ORIGINAL ARTICLE

Evaluation of Histopathological Changes in Isoniazid and Rifampicin induced liver injury and protective role of Zinc Sulfate in Albino rats

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ABSTRACT

Background: Hepatic disorders are becoming major health issue. Presently available treatment options in hepatic failure cases are not 100% curative except organ transplantation which is not cost effective. Development of inexpensive treatment option is needed so regenerative supplements offer good approach for prevention of hepatic dysfunction. Zinc sulfate supplementation can prevent liver damage by antioxidant effects.

Aim: To find out histoprotective effect of Zinc Sulfate7mg /kg/day against Isoniazid 50mg/kg/day and Rifampicin 100 mg/kg/day induced histopathological changes.

Methods/results: Twenty one albino male rats were included in study. All are divided in GX, GY and GZ (Seven rats in each group). Histopathological changes were induced by Isoniazid and Rifampicin in GY, Z. Histoprotection of Zinc sulfate supplementation was evaluated in GZ by microscopy of following features eosinophilic infiltrate, lobular lymphocytic infiltrate, portal lymphocytic infiltrate, portal and lobular plasma cellular infiltrate, perivenular necrosis, bridging/ confluent necrosis, steatosis, fibrosis, neutrophils, sinusoidal distension, hepatocytes enlargement, inflammed portal area, congestion, prominent kuppfer cells and mast cells. Significant changes in parameters like lobular lymphocytic infiltrate, portal lymphocytic infiltrate, portal and lobular plasma cellular infiltrate, steatosis, neutrophils, sinusoidal distension, hepatocytes enlargement, inflammed portal area, congestion, prominent kuppfer cells and mast cells (p-value 0.05) were observed among various groups.

Conclusion: This study provided histopathological evidence of hepatoprotective effect of Zinc sulfate supplementation.

Keywords: Hepatotoxicity, Histopathology, Histoprotection, Hepatoprotaction, Isonazid, Rifampin, Zinc sulfate

INTRODUCTION

Liver toxicity is defined as impaired liver function and histopathological changes[1]. Xenobiotics/ drugs induced hepatic damage is one of the main cause of hepatic failure. (2) Thousands of marketed drugs are associated with liver damage[3]. Hepatotoxicity induced by first line anti-TB drugs (Isonazid, Rifampin**)** is a serious health problem[4]. Only organ transplantation is available treatment modality for cure of hepatic failure[5]. Its practical application is restricted due to economic issues, limited availability of donors and immunological rejections. Development of newer approaches for prevention of hepatic failure are direly needed. So during the last 20–30 years use of regenerative supplemental medicines are increasing[5]. At present no promising option is available for treatment of hepatotoxicity. (6) An essential trace element Zinc is used in prophylaxis and treatment of liver dysfunctions[7]. Zinc is required for normal functioning of enzymes and thousand transcription factors in human body[8]. various enzymes like oxidoreductases, hydrolases, transferases, lyases, isomerases and ligases requires Zinc for proper functioning[9]. It has antioxidant properties[10]. It plays important role in anti-inflammatory processes, signaling pathways, cellular metabolism such as structural, regulatory or catalytic metabolism and immune system modulation. Its antioxidant action is due to induction of glutathione, catalase, sulfhydryls and metallothionine (cysteine rich protein which is involved in electrophilic scavenging and Zinc homeostasis)[11].

MATERIAL AND METHODS

Study design: Animal experimental study.

Sampling technique: Simple random sampling was done by lottery method.

Sample size: twenty one albino rats (seven rats in each group) were included in study.

Inclusion criteria: Healthy, male albino rats weighing 150-200g

Animals keeping: Rats, according to inclusion criteria were purchased and divided into three groups GX, GY and GZ from University Of Veterinary and Animal Sciences Lahore and kept in hygienic environmental conditions, under natural light and dark cycles, at 23±2 degree centigrade, in iron cages. All animals were properly labeled and were provided rodent chow and water.

Preparation of doses: The calculated doses of Isoniazid 50mg/kg/day (12), Rifampicin 100 mg/kg/day (12) and Zinc Sulfate 7mg/kg/day (13) according to the weights of animals were dissolved in calculated amount of distilled water (0.3 ml per rat) and were given through oral route for 14 days (from day 0-13).

GX (Normal Control): Administered distilled water equivalent to amount given to experimental group (0.3 ml).
GY (Positive Control): Administered Isoniazid and Rifampicin (hepatotoxic agents) simultaneously.
GZ: Administered Isoniazid, Rifampicin along with Zinc Sulfate (30 min before hepatotoxic agents).
LFTs were performed on day 6 by collecting blood sample through cardiac puncture to check induction of hepatotoxicity. Animals were also weighed weekly for dose adjustment of drugs.
Euthanization: Twenty four hours after last dose all rats were sacrificed on 14th day by cervical dislocation.
Histological examination: Each albino rat was sacrificed on 14th day and Liver was removed and sliced. Slices were fixed in 10% formalin solution. Liver tissues passed through automatic processor for dehydration in ascending grades of ethanol (70, 80, and 90) and absolute alcohol. Tissues were washed in Xylene and dipped in paraffin wax. Sections of 5 micrometer thickness were obtained by the use of microtome. Slides were numbered and tissues were mounted. Dewaxing was done in incubator and dipped in xylene again. Slides were hydrated by passing through decreasing concentration of alcohol (100%, 90%, 80% and 70%). All slides were dipped in haematoxylin for 3-5 min and washed in running water. Then slides were placed in 1% acid alcohol for 5 min and again washed in tap water and put in 1% ammonia solution for 1-2 min followed by water wash, and putted in eosin stain for 5 min. The stained sections were washed in tap water for 2-3min and their dehydration was done by placing the slides in increasing concentration of alcohol and cleared in xylene. The stained sections were mounted with DPX and examined under microscope to evaluate liver parenchymal changes such as eosinophilic infiltrate, lobular lymphocytic infiltrate, portal lymphocytic infiltrate, portal and lobular plasma cellular infiltrate, perivenular necrosis, bridging/ confluent necrosis, steatosis, fibrosis, neutrophils, sinusoidal distension, hepatocytes enlargement, inflammed portal area, congestion, prominent kuppfer cells and mast cells[14,15].
Data analysis: All the qualitative and quantitative data was entered in SPSS version 20 and graph pad prism version 5 respectively for analysis. Quantitative data was expressed as Mean ± S.D. Mean plots were used for graphical presentation to see changes in the parameters. The data was evaluated by one way analysis of variance followed by Tukeys multiple comparison tests. Histopathological changes were expressed as frequencies and percentages; Chi-square test was used for evaluation. P-value of less than 0.05 was considered significant.

RESULTS AND DISCUSSION

Effect on body weight: Changes in weight of animals of different groups are shown in (table-1, fig-1). Only mathematical increase was found in GY and GZ as compared to GX. Comparing GY and GZ mild mathematical reduction in body weight was observed. But statistically weight changes were not significant. Zinc sulfate administration has shown weight gain against Nickle and Lithium induced hepatotoxicity.(16) Weight gain was also observed in GY even after administration of hepatotoxic drugs (Isoniazid and Rifampicin) as these results are in consistence with previous study results conducted by Harsh Wardhan[17].

Total 21 liver specimens were examined for various histopathological parameters in liver. The frequency and percentage 14, 66.666% respectively for all parameters has been summarized in table 2. The maximum frequency and percentage is observed for lobular lymphocytic infiltrate, portal lymphocytic infiltrate, hepatocytes enlargement, portal and lobular plasma cellular infiltrate and neutrophils. Minimum frequency and percentage (0, 0%) was observed for parameters like perivenular necrosis, bridging/ confluent necrosis and fibrosis.

When chi-square test was applied p-value found to be significant for lobular lymphocytic infiltrate, portal lymphocytic infiltrate, portal and lobular plasma cellular infiltrate, steatosis, neutrophils, sinusoidal distension, hepatocytes enlargement, inflammed portal area, congestion, prominent kuppfer cells, mast cells with p-value .000 ($p < 0.05$) and non-significant for eosinophilic infiltrate, perivenular necrosis, bridging/ confluent necrosis, fibrosis as summarized in table- 3.

Table-1: Comparison of mean body weight (grams) between GX, GY and GZ.

Body weight (grams)	GX		GY		GZ		P. value
	Mean± S.D	(n)	Mean± S.D	(n)	Mean± S.D	(n)	
Day 0	152.7± 2.812	7	164.1± 15.43	7	163.3± 13.02	7	0.1581
Day 6	203.4± 21.12	7	189.0± 20.78	7	188.3± 11.63	7	0.2469
Day 13	229.7± 22.74	7	205.3± 22.87	7	203.3± 15.50	7	0.0501

*** P-value ≤ 0.001, ** p-value ≤ 0.01,* p-value- 0.05
GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group

Table-2: Histopathological parameters frequency and percentage in liver among GX, GY and GZ.
GX = normal control group, GY = positive control group, GZ = Zinc

Histopathological parameters		Groups			Total	Total %age
		GX	GY	GZ		
Eosinophilic infiltrate	Present	0	1	0	1	4.761%
	Absent	7	6	7	20	95.238%
Lobular lymphocytic infiltrate	Present	0	7	7	14	66.666%
	Absent	7	0	0	7	33.333%
Portal lymphocytic infiltrate	Present	0	7	7	14	66.666%
	Absent	7	0	0	7	33.333%
Portal and lobular plasma cellular infiltrate	Present	0	7	7	14	66.666%
	Absent	7	0	0	7	33.333%
Perivenular necrosis	Present	0	0	0	0	0%
	Absent	7	7	7	21	100%
Bridging/ confluent necrosis	Present	0	0	0	0	0%
	Absent	7	7	7	21	100%
steatosis	Present	0	7	4	11	52.38%
	Absent	7	0	3	10	47.619%
fibrosis	Present	0	0	0	0	0%
	Absent	7	7	7	21	100%
Neutrophils	Present	0	7	7	14	66.666%
	Absent	7	0	0	7	33.333%
Sinusoidal distension	Present	0	7	0	7	33.333%
	Absent	7	0	7	14	66.666%
Hepatocytes enlargement	Present	0	7	7	14	66.666%
	Absent	7	0	0	7	33.333%
Inflammed portal area	Present	0	7	6	13	61.904%
	Absent	7	0	1	8	38.095%
congestion	Present	0	7	0	7	33.333%
	Absent	7	0	7	14	66.666%
Prominent kuppfer cells	Present	0	7	0	7	33.333%
	Absent	7	0	7	14	66.666%
Mast cells	Present	0	7	0	7	33.333%
	Absent	7	0	7	14	66.666%

Sulfate treated group

Table 3: Chi- square test for histopathological parameters in liver among group GX, GY and GZ.

Histological Parameters	Chi square test	Value	Asymp. Sig. (2-sided)
Eosinophilic infiltrate	Pre Pearson Chi-Square, N of Valid Cases	2.100[a]21	.350
	a.3cell (50.0%) have expected count less than 5.the minimum expected count is .33.		
Lobular lymphocytic infiltrate	Pre Pearson Chi-Square, N of Valid Cases	21.00[a]21	.000
	a.6cell (100.0%) have expected count less than 5.the minimum expected count is 2.33.		
Portal lymphocytic infiltrate	Pre Pearson Chi-Square N of Valid Cases	21.00[a]21	.000
	a.6cell (100.0%) have expected count less than 5.the minimum expected count is 2.33.		
Portal and lobular plasma cellular infiltrate	Pre Pearson Chi-Square N of Valid Cases	21.00[a]21	.000
	a.6cell (100.0%) have expected count less than 5.the minimum expected count is 2.33.		
Perivenular necrosis	Pre Pearson Chi-Square N of Valid Cases	.a 21	
	a. No statistics are computed because perivenular necrosis is a constant.		
Bridging/confluent necrosis	Pre Pearson Chi-Square, N of Valid Cases	.a 21	
	a. No statistics are computed because bridging/ confluent necrosis is a constant.		
steatosis	Pre Pearson Chi-Square N of Valid Cases	14.127[a]21	.001
	a.6cell (100.0%) have expected count less than 5.the minimum expected count is 2.33.		
fibrosis	Pre Pearson Chi-Square N of Valid Cases	.a 21	
	a. No statistics are computed because fibrosis is a constant.		
Neutrophils	Pre Pearson Chi-Square N of Valid Cases	21.00[a] 21	.000
	a.6cell (100.0%) have expected count less than 5.the minimum expected count is 2.33.		
Sinusoidal distension	Pre Pearson Chi-Square N of Valid Cases	21.00[a] 21	.000
	a.6cell (100.0%) have expected count less than 5.the minimum expected count is 2.33.		
Hepatocytes enlargement	Pre Pearson Chi-Square N of Valid Cases	21.00[a]21	.000
	a.6cell (100.0%) have expected count less than 5.the minimum expected count is 2.33.		
Inflammed portal area	Pre Pearson Chi-Square N of Valid Cases	21.00[a] 21	.000
	a.6cell (100.0%) have expected count less than 5.the minimum expected count is 2.33.		
congestion	Pre Pearson Chi-Square N of Valid Cases	21.00[a] 21	.000
	a.6cell (100.0%) have expected count less than 5.the minimum expected count is 2.33.		
Prominent kuppfer cells	Pre Pearson Chi-Square N of Valid Cases	21.00[a] 21	.000
	a.6cell (100%) have expected count less than 5.the minimum expected count is 2.33.		
Mast cells	Pre Pearson Chi-Square N of Valid Cases	21.00[a] 21	.000
	a.6cell (100%) have expected count less than 5.the minimum expected count is 2.33.		

Value of $p < 0.05$ is considered significant

Figure 1: GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group

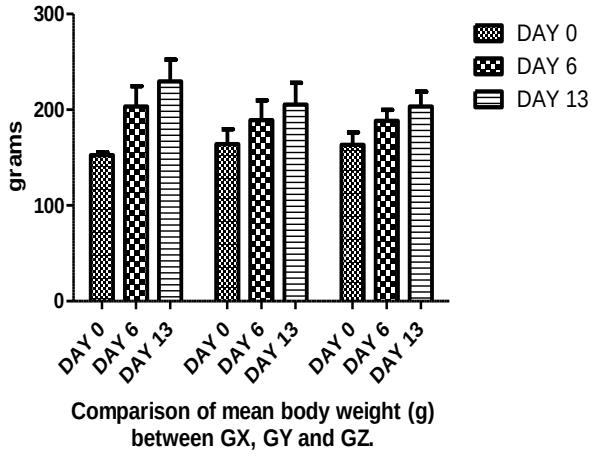


Figure 2: **Comparison of eosinophilic infiltrate in liver among group GX, GY and GZ.**
GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group

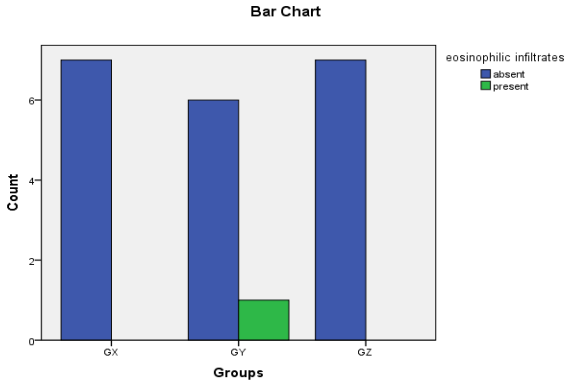


Figure 3: Comparison of lobular lymphocytic infiltrate in liver among group GX, GY and GZ.
GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group

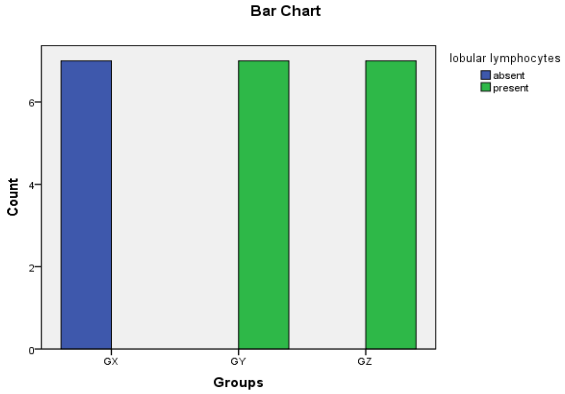


Figure 4: Comparison of portal lymphocytic infiltrate in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group)

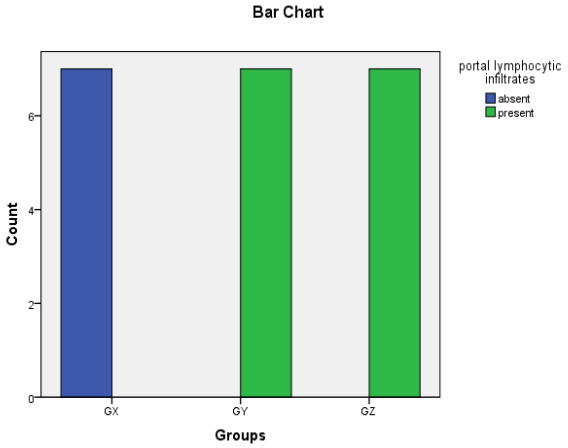


Figure 5: Comparison of portal and lobular plasma cellular in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group

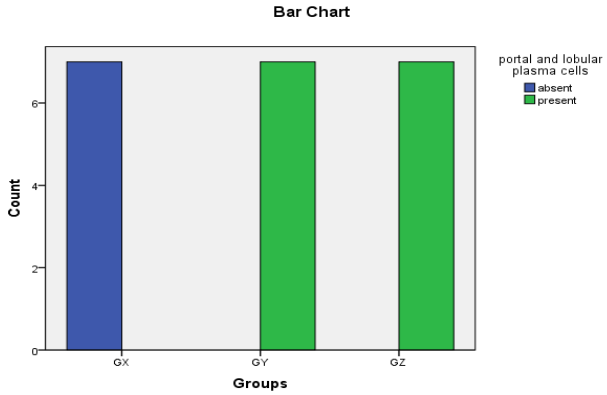


Figure 6: Comparison of Perivenular necrosis in liver among group GX, GY and GZ.
GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group

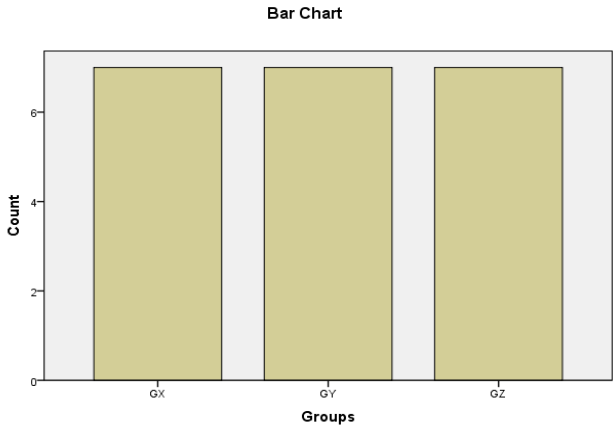


Figure 7: Comparison of bridging/confluent necrosis in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group)

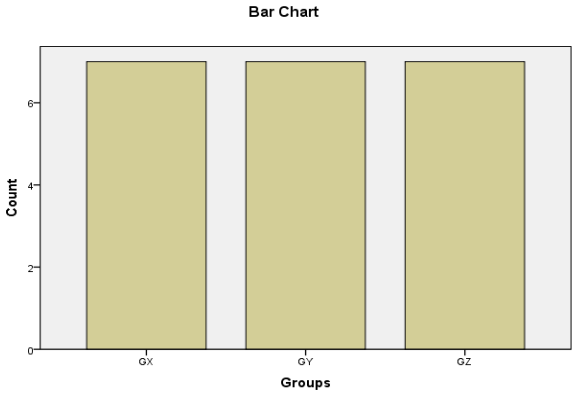


Figure 8: Comparison of steatosis in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group)

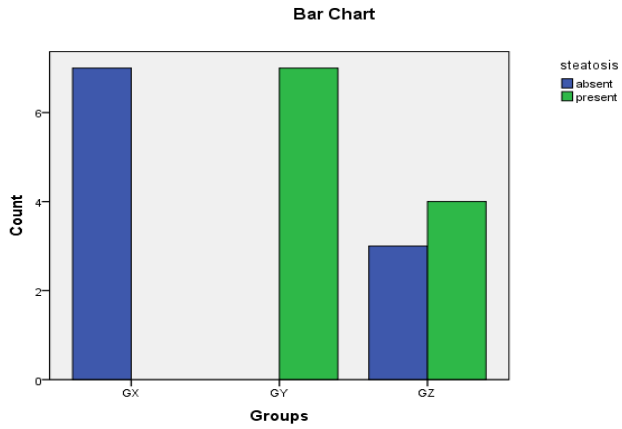


Fig. 9: Comparison of fibrosis in liver among group GX, GY, GZ. GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group

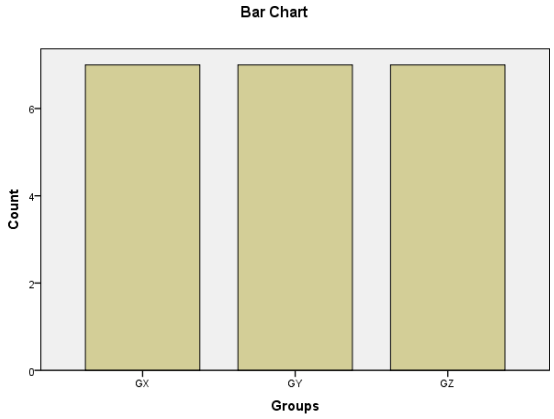


Figure 10: Comparison of neutrophils in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group)

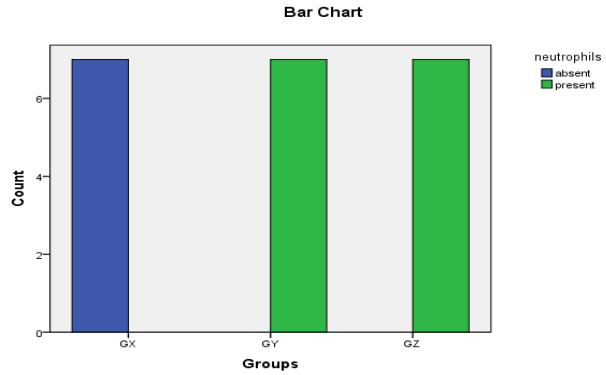


Figure 11: Comparison of Sinusoidal distension in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group)

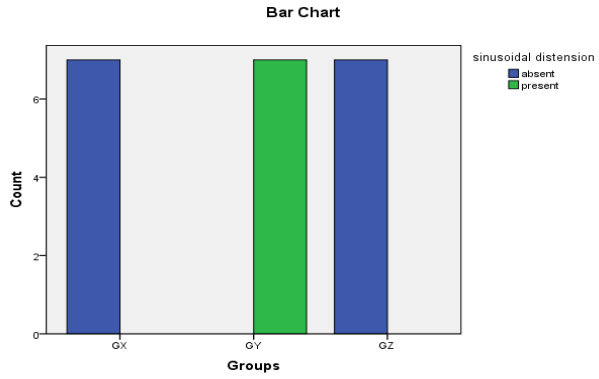


Figure- 12: Comparison of hepatocytes enlargement in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group)

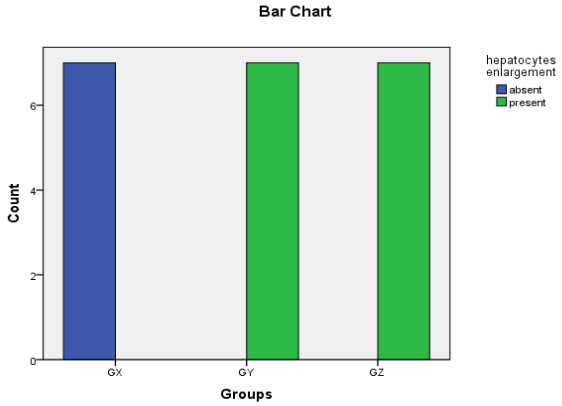


Figure- 13: Comparison of inflamed portal area in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group)

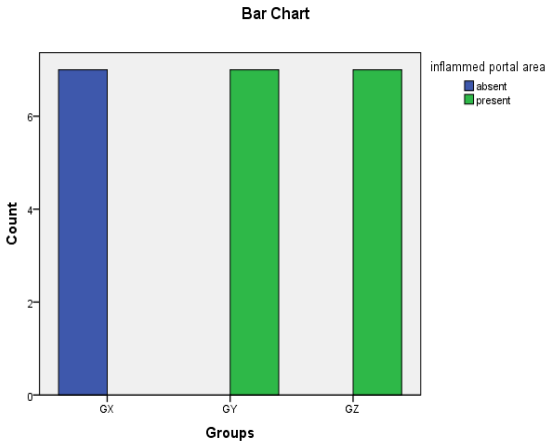


Figure- 14: Comparison of congestion in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group)

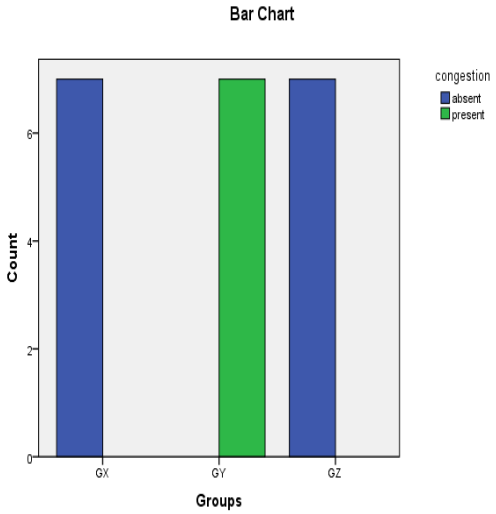


Fig.15:

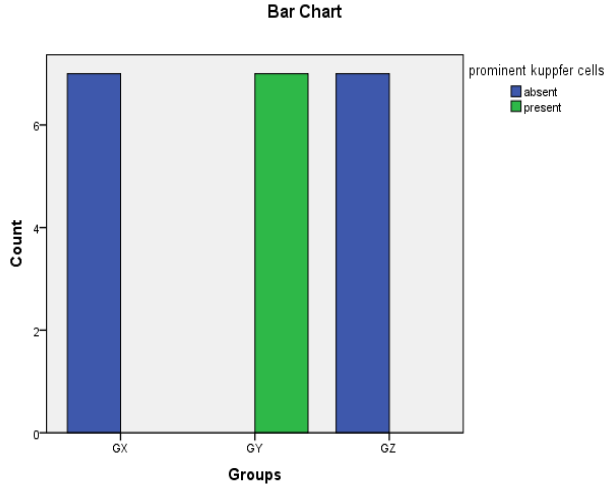
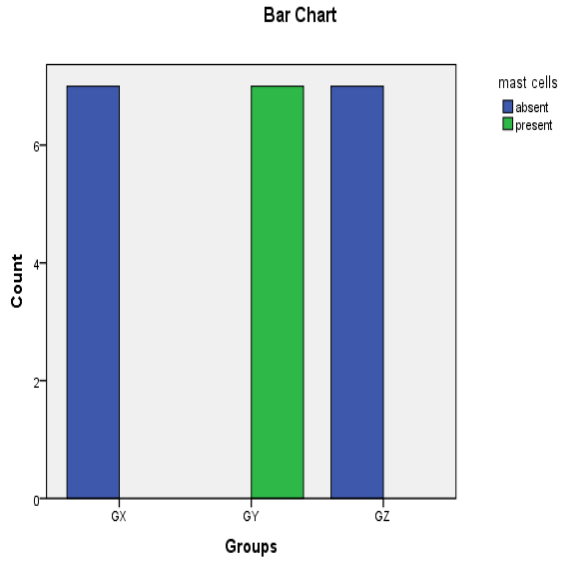


Figure- 16: Comparison of mast cells in liver among group GX, GY and GZ (GX = normal control group, GY = positive control group, GZ = Zinc Sulfate treated group)



The study had shown that there was no significant infiltration of eosinophils by Isoniazid and Rifampicin combination induced hepatotoxicity in GY and GZ. The article on case reports by Dominique Pessayre showed Isoniazid Rifampicin-Ethambutol treatment reported to cause no eosinophilia[18]. Current study had shown that the incidence of lobular and portal lymphocyte infiltration was significantly increased in all groups administered Isoniazid and Rifampicin. In Anand study it was found that the group administered Isoniazid (INH) showed lymphocytic portal and lobular inflammation[19]. Similarly incidence of lobular and portal plasma cellular infiltration was significantly increased in all groups administered Isoniazid and Rifampicin. The results are in accordance with findings of LIVER PATHOLOGY An Atlas and Concise Guide[14]. According to Sergio Duarte article inflammatory leukocytes infiltration occurs as a result of release of pro-inflammatory mediators and reactive oxygen and nitrogen species[20]. Perivenular, bridging/confluent necrosis and fibrosis were not significantly increased in groups administered Isoniazid and Rifampicin. The results are inconsistence with findings mentioned in LIVER PATHOLOGY An Atlas and Concise Guide and with findings of Sude Eminzade study respectively[14,15]. According to review by Vidyasagar Ramappa necrosis occurred only by profound anti-oxidant glutathione depletion. Nrf2-directed antioxidant systems in the liver may reduce the damaging effect of reactive metabolites[21]. A unique property of liver is its ability to regenerate, which allows the liver to continue to perform its normal functions. Cytokines and growth factors are mainly involved in liver regeneration[20]. Only sustained injury for long duration can cause fibrosis by accumulation of extracellular matrix (ECM)[22]. Growth factors and cytokines found to be involved as liver regeneration[23]. The present study had shown that the incidence of steatosis was significantly increased in GY. While other group receiving Zinc Sulfate showed significant improvement in steatosis. The results of induction of steatosis in GY were inconsistence with findings mentioned in LIVER PATHOLOGY An Atlas and Concise Guide[14]. Antioxidant nature of Zinc Sulfate in GZ had shown preservation of hepatic structure against Cadmium induced hepatotoxicity[25]. Incidence of congestion was significantly increased in GY. The results are in consistence with findings of Sangamithira study results[4]. While group receiving Zinc Sulfate GZ showed significant improvement in congestion. Anti-tuberculosis drugs cause congestion of liver via oxidative stress while the group receiving Zinc Sulfate showed preservation of hepatic structure against Cadmium induced hepatotoxicity[25]. Incidence of hepatocytes enlargement was significantly increased in groups administered Isoniazid and Rifampicin. The results were in agreement with results of Yong Lian study[26]. While GZ showed decrease in hepatocytes enlargement. Antioxidant action of zinc superoxide dismutase and induction of metallothionine protects liver against Isoniazid and Rifampicin induced injury[27]. Sinusoidal distension was significantly increased in GY while group receiving Zinc Sulfate GZ, showed improvement in sinusoidal distension. Anti-tuberculosis drugs cause sinusoidal distension of liver via oxidative stress[28]. Rasha H.G Hasan study proved that Zinc Sulfate correct sinusoidal distension by anti-oxidant effect against CCl_4 induced sinusoidal distension[27] Kuppfer cells were significantly increased in GY. Group receiving Zinc Sulfate GZ showed no prominent kuppfer cells. According to Benjamin L. Woolbright cytochrome P450 enzymes system of liver effectively detoxify xenobiotics leading to liver toxicity and inflammatory process activation. Kupffer cells also contain small amount of cytochrome P450 (2E1) act as first defense line against xenobiotics[28]. Sergio Duarte article described that as a result of release of pro-inflammatory mediators and reactive oxygen and nitrogen species (oxidative stress), causes activation of Kupffer cells[22]. Zinc Sulfate also protects by anti-oxidant effect against CCl_4 oxidative stress[27].

Figure- 17: Histology of liver of GX (40X)

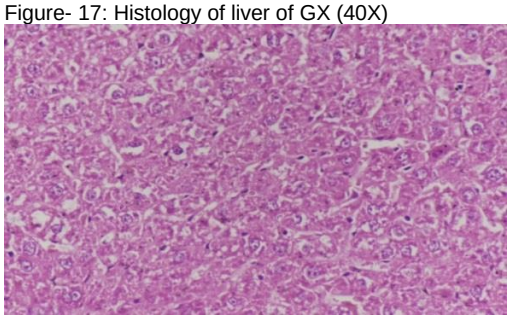


Figure- 18: Histology of liver of GY (40X)

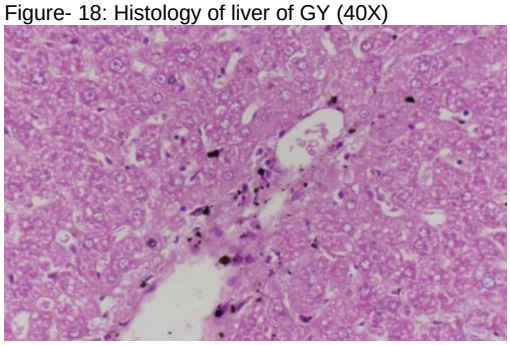
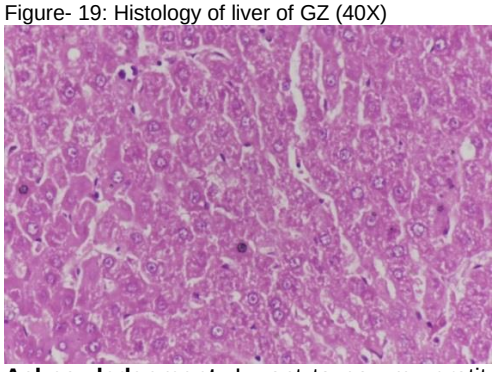


Figure- 19: Histology of liver of GZ (40X)



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