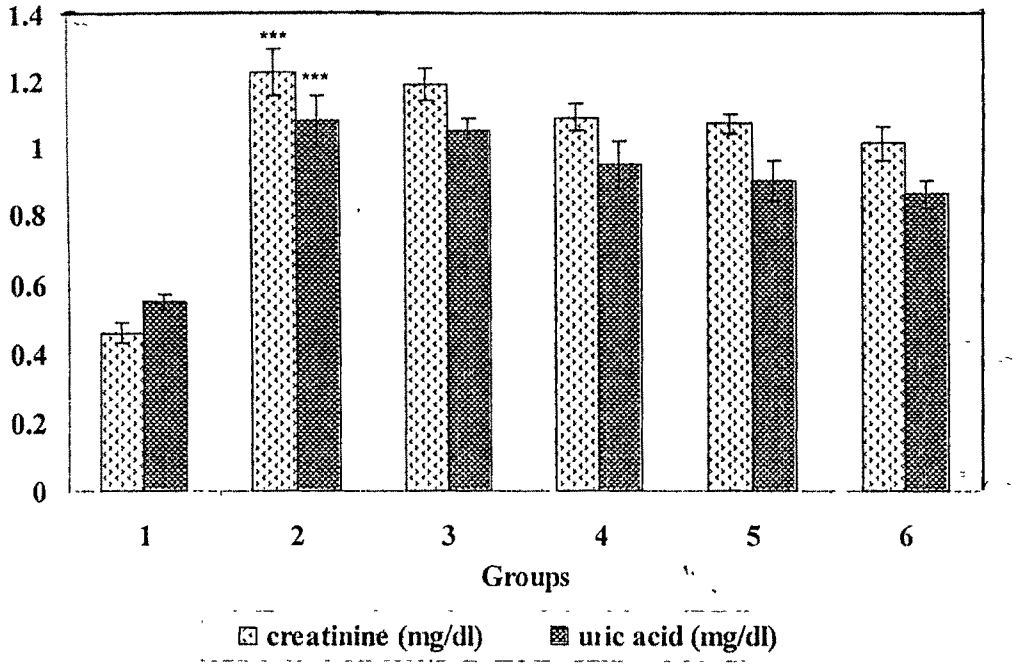


Fig. 4.44.

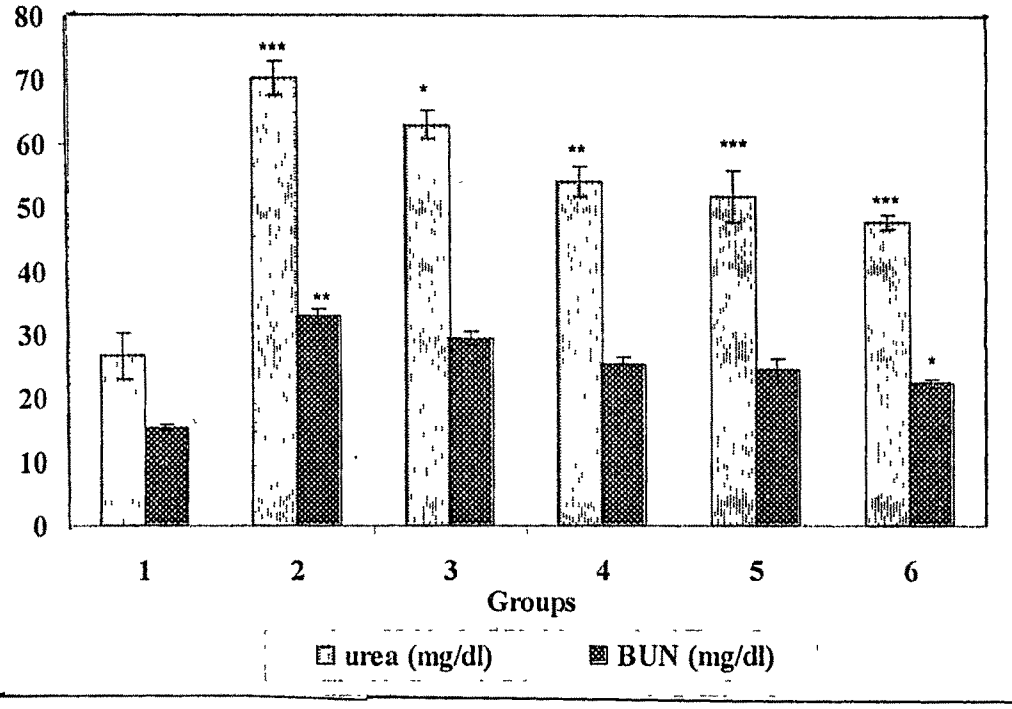


Fig. 4.45. Effect of Pepticare on the serum levels of creatinine and uric acid in cisplatin-induced nephrotoxicity (acute model) in rats.

Fig. 4.46. Effect of Pepticare on the serum levels of urea and BUN in cisplatin-induced nephrotoxicity (acute model) in rats.

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: Pepticare (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Pepticare (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.45.

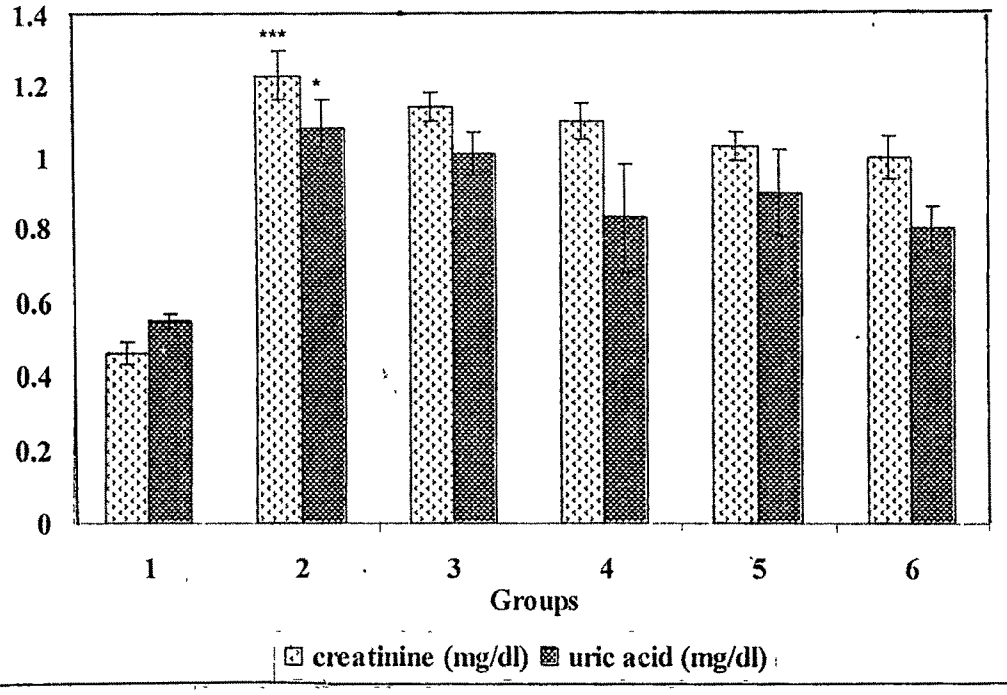


Fig. 4.46.

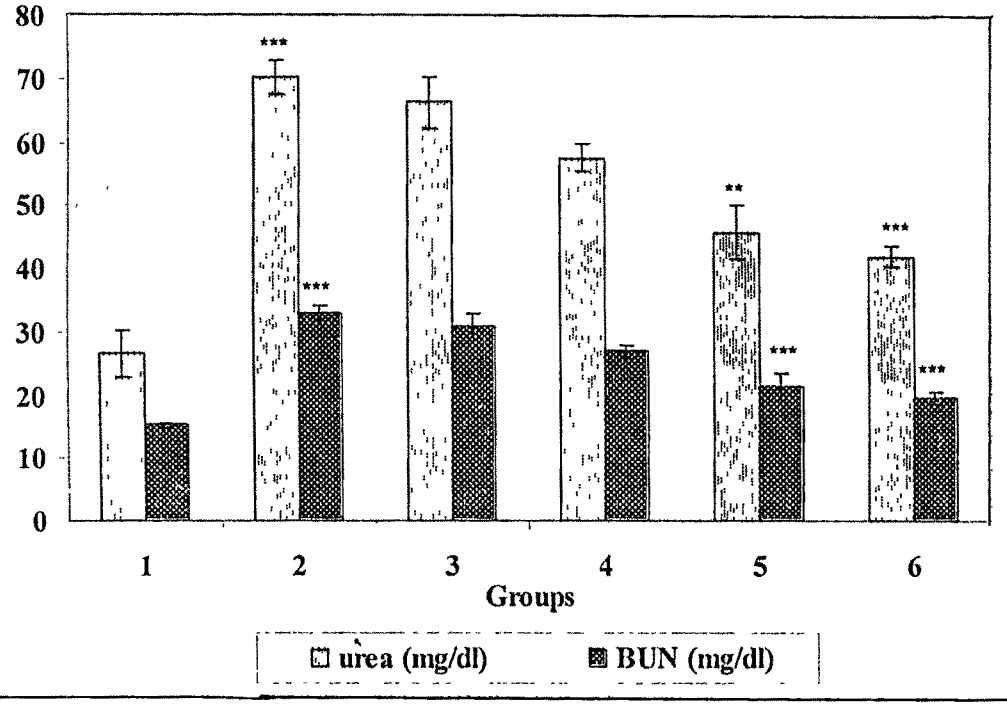


Fig. 4.47. Effect of Normacid on the serum levels of creatinine and uric acid in cisplatin-induced nephrotoxicity (acute model) in rats.

Fig. 4.48. Effect of Normacid on the serum levels of urea and BUN in cisplatin-induced nephrotoxicity (acute model) in rats.

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: Normacid (125 mg/kg, p.o.) followed by cisplatin treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6. Normacid (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.47.

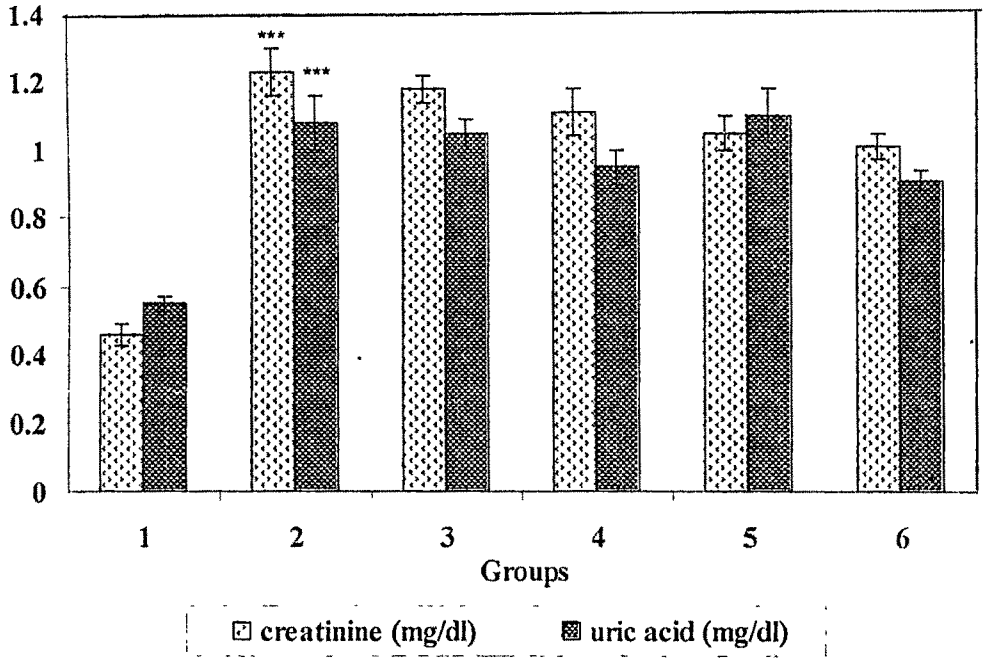
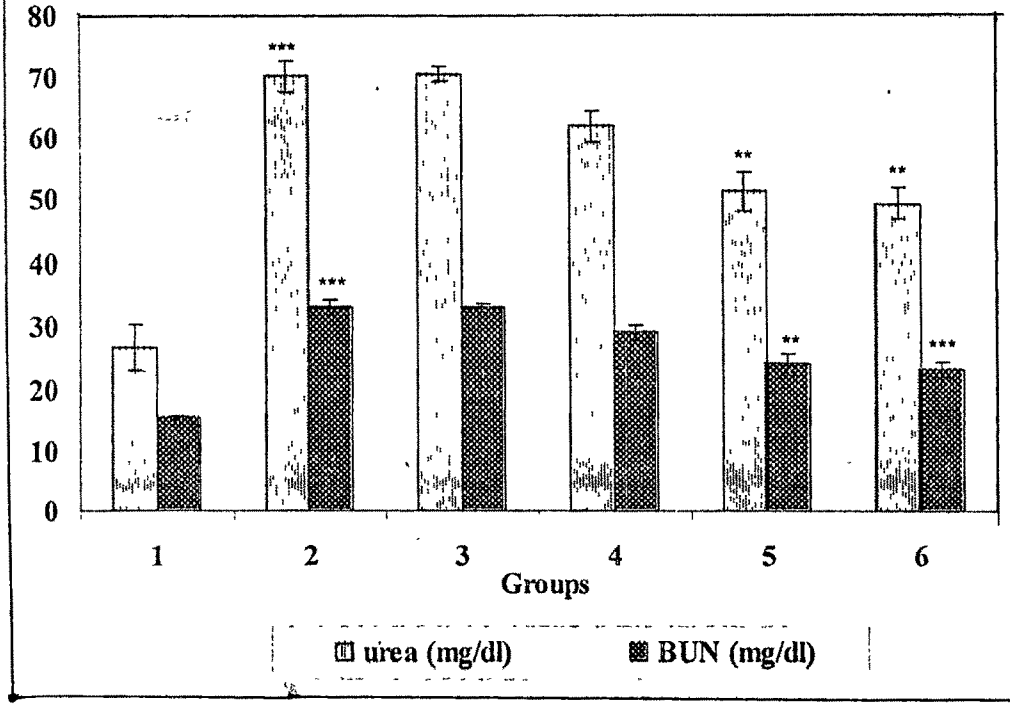


Fig. 4.48.



4.2.4.2 TISSUE PARAMETERS

4.2.4.2.1 Effect on lipid peroxidation

Cisplatin treatment (Group 2) to rats led to a significant ($p<0.001$) increase in lipid peroxidation or MDA content in kidneys as compared to the control group (Group 1).

Administration of DHC-1, Activit, Pepticare and Normacid followed by cisplatin treatment did not significantly alter the levels of MDA at any of the four doses (125, 250, 500 and 1000 mg/kg) as compared to cisplatin control (Tables 4.25, 4.26, 4.27 and 4.28).

4.2.4.2.2 Effect on endogenous antioxidants

4.2.4.2.2.1 Effect on Superoxide dismutase

Cisplatin treatment (Group 2) reduced the SOD activity significantly ($p<0.001$) in kidneys of rats as compared to control group (Group 1).

Administration of DHC-1 and Normacid followed by cisplatin treatment did not significantly affect the levels of SOD, at any of the four doses (125, 250, 500 and 1000 mg/kg) as compared to the cisplatin control group (Tables 4.25 and 4.28).

Administration of Activit at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not produce any significant change in the levels of SOD; but at the higher dose i.e. 1000 mg/kg it significantly ($p<0.05$) increased the levels of SOD as compared to cisplatin control (Table 4.26).

Administration of Pepticare (125 and 250 mg/kg) followed by cisplatin treatment did not produce any significant change in the levels of SOD; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.05$) increased the levels of SOD as compared to cisplatin control (Table 4.27).

4.2.4.2.2.2 Effect on Catalase

The catalase activity in cisplatin treated control group (Group 2) was significantly ($p<0.001$) reduced as compared to control group (Group 1).

Administration of DHC-1 followed by cisplatin treatment did not significantly alter the levels of catalase at any of the four doses (125, 250, 500 and 1000 mg/kg) as compared to the cisplatin control group (Table 4.25).

Administration of Activit, at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not produce any significant change in the level of catalase enzyme; but at the dose of 1000 mg/kg ($p<0.05$) it significantly increased these levels as compared to cisplatin control (Table 4.26).

Administration of Pepticare and Normacid, followed by cisplatin treatment did not affect the levels of catalase at any of the four doses, namely 125 mg/kg, 250 mg/kg, 500 mg/kg and 1000 mg/kg as compared to the cisplatin control group (Tables 4.27 and 4.28).

4.2.4.2.1.3 Effect on Reduced glutathione

A significant ($p<0.001$) reduction in reduced glutathione concentration was observed in cisplatin treated rats (Group 2) as compared to the normal control group (Group 1).

Administration of DHC-1, Activit or Normacid followed by cisplatin treatment did not significantly change the levels of GSH at any of the four doses (125, 250, 500 and 1000 mg/kg) as compared to the cisplatin control group (Tables 4.25, 4.26 and 4.28).

Similarly, administration of Pepticare at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not produce any significant change in the level of GSH; but at the higher dose of 1000 mg/kg it significantly ($p<0.05$) increased these levels as compared to cisplatin control (Table 4.27).

Table 4.25: Effect of DHC-1 on the levels of lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the kidney of rats in cisplatin-induced nephrotoxicity (acute model).

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	2.50 ± 0.08	1.71 ± 0.13	2.61 ± 0.10	3.11 ± 0.07
Group 2	5.28 ± 0.17***	0.72 ± 0.04***	2.17 ± 0.04***	2.41 ± 0.09***
Group 3	5.22 ± 0.19NS	0.73 ± 0.04NS	2.19 ± 0.01NS	2.45 ± 0.06NS
Group 4	5.10 ± 0.07NS	0.78 ± 0.03NS	2.19 ± 0.05NS	2.54 ± 0.05NS
Group 5	4.68 ± 0.18NS	0.90 ± 0.01NS	2.22 ± 0.04NS	2.60 ± 0.03NS
Group 6	4.56 ± 0.19NS	0.95 ± 0.02NS	2.31 ± 0.02NS	2.68 ± 0.02NS
F value	46.340	38.594	10.828	18.921
P value	<0.0001	<0.0001	0.0004	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: DHC-1 (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: DHC-1 (250 mg/kg, p.o.) followed by cisplatin treatment.

Group 5: DHC-1 (500 mg/kg, p.o.) followed by cisplatin treatment.

Group 6. DHC-1 (1000 mg/kg, p.o.) followed by cisplatin treatment.

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.26: Effect of Activit on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the kidney of rats in cisplatin-induced nephrotoxicity (acute model).

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	2.50 ± 0.08	1.71 ± 0.13	2.61 ± 0.10	3.11 ± 0.07
Group 2	5.28 ± 0.17***	0.72 ± 0.04***	2.17 ± 0.04***	2.41 ± 0.09***
Group 3	5.67 ± 0.24NS	0.74 ± 0.02NS	2.28 ± 0.04NS	2.45 ± 0.03NS
Group 4	5.20 ± 0.47NS	0.80 ± 0.02NS	2.32 ± 0.02NS	2.57 ± 0.02NS
Group 5	4 26 ± 0.20NS	0.86 ± 0 02NS	2.35 ± 0.02NS	2.64 ± 0.03NS
Group 6	4.06 ± 0.33NS	0.93 ± 0.02NS	2.43 ± 0.03*	2.71 ± 0.05*
F value	17.740	41.541	9.134	21.195
P value	<0.0001	<0.0001	0.0009	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: Activit (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Activit (250 mg/kg, p.o.) followed by cisplatin treatment.

Group 5: Activit (500 mg/kg, p.o.) followed by cisplatin treatment.

Group 6: Activit (1000 mg/kg, p.o.) followed by cisplatin treatment.

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.27: Effect of Pepticare on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the kidney of rats in cisplatin-induced nephrotoxicity (acute model).

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	2.50 ± 0.08	1.71 ± 0.13	2.61 ± 0.10	3.11 ± 0.07
Group 2	5.28 ± 0.17***	0.72 ± 0.04***	2.17 ± 0.04***	2.41 ± 0.09***
Group 3	5.53 ± 0.31NS	0.88 ± 0.01NS	2.31 ± 0.03NS	2.43 ± 0.02NS
Group 4	5.03 ± 0.06NS	0.90 ± 0.02NS	2.36 ± 0.02NS	2.46 ± 0.04NS
Group 5	4.85 ± 0.20NS	0.98 ± 0.01NS	2.44 ± 0.04*	2.55 ± 0.02NS
Group 6	4.72 ± 0.17NS	1.02 ± 0.01*	2.46 ± 0.06*	2.60 ± 0.03NS
F value	34.945	36.815	7.607	24.446
P value	<0.0001	<0.0001	0.0020	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: Pepticare (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Pepticare (250 mg/kg, p.o.) followed by cisplatin treatment.

Group 5: Pepticare (500 mg/kg, p.o.) followed by cisplatin treatment.

Group 6: Pepticare (1000 mg/kg, p.o.) followed by cisplatin treatment.

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.28: Effect of Normacid on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the kidney of rats in cisplatin-induced nephrotoxicity (acute model).

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	2.50 ± 0.08	1.71 ± 0.13	2.61 ± 0.10	3.11 ± 0.07
Group 2	5.28 ± 0.17***	0.72 ± 0.04***	2.17 ± 0.04***	2.41 ± 0.09***
Group 3	5.63 ± 0.30NS	0.72 ± 0.03NS	2.20 ± 0.03NS	2.42 ± 0.04NS
Group 4	5.06 ± 0.16NS	0.83 ± 0.01NS	2.22 ± 0.03NS	2.52 ± 0.02NS
Group 5	5.19 ± 0.32NS	0.92 ± 0.01NS	2.27 ± 0.03NS	2.58 ± 0.03NS
Group 6	4.34 ± 0.22NS	0.97 ± 0.01NS	2.32 ± 0.02NS	2.61 ± 0.01NS
F value	26.345	40.749	10.933	24.982
P value	<0.0001	<0.0001	0.0004	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: Normacid (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Normacid (250 mg/kg, p.o.) followed by cisplatin treatment.

Group 5: Normacid (500 mg/kg, p.o.) followed by cisplatin treatment.

Group 6: Normacid (1000 mg/kg, p.o.) followed by cisplatin treatment.

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

4.2.4.2.3 Effect on membrane bound enzymes

4.2.4.2.3.1 Effect on Sodium Potassium ATPase

In the kidneys of cisplatin-treated rats (Group 2) the activity of Na^+K^+ATPase enzyme was significantly ($p<0.001$) reduced as compared to the control group 1.

Administration of DHC-1, at all the four doses, namely 125 mg/kg, 250 mg/kg, 500 mg/kg and 1000 mg/kg followed by cisplatin treatment did not significantly change the levels of Na^+K^+ATPase enzyme as compared to the cisplatin control group (Table 4.29).

Administration of Activit (125 and 250 mg/kg) followed by cisplatin treatment did not produce any significant increase in Na^+K^+ATPase levels; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) it significantly increased the levels of the enzyme as compared to cisplatin control (Table 4.30).

Administration of Pepticare and Normacid followed by cisplatin treatment did not produce any significant increase in the levels of Na^+K^+ATPase at any of the dose levels as compared to the cisplatin treated control group (Tables 4.31 and 4.32).

4.2.4.2.3.2 Effect on Calcium ATPase

Treatment with cisplatin (Group 2) resulted in a significant ($p<0.001$) decrease in the Ca^{2+}ATPase activity as compared to the control group (Group 1).

Administration of DHC-1 and Activit, at all the four doses (125, 250, 500 and 1000 mg/kg) followed by cisplatin treatment did not produce any significant increase in Ca^{2+}ATPase levels as compared to the cisplatin control (Tables 4.29 and 4.30).

Administration of Pepticare and Normacid at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not produce any significant change in the level of Ca^{2+}ATPase; but at the dose of 1000 mg/kg they significantly ($p<0.001$) increased these levels as compared to cisplatin control (Table 4.31 and 4.32).

4.2.4.2.3.3 Effect on Magnesium ATPase

Ttreatment with cisplatin (Group 2) resulted in a significant ($p<0.001$) decrease in the Mg^{2+}ATPase activity as compared to the control group (Group 1).

Administration of DHC-1 at all the four doses (125, 250, 500 and 1000 mg/kg) followed by cisplatin treatment did not produce any significant increase in Ca^{2+}ATPase levels as compared to the cisplatin control (Table 4.29).

Administration of Activit at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not produce any significant increase in Mg^{2+}ATPase levels; but at the dose of 1000 mg/kg it significantly ($p<0.01$) increased the levels of the enzyme as compared to cisplatin control (Table 4.30).

Administration of Pepticare and Normacid followed by cisplatin treatment did not produce any significant increase in the levels of Mg^{2+}ATPase at any of the dose levels as compared to the cisplatin treated control group (Table 4.31 and 4.32).

Table 4.29: Effect of DHC-1 on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the kidney of rats in cisplatin-induced nephrotoxicity (acute model).

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	10.98 ± 0.34	4.41 ± 0 09	6.57 ± 0.18
Group 2	5.75 ± 0.19***	2.72 ± 0 20***	3.70 ± 0.24***
Group 3	5.82 ± 0.41NS	2.80 ± 0.05NS	3.75 ± 0.07NS
Group 4	6.26 ± 0.16NS	2.84 ± 0.09NS	3.86 ± 0.08NS
Group 5	6.49 ± 0.19NS	2.87 ± 0.07NS	4.14 ± 0.09NS
Group 6	6.80 ± 0.10NS	3.05 ± 0.04NS	4.26 ± 0.21NS
F value	59.159	37.404	48.392
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: DHC-1 (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: DHC-1 (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.30: Effect of Activit on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the kidney of rats in cisplatin-induced nephrotoxicity (acute model).

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	10.98 ± 0.34	4.41 ± 0.09	6.57 ± 0.18
Group 2	5.75 ± 0.19***	2.72 ± 0.20***	3.70 ± 0.24***
Group 3	6.17 ± 0.03NS	2.83 ± 0.03NS	3.85 ± 0.17NS
Group 4	6.43 ± 0.06NS	2.87 ± 0.09NS	4.25 ± 0.06NS
Group 5	6.73 ± 0.23*	2.98 ± 0.07NS	4.43 ± 0.12NS
Group 6	7.04 ± 0.04**	3.05 ± 0.04NS	4.80 ± 0.16**
F value	103.35	35.868	41.009
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: Activit (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Activit (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Activit (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.31: Effect of Pepticare on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the kidney of rats in cisplatin-induced nephrotoxicity (acute model).

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	10.98 ± 0.34	4.41 ± 0.09	6.57 ± 0.18
Group 2	5.75 ± 0.19***	2.72 ± 0.20***	3.70 ± 0.24***
Group 3	6.16 ± 0.12NS	2.77 ± 0.05NS	3.71 ± 0.08NS
Group 4	6.34 ± 0.06NS	2.91 ± 0.07NS	3.92 ± 0.05NS
Group 5	6.48 ± 0.06NS	3.17 ± 0.03NS	4.03 ± 0.05NS
Group 6	6.49 ± 0.04NS	3.62 ± 0.05***	4.25 ± 0.07NS
F value	78.50	41.235	70.836
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: Pepticare (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Pepticare (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.32: Effect of Normacid on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the kidney of rats in cisplatin-induced nephrotoxicity (acute model).

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	10.98 ± 0.34	4.41 ± 0.09	6.57 ± 0.18
Group 2	5.75 ± 0.18***	2.72 ± 0.20***	3.70 ± 0.24***
Group 3	6.12 ± 0.13NS	2.76 ± 0.14NS	3.70 ± 0.06NS
Group 4	6.22 ± 0.14NS	2.86 ± 0.07NS	3.88 ± 0.06NS
Group 5	6.45 ± 0.06NS	3.07 ± 0.04NS	4.12 ± 0.07NS
Group 6	6.58 ± 0.06NS	3.13 ± 0.07***	4.72 ± 0.43NS
F value	117.88	29.527	26.491
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3mg/kg, i.p.; single dose).

Group 3: Normacid (125 mg/kg, p.o.) followed by cisplatin treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6. Normacid (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

4.2.4.3 EFFECT OF DRUGS ON BODY WEIGHT (Table 4.33)

When the animals were given cisplatin (Group 2), the weight of the animals decreased significantly. There was a percentage decrease of 7.81% on day 5 compared to control animals (Group 1), which gained 5.06% during the same period.

Administration of DHC-1, at the doses of 125, 250, 500 and 1000 mg/kg, 1 h before cisplatin did not reverse the decrease in body weight significantly as compared to the cisplatin control.

The animals treated with Activit, at the doses of 125, 250, 500 and 1000 mg/kg, 1 h before cisplatin, did not record a significant change in the body weight as compared to cisplatin control.

When the animals were administered Pepticare (125, 250 and 500 mg/kg) 1 h before cisplatin the decrease in body weight was not reversed significantly as compared to the cisplatin control. Pepticare at the dose of 1000 mg/kg produced an increase in body weight rather than a decrease but the change in body weight was not significant as compared to the cisplatin control group.

The animals treated with Normacid (125, 250, 500 and 1000 mg/kg) 1 h before cisplatin, did not record a significant change in body weight as compared to the cisplatin control group.

Table 4.33: Effect of DHC-1, Activit, Pepticare and Normacid on % change in body weight of rats in cisplatin-induced nephrotoxicity (acute model).

Groups	% change in body weight				
Normal Control	168.1 ± 3.2 (+5.06)				
Cisplatin Control	147.5 ± 7.6*** (-7.81)				
		Dose (mg/kg)			
		125	**250**	**500**	**1000**
DHC-1	-	-7.38^{NS}	-7.13^{NS}	-8.00^{NS}	-6.50^{NS}
Activit	-	-6.69^{NS}	-5.50^{NS}	-5.50^{NS}	-5.88^{NS}
Pepticare	-	-6.06^{NS}	-4.56^{NS}	-4.38^{NS}	-5.12^{NS}
Normacid	-	-5.75^{NS}	-1.50^{NS}	+0.06^{NS}	-2.56^{NS}

Values are expressed as mean ± SEM.

Cisplatin control group was compared with the Normal control group.

DHC-1, Activit, Pepticare and Normacid treated groups were compared with Cisplatin control group.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Values in the drug treated groups indicate the % change in relation to the Cisplatin control group; + denotes increase and – denotes decrease

4.2.5 CISPLATIN-INDUCED NEPHROTOXICITY (CHRONIC MODEL)

4.2.5.1 SERUM PARAMETERS

4.2.5.1.1 Effect of drugs on creatinine

Treatment with cisplatin (3 mg/kg, i.p.) every week for 28 days (days 1, 7, 14, 21 and 28) resulted in a significant ($p<0.001$) increase in the serum concentration of creatinine in rats (Group 2) as compared to control group (Group 1).

Administration of DHC-1 (125, 250, 500 and 1000 mg/kg) followed by cisplatin treatment produced a significant ($p<0.001$) decrease in the levels of serum creatinine as compared to cisplatin control (Fig. 4.49).

Administration of Activit followed by cisplatin treatment also significantly reduced the levels of creatinine at all the doses namely, 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to cisplatin control (Fig. 4.51).

Administration of Pepticare (125 mg/kg) followed by cisplatin treatment did not produce any significant reduction in the level of serum creatinine; but at the higher doses, namely 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly decreased the creatinine levels as compared to cisplatin control (Fig. 4.53).

Administration of Normacid (125, 250, 500 and 1000 mg/kg) followed by cisplatin treatment produced a significant ($p<0.001$) decrease in the levels of serum creatinine as compared to cisplatin control (Fig. 4.55).

4.2.5.1.2 Effect of drugs on uric acid

Cisplatin treatment (Group 2) resulted in a significant ($p<0.001$) increase in the serum concentration of uric acid as compared to control group (Group 1).

Administration of DHC-1 followed by cisplatin treatment produced a significant ($p<0.001$) decrease in the levels of serum BUN at all the four doses (125, 250, 500 and 1000 mg/kg) as compared to the cisplatin control group (Fig. 4.49).

Administration of Activit, Pepticare and Normacid, at the doses of 125 mg/kg followed by cisplatin treatment did not produce any significant change in the level of serum uric acid; but at the higher doses of 250, 500 and 1000 mg/kg they significantly ($p<0.001$) decreased the uric acid levels as compared to cisplatin control (Fig. 4.51, Fig. 4.53 and Fig. 4.55).

4.2.5.1.3 Effect of drugs on urea

Cisplatin treatment (Group 2) resulted in a significant ($p<0.001$) increase in the serum concentration of urea as compared to normal control group (Group 1).

Administration of DHC-1 and Normacid followed by cisplatin treatment produced a significant ($p<0.001$) decrease in the levels of serum urea at all the four doses (125, 250, 500 and 1000 mg/kg) as compared to cisplatin control (Fig. 4.50 and 4.56).

Administration of Activit (125 mg/kg) followed by cisplatin treatment did not produce any significant reduction in the level of serum urea; but at the higher doses of 250, 500 and 1000 mg/kg it significantly ($p<0.001$) decreased the urea levels as compared to cisplatin control (Fig. 4.52).

Administration of Pepticare (125 and 250 mg/kg) followed by cisplatin treatment did not produce any significant change in the levels of serum urea; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) it significantly decreased the levels of urea as compared to cisplatin control (Fig. 4.54).

4.2.5.1.4 Effect of drugs on blood urea nitrogen

Cisplatin treatment (Group 2) resulted in a significant ($p<0.001$) increase in the serum concentration of urea as compared to the normal control (Group 1).

Administration of DHC-1 or Normacid followed by cisplatin treatment produced a significant ($p<0.001$) decrease in the levels of serum BUN at all the four dose levels as compared to cisplatin control group (Fig. 4.50 and Fig.4.56).

Administration of Activit (125 mg/kg) followed by cisplatin treatment did not produce any significant change in the level of serum BUN; but at the higher doses, namely 250 mg/kg, 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$) decreased the BUN levels as compared to cisplatin control (Fig. 4.52).

Administration of Pepticare (125 and 250 mg/kg) followed by cisplatin treatment did not produce any significant change in the levels of serum BUN; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) it significantly decreased the levels of BUN as compared to cisplatin control (Fig. 4.54).

Fig. 4.49. Effect of DHC-1 on the serum levels of creatinine and uric acid in cisplatin-induced nephrotoxicity (chronic model) in rats.

Fig. 4.50. Effect of DHC-1 on the serum levels of urea and BUN in cisplatin-induced nephrotoxicity (chronic model) in rats.

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: DHC-1 (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: DHC-1 (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.49.

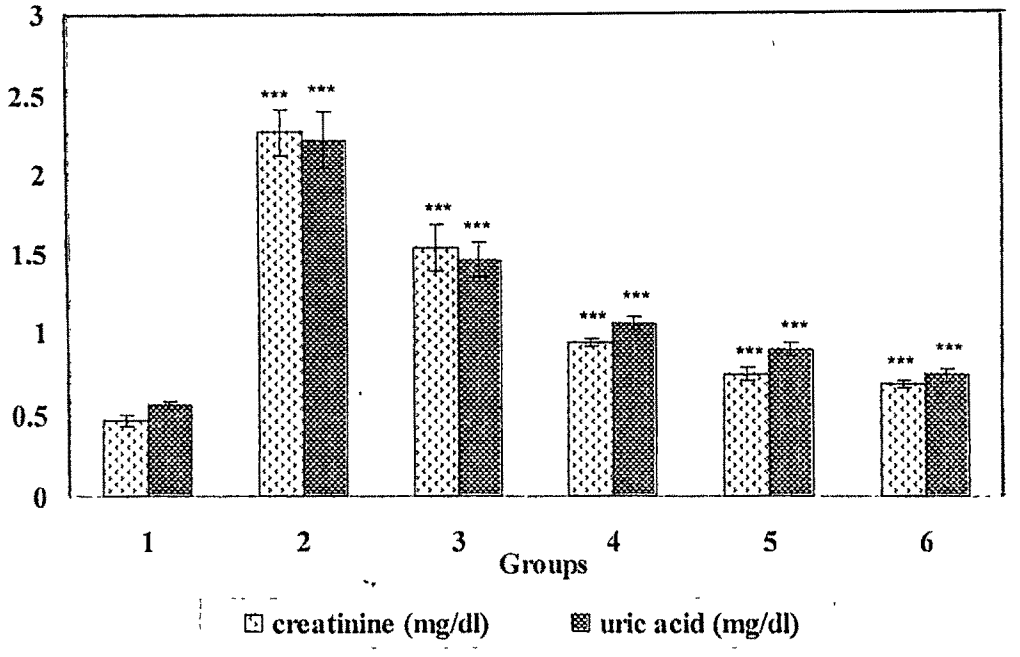


Fig. 4.50.

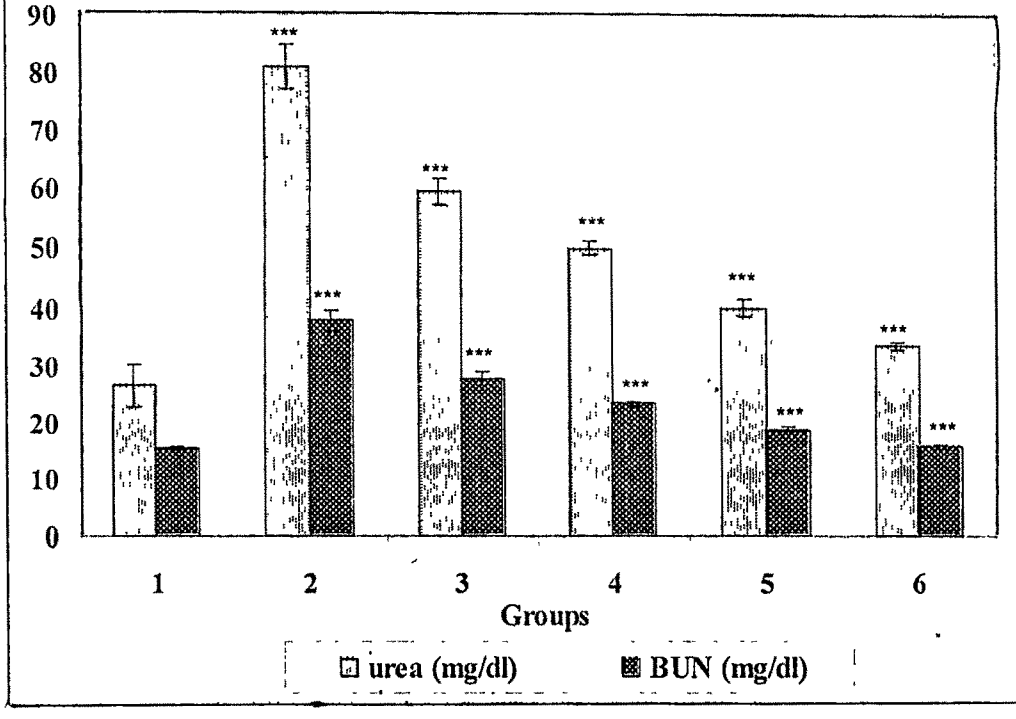


Fig. 4.51. Effect of Activit on the serum levels of creatinine and uric acid in cisplatin-induced nephrotoxicity (chronic model) in rats.

Fig. 4.52. Effect of Activit on the serum levels of urea and BUN in cisplatin-induced nephrotoxicity (chronic model) in rats.

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: Activit (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Activit (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Activit (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.51.

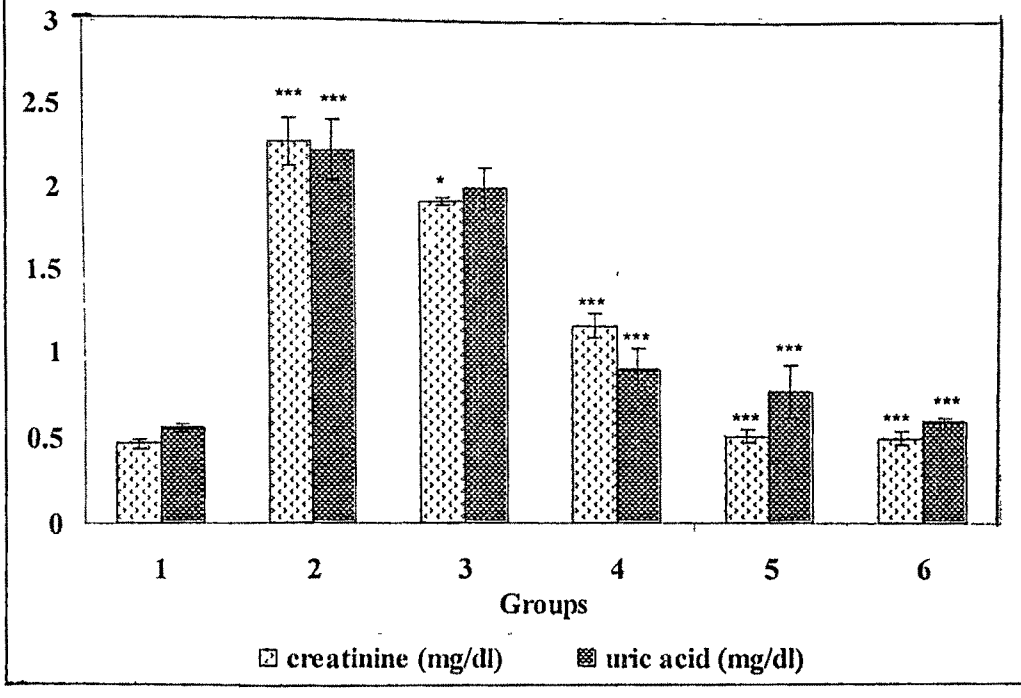


Fig. 4.52.

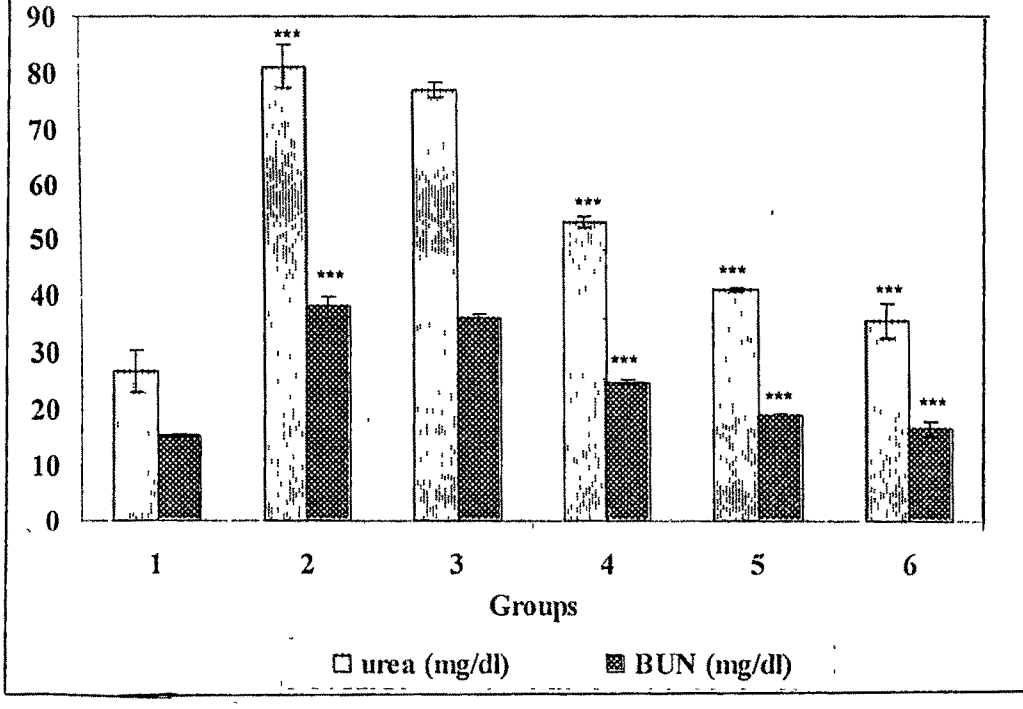


Fig. 4.53. Effect of Pepticare on the serum levels of creatinine and uric acid in cisplatin-induced nephrotoxicity (chronic model) in rats.

Fig. 4.54. Effect of Pepticare on the serum levels of urea and BUN in cisplatin-induced nephrotoxicity (chronic model) in rats.

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: Pepticare (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Pepticare (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.53.

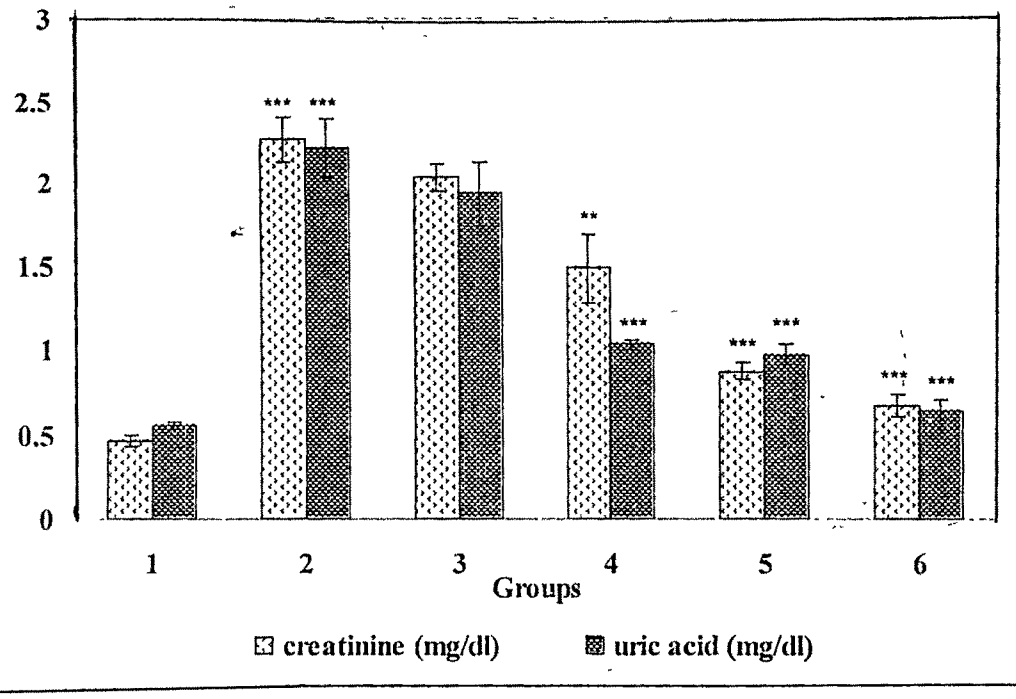


Fig. 4.54.

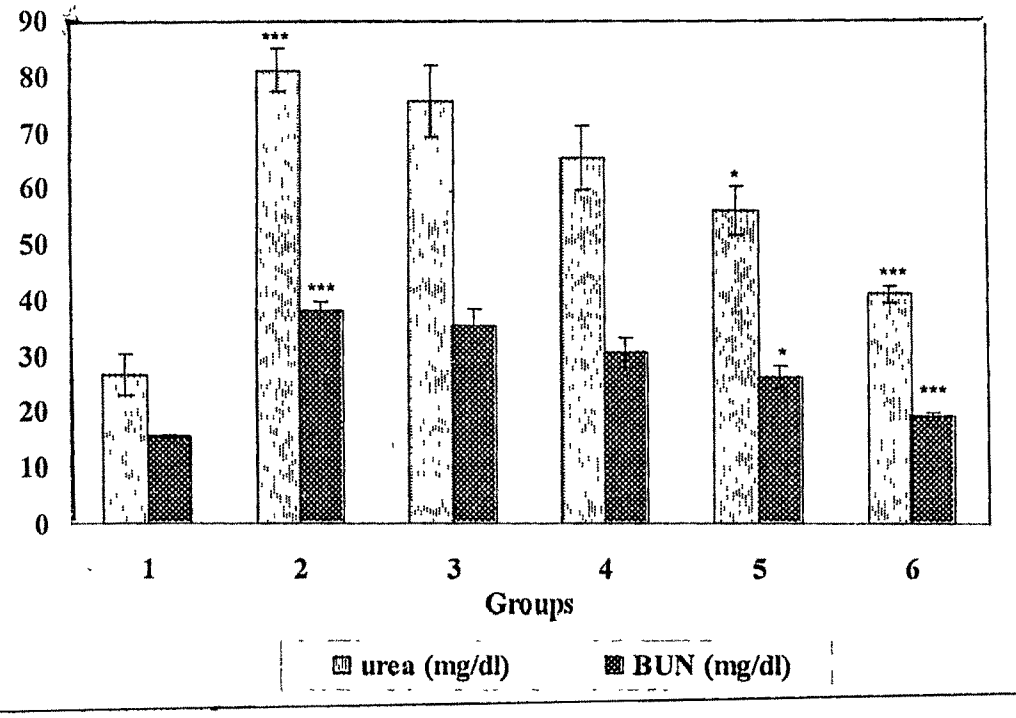


Fig. 4.55. Effect of Normacid on the serum levels of creatinine and uric acid in cisplatin-induced nephrotoxicity (chronic model) in rats.

Fig. 4.56. Effect of Normacid on the serum levels of urea and BUN in cisplatin-induced nephrotoxicity (chronic model) in rats.

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: Normacid (125 mg/kg, p.o.) followed by cisplatin treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.55.

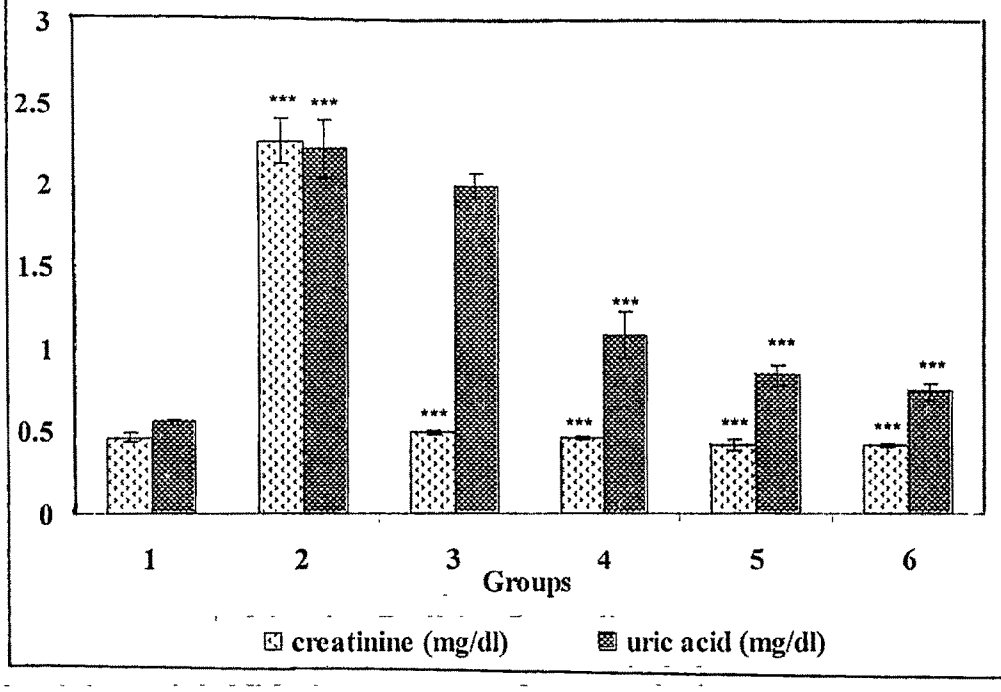
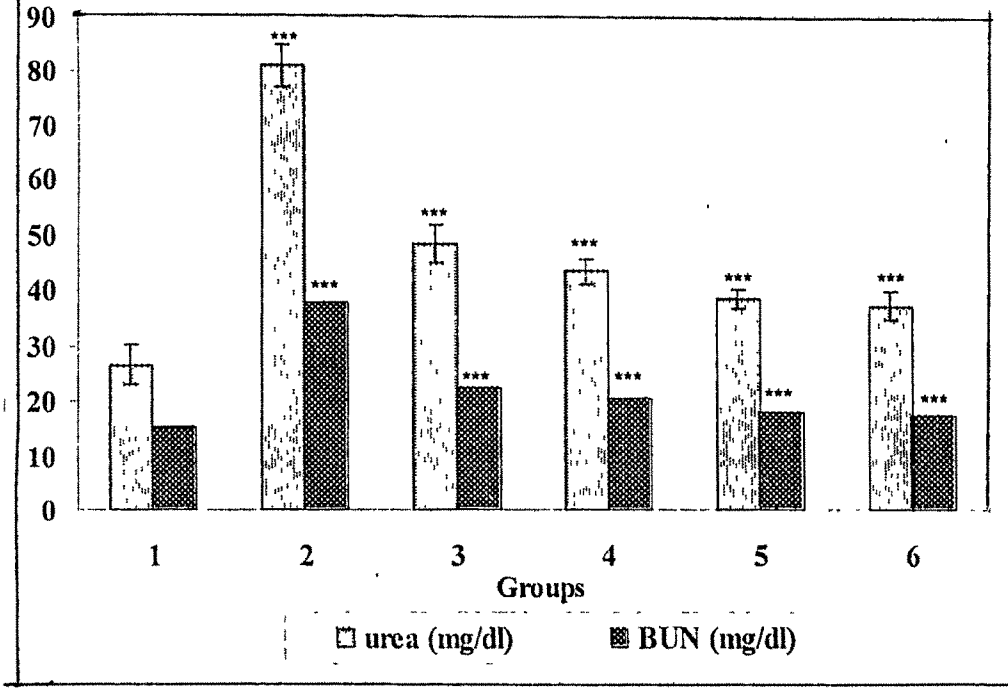


Fig. 4.56.



4.2.5.2 TISSUE PARAMETERS

4.2.5.2.1 Effect on lipid peroxidation

Cisplatin treatment (Group 2) led to a significant ($p<0.001$) increase in lipid peroxidation or MDA content in kidneys of rats as compared to the normal control group (Group 1).

Administration of DHC-1 (125 mg/kg) followed by cisplatin treatment did not produce any significant change in the level of MDA in kidneys; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.01$) it significantly decreased the MDA levels as compared to cisplatin control (Table 4.34).

Administration of Activit (125 mg/kg) followed by cisplatin treatment did not produce any significant change in the level of lipid peroxidation in kidneys; but at the higher doses of 250, 500 and 1000 mg/kg it significantly ($p<0.001$) decreased the MDA levels as compared to cisplatin control (Table 4.35).

Administration of Pepticare at the doses of 125 and 250 mg/kg followed by cisplatin treatment did not produce any significant change in the levels of MDA; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$) decreased the levels of MDA as compared to cisplatin control (Table 4.36).

Administration of Normacid followed by cisplatin treatment significantly reduced the levels of lipid peroxidation (MDA) at all the doses namely, 125 mg/kg ($p<0.01$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to cisplatin control (Table 4.37).

4.2.5.2.2 Effect on endogenous antioxidants

4.2.5.2.2.1 Effect on Superoxide dismutase

Cisplatin treatment (Group 2) reduced the SOD activity significantly ($p<0.01$) in kidneys of rats as compared to the normal control (Group 1).

Administration of DHC-1 at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not affect the SOD content in kidneys as compared to the cisplatin control group. At the higher dose i.e. 1000

mg/kg, the drug led to a significant ($p<0.01$) rise in SOD content as compared to cisplatin control (Table 4.34).

Administration of Activit at the doses of 125 and 250 mg/kg followed by cisplatin treatment did not produce any significant change in the levels of SOD; but at the higher doses of 500 and 1000 mg/kg it significantly ($p<0.05$) increased the levels of SOD as compared to cisplatin control (Table 4.35).

Administration of Pepticare (125 and 250 mg/kg) followed by cisplatin treatment did not produce any significant change in the levels of SOD; but at the higher doses (500 and 1000 mg/kg) it significantly ($p<0.01$) increased the levels of SOD as compared to cisplatin control (Table 4.36).

Administration of Normacid at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not affect the SOD content in kidneys as compared to the cisplatin control group. At the higher dose i.e. 1000 mg/kg, the drug led to a significant ($p<0.01$) rise in SOD content as compared to cisplatin control (Table 4.37).

4.2.5.2.2.2 Effect on Catalase

The catalase activity in cisplatin treated control group (Group 2) was significantly ($p<0.001$) reduced as compared to control group (Group 1).

Administration of DHC-1 at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not affect the catalase content in kidneys as compared to the cisplatin control group. At the higher dose i.e. 1000 mg/kg, the drug led to a significant ($p<0.001$) rise in catalase levels as compared to cisplatin control (Table 4.34).

Administration of Activit, at the doses of 125 and 250 mg/kg followed by cisplatin treatment did not produce any significant change in the level of catalase enzyme; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased these levels as compared to cisplatin control (Table 4.35).

Similarly, administration of Pepticare (125 and 250 mg/kg) followed by cisplatin treatment did not produce any significant change in the level of catalase enzyme; but at the higher doses of 500 and 1000 mg/kg it

significantly ($p<0.01$) increased these levels as compared to cisplatin control (Table 4.36).

Administration of Normacid at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not affect the catalase content in kidneys as compared to the cisplatin control group; but at the higher dose i.e. 1000 mg/kg, the drug led to a significant ($p<0.01$) rise in catalase levels as compared to cisplatin control (Table 4.37).

4.2.5.2.1.3 Effect on Reduced glutathione

A significant ($p<0.001$) reduction in reduced glutathione concentration was observed in cisplatin treated rats (Group 2) as compared to control group 1.

Administration of DHC-1 (125 mg/kg) followed by cisplatin treatment did not produce any significant increase in GSH content; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly increased the GSH content as compared to cisplatin control (Table 4.34).

Administration of Activit at the doses of 125 and 250 mg/kg followed by cisplatin treatment did not produce any significant change in the level of GSH; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) it significantly increased these levels as compared to cisplatin control (Table 4.35).

Similarly, administration of Pepticare (125 and 250 mg/kg) followed by cisplatin treatment did not produce any significant change in the level of GSH; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased these levels as compared to cisplatin control (Table 4.36).

Administration of Normacid at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not affect the GSH content in kidneys as compared to the cisplatin control group; but at the higher dose i.e. 1000 mg/kg, the drug led to a significant ($p<0.001$) rise in GSH levels as compared to cisplatin control (Table 4.37).

Table 4.34: Effect of DHC-1 on the levels of lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the kidney of rats in cisplatin-induced nephrotoxicity (chronic model).

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	2.50 ± 0.08	1.71 ± 0.13	2.61 ± 0.10	3.11 ± 0.07
Group 2	5.64 ± 0.27**	0.61 ± 0.03***	1.94 ± 0.11***	2.00 ± 0.14***
Group 3	4.52 ± 0.59^{NS}	0.69 ± 0.03^{NS}	2.06 ± 0.08^{NS}	1.97 ± 0.06^{NS}
Group 4	3.73 ± 0.57*	1.12 ± 0.07*	2.11 ± 0.02^{NS}	2.21 ± 0.08^{NS}
Group 5	2.93 ± 0.34**	1.32 ± 0.10***	2.27 ± 0.07^{NS}	2.33 ± 0.04^{NS}
Group 6	2.53 ± 0.27**	1.39 ± 0.09***	2.43 ± 0.03**	2.78 ± 0.07***
F value	10.058	25.132	10.935	30.469
P value	0.0006	<0.0001	0.0004	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: DHC-1 (125 mg/kg, p.o.) followed by cisplatin treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Table 4.35: Effect of Activit on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the kidney of rats in cisplatin-induced nephrotoxicity (chronic model).

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	2.50 ± 0.08	1.71 ± 0.13	2.59 ± 0.36	3.11 ± 0.07
Group 2	5.64 ± 0.27***	0.61 ± 0.03***	1.94 ± 0.11**	2.00 ± 0.14***
Group 3	4.59 ± 0.34NS	0.67 ± 0.04 NS	2.17 ± 0.11 NS	2.11 ± 0.12 NS
Group 4	3.49 ± 0.29***	0.79 ± 0.04 NS	2.23 ± 0.12 NS	2.20 ± 0.12 NS
Group 5	2.68 ± 0.28***	0.98 ± 0.05*	2.44 ± 0.05*	2.78 ± 0.06**
Group 6	2.54 ± 0.15***	1.27 ± 0.09***	2.50 ± 0.04*	2.94 ± 0.06***
F value	26.738	33.322	6.925	23.176
P value	<0.0001	<0.0001	0.0029	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: Activit (125 mg/kg, p.o.) followed by cisplatin treatment

Group 4: Activit (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Activit (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*$p<0.05$; **$p<0.01$; ***$p<0.001$; NS = Non Significant

Table 4.36: Effect of Pepticare on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the kidney of rats in cisplatin-induced nephrotoxicity (chronic model).

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	2.50 ± 0.08	1.71 ± 0.13	2.59 ± 0.36	3.11 ± 0.07
Group 2	5.64 ± 0.27***	0.61 ± 0.03***	1.94 ± 0.11***	2.00 ± 0.14***
Group 3	4.99 ± 0.20NS	0.67 ± 0.04NS	2.02 ± 0.05NS	2.14 ± 0.12NS
Group 4	4.68 ± 0.22NS	0.84 ± 0.06NS	2.12 ± 0.07NS	2.23 ± 0.07NS
Group 5	3.59 ± 0.25***	1.12 ± 0.04**	2.44 ± 0.05**	2.73 ± 0.12**
Group 6	2.45 ± 0.23***	1.40 ± 0.09***	2.45 ± 0.04**	2.87 ± 0.12**
F value	38.726	35.060	13.292	17.021
P value	<0.0001	<0.0001	0.0002	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: Pepticare (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Pepticare (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.37: Effect of Normacid on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the kidney of rats in cisplatin-induced nephrotoxicity (chronic model).

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	2.50 ± 0.08	1.71 ± 0.13	2.59 ± 0.36	3.11 ± 0.07
Group 2	5.64 ± 0.27***	0.61 ± 0.03***	1.94 ± 0.11**	2.00 ± 0.14***
Group 3	4.54 ± 0.15**	0.61 ± 0.05 NS	2.09 ± 0.12 NS	2.07 ± 0.05NS
Group 4	3.76 ± 0.21***	0.77 ± 0.01 NS	2.21 ± 0.09 NS	2.14 ± 0.03NS
Group 5	3.03 ± 0.06***	0.90 ± 0.03 NS	2.34 ± 0.05 NS	2.31 ± 0.04NS
Group 6	2.89 ± 0.08***	1.22 ± 0.06***	2.56 ± 0.06**	2.63 ± 0.18**
F value	55.507	42.534	8.320	17.419
P value	<0.0001	<0.0001	0.0013	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: Normacid (125 mg/kg, p.o.) followed by cisplatin treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

4.2.5.2.3 Effect on membrane bound enzymes

4.2.5.2.3.1 Effect on Sodium Potassium ATPase

In the kidneys of cisplatin-treated rats (Group 2) the activity of Na^+K^+ATPase enzyme was significantly ($p<0.001$) reduced as compared to the control group (Group 1).

Administration of DHC-1 at all the doses, namely 125 mg/kg ($p<0.01$), 500 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) followed by cisplatin treatment resulted in a significant increase in Na^+K^+ATPase levels as compared to cisplatin control (Table 4.38).

Administration of Activit (125 mg/kg) followed by cisplatin treatment did not produce any significant increase in Na^+K^+ATPase levels; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly increased the levels of the enzyme as compared to cisplatin control (Table 4.39).

Administration of Pepticare followed by cisplatin treatment did not produce any significant increase in the levels of Na^+K^+ATPase at any of the four dose levels as compared to the cisplatin treated control group (Table 4.40).

Administration of Normacid at the doses of 125 and 250 mg/kg followed by cisplatin treatment did not affect the Na^+K^+ATPase levels; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.01$) it significantly increased the levels of Na^+K^+ATPase as compared to cisplatin control (Table 4.41).

4.2.5.2.3.2 Effect on Calcium ATPase

Treatment with cisplatin (Group 2) resulted in a significant ($p<0.001$) decrease in the Ca^{2+}ATPase activity as compared to the normal control group (Group 1).

Administration of DHC-1 at all the four doses (125, 250, 500 and 1000 mg/kg) followed by cisplatin treatment produced a significant ($p<0.001$) increase in Ca^{2+}ATPase levels as compared to the cisplatin control (Table 4.38).

Similarly, administration of 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) of Activit followed by cisplatin treatment produced a significant elevation in the levels of Ca^{2+}ATPase levels as compared to cisplatin control (Table 4.39).

Administration of Pepticare at the doses of 125 and 250 mg/kg followed by cisplatin treatment did not produce any significant change in the level of Ca^{2+}ATPase; but at the higher doses of 500 and 1000 mg/kg it significantly ($p<0.001$) increased these levels as compared to cisplatin control (Table 4.40).

Administration of Normacid (125 mg/kg) followed by cisplatin treatment did not produce any significant increase in Ca^{2+}ATPase levels; but at the higher doses of 250, 500 and 1000 mg/kg it significantly ($p<0.001$) increased the levels of the enzyme as compared to cisplatin control (Table 4.41).

4.2.5.2.3.3 Effect on Magnesium ATPase

Treatment with cisplatin (Group 2) resulted in a significant ($p<0.001$) decrease in the Mg^{2+}ATPase activity as compared to the normal control group (Group 1).

Administration of DHC-1 (125, 250, 500 and 1000 mg/kg) followed by cisplatin treatment produced a significant ($p<0.001$) increase in Mg^{2+}ATPase levels as compared to the cisplatin control (Table 4.38).

Administration of Activit followed by cisplatin treatment did not produce a significant increase in Mg^{2+}ATPase levels at the dose of 125 mg/kg; but at the higher doses of 250, 500 and 1000 mg/kg it significantly ($p<0.001$) increased the levels of the enzyme as compared to cisplatin control (Table 4.39).

Administration of Pepticare at the doses of 125, 250 and 500 mg/kg followed by cisplatin treatment did not affect the Mg^{2+}ATPase levels in kidneys as compared to the cisplatin control group; however at the higher dose of 1000 mg/kg, the drug led to a significant ($p<0.05$) rise in Mg^{2+}ATPase levels as compared to cisplatin control (Table 4.40).

Administration of Normacid (125 mg/kg) followed by cisplatin treatment did not produce any significant increase in Mg^{2+}ATPase levels;

but at the higher doses, namely 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly increased the levels of the enzyme as compared to cisplatin control (Table 4.41).

Table 4.38: Effect of DHC-1 on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the kidney of rats in cisplatin-induced nephrotoxicity (chronic model).

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	10.98 ± 0.34	4.41 ± 0.09	6.57 ± 0.18
Group 2	3.07 ± 0.70***	1.35 ± 0.14***	1.43 ± 0.24***
Group 3	5.26 ± 0.19**	2.46 ± 0.10***	2.82 ± 0.08***
Group 4	5.89 ± 0.21**	3.22 ± 0.14***	4.17 ± 0.11***
Group 5	7.10 ± 0.18***	3.63 ± 0.13***	4.54 ± 0.12***
Group 6	7.59 ± 0.20***	4.03 ± 0.10***	6.01 ± 0.11***
F value	54.918	93.596	169.76
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: DHC-1 (125 mg/kg, p.o.) followed by cisplatin treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.39: Effect of Activit on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the kidney of rats in cisplatin-induced nephrotoxicity (chronic model).

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	10.98 ± 0.34	4.41 ± 0.09	6.57 ± 0.18
Group 2	3.07 ± 0.70***	1.35 ± 0.14***	1.43 ± 0.24***
Group 3	4.28 ± 0.04 NS	2.25 ± 0.19*	2.24 ± 0.23 NS
Group 4	6.37 ± 0.22*	3.55 ± 0.12***	3.74 ± 0.14***
Group 5	8.14 ± 0.35***	4.02 ± 0.23***	4.46 ± 0.18***
Group 6	8.85 ± 1.10***	4.15 ± 0.19***	5.99 ± 0.21***
F value	26.308	54.268	104.17
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: Activit (125 mg/kg, p.o.) followed by cisplatin treatment

Group 4: Activit (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Activit (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.40: Effect of Pepticare on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the kidney of rats in cisplatin-induced nephrotoxicity (chronic model).

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	10.98 ± 0.34	4.41 ± 0.09	6.57 ± 0.18
Group 2	3.07 ± 0.70***	1.35 ± 0.14***	1.43 ± 0.24***
Group 3	3.14 ± 0.18NS	1.63 ± 0.08NS	1.56 ± 0.19NS
Group 4	3.57 ± 0.10NS	1.81 ± 0.24NS	1.77 ± 0.12NS
Group 5	3.94 ± 0.08NS	2.45 ± 0.09***	2.11 ± 0.07NS
Group 6	4.21 ± 0.32NS	2.65 ± 0.06***	2.21 ± 0.09*
F value	72.894	70.579	151.94
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: Pepticare (125 mg/kg, p.o.) followed by cisplatin treatment.

Group 4: Pepticare (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.41: Effect of Normacid on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the kidney of rats in cisplatin-induced nephrotoxicity (chronic model).

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	10.98 ± 0.34	4.41 ± 0.09	6.57 ± 0.18
Group 2	3.07 ± 0.70***	1.35 ± 0.14***	1.43 ± 0.24***
Group 3	4.42 ± 0.26NS	1.79 ± 0.13NS	2.19 ± 0.14NS
Group 4	4.57 ± 0.20NS	2.54 ± 0.09***	2.70 ± 0.18**
Group 5	4.83 ± 0.09*	2.61 ± 0.07***	3.29 ± 0.15***
Group 6	5.80 ± 0.11**	2.94 ± 0.11***	4.11 ± 0.26***
F value	62.328	98.839	84.771
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: Cisplatin control (3 mg/kg, i.p.) every week for 28 days

Group 3: Normacid (125 mg/kg, p.o.) followed by cisplatin treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by cisplatin treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by cisplatin treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by cisplatin treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*$p<0.05$; **$p<0.01$; ***$p<0.001$; NS = Non Significant

4.2.5.3 EFFECT OF DRUGS ON BODY WEIGHT (Table 4.42)

At the end of the experimental period, there was a percentage decrease of 19.35% in the control group (Group 2), which was significant ($p<0.001$) as compared to the normal group (Group 1), which recorded a percentage increase in body weight of 40.24%.

The animals administered with DHC-1 at the dose of 125 mg/kg, p.o. did not record a significant change in body weight as compared to cisplatin control group. However, upon administration of DHC-1 at the higher doses of 250 ($p<0.01$), 500 ($p<0.001$) and 1000 mg/kg ($p<0.001$) there was a significant increase in body weight as compared to cisplatin control group.

When the animals were given Activit (125 and 250 mg/kg) the decrease in the body weight was not reversed significantly as compared to the cisplatin control group. However, administration of Activit at 500 ($p<0.05$) and 1000 mg/kg ($p<0.01$), showed a significant increase in body weight as compared to cisplatin control group.

The animals pretreated with Pepticare at the dose of 125 mg/kg p.o., recorded no significant change in body weight; whereas administration of Pepticare at the doses of 250 ($p<0.05$), 500 ($p<0.01$) and 1000 mg/kg ($p<0.001$), recorded a significant increase in body weight as compared to cisplatin control group.

Pretreatment with Normacid at the dose of 125 mg/kg p.o., showed no significant change in body weight. However, on administration of Normacid at the doses of 250 ($p<0.01$), 500 ($p<0.001$) and 1000 mg/kg ($p<0.001$), there was a significant increase in body weight as compared to cisplatin control group.

Table 4.42: Effect of DHC-1, Activit, Pepticare and Normacid on body weight of rats in cisplatin-induced nephrotoxicity (chronic model).

Groups	% change in body weight				
Normal Control	235.6 ± 12.2 (+40.24)				
Cisplatin Control	135.5 ± 9.7*** (-19.35)				
		Dose (mg/kg)			
		125	250	500	1000
DHC-1	-	-6.43^{NS}	-11.13^{NS}	-13.27^{NS}	-7.74^{NS}
Activit	-	-2.74**	-5.65^{NS}	-1.07*	+8.10**
Pepticare	-	+19.17***	-2.20*	+5.06**	+17.14***
Normacid	-	+28.33***	+9.82**	+20.00***	+26.96***

Values are expressed as mean ± SEM.

Cisplatin control group was compared with the Normal control group.

DHC-1, Activit, Pepticare and Normacid treated groups were compared with Cisplatin control group.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Values in the drug treated groups indicate the % change in relation to the Cisplatin control group; + denotes increase and – denotes decrease

4.2.5.4 HISTOPATHOLOGY

Fig. 4.57(A) showed kidney from control male rats with normal morphology of the proximal tubule located in the outer stripe of the outer medulla. The tubules were lined up with cells forming a proper lumen inside.

Rats dosed i.p. with cisplatin (3 mg/kg/day) exhibited no drug-related histopathology in kidneys after 24 h (acute model) (data not shown). However, administration of cisplatin every week for 28 days (days 1, 7, 14, 21 and 28) (chronic model) resulted in severe necrosis of kidneys, which occurred in the proximal tubular epithelial cells [Fig. 4.57(B)]. Necrosis was accompanied by ballooning degeneration of cells leading to contraction of the lumen. Lumen also exhibited cytoplasmic intrusions. Widespread necrosis and sloughing of proximal tubular epithelial cells was noted.

Administration of DHC-1 [Fig. 4.57(C) to Fig. 4.57(F)] decreased the necrosis and maintained the normal cell size in the kidneys. Progressively there was lesser ballooning degeneration of cells and maintenance of the normal lumen. Thus the renal structure was maintained in DHC-1 treated groups.

Activit [Fig. 4.58(A) to Fig. 4.58(D)] also decreased the necrosis with increasing doses and maintained the normal lumen. A well maintained renal structure was observed.

Pretreatment with Pepticare [Fig. 4.59(A) to Fig. 4.59(D)] decreased the necrosis with increasing doses and the cell structure regained to normal with the increasing doses of the drug. No ballooning degeneration of cells was observed in any of the groups administered with Pepticare.

Administration of Normacid [Fig. 4.60(A) to Fig. 4.60(D)] showed progressively lesser necrosis as compared to the cisplatin control. Ballooning degeneration of cells and contraction of the lumen was observed at the doses of 125 and 250 mg/kg [Fig. 4.60 (A) and Fig. 4.60 (B)]; whereas Normacid at the higher doses [Fig. 4.60 (C) and Fig. 4.60 (D)] showed lesser ballooning degeneration of cells and contraction of the lumen.

Fig. 4.57. Photomicrographs showing effect of DHC-1 on the kidney of cisplatin-treated rats.

(Magnification 40 X)

A. Normal control

B. Cisplatin control (3 mg/kg, i.p.) every week for 28 days

C. DHC-1 (125 mg/kg, p.o.)

D. DHC-1 (250 mg/kg, p.o.)

E. DHC-1 (500 mg/kg, p.o.)

F. DHC-1 (1000 mg/kg, p.o.)

○ **Cytoplasmic intrusions**

→ **Lumen**

△ **Ballooning degeneration**

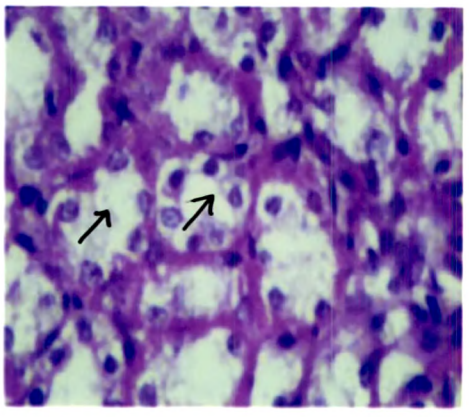


Fig. 4.57 (A)

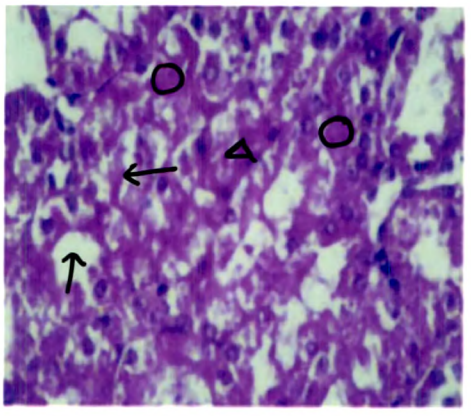


Fig. 4.57 (B)

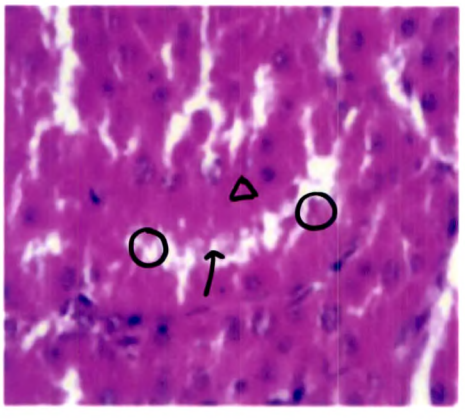


Fig. 4.57 (C)

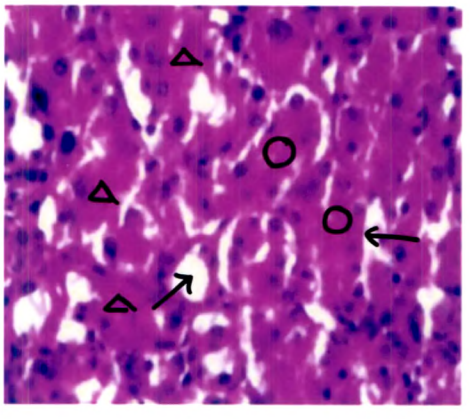


Fig. 4.57 (D)

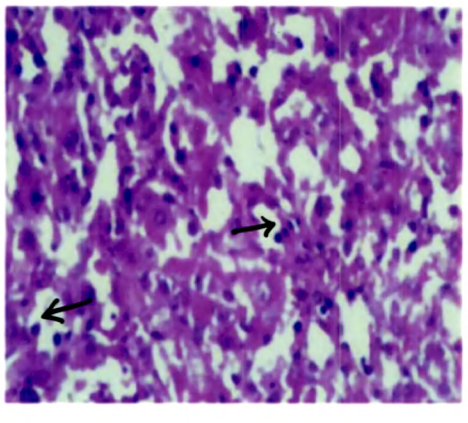


Fig. 4.57 (E)

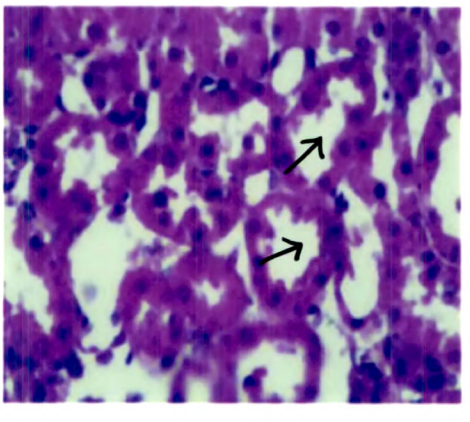


Fig. 4.57 (F)

Fig. 4.58. Photomicrographs showing effect of Activit on the kidney of cisplatin-treated rats.

(Magnification 40 X)

A. Activit (125 mg/kg, p.o.)

B. Activit (250 mg/kg, p.o.)

C. Activit (500 mg/kg, p.o.)

D. Activit (1000 mg/kg, p.o.)

○ **Cytoplasmic intrusions**

→ **Lumen**

△ **Ballooning degeneration**

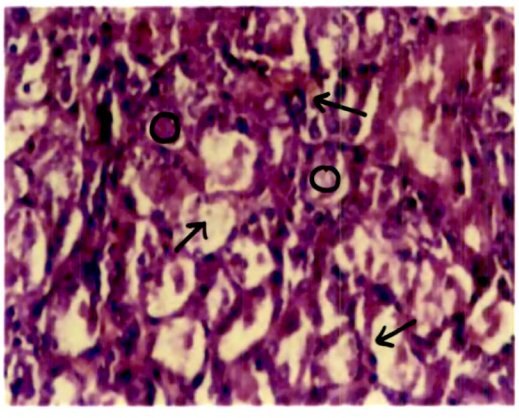


Fig. 4.58 (A)

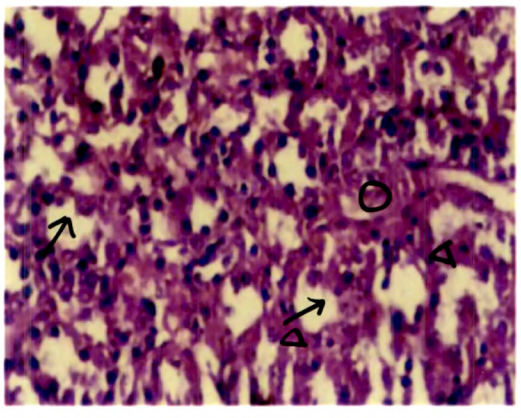


Fig. 4.58 (B)

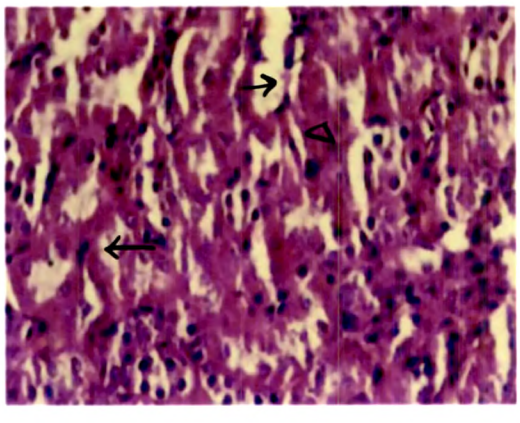


Fig. 4.58 (C)

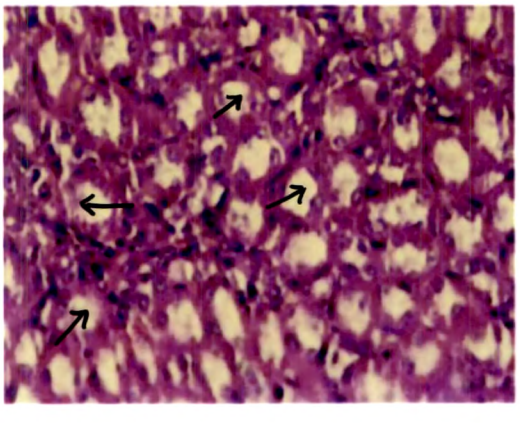


Fig. 4.58 (D)

Fig. 4.59. Photomicrographs showing effect of Pepticare on the kidney of cisplatin-treated rats.

(Magnification 40 X)

A. Pepticare (125 mg/kg, p.o.)

B. Pepticare (250 mg/kg, p.o.)

C. Pepticare (500 mg/kg, p.o.)

D. Pepticare (1000 mg/kg, p.o.)

○ **Cytoplasmic intrusions**

→ **Lumen**

△ **Ballooning degeneration**

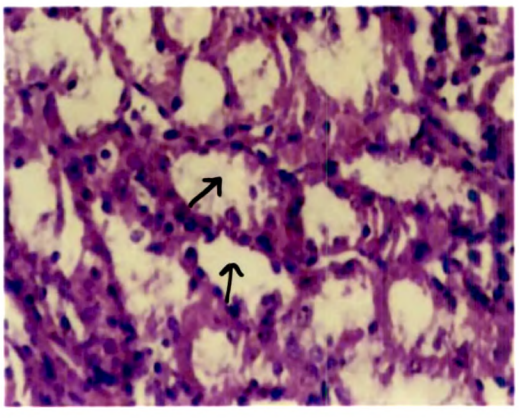


Fig. 4.59 (A)

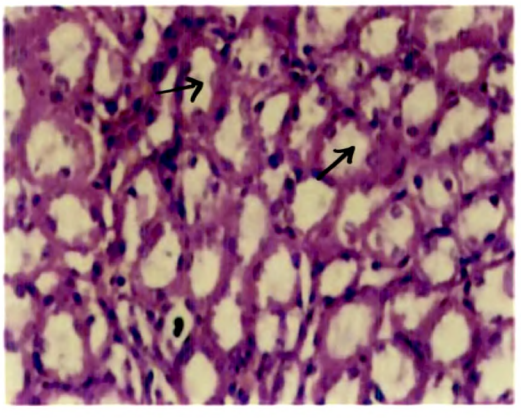


Fig. 4.59 (B)

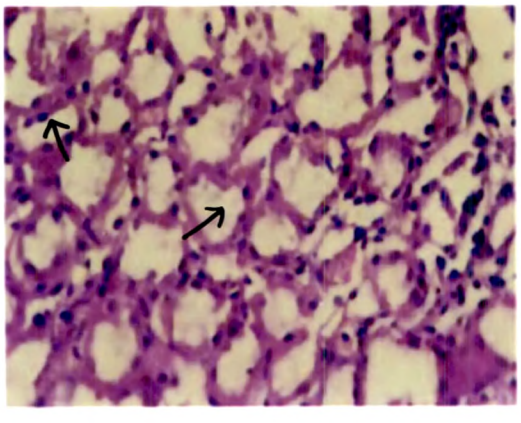


Fig. 4.59 (C)

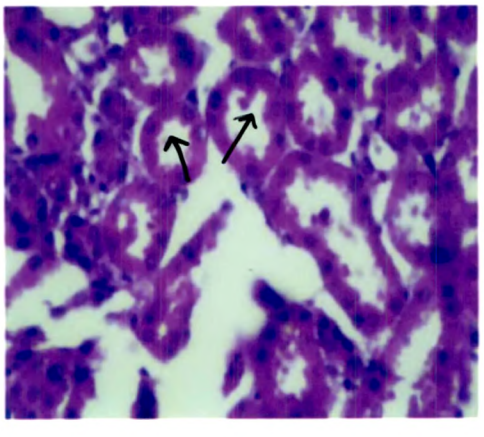


Fig. 4.59 (D)

Fig. 4.60. Photomicrographs showing effect of Normacid on the kidney of treated rats.

(Magnification 40 X)

A. Normacid (125 mg/kg, p.o.)

B. Normacid (250 mg/kg, p.o.)

C. Normacid (500 mg/kg, p.o.)

D. Normacid (1000 mg/kg, p.o.)

○ **Cytoplasmic intrusions**

→ **Lumen**

△ **Ballooning degeneration**

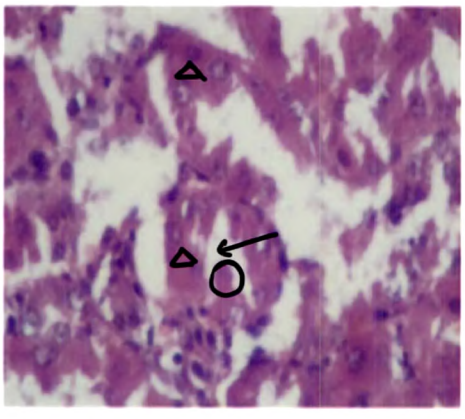


Fig. 4.60 (A)

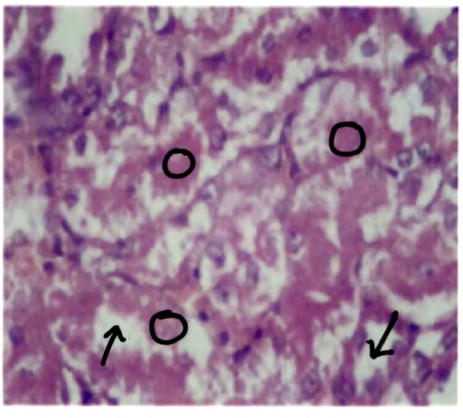


Fig. 4.60 (B)

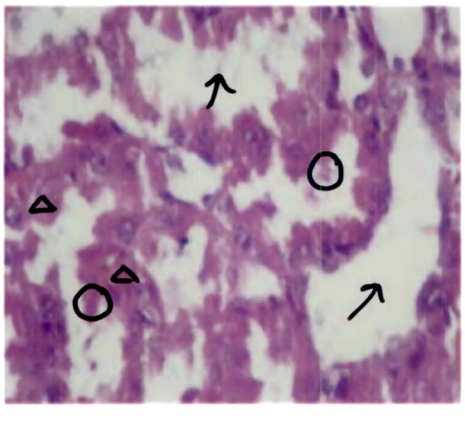


Fig. 4.60 (C)

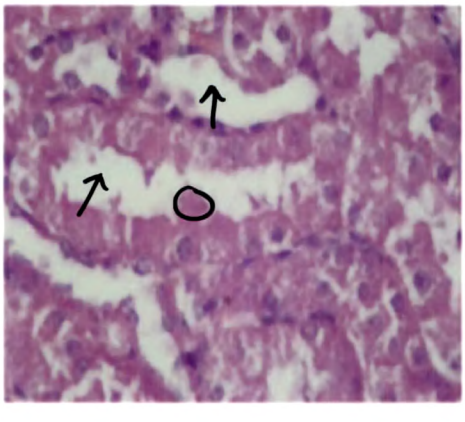


Fig. 4.60 (D)

SET 5:

CARBON-TETRACHLORIDE-INDUCED HEPATOTOXICITY.

4.2.6 CARBON TETRACHLORIDE-INDUCED LIVER DAMAGE

4.2.6.1 SERUM PARAMETERS

4.2.6.1.1 Effect of drugs on SGPT

CCl_4 treatment [2.5ml/kg, p.o. in olive oil (1:1) led to a significant ($p<0.001$) increase in level of SGPT in rats (Group 2) as compared to control group (Group 1).

Administration of DHC-1 followed by CCl_4 treatment did not produce any significant change in the level of SGPT at the doses of 125 and 250 mg/kg; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) it significantly decreased these levels as compared to CCl_4 treated control (Fig. 4.61).

Administration of Activit, Pepticare and Normacid followed by CCl_4 treatment did not reduce the levels of SGPT significantly at any of the four doses (125, 250, 500 and 1000 mg/kg) as compared to CCl_4 control (Fig. 4.63, Fig. 4.65, Fig. 4.67).

4.2.6.1.2 Effect of drugs on SGOT

CCl_4 treatment (Group 2) led to a significant ($p<0.001$) increase in level of SGOT as compared to control group (Group 1).

Administration of DHC-1 at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not produce any significant change in the level of SGOT; but at the higher doses of 500 and 1000 mg/kg it significantly ($p<0.05$) decreased these levels as compared to CCl_4 control (Fig. 4.61).

Administration of Activit (125 and 250 mg/kg) followed by CCl_4 treatment did not produce any significant change in the level of SGOT; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) it significantly decreased these levels as compared to CCl_4-treated control group (Fig. 4.63).

Administration of Pepticare followed by CCl_4 treatment did not affect the levels of SGOT, at any of the four doses (125, 250, 500 and 1000 mg/kg) as compared to CCl_4 control (Fig. 4.65).

Administration of Normacid at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not produce any significant change in the level of SGOT; but at the higher doses of 500 and 1000 mg/kg it significantly ($p<0.01$) decreased these levels as compared to CCl_4 control (Fig. 4.67).

4.2.6.1.3 Effect of drugs on alkaline phosphatase

CCl_4 treatment (Group 2) led to a significant ($p<0.001$) increase in level of alkaline phosphatase as compared to control group (Group 1).

Administration of DHC-1 followed by CCl_4 treatment significantly reduced the levels of alkaline phosphatase at all the doses namely, 125 mg/kg ($p<0.01$), 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to CCl_4 control (Fig. 4.61).

Administration of Activit at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not produce any significant change in the level of alkaline phosphatase; but at the higher doses, namely 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$) it significantly decreased these levels as compared to CCl_4 control (Fig. 4.63).

Administration of Pepticare followed by CCl_4 treatment significantly reduced the levels of alkaline phosphatase at all the doses namely, 125 mg/kg ($p<0.01$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to CCl_4 control (Fig. 4.65).

Administration of Normacid at the doses of 125, 250 and 500 mg/kg followed by CCl_4 treatment did not produce any significant change in the level of alkaline phosphatase; but at the higher dose of 1000 mg/kg ($p<0.01$) it significantly decreased these levels as compared to CCl_4 control (Fig. 4.67).

4.2.6.1.4 Effect of drugs on total bilirubin

CCl_4 treatment (Group 2) led to a significant ($p<0.001$) increase in level of total bilirubin as compared to control group (Group 1).

Administration of DHC-1 followed by CCl_4 treatment significantly reduced the levels of total bilirubin at all the doses namely, 125 mg/kg

($p<0.01$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to CCl_4 control (Fig. 4.62).

Administration of Activit followed by CCl_4 treatment did not significantly affect the levels of total bilirubin at any of the doses when compared to CCl_4 control (Group 2) (Fig. 4.64).

Administration of Pepticare followed by CCl_4 treatment significantly reduced the levels of total bilirubin at all the doses namely, 125 mg/kg ($p<0.01$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to CCl_4 control (Fig. 4.66).

Administration of Normacid (125, 250, 500 and 1000 mg/kg) followed by CCl_4 treatment did not produce any significant change in the level of total bilirubin as compared to CCl_4 control (Fig. 4.68).

Fig. 4.61. Effect of DHC-1 on the serum levels of SGPT, SGOT and alkaline phosphatase in CCl_4-induced liver damage in rats.

Fig. 4.62. Effect of DHC-1 on the serum levels of total bilirubin in CCl_4-induced liver damage in rats.

Group 1: Normal control

Group 2: CCl_4control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: DHC-1 (125 mg/kg, p.o.) followed by CCl_4 treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.61.

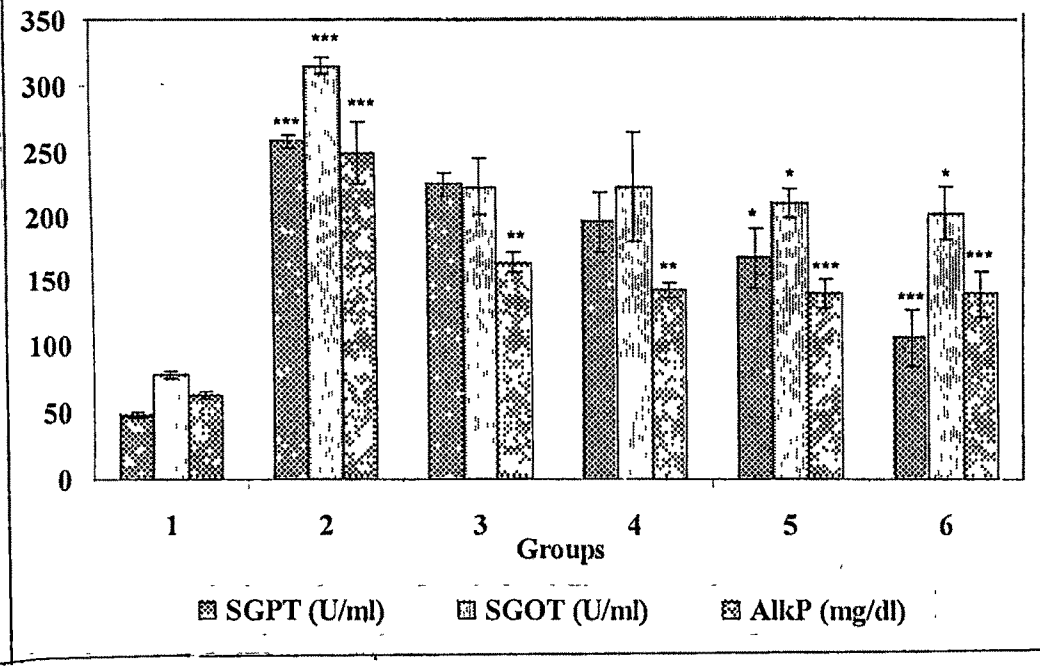


Fig. 4.62.

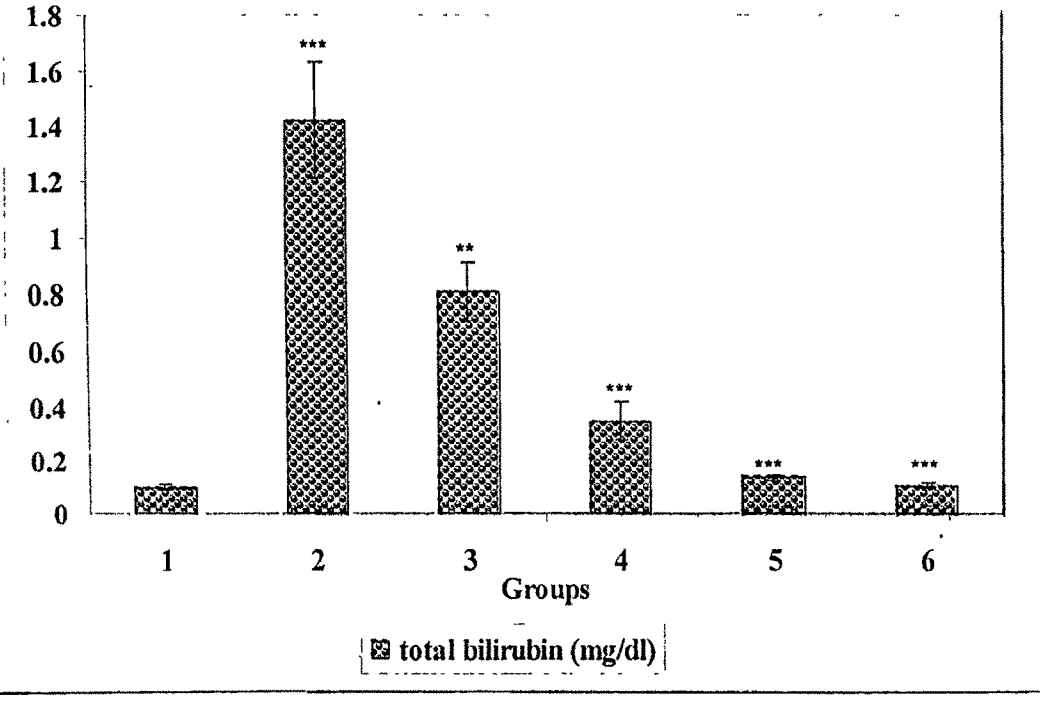


Fig. 4.63. Effect of Activit on the serum levels of SGPT, SGOT and alkaline phosphatase in CCl_4-induced liver damage in rats.

Fig. 4.64. Effect of Activit on the serum levels of total bilirubin in CCl_4-induced liver damage in rats.

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: Activit (125 mg/kg, p.o.) followed by CCl_4 treatment

Group 4: Activit (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: Activit (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.63.

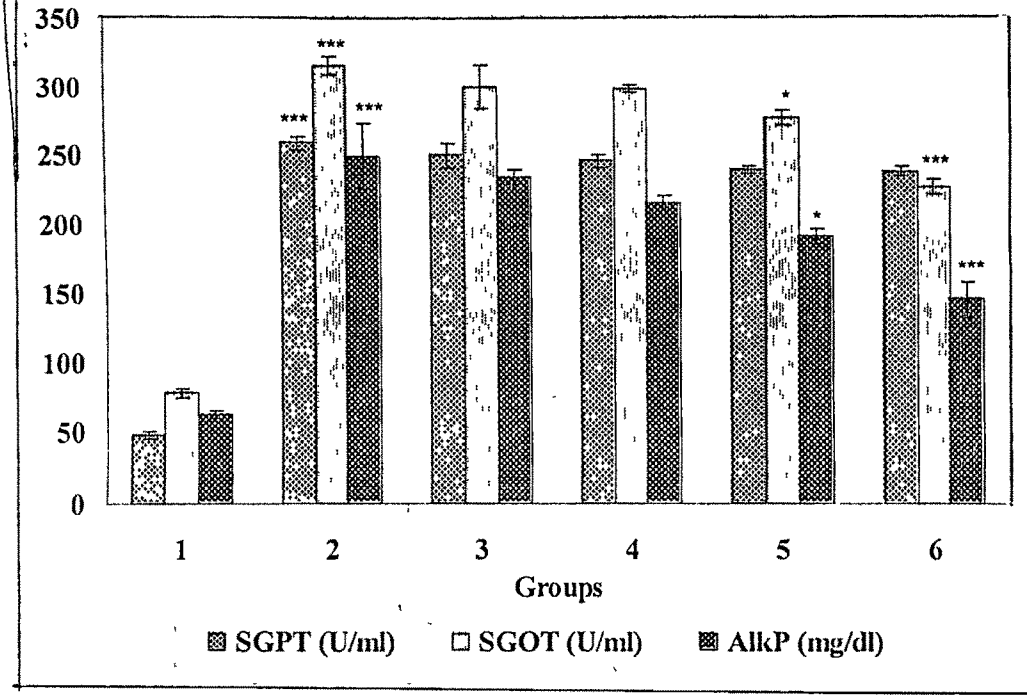


Fig. 4.64.

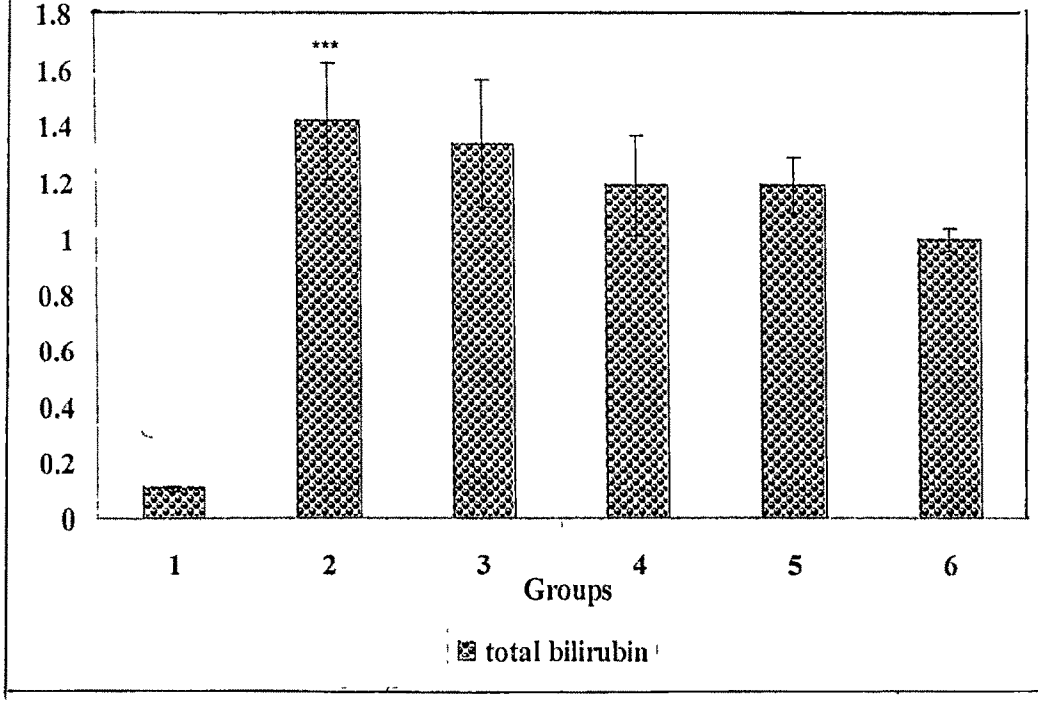


Fig. 4.65. Effect of Pepticare on the serum levels of SGPT, SGOT and alkaline phosphatase in CCl_4-induced liver damage in rats.

Fig. 4.66. Effect of Pepticare on the serum levels of total bilirubin in CCl_4-induced liver damage in rats.

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: Pepticare (125 mg/kg, p.o.) followed by CCl_4 treatment.

Group 4: Pepticare (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig.4.65.

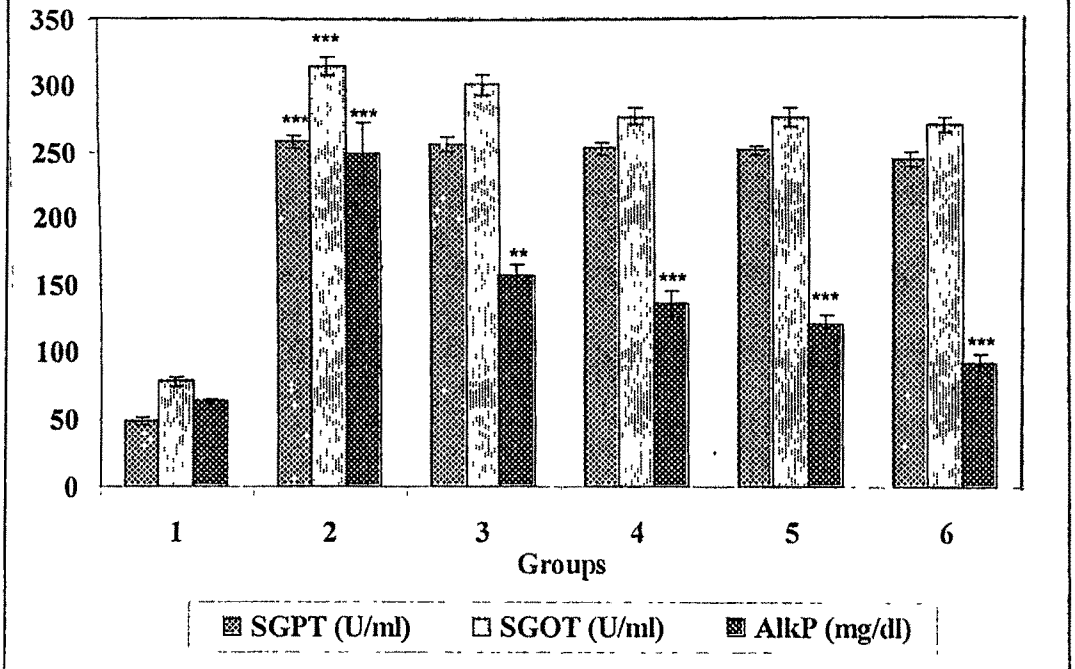


Fig. 4.66.

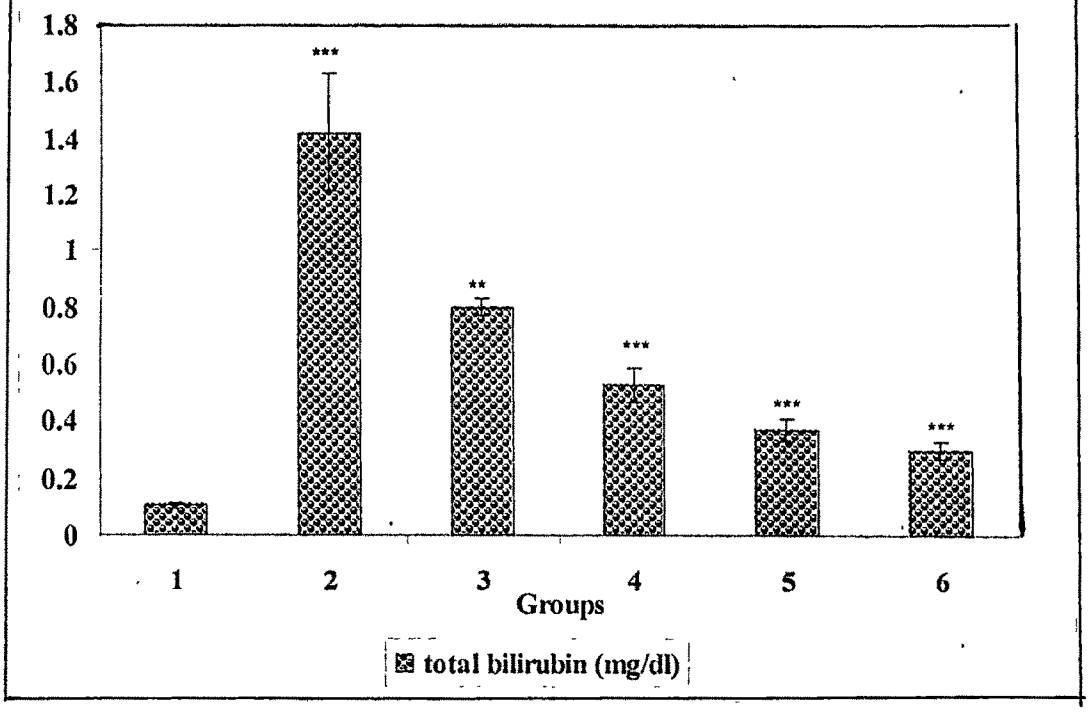


Fig. 4.67. Effect of Normacid on the serum levels of SGPT, SGOT and alkaline phosphatase in CCl_4-induced liver damage in rats.

Fig. 4.68. Effect of Normacid on the serum levels of total bilirubin in CCl_4-induced liver damage in rats.

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: Normacid (125 mg/kg, p.o.) followed by CCl_4 treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.67.

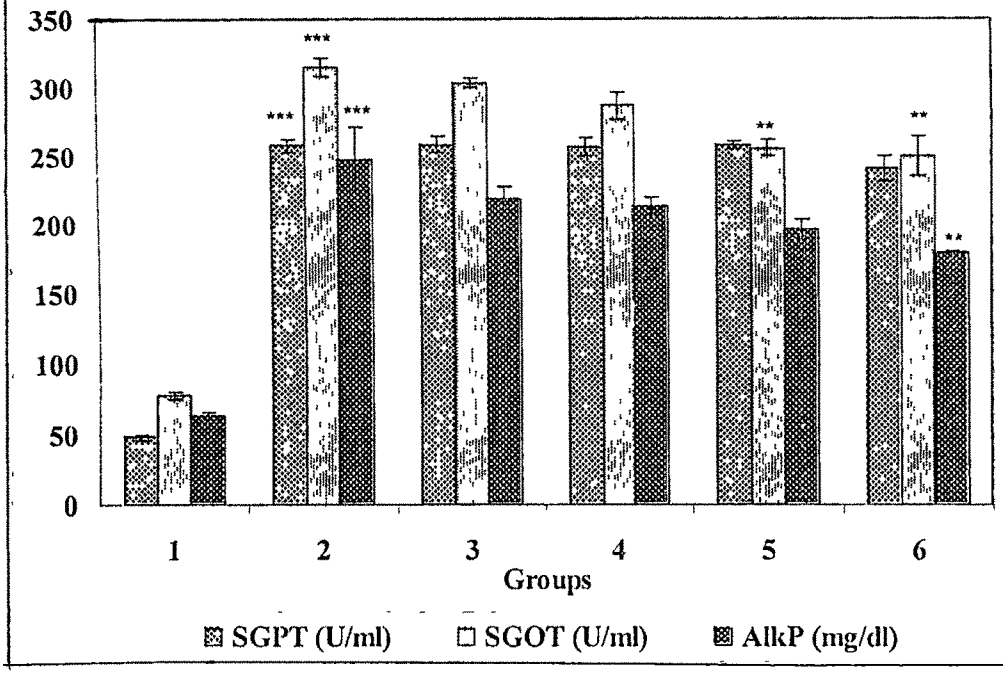
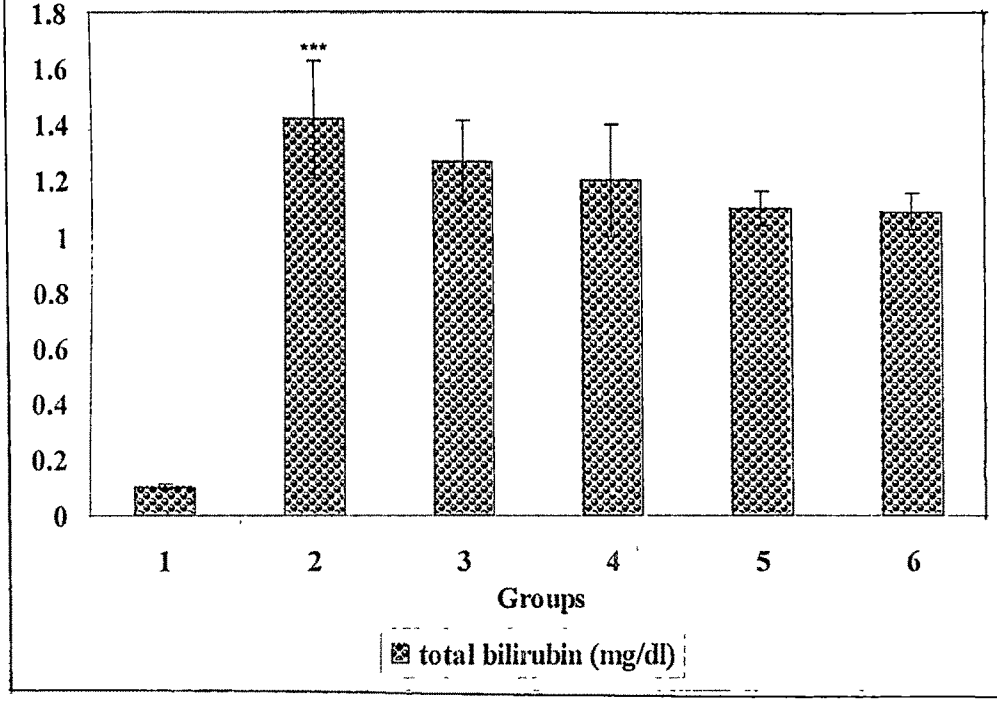


Fig. 4.68.



4.2.6.2 TISSUE PARAMETERS

4.2.6.2.1 Effect on lipid peroxidation

CCl_4 treatment of (Group 2) led to a significant ($p<0.001$) increase in lipid peroxidation (MDA content) in liver of rats as compared to the control group (Group 1).

Administration of DHC-1 (125 mg/kg) followed by CCl_4 treatment did not produce any significant change in the level of MDA in liver; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly decreased the MDA levels as compared to CCl_4 control (Table 4.43).

Administration of Activit, Pepticare and Normacid at the doses of 125, 250, 500 and 1000 mg/kg followed by CCl_4 treatment did not produce any significant change in the level of lipid peroxidation in liver as compared to CCl_4 control (Tables 4.44, 4.45 and 4.46).

4.2.6.2.2 Effect on endogenous antioxidants

4.2.6.2.2.1 Effect on Superoxide dismutase

CCl_4 treatment (Group 2) reduced the SOD activity significantly ($p<0.001$) in liver of rats as compared to control group (Group 1).

Administration of DHC-1 at the dose of 125 mg/kg followed by CCl_4 treatment did not affect the SOD content in liver as compared to the CCl_4 control group; however at the higher doses i.e. 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$), the drug led to a significant rise in SOD content as compared to CCl_4 control (Table 4.43).

Administration of Activit, Pepticare and Normacid, at the doses of 125, 250, 500 and 1000 mg/kg followed by CCl_4 treatment did not produce any significant change in the level of SOD in liver as compared to CCl_4 control (Tables 4.44, 4.45 and 4.46).

4.2.6.2.2.2 Effect on Catalase

CCl_4 treatment (Group 2) reduced the catalase activity significantly ($p<0.001$) in liver as compared to vehicle control (Group 1).

Administration of DHC-1 at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not affect the catalase content in liver as compared to the CCl_4 control group. At the higher doses i.e. 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$), the drug led to a significant rise in catalase content as compared to CCl_4 control (Table 4.43).

Administration of Activit, Pepticare and Normacid, at the doses of 125, 250, 500 and 1000 mg/kg followed by CCl_4 treatment did not produce any significant change in the level of catalase in liver as compared to CCl_4 control (Tables 4.44, 4.45 and 4.46).

4.2.6.2.1.3 Effect on Reduced glutathione

CCl_4 treatment (Group 2) reduced the GSH content significantly ($p<0.001$) in liver of rats as compared to the vehicle control (Group 1).

Administration of DHC-1 (125 mg/kg) followed by CCl_4 treatment did not affect the GSH content of liver as compared to the CCl_4 control group. At the higher doses i.e. 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$), the drug led to a significant rise in GSH content as compared to CCl_4 control (Table 4.43).

Administration of Activit and Pepticare, followed by CCl_4 treatment significantly increased the levels of GSH at all the doses namely, 125 mg/kg ($p<0.01$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to CCl_4 control (Tables 4.44 and 4.45)

Administration of Normacid followed by CCl_4 treatment also significantly increased the levels of GSH at all the doses namely, 125 mg/kg ($p<0.05$), 250 mg/kg ($p<0.001$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) as compared to CCl_4 control (Table 4.46).

Table 4.43: Effect of DHC-1 on the levels of lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the liver of rats in CCl_4-induced hepatotoxicity.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	1.53 ± 0.05	3.76 ± 0.10	3.10 ± 0.09	3.78 ± 0.20
Group 2	5.33 ± 0.10***	0.47 ± 0.04***	1.50 ± 0.08***	1.52 ± 0.16***
Group 3	4.34 ± 0.50NS	1.85 ± 0.18NS	1.83 ± 0.07 NS	1.63 ± 0.13 NS
Group 4	4.03 ± 0.15*	3.07 ± 0.59**	2.05 ± 0.11*	1.88 ± 0.07 NS
Group 5	2.56 ± 0.17***	4.29 ± 0.39***	2.18 ± 0.08**	2.26 ± 0.06*
Group 6	1.59 ± 0.31***	4.47 ± 0.40***	2.51 ± 0.11***	2.63 ± 0.06***
F value	36.297	20.897	37.224	43.980
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: DHC-1 (125 mg/kg, p.o.) followed by CCl_4 treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.44: Effect of Activit on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the liver of rats in CCl_4-induced hepatotoxicity.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	1.53 ± 0.05	3.76 ± 0.10	3.10 ± 0.09	3.76 ± 0.20
Group 2	5.33 ± 0.10***	0.47 ± 0.04***	1.50 ± 0.08***	1.52 ± 0.16***
Group 3	5.27 ± 0.24NS	1.38 ± 0.11**	1.47 ± 0.13NS	1.45 ± 0.04 NS
Group 4	5.17 ± 0.10NS	2.04 ± 0.10***	1.56 ± 0.16NS	1.66 ± 0.05 NS
Group 5	5.16 ± 0.11NS	2.35 ± 0.17***	1.73 ± 0.03NS	1.63 ± 0.13NS
Group 6	4.85 ± 0.21NS	2.40 ± 0.12***	1.74 ± 0.10NS	1.88 ± 0.07NS
F value	98.704	60.554	34.865	50.150
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: Activit (125 mg/kg, p.o.) followed by CCl_4 treatment

Group 4. Activit (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5· Activit (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6. Activit (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.45: Effect of Pepticare on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the liver of rats in CCl_4-induced hepatotoxicity.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	1.53 ± 0.05.	3.76 ± 0.10	3.10 ± 0.09	3.76 ± 0.20
Group 2	5.33 ± 0.10***	0.47 ± 0.04***	1.50 ± 0.08***	1.52 ± 0.16***
Group 3	5 33 ± 0.11NS	1.41 ± 0.10**	1.50 ± 0.09NS	1.46 ± 0.10 NS
Group 4	4.97 ± 0.18 NS	1.83 ± 0.12***	1.55 ± 0.11NS	1.60 ± 0.09 NS
Group 5	4.94 ± 0.06 NS	2.02 ± 0.10***	1.67 ± 0.08NS	1.76 ± 0.08NS
Group 6	4.90 ± 0.09 NS	2.15 ± 0.09***	1.76 ± 0.12NS	1.94 ± 0.05NS
F value	192.62	68.592	42.806	49.731
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: Pepticare (125 mg/kg, p o.) followed by CCl_4 treatment.

Group 4: Pepticare (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.46: Effect of Normacid on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the liver of rats in CCl_4-induced hepatotoxicity.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	1.53 ± 0.05	3.76 ± 0.10	3.10 ± 0.09	3.76 ± 0.20
Group 2	5.33 ± 0.10***	0.47 ± 0.04***	1.50 ± 0.08***	1.52 ± 0.16***
Group 3	5.36 ± 0.09NS	1.09 ± 0.07*	1.43 ± 0.06NS	1.42 ± 0.04 NS
Group 4	5.15 ± 0.12 NS	2.18 ± 0.07***	1.54 ± 0.06NS	1.58 ± 0.08 NS
Group 5	4.95 ± 0.12 NS	2.29 ± 0.07***	1.69 ± 0.10NS	1.72 ± 0.08NS
Group 6	4.91 ± 0.08 NS	3.23 ± 0.16***	1.81 ± 0.08NS	1.98 ± 0.08NS
F value	230.95	96.018	63.778	54.181
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: Normacid (125 mg/kg, p.o.) followed by CCl_4 treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

4.2.6.2.3 Effect on membrane bound enzymes

4.2.6.2.3.1 Effect on Sodium Potassium ATPase

In the liver of CCl_4-treated rats (Group 2) the activity of Na^+K^+ATPase enzyme was significantly ($p<0.001$) reduced as compared to the normal control group (Group 1).

Administration of DHC-1 at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not affect the Na^+K^+ATPase levels; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased the levels of Na^+K^+ATPase as compared to CCl_4 control (Table 4.47).

Administration of Activit (125 mg/kg) followed by CCl_4 treatment did not produce any significant increase in Na^+K^+ATPase levels; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased the levels of the enzyme as compared to CCl_4 control (Table 4.48).

Administration of Pepticare at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not affect the Na^+K^+ATPase levels; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased the levels of Na^+K^+ATPase as compared to CCl_4 control (Table 4.49).

Administration of Normacid at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not affect the Na^+K^+ATPase levels; but at the doses of 500 and 1000 mg/kg it significantly ($p<0.01$) increased the levels of Na^+K^+ATPase as compared to CCl_4 control (Table 4.50).

4.2.6.2.3.2 Effect on Calcium ATPase

Treatment with CCl_4 (Group 2) resulted in a significant ($p<0.001$) decrease in the Ca^{2+}ATPase activity as compared to the control group (Group 1).

Administration of DHC-1 (125 mg/kg) followed by CCl_4 treatment did not produce any significant change in the levels of Mg^{2+}ATPase; but at the doses of 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg

($p<0.001$) it significantly increased the levels of the enzyme as compared to CCl_4 control (Table 4.47).

Administration of Activit (125 mg/kg) followed by CCl_4 treatment did not produce any significant increase in Mg^{2+}ATPase levels; but at the higher doses, namely 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly increased the levels of the enzyme as compared to CCl_4 control (Table 4.48).

Similarly, administration of Pepticare at the dose of 125 mg/kg followed by CCl_4 treatment did not produce any significant increase in Mg^{2+}ATPase levels; but at the higher doses, namely 250 mg/kg ($p<0.05$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly increased the levels of the enzyme as compared to CCl_4 control (Table 4.49).

Administration of Normacid at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not produce any significant change in the level of Mg^{2+}ATPase; but at the higher doses, namely 500 mg/kg and 1000 mg/kg it significantly ($p<0.001$) increased these levels as compared to CCl_4 control (Table 4.50).

4.2.6.2.3.3 Effect on Magnesium ATPase

Treatment with CCl_4 (Group 2) resulted in a significant ($p<0.001$) decrease in the Mg^{2+}ATPase activity as compared to the control group (Group 1).

Administration of DHC-1 at the doses of 125, 250 and 500 mg/kg followed by CCl_4 treatment did not affect the Mg^{2+}ATPase levels in liver; however at the higher dose i.e. 1000 mg/kg, the drug led to a significant ($p<0.01$) rise in Mg^{2+}ATPase levels as compared to CCl_4 control (Table 4.47).

Administration of Activit (125 mg/kg) followed by CCl_4 treatment did not produce any significant increase in Mg^{2+}ATPase levels; but at the higher doses, namely 250 mg/kg ($p<0.01$), 500 mg/kg ($p<0.001$) and 1000 mg/kg ($p<0.001$) it significantly increased the levels of the enzyme as compared to CCl_4 control (Table 4.48).

Administration of Pepticare at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not affect the Mg^{2+}ATPase levels in liver as

compared to the CCl_4 control group. At the higher doses i.e. 500 mg/kg ($p<0.05$) and 1000 mg/kg ($p<0.001$), the drug led to a significant rise in Mg^{2+}ATPase levels as compared to CCl_4 control (Table 4.49).

Administration of Normacid at the doses of 125 and 250 mg/kg followed by CCl_4 treatment did not produce any significant increase in Mg^{2+}ATPase levels; but at the higher doses, namely 500 mg/kg ($p<0.01$) and 1000 mg/kg ($p<0.001$) it significantly increased the levels of the enzyme as compared to CCl_4 control (Table 4.50).

Table 4.47: Effect of DHC-1 on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the liver of rats in CCl_4-induced hepatotoxicity.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	4.68 ± 0.14	3.26 ± 0.06	3.13 ± 0.07
Group 2	2.50 ± 0.09***	1.56 ± 0.04***	2.17 ± 0.08***
Group 3	2.64 ± 0.09NS	1.70 ± 0.10NS	2.33 ± 0.04NS
Group 4	2.88 ± 0.11NS	2.14 ± 0.09*	2.46 ± 0.12NS
Group 5	3.27 ± 0.20**	2.48 ± 0.07***	2.58 ± 0.11NS
Group 6	3.98 ± 0.07***	3.02 ± 0.17***	2.84 ± 0.08**
F value	48.174	51.031	16.290
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: DHC-1 (125 mg/kg, p.o.) followed by CCl_4 treatment

Group 4: DHC-1 (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: DHC-1 (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: DHC-1 (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.48: Effect of Activit on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the liver of rats in CCl_4-induced hepatotoxicity.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	4.68 ± 0.14	3.26 ± 0.06	3.13 ± 0.07
Group 2	2.50 ± 0.09***	1.56 ± 0.04***	2.17 ± 0.08***
Group 3	2.98 ± 0.07NS	1.85 ± 0.04NS	2.39 ± 0.09NS
Group 4	3.14 ± 0.08*	2.14 ± 0.08**	2.70 ± 0.10**
Group 5	3.57 ± 0.10**	2.37 ± 0.07***	2.82 ± 0.06***
Group 6	4.41 ± 0.24***	3.45 ± 0.19***	3.06 ± 0.04***
F value	41.461	64.383	24.622
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: Activit (125 mg/kg, p.o.) followed by CCl_4 treatment

Group 4: Activit (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: Activit (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: Activit (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.49: Effect of Pepticare on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the liver of rats in CCl_4-induced hepatotoxicity.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	4.68 ± 0.14	3.26 ± 0.06	3.13 ± 0.07
Group 2	2.50 ± 0.09***	1.56 ± 0.04***	2.17 ± 0.08***
Group 3	2.51 ± 0.12NS	1.70 ± 0.10NS	2.38 ± 0.12NS
Group 4	2.85 ± 0.05NS	2.06 ± 0.07*	2.55 ± 0.09NS
Group 5	3.15 ± 0.07**	2.85 ± 0.13***	2.67 ± 0.07*
Group 6	3.33 ± 0.06***	3.29 ± 0.11***	2.94 ± 0.05***
F value	75.791	78.779	17.312
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: Pepticare (125 mg/kg, p.o.) followed by CCl_4 treatment.

Group 4: Pepticare (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: Pepticare (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: Pepticare (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

Table 4.50: Effect of Normacid on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the liver of rats in CCl_4-induced hepatotoxicity.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	4.68 ± 0.14	3.26 ± 0.06	3.13 ± 0.07
Group 2	2.50 ± 0.09***	1.56 ± 0.04***	2.17 ± 0.08***
Group 3	2.68 ± 0.14NS	1.62 ± 0.10NS	2.33 ± 0.11NS
Group 4	3.00 ± 0.06NS	2.03 ± 0.13NS	2.47 ± 0.05NS
Group 5	3.28 ± 0.11**	2.45 ± 0.11***	2.87 ± 0.09**
Group 6	3.33 ± 0.13**	3.23 ± 0.13***	3.18 ± 0.12***
F value	47.011	56.975	22.546
P value	<0.0001	<0.0001	<0.0001

Group 1: Normal control

Group 2: CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

Group 3: Normacid (125 mg/kg, p.o.) followed by CCl_4 treatment

Group 4: Normacid (250 mg/kg, p.o.) followed by CCl_4 treatment

Group 5: Normacid (500 mg/kg, p.o.) followed by CCl_4 treatment

Group 6: Normacid (1000 mg/kg, p.o.) followed by CCl_4 treatment

Values are expressed as mean ± SEM.

Group 2 was compared with Group 1.

Groups 3, 4, 5 and 6 were compared with Group 2.

*p<0.05; **p<0.01; ***p<0.001; NS = Non Significant

4.2.6.3 HISTOPATHOLOGY

Liver section of normal control rats showed cellular architecture with distinct hepatic cells, sinusoidal spaces and central vein [Fig. 4.69(A)].

Histopathological examination of liver challenged with CCl_4 showed complete disarrangement of normal hepatic cells with centrilobular necrosis, degeneration and loss of cell boundaries which were not found in the normal animals. Inflammatory cells and pyknotic nuclei were also present [Fig. 4.69(B)].

In animals treated with DHC-1 and subsequently given CCl_4, there was less hepatocellular necrosis. Inflammatory cells and pyknosis of the nuclei were not observed in the DHC-1-treated groups [Fig. 4.69(D)-4.69(F)]. Liver sections of rats treated with DHC-1 also showed a well-preserved architecture when compared with liver of rats treated only with CCl_4 [Fig. 4.69(C)-4.69(F)].

Activit treated groups showed necrosis alongwith the presence of larger areas of inflammatory cells. Loss of cell boundaries and presence of pyknotic nuclei were also observed. [Fig. 4.70(A)-4.70(D)].

Histopathology revealed that Pepticare at the lower dose showed centrilobular necrosis alongwith the presence of inflammatory cells and pyknotic nuclei [Fig. 4.71 (A)]. The necrosis was less extensive in the animals treated with the higher doses of the drug. No inflammatory cells were found and the nuclei were not found to be pyknotic [Fig. 4.71(B)-Fig. 4.71(D)].

Normacid treated groups showed necrosis with the presence of inflammatory cells and pyknotic nuclei. Cell boundaries were lost. Hepatic structure was not maintained in these groups [Fig. 4.72(A)-Fig. 4.72(D)].

Fig. 4.69. Photomicrographs showing effect of DHC-1 on the liver of CCl_4-treated rats.

(Magnification 40 X)

A- Normal control

B- CCl_4 control [2.5ml/kg, p.o. in olive oil (1:1)

C- DHC-1 (125 mg/kg, p.o.)

D- DHC-1 (250 mg/kg, p.o.)

E- DHC-1 (500 mg/kg, p.o.)

F- DHC-1 (1000 mg/kg, p.o.)

○ **Inflammatory cells**

→ **Pyknotic nucleus**

△ **Hydropic changes**

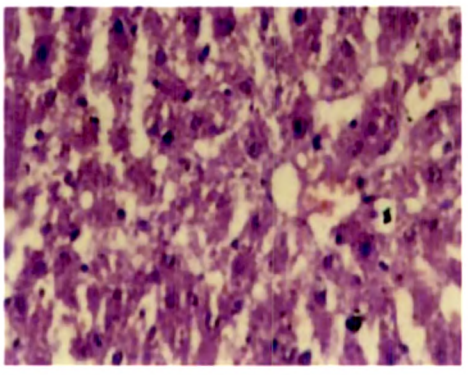


Fig. 4.69 (A)

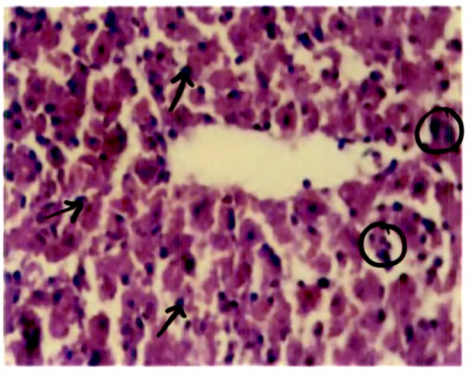


Fig. 4.69 (B)

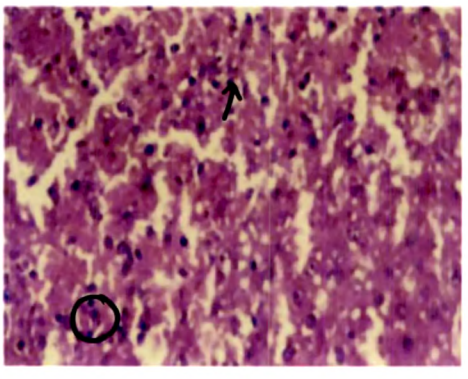


Fig. 4.69 (C)

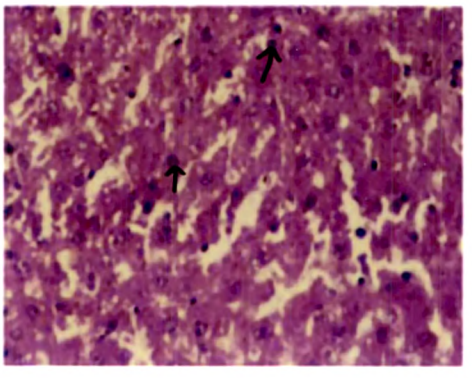


Fig. 4.69 (D)

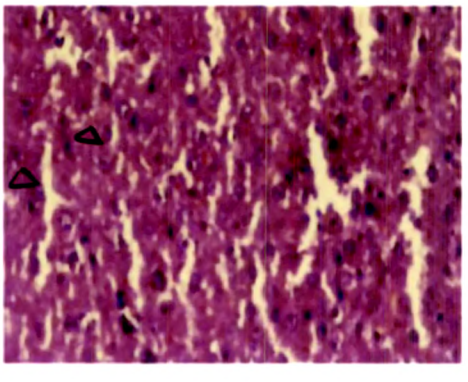


Fig. 4.69 (E)

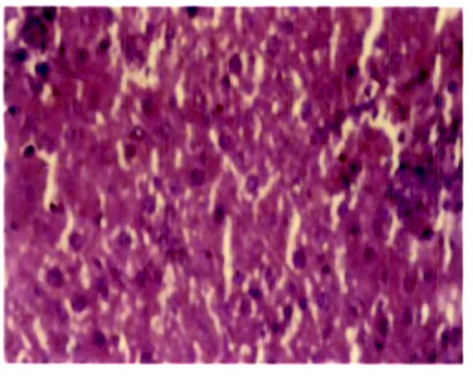


Fig. 4.69 (F)

Fig. 4.70. Photomicrographs showing effect of Activit on the liver of CCl_4-treated rats.

(Magnification 40 X)

A. Activit (125 mg/kg, p.o.)

B. Activit (250 mg/kg, p.o.)

C. Activit (500 mg/kg, p.o.)

D. Activit (1000 mg/kg, p.o.)

○ **Inflammatory cells**

→ **Pyknotic nucleus**

△ **Hydropic changes**

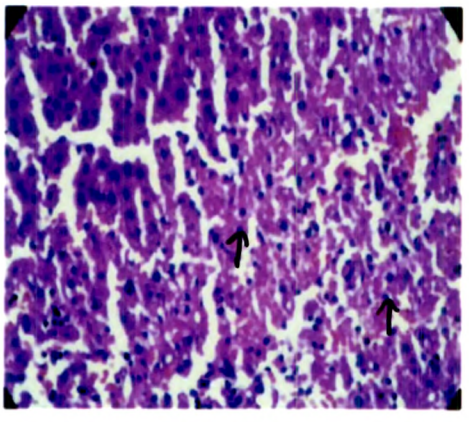


Fig. 4.70 (A)

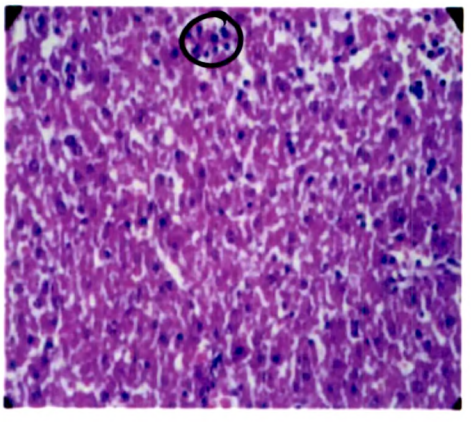


Fig. 4.70 (B)

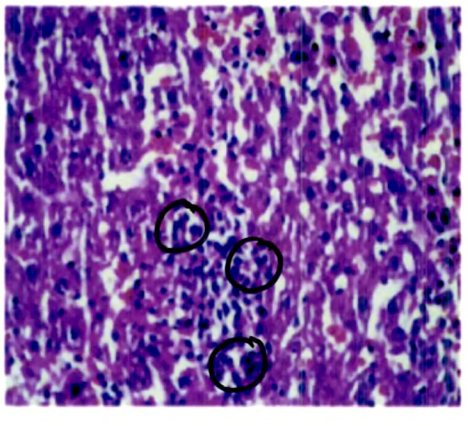


Fig. 4.70 (C)

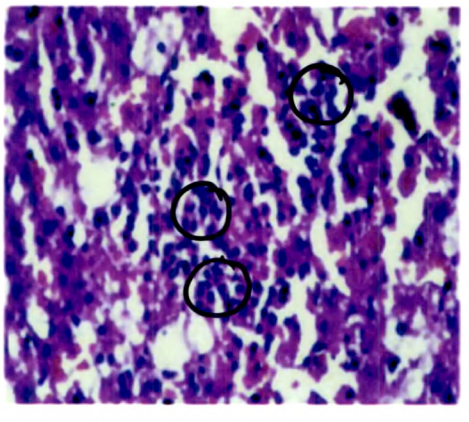


Fig. 4.70 (D)

Fig. 4.71. Photomicrographs showing effect of Pepticare on the liver of CCl_4-treated rats.

(Magnification 40 X)

A. Pepticare (125 mg/kg, p.o.)

B. Pepticare (250 mg/kg, p.o.)

C. Pepticare (500 mg/kg, p.o.)

D. Pepticare (1000 mg/kg, p.o.)

○ **Inflammatory cells**

→ **Pyknotic nucleus**

△ **Hydropic changes**

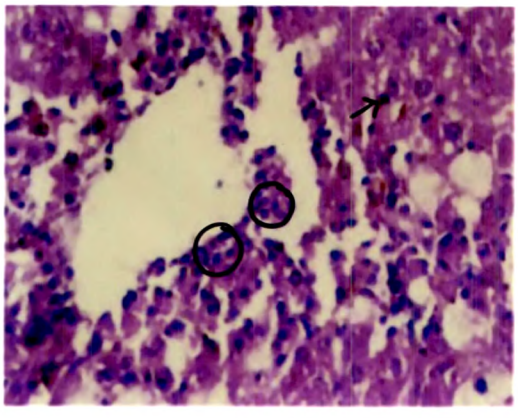


Fig. 4.71 (A)

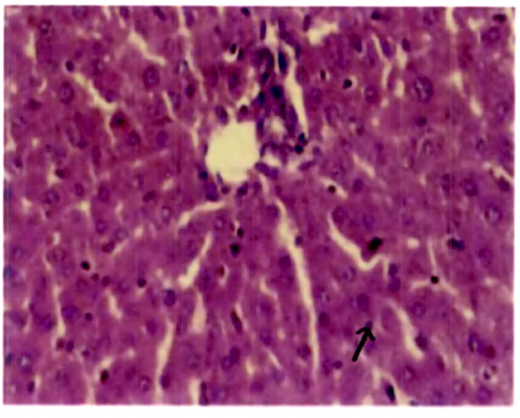


Fig. 4.71 (B)

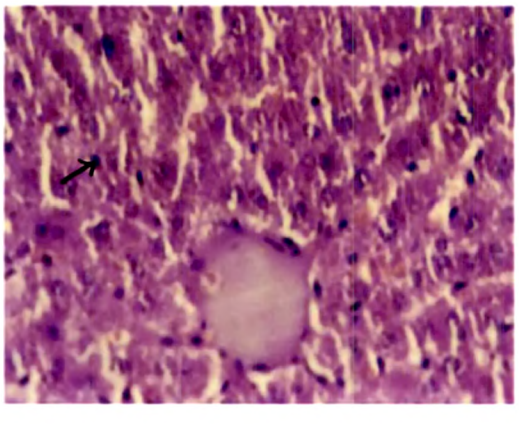


Fig. 4.71 (C)

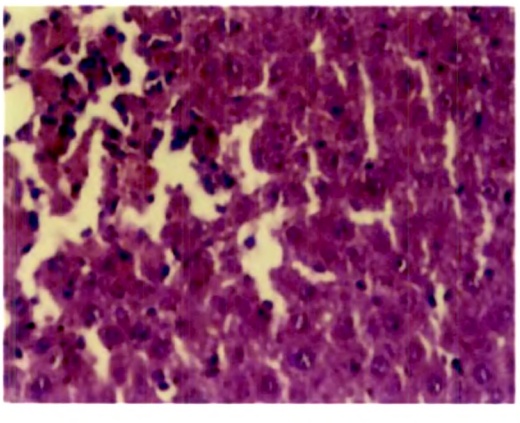


Fig. 4.71 (D)

Fig. 4.72. Photomicrographs showing effect of Normacid on the liver of CCl_4-treated rats.

(Magnification 40 X)

A. Normacid (125 mg/kg, p.o.)

B. Normacid (250 mg/kg, p.o.)

C. Normacid (500 mg/kg, p.o.)

D. Normacid (1000 mg/kg, p.o.)

○ **Inflammatory cells**

→ **Pyknotic nucleus**

△ **Hydropic changes**

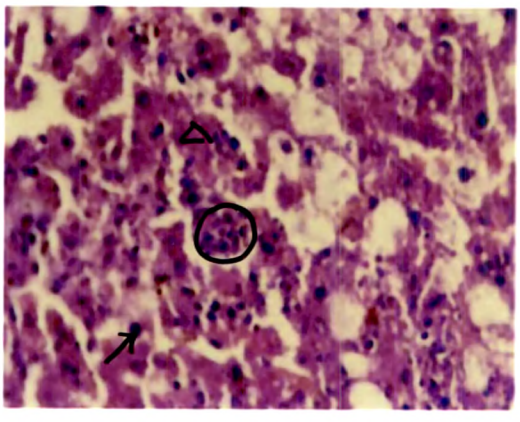


Fig. 4.72 (A)

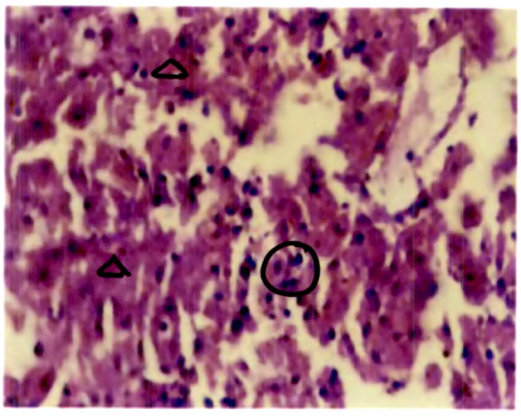


Fig. 4.72 (B)

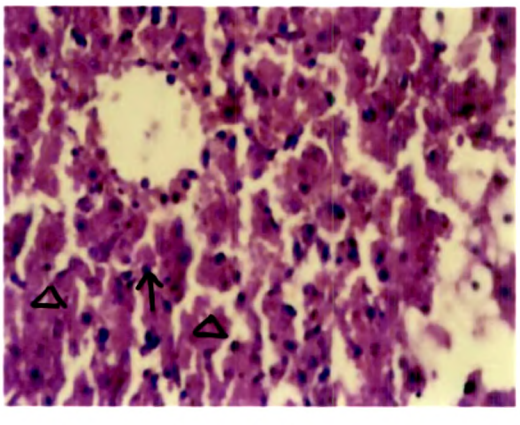


Fig. 4.72 (C)

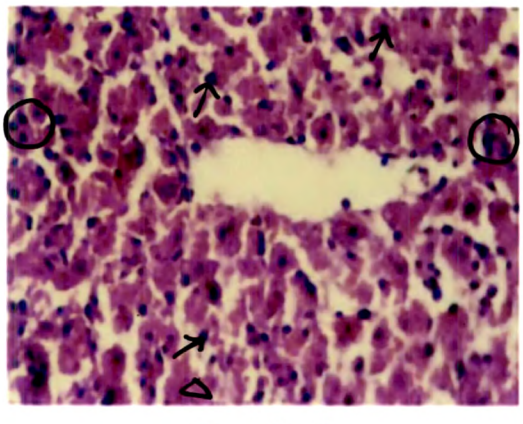


Fig. 4.72 (D)

SET 6:

HYPO-CHOLESTEROLEMIC AND ANTIOXIDANT ACTIVITY OF DRUG-X IN NORMAL AND HYPERCHOLESTEROLEMIC RABBITS.

4.2.7 HYPOCHOLESTEROLEMIC AND ANTIOXIDANT ACTIVITY OF DRUG-X

4.2.7.1 SERUM PARAMETERS

4.2.7.1.1 Effect of Drug X on total cholesterol (Chol.)

Feeding hypercholesterolemic diet (Group 3) for a period of 120 days to rabbits increased the serum total cholesterol levels significantly ($p<0.001$) as compared to the normal control group (SLD control, Group 1). Administration of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) for a period of 120 days decreased the serum total cholesterol significantly ($p<0.001$) as compared to the respective control groups 1 and 3 (Fig. 4.73).

4.2.7.1.2 Effect of Drug X on triglyceride (TGL)

The serum triglyceride levels were significantly ($p<0.001$) increased in hypercholesterolemic control group (Group 3) as compared to the normal control group (Group 1). Treatment with Drug X of normal (Group 2) ($p<0.01$) and hypercholesterolemic (Group 4) ($p<0.001$) rabbits showed a significant decrease in the serum triglyceride levels as compared to the respective control groups 1 and 3 (Fig. 4.73).

4.2.7.1.3 Effect of Drug X on phospholipid (PL)

Feeding hypercholesterolemic diet (Group 3) increased the serum phospholipid levels significantly ($p<0.001$) as compared to the SLD control (Group 1). Administration of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) for a period of 120 days decreased the serum phospholipid significantly ($p<0.001$) as compared to normal control (Group 1) and hypercholesterolemic control (Group 3) groups (Fig. 4.73).

4.2.7.1.4 Effect of Drug X on total lipid (TL)

The serum total lipid levels significantly ($p<0.001$) increased in hypercholesterolemic control rabbits of group 3 as compared to the normal control (SLD control, Group 1). Administration of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) for a period of 120 days decreased the serum total lipid significantly ($p<0.001$) as compared to the respective control groups 1 and 3 (Fig. 4.74).

4.2.7.1.5 Effect of Drug X on HDL

The serum HDL levels significantly ($p<0.001$) increased in hypercholesterolemic control group (Group 3) as compared to the normal control (SLD control, Group 1). Administration of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) for a period of 120 days decreased the serum HDL levels significantly ($p<0.001$) as compared to the control group 1; whereas in rabbits fed with hypercholesterolemic diet Drug X treatment (Group 4) resulted in a significant ($p<0.001$) increase in HDL levels as compared to the hypercholesterolemic control (Fig. 4.75).

4.2.7.1.6 Effect of Drug X on LDL

Rabbits fed with hypercholesterolemic diet (Group 3) showed a significant ($p<0.001$) increase in the serum LDL levels as compared to the normal control (SLD control, Group 1). Administration of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) for a period of 120 days decreased the serum LDL levels significantly ($p<0.001$) as compared to the respective control groups 1 and 3 (Fig. 4.75).

4.2.7.1.7 Effect of Drug X on VLDL

The serum VLDL levels significantly ($p<0.001$) increased on feeding hypercholesterolemic diet (Group 3) to rabbits as compared to the normal control (Group 1). Treatment of Drug X to rabbits fed with standard laboratory diet (Group 2) ($p<0.01$) or hypercholesterolemic diet (Group 4)

($p<0.001$) decreased the serum VLDL levels significantly as compared to the respective control groups 1 and 3 (Fig. 4.75).

Fig. 4.73. Effect of Drug X on serum total cholesterol (Chol.), triglyceride (TGL) and phospholipids (PL) in rabbits fed with standard laboratory diet (SLD) or hypercholesterolemic diet (HCD).

Fig. 4.74. Effect of Drug X on serum total lipid (TL) in rabbits fed with standard laboratory diet (SLD) or hypercholesterolemic diet (HCD).

Values are expressed as mean ± SEM.

Group 3 is compared to Group 1.

Group 2 is compared to group 1.

Group 4 is compared to Group 3

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.73.

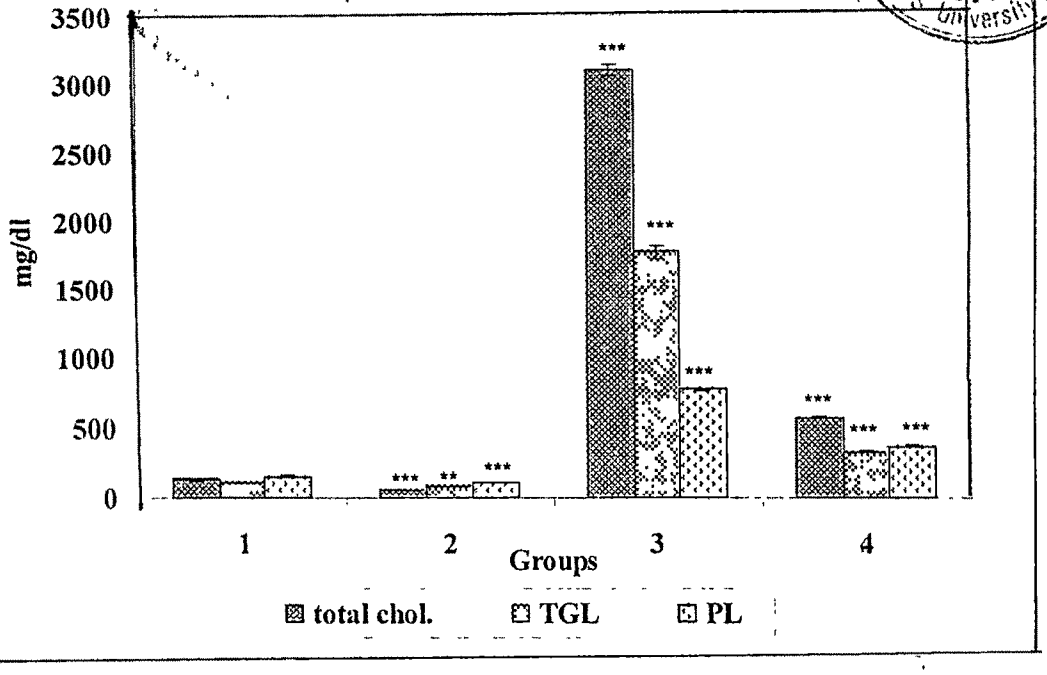


Fig. 4.74.

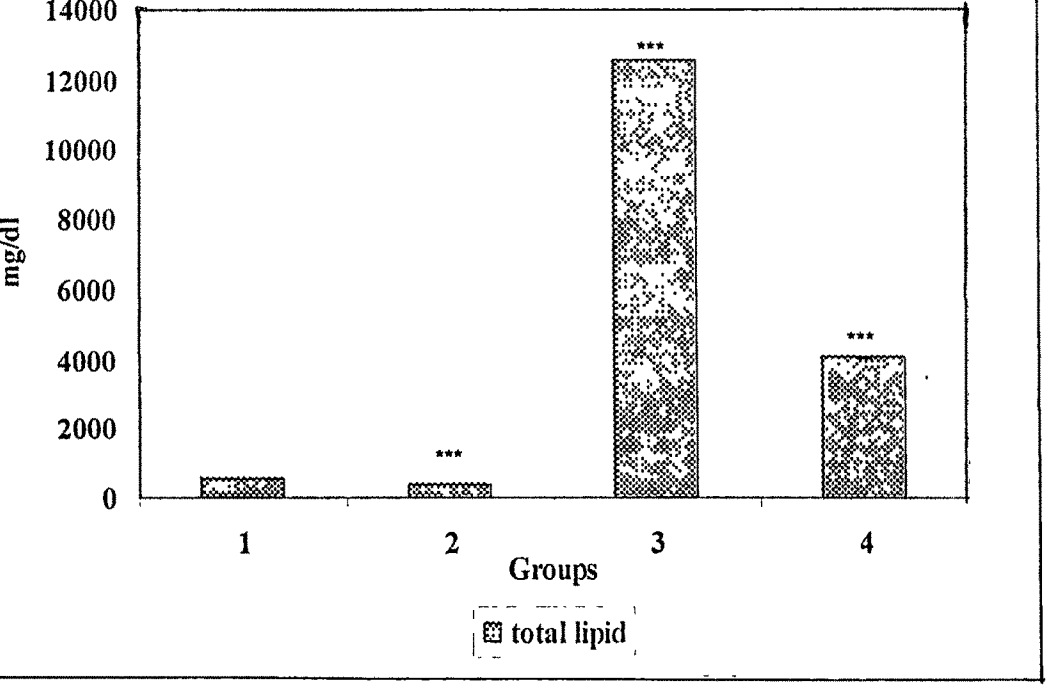


Fig. 4.75. Effect of Drug X on serum HDL, VLDL and LDL in rabbits fed with standard laboratory diet (SLD) or hypercholesterolemic diet (HCD).

Values are expressed as mean ± SEM.

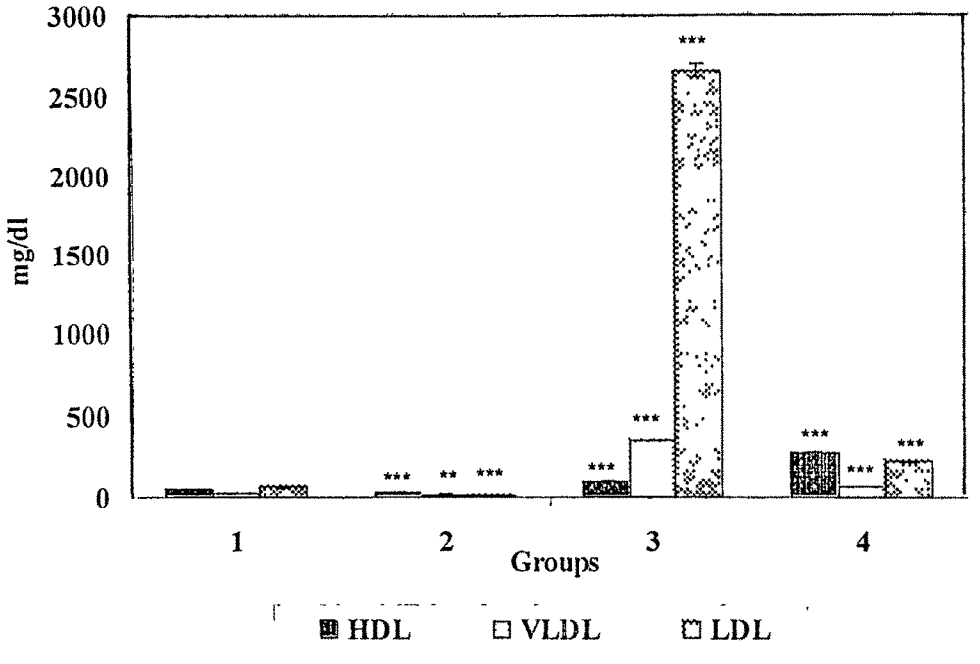
Group 3 is compared to Group 1.

Group 2 is compared to group 1.

Group 4 is compared to Group 3

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.75.



4.2.7.2 TISSUE PARAMETERS

4.2.7.2.1 LIPID PARAMETERS

4.2.7.2.1.1 Effect of Drug X on total cholesterol (Chol.)

Feeding hypercholesterolemic diet (Group 3) for a period of 120 days increased the total cholesterol levels in heart significantly ($p<0.001$) as compared to the normal control (Group 1). Administration of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) ($p<0.01$) or hypercholesterolemic diet (Group 4) ($p<0.001$) for a period of 120 days decreased the total cholesterol significantly as compared to the respective control groups 1 and 3 (Fig. 4.76).

Feeding hypercholesterolemic diet (Group 3) also increased the total cholesterol levels in liver significantly ($p<0.001$) as compared to the normal control (SLD control, Group 1). Administration of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) for a period of 120 days decreased the total cholesterol significantly ($p<0.001$) as compared to the respective control groups 1 and 3 (Fig. 4.77).

4.2.7.2.1.2 Effect of Drug X on triglyceride (TGL)

Hypercholesterolemic diet (Group 3) led to a significantly ($p<0.001$) increase in the triglyceride levels as compared to the normal control (SLD control, Group 1). Treatment of normal (Group 2) rabbits with Drug X for a period of 120 days did not significantly alter the levels of triglyceride in heart; whereas similar treatment to hypercholesterolemic (Group 4) rabbits showed a significant ($p<0.001$) reduction in triglyceride levels as compared to the respective control groups 1 and 3 (Fig. 4.76).

Hypercholesterolemic diet (Group 3) also significantly ($p<0.001$) increased the triglyceride levels as compared to the normal control (SLD control, Group 1). Treatment of normal (Group 2) rabbits with Drug X for a period of 120 days significantly ($p<0.05$) decreased the levels of triglyceride in liver as compared to the control group 1. Similar treatment to hypercholesterolemic (Group 4) rabbits also showed a significant ($p<0.001$)

reduction in triglyceride levels as compared to the hypercholesterolemic control group 3 (Fig. 4.77).

4.2.7.2.1.3 Effect of Drug X on phospholipid (PL)

A significant ($p<0.001$) increase in the phospholipid levels in heart was observed in hypercholesterolemic control group (Group 3) as compared to the normal control (SLD control, Group 1). Treatment of normal (Group 2) rabbits with Drug X did not significantly alter the levels of phospholipid in heart; whereas similar treatment to hypercholesterolemic (Group 4) rabbits showed a significant ($p<0.001$) reduction in phospholipid levels as compared to the respective control groups 1 and 3 (Fig. 4.76).

A significant ($p<0.001$) increase in the phospholipid levels in liver was also observed in hypercholesterolemic control group (Group 3) as compared to the normal control (SLD control, Group 1). The levels of phospholipid in liver after treatment with Drug X of normal (Group 2) ($p<0.01$) and hypercholesterolemic (Group 4) ($p<0.001$) rabbits for a period of 120 days significantly decreased as compared to the respective control groups 1 and 3 (Fig. 4.77).

4.2.7.2.1.4 Effect of Drug X on total lipid (TL)

The total lipid levels significantly ($p<0.001$) increased in hypercholesterolemic control rabbits of group 3 as compared to the normal control (SLD control, Group 1). Administration of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) decreased the total lipid in heart significantly ($p<0.001$) as compared to the respective control groups 1 and 3 (Fig. 4.76).

The total lipid levels significantly ($p<0.001$) increased in group 3 (HCD control) as compared to the normal control (SLD control, Group 1). Administration of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) decreased the total lipid in liver significantly ($p<0.001$) as compared to the respective control groups 1 and 3 (Fig. 4.77).

Fig. 4.76. Effect of Drug X on total cholesterol (Chol.), triglyceride (TGL), phospholipids (PL) and total lipid (TL) in heart of rabbits fed with standard laboratory diet (SLD) or hypercholesterolemic diet (HCD).

Fig. 4.77. Effect of Drug X on total cholesterol (Chol.), triglyceride (TGL), phospholipids (PL) and total lipid (TL) in liver of rabbits fed with standard laboratory diet (SLD) or hypercholesterolemic diet (HCD).

Values are expressed as mean ± SEM.

Group 3 is compared to Group 1.

Group 2 is compared to group 1.

Group 4 is compared to Group 3

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Fig. 4.76.

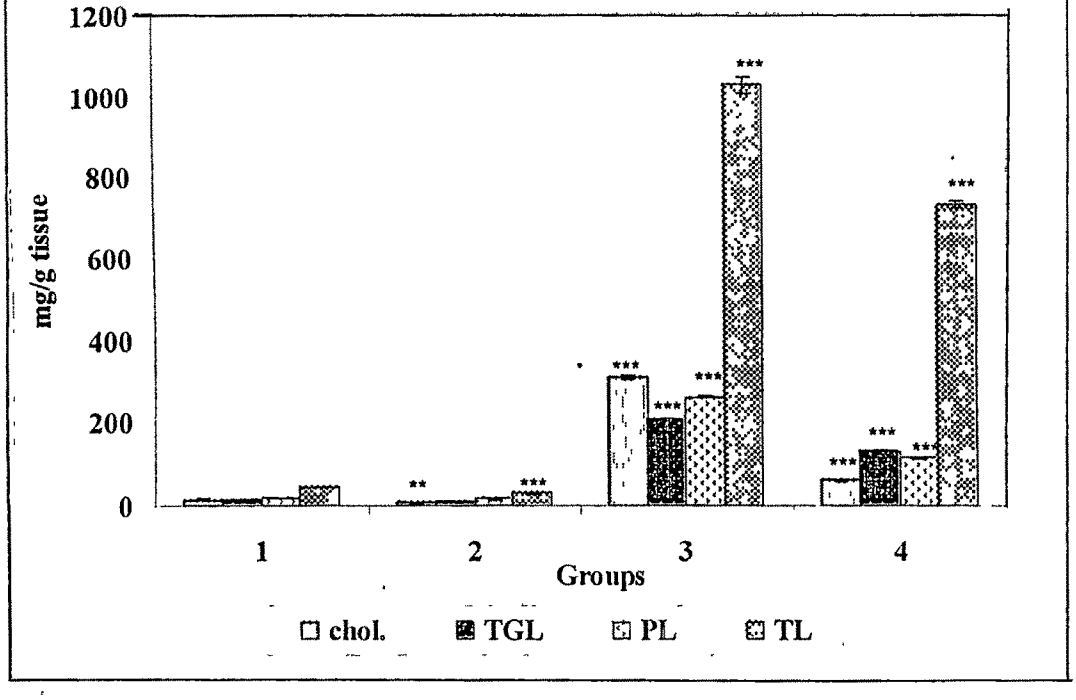
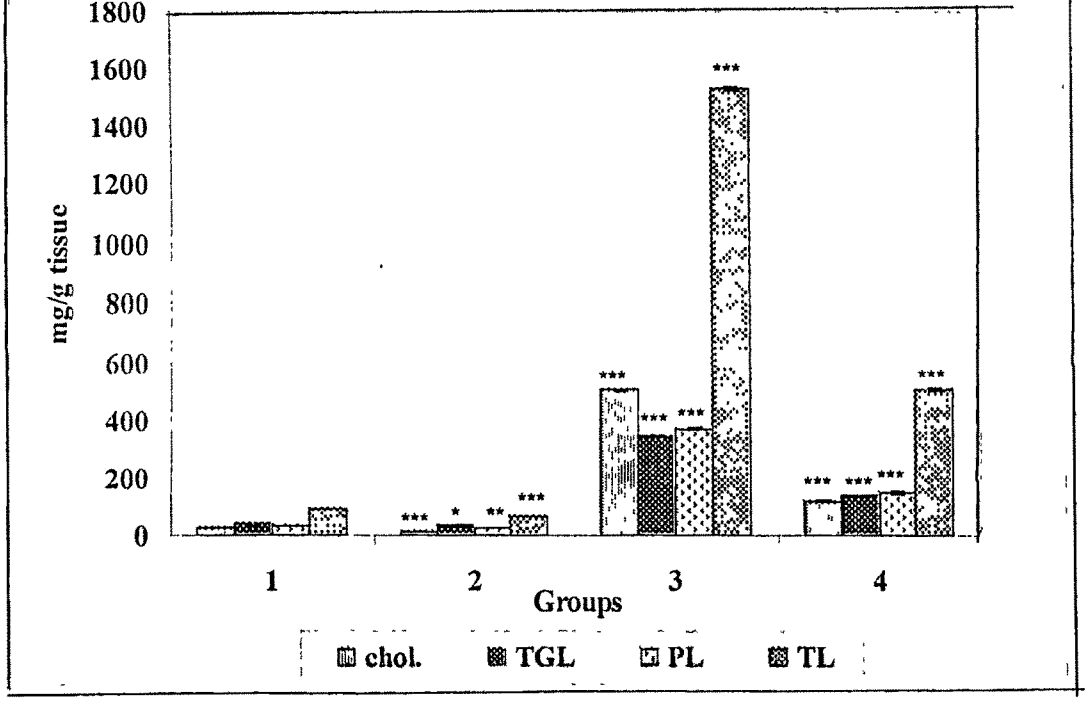


Fig. 4.77.



4.2.7.2.2 ANTIOXIDANT PARAMETERS

4.2.7.2.2.1. Effect on lipid peroxidation

Lipid peroxidation or MDA content in heart and liver of rabbits of hypercholesterolemic control group (Group 3) was significantly ($p<0.001$) higher as compared to the normal control group (Group 1) (Tables 4.51 and 4.52).

Treatment of Drug X (200 mg/kg/day, p.o.) to rabbits fed with standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) for a period of 120 days did not produce any significant change in the levels of MDA in heart and liver as compared to the respective control groups 1 and 3 (Tables 4.51 and 4.52).

4.2.7.2.2.2 Effect on endogenous antioxidants

4.2.7.2.2.2.1 Effect on Superoxide dismutase

The SOD content in heart and liver of rabbits of hypercholesterolemic control group (Group 3) was significantly ($p<0.001$) higher as compared to the normal control group (Group 1) (Table 4.51 and 4.52).

Treatment of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) for a period of 120 days neither produced any significant change in the levels of SOD in heart nor in liver as compared to the respective control groups 1 and 3 (Table 4.51 and 4.52).

4.2.7.2.2.2.2 Effect on Catalase

The catalase content in heart and liver of rabbits of hypercholesterolemic control group (Group 3) was significantly ($p<0.001$) higher as compared to the normal control group (Group 1) (Table 4.51 and 4.52).

Treatment of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) for a period of 120 days neither produced any significant change in the

levels of catalase in heart nor in liver as compared to the respective control groups 1 and 3 (Table 4.51 and 4.52).

4.2.7.2.2.2.3 Effect on Reduced glutathione

The GSH content in heart and liver of rabbits of hypercholesterolemic control group (Group 3) was significantly ($p<0.001$) higher as compared to the normal control group (Group 1) (Table 4.51 and 4.52).

Treatment of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) for a period of 120 days neither produced any significant change in the levels of GSH in heart nor in liver as compared to the respective control groups 1 and 3 (Table 4.51 and 4.52).

Table 4.51: Effect of Drug X on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the heart of rabbits fed standard laboratory diet and hypercholesterolemic diet for 120 days.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	0.75 ± 0.09	2.07 ± 0.09	3.12 ± 0.06	2.16 ± 0.04
Group 2	0.73 ± 0.04^{NS}	2.32 ± 0.06^{NS}	3.22 ± 0.08^{NS}	2.23 ± 0.04^{NS}
Group 3	5.05 ± 0 13***	1.22 ± 0.09***	2.30 ± 0.07***	1.28 ± 0.06***
Group 4	4.85 ± 0.10 ^{NS}	1.48 ± 0.11^{NS}	2.82 ± 0.11 ^{NS}	1.34 ± 0.05^{NS}
F value	230.95	31.88	25.41	116.14
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: SLD (Control)

Group 2: SLD + Drug X

Group 3: HCD

Group 4: HCD + Drug X

SLD = Standard Laboratory Diet.

HCD = Hypercholesterolemic Diet

Values are expressed as mean ± SEM.

Group 3 is compared to Group 1.

Group 2 is compared to Group 1

Group 4 is compared to Group 3.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

Table 4.52: Effect of Drug X on lipid peroxidation (MDA content), endogenous antioxidant enzymes (superoxide dismutase and catalase) and reduced glutathione in the liver of rabbits fed standard laboratory diet and hypercholesterolemic diet for 120 days.

GROUPS	Lipid Peroxidation (nmoles of MDA/ mg protein)	Reduced Glutathione (µg of GSH/ mg protein)	Superoxide Dismutase (Units/ mg protein)	Catalase (µmoles of H_2O_2 consumed/ min/ mg protein)
Group 1	0.98 ± 0.04	3.07 ± 0.09	3.27 ± 0.09	3.19 ± 0.13
Group 2	1.09 ± 0.10^{NS}	3.12 ± 0.09^{NS}	3.21 ± 0.08 ^{NS}	3.31 ± 0.12^{NS}
Group 3	4.99 ± 0.09***	1.05 ± 0.09***	1.74 ± 0.08***	1.96 ± 0.07***
Group 4	4.99 ± 0.05 ^{NS}	1.22 ± 0.11^{NS}	2.01 ± 0.05^{NS}	2.15 ± 0.13^{NS}
F value	878.23	136.98	92.25	36.79
P value	<0.0001	<0.0001	<0.0001	<0.0001

Group 1: SLD (Control)

Group 2: SLD + Drug X

Group 3: HCD

Group 4: HCD + Drug X

SLD = Standard Laboratory Diet.

HCD = Hypercholesterolemic Diet.

Values are expressed as mean ± SEM.

Group 3 is compared to Group 1.

Group 2 is compared to Group 1

Group 4 is compared to Group 3.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

4.2.7.2.2.3 Effect on membrane bound enzymes

4.2.7.2.2.3.1 Effect on Sodium Potassium ATPase

The Na^+K^+ATPase content in heart and liver of rabbits of hypercholesterolemic control group (Group 3) was significantly ($p<0.001$) higher as compared to the normal control group (Group 1) (Table 4.53 and 4.54).

Treatment of Drug X (200 mg/kg/day, p.o.) to normal rabbits fed a standard laboratory diet (Group 2) for a period of 120 days did not produce any significant change in the levels of Na^+K^+ATPase in heart but treatment with the same in hypercholesterolemic rabbits produced a significant ($p<0.01$) increase in Na^+K^+ATPase levels in heart (Table 4.53).

Treatment of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) produced no significant change in the levels of Na^+K^+ATPase in liver as compared to the respective control groups 1 and 3 (Table 4.54).

4.2.7.2.2.3.1 Effect on Calcium ATPase

The Ca^{2+}ATPase content in heart and liver of rabbits of hypercholesterolemic control group (Group 3) was significantly ($p<0.001$) higher as compared to the normal control group (Group 1) (Table 4.53 and 4.54).

Treatment of Drug X (200 mg/kg/day, p.o.) to normal rabbits fed a standard laboratory diet (Group 2) for a period of 120 days did not produce any significant change in the levels of Ca^{2+}ATPase in heart but treatment with the same in hypercholesterolemic rabbits produced a significant ($p<0.05$) increase in Ca^{2+}ATPase levels in heart (Table 4.53).

Whereas, treatment of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) produced no significant change in the levels of Ca^{2+}ATPase in liver as compared to the respective control groups 1 and 3 (Table 4.54).

4.2.7.2.2.3.1 Effect on Magnesium ATPase

The Mg^{2+}ATPase content in heart and liver of rabbits of hypercholesterolemic control group (Group 3) was significantly ($p<0.001$) higher as compared to the normal control group (Group 1) (Table 4.53 and 4.54).

Treatment of Drug X (200 mg/kg/day, p.o.) to normal rabbits fed a standard laboratory diet (Group 2) for a period of 120 days did not produce any significant change in the levels of Mg^{2+}ATPase in heart but treatment with the same in hypercholesterolemic rabbits produced a significant ($p<0.01$) increase in Mg^{2+}ATPase levels in heart (Table 4.53).

Whereas, treatment of Drug X (200 mg/kg/day, p.o.) to rabbits fed a standard laboratory diet (Group 2) or hypercholesterolemic diet (Group 4) produced no significant change in the levels of Mg^{2+}ATPase in liver as compared to the respective control groups 1 and 3 (Table 4.54).

Table 4.53: Effect of Drug X on membrane bound enzymes, namely Na^+K^+ATPase, Ca^{2+}ATPase and Mg^{2+}ATPase in the heart of rabbits fed standard laboratory diet and hypercholesterolemic diet for 120 days.

GROUPS	Na^+K^+ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Ca^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)	Mg^{2+}ATPase (µmoles of inorganic phosphorus liberated/min/ mg protein)
Group 1	4.89 ± 0.11	3.23 ± 0.08	3.01 ± 0.10
Group 2	4.61 ± 0.10^{NS}	3.31 ± 0.11^{NS}	3.02 ± 0.11^{NS}
Group 3	2.58 ± 0.13***	1.84 ± 0.08***	1.62 ± 0.15***
Group 4	3.46 ± 0.16**	2.33 ± 0.12*	2.39 ± 0.10**
F value	68.78	51.31	33.34
P value	<0.0001	<0.0001	<0.0001

Group 1: SLD (Control)

Group 2: SLD + Drug X

Group 3: HCD

Group 4: HCD + Drug X

SLD = Standard Laboratory Diet.

HCD = Hypercholesterolemic Diet.

Values are expressed as mean ± SEM.

Group 3 is compared to Group 1.

Group 2 is compared to Group 1.

Group 4 is compared to Group 3.

$^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; NS = Non Significant

4.2.7.3 EFFECT OF DRUG X ON BODY WEIGHT (Table 4 55)

There was a significant ($p<0.001$) increase in the body weight of rabbits after feeding hypercholesterolemic diet (Group 3) for a period of 120 days as compared to those fed with standard laboratory diet (Group 1).

Treatment with Drug X (*Moringa oleifera*) for 120 days to normal rabbits (Group 2) did not result in any significant change in body weight as compared to normal rabbits (Group 1).

However, treatment of hypercholesterolemic rabbits with Drug X (Group 4) for similar period resulted in a significant ($p<0.001$) decrease in body weight as compared to the hypercholesterolemic control animals (Group 3)

Table 4.55: Effect of Drug X (*Moringa oleifera*) on change in body weight in rabbits fed standard laboratory diet and hypercholesterolemic diet daily for 120 days.

Groups	Change in body weight (kg)
Group 1	0.317 ± 0.025
Group 2	-18.61^{NS}
Group 3	0.992 ± 0.09***
Group 4	-89.11***

Group 1: SLD (Control)
Group 2: SLD + Drug X
Group 3: HCD
Group 4: HCD + Drug X
SLD = Standard Laboratory Diet.
HCD = Hypercholesterolemic Diet.

Control values are expressed as mean ± SEM.
Groups 2 and 3 are compared to group 1;
Group 4 is compared to group 3
$^{***}p<0.001$; $^{**}p<0.01$; $^{*}p<0.05$
Values in rows 2 and 4 indicate the % change in relation to the corresponding controls; + denotes increase and – denotes decrease