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REVIEW ARTICLE

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Lithium Carbonate Induced Hepatotoxicity and its Alleviation with Ascorbic Acid in Wistar Albino Rats

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ABSTRACT

Lithium carbonate has been used for prolonged treatment of psychiatric disorders, and accompanied by side effects. The objective of this study was to assess the toxicity of lithium carbonate and to compare it with its use, accompanied by ascorbic acid as an antioxidant, in Wistar Albino rats. The measured variables were serum, oxidative stress markers, and histopathological of liver tissue. A complete randomized design was used and the data obtained was subjected to the analysis of variance (ANOVA) by Duncan's Multiple Range Test (DMRT) and the student T test was used to detect the significant interactions between the means, this was performed SPPS package program. Ninty rats were used in two experiments. In experiment 1, forty rats were used and divided to four groups, three groups were subjected to different oral doses of lithium carbonate (9, 17 and 34 mg/kg/BW) daily and the fourth was kept as control group. In experiment 2, fifty rats were used and divided to five groups, ascorbic acid, (7mg/kg BW) as antioxidant was added to the different doses of lithium carbonate during the experimental period.

The experiment was performed in three months and blood samples were collected monthly, then specimen of the liver, was used for histopathological examination and the liver homogenate preparations were used to assay antioxidant markers. The overall means of the serum levels of total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), showed significantly (P≤0.005) higher levels in the groups used different doses of the lithium carbonate compared to the control group. For the oxidative stress markers, the hepatocyte superoxide dismutase (SOD) was insignificantly decreased, the hepatocyte catalase (CAT) was significantly (P=0.040) increased and the hepatocytemalonodialdhyde (MDA) was insignificantly increased in the treated groups compared to the control group. Histopathological findings in the liver showed massive necrosis, congestion of the central vein and infiltration of inflammatory cells. In experiment 2, fifty rats, ascorbic acid, (7mg/kg BW) as antioxidant was added to the different doses of drug during the experimental period. The serum levels of total protein, (AST), were significantly (p≤0.004) increased in all groups of the treated rats compared to the control group. The serum albumin was of similar levels in all treated groups. The serum (ALT) was insignificantly lower in all treated groups compared to control group. Less oxidative stress was observed in hepatocyte markers SOD and MDA showed insignificantly decreased levels and the hepatocyte CAT was insignificantly increased compared to the control group. For histopatholgical changes, when drug was accompanied by L-ascorbic acid, the infiltration of inflammatory cells was less in the liver compared to the groups treated with lithium carbonate alone. It was concluded that, lithium carbonate treatment in rats caused altered biochemical values, increased oxidative stress and resulted in histopatholgical changes in liver, and all these effects were reduced when drug was accompanied by ascorbic acid. The study recommended that patients on lithium carbonate should be periodically evaluated for hepatic, dysfunction and also advised to be supplied with ascorbic acid, to reduce the toxicity of lithium carbonate. Future studies should investigate the effect of different doses of the ascorbic acid on responses to lithium carbonate therapy. Also the effects of other antioxidants on drug responses should be tested.

Key words: Liver Toxicity, Lithium Carbonate, Ascorbic Acid, Antioxidants, Albino Rats and Lithium Therapy.

INTRODUCTION

Lithium is the lightest alkali metal used effectively to treat manic disorders and in preventing recurring manic depressive episodes (Groleau, 1994; Sharma and Iqbal, 2005), since it has a narrow therapeutic range which makes blood serum lithium levels monitoring mandatory to avoid lithium intoxication (Dehpour *et al*., 1998), but has narrow therapeutic index (Jefferson *et al*., 1987). Lithium is well absorbed by the stomach and doudeneum with no absorption in the large intestine, after ingestion peak serum lithium levels are seen after two and a half hour and completed within 6-8 hours (Goodman and Gillman, 1996). Lithium does not bind to plasma protein but binds to some legend (Clarke *et al*., 1998), as it moves slowly from extra- cellular compartment to intracellular space it may require 6-10 days to reach steady blood concentration and the desired therapeutic responses (Groleau, 1994). Distribution of lithium in the human organs is almost uniform; it concentrates in tissues like brain, kidney, thyroid, bone, liver and muscle cells against a concentration gradient. The body distribution of lithium is quite similar to that of sodium and greater part of it is contained in the cells probably at the response of potassium (Javaid, 1985). Lithium effects

have been investigated in details in the brain, intestine, liver and thyroid gland, and revealed many deformities and histological alteration (Tendon *et al*., 1997; Klemfus, 1992). The reactive oxygen species (ROS) are particles generated in metabolic processes as a consequence of incomplete reduction of the oxygen molecule (Drew *et al*., 2002). Numerous investigations revealed that they cause damage to the organism and can be involved in pathogenesis of severe diseases (Song *et al*., 1994; Sontakkea and Tarer, 2002). One of the oxidative processes is lipid per-oxidation, succeeded by the increase of malondialdehyde (MDA) concentration (Ynalm *et al*., 2001; Cirak *et al*., 2003). Lithium alters the activities of enzymes superoxide dismutase (SOD) and glutathione peroxidase in the brain (Kielczykowska *et al*., 2004). Furthermore, malondi-aldehyde (MDA) levels, a marker for lipid peroxidatio, were found to be significantly increased in kidney following lithium treatment (Oktem *etal*., 2005). Alterations in the levels of essential and non-essential elements in the rat liver and brain following administration of lithium carbonate have been also reported (Dhawan *et al*., 1999; Singh *et al*., 1995). Antioxidant supplements may include a number of different free radical-fighting compounds. It is thought that antioxidants, such as vitamin C, E and beta carotene, may reduce the damage caused by free radical in the bodies by inhibiting their formation (Frei *et al*., 1989). The objectives of this study was to evaluate the oxidative stress of lithium carbonate by measuring the activities of the enzymes catalase (CAT), superoxide dismutase (SOD), in hepatocytes of rats supplied with lithium carbonate, In addition to estimate the level of malondialdehyde (MDA) concentration as a marker of lipid peroxidation in the hepatic tissues. And also aims to investigate the influence of lithium carbonate on liver function test Then in other experiment the addition of ascorbic acid, as a known anti oxidant, together with the different doses of litium carbonate will be tested for the same parameters. Finally to examine the histopathological effects of the administration of different doses of lithium carbonate on the liver tissue in Wistar albino rats.

MATERIALS AND METHODS

Animals

This research was carried on 90 adult male rats obtained from the Faculty of Pharmacy, University of Khartoum, Sudan, reared in the premises of the Department of Biochemistry, Faculty of Veterinary Medicine, University of Khartoum. All animals were maintained on standard rat diet and water and used for two experiments.

Chemicals

Lithium preparation used in this study is Li_2Co_3. (El-Nile Company, Egypt with the trade name Prianil CR) presented in the form of tablets of 400 mg. The dose of the drug was calculated by converting adult human therapeutic dose (600-2400 mg/day) to animal dose (Sharif *et al*., 2011; Toghiani *et al*., 2012).

L-ascorbic acid made in the European Union (Scharlauchemie S.A) in the form of powder. Each of the Li_2Co_3 and the ascorbic acid were dissolved in distilled water before use and the calculated doses were given orally using stomach tubes.

Experiment I (The effect of adding different doses of lithium carbonate inWistar albino rats)

Forty male adult rats weighed between (125-217g). Food and water provided *ad libitum* for two weeks, before experiment, as adaptation periods, were allotted random to four groups, each of 10 rats; group 1, were to be fed the basal rat diet and water, served as control

group. Groups (2, 3, and 4) received the diet and water and treated by lithium carbonate (Li_2Co_3) at doses of 9 mg/kg BW, 17mg/kg BW 34 mg/kg BW respectively. The Li_2Co_3 was dissolved in distilled water and the calculated doses were given orally using stomach tubes. The duration of experiment is three months. After two weeks of adaptation period. Blood was collected and body weights of animals were measured at the zero time, after 1month, 2month and at the end of the experiment. The animals were anaesthetized with diethyl ether and sacrificed at end of the experiment. The liver, was removed and specimens were fixed in 10% neutral buffered formalin for histopathology. The liver was removed and a homogenate was prepared for the assay of antioxidant parameters.

Experiment II (The effect of adding different doses of lithium carbonate pluse L- ascorbic acidin Wister albino rats)

Fifty male adult rats weighted between (100-200g) were used in this experiment. Food and water provided *ad libitum* for two weeks before the start of the experiment as adaptation period.

The rats were allotted at random to five groups, each of 10 rats; group 1 continued to be fed the basal rat diet and water, and served as control group (negative control). Group 2 (positive control) received ascorbic acid (7mg/kg BW). Group 3 received lithium carbonate and ascorbic acid (9 mg/kg BW li_2Co_3+7mg/kg BW ascorbic acid). Group 4 received lithium carbonate and ascorbic acid (17mg/kg BW li_2Co_3+7mg/kg BW ascorbic acid). Group 5 received lithium carbonate and ascorbic acid (34mg/kg BW li_2Co_3+7mg/kg BW ascorbic acid). The Li_2Co_3 and ascorbic acid were dissolved in distilled water and the calculated doses were given orally using stomach tube. The duration of this experiment was three months. After two weeks of the adaptation period the blood sample were collected at zero time, then blood was collected monthly to assay biochemical parameters, after one month, two month and at the end of the experiment.

The animals were anaesthetized with diethyl ether and sacrificed at end of the experiment. the liverspecimen were removed and were fixed in 10% neutral buffered formalin for histopathology. The liver was removed for homogenate preparation, to assay antioxidant parameters.

Serum biochemical analysis

The blood samples were allowed to clot, and the sera were separated by centrifugation at 3000 rpm for 5 min and stored at -20^{o}C until the analysis was performed. The estimation of serum chemistry was performed using spectro-photometric methods and commercial kits. The parameters determined were Aspartate transaminase (AST), Alanine transaminase (ALT), the concentration of total protein, albumin, urea, creatinine and uric acid.

Tissue homogenate

Livers were stored at -20^{o}C until used for homogenization. One gram from each liver tissue was cut into small pieces, and immersed in ice-cold Tris buffer saline (TBS pH 7.4) to be homogenized. The homogenate was centrifuged at 300g for 15 min at 4^{o}C. The supernatant was collected and stored at -80^{o}C until used of the estimation of the antioxidant parameters.

Histological investigations

The method described by Turner *et al*. (1996) was used for histological investigations**.** Tissue specimen was obtained from the liver, of rats for histological examination. After sacrificing the rats the specimens were immediately preserved in 10 % formalin. The specimens were then processed in paraffin using an automatic tissue processor (Elliot tissue processor,

London). The specimens were then cut to sections, and stained with haematoxylin and eosin.

Statistical analysis

Mean values in body weight, blood and antioxidant data were expressed as (Mean ±SE) and statistical analysis was carried using computerized SPSS program version (21) with one way ANOVA. One-way Analysis of Variance (ANOVA) was used for determining the significance (Snedecor and Cochran, 1989). One-way analysis of variance (ANOVA) assessed for biochemical parameters; and then means were separated using DMRT. The animal experiments were designed by the complete randomized design (CRD); factorial arrangement 4×4. Where 4 indicate four groups (A; control, B, C and D; treated) and the other 4 indicate times (0, 1, 2,3months) for experiment one, and also factorial arrangement 4×5. Where 4 indicate five groups (A; control, B, C, D and E; treated) and the other 4 indicate times (0, 1, 2,3 months)for experiment two.

RCD ≡ Randomized Complete Design

ANOVA ≡ Analysis of variance

DMRT ≡ Duncan multiple range test

RESULTS

Key:

For experiment one

A ≡ control group

B≡ treated with 9 mg/kg/BW lithium carbonate

C ≡ treated with 17mg/kg/BW lithium carbonate

D ≡ treated with 34mg/kg/BW lithium carbonate

For experiment two

A ≡ control group (negative control).

B ≡ treated with 7 mg/kg/BW L-ascorbic acid (positive control).

C ≡ treated with 17mg/kg/BW lithium carbonate and 7 mg/kg/BW L-ascorbic acid.

D ≡ treated with 34mg/kg/BW lithium carbonate and 7 mg/kg/BW L-ascorbic acid

E ≡ treated with 34 mg Li_2Co_3 + 7mg/kg ascorbic acid

DISCUSSION

Since lithium carbonate is highly effective in controlling and preventing recurring of manic depressive episodes, its use in psychiatry to rehabilitate patients continues despite its complications (Csutora *et al*., 2005). Structural and functional effects of lithium carbonate have been studied by various workers from time to time (Yip and Yenng, 2007). Chronic lithium intoxication is more common. There is gradual accumulation of lithium, usually due to decreased excretion. Lithium exerts its effects on a wide range of cellular functions by inhibiting inositol production, affects the protein kinase C signaling pathway, and inhibits glycogen synthase kinase (Pilcher, 2003). Early recognition and management of lithium induced organ toxicity can save lives and reduce significant morbidity.

In the current study the total mean of serum total protein in different doses of lithium carbonate showed significantly increase (p=0.000) compared to the control group. The results disagreed with Sharma and Iqbal, (2005) who reported that lithium therapy treated rats got decreased serum total protein. The results also agreed with Kielczykowska *et al*.,(2014) who reported that lithium carbonate treated rats by a form solved in water by stomach tube for 6 weeks caused an increase of serum total protein. They suggested that, it can be attributed to the fact that a significant change in serum proteins seems that related

to the observed kidney damage. In the present study the total mean of serum total protein in different doses of lithium carbonate and L-ascorbic acid showed significantly (p=0.000) higher levels compared to the control group. A similar study conducted by Kielczykowska *et al*., (2014) revealed that lithium carbonate treated rats and co administration of antioxidant in the form of water solution by stomach tube for 6 weeks a caused an increase of serum total protein. This can be attributed to the fact that a significant change in serum proteins seems that related to a renal insufficiency due to long term treatment with lithium carbonate which was reported by Kielczykowska *et al*., (2014). In the current study the total mean of serum albumin in different doses of lithium carbonate showed significant (p=0.000) increase compared to the control group. The result disagreed with Kielczykowska *et al*., (2014) who reported that lithium carbonate treated rats in the form of water solution by stomach tube for 6 weeks caused a decrease in serum albumin. They suggested that, it can be attributed to the fact that a significant change in serum proteins seems that related to the observed kidney damage. In the present study the total mean of serum albumin in different doses of lithium carbonate and L-ascorbic acid showed significantly(p=0.000) higher levels compared to the control group, except group E treated with 34 mg Li_2Co_3 + 7mg/kg ascorbic acid) that showed significant decrease. The result in this study agreed with Kielczykowska *et al*., (2014) who revealed that lithium carbonate treated rats subjected to co administration of antioxidant in the form of water solution by stomach tube for 6 weeks caused increased serum albumin. The significant (p=0.000) change in serum albumin especially in group E, seems that be related to the histopathological lesions was observed were in the present study as histopathological findings. In the current study the total mean of serum alanine aminotransferase in different doses of lithium carbonate showed a highly significant (P=0.000) increase compared to the control group. That agreed with Devesh *et al*., (2013) who reported that the activity of SGPT was significantly increased in serum of lithium treated rats. Results in the present work contradicted with Mohammad *et al*., (2011) who found that, the activity of ALT was significantly decreased in serum of lithium treated rats. The results also agreed with Sharma and Iqbal, (2005). Who stated that, the activity of ALT was significantly increased in serum of rats treated by different doses of lithium. Which might be due to the liver dysfunction resulting into disturbance in the biosynthesis of these enzymes which alteration in the permeability of liver membranes. Any increased in these enzymes leads to biochemical impairment and lesions of the tissues and cellular function, Rahman *et al*., (2000). Also Rahman *et al*., (2000).Reported that the increase level of these enzymes in blood might be due to the necrosis of liver and kidney. They suggested that, blood serum enzymes like ALT and AST can be used as biomarker enzymes for detecting lithium toxicity. Generally and logically such tissue damages should result in a leak of the studied enzymes from the damaged tissues in the serum (Hines and Henslee, 1986). The serum liver enzyme ALT was observed to increase in the present study suggesting tissue damage in the treated groups.

In the present study the total mean of serum aspartate aminotransferase (AST) in different doses of lithium carbonate showed significant (P=0.000) increase in all treated rats compared to control group. The results agreed with Devesh *et al*., (2013) who found that the activity of SGOT was significantly increased in serum of lithium treated rats. Although the results disagreed with the findings of Mohammad *et al*., (2011) when reported that, the activity of AST was significantly decreased in serum of lithium treated rats. The results agreed with Sharma and Iqbal, (2005). Who reported that, the activity of AST was significantly increased in serum of lithium treated rats. Which might be due to the liver

dysfunction resulting into disturbance in the biosynthesis of these enzymes which alteration in the permeability of liver membranes. Any increase in these enzymes leads to biochemical impairment and lesions of the tissues and cellular function Rahman *et al*.,(2000). Also, Rahman *et al*., (2000) reported that the increase level of these enzymes in blood might be due to the necrosis of liver and kidney and suggested that, blood serum enzymes like ALT and AST can be used as biomarker enzymes for detecting lithium toxicity. In the present study the total mean of serum alanine aminotransferase (ALT) in different doses of lithium carbonate and L-ascorbic acid showed slight decrease compared to the control groups. The results disagreed with Kielczykowska *et al*., (2014) when reported that lithium carbonate with co administration of antioxidant treated rats in the form of water solution by stomach tube for 6 weeks caused increase in serum alanine aminotransferase (ALT). Ahmad *et al*.,(2011) observed that a significant decrease in these enzymes activities in rats receiving lithium only. However, the period of the experiment was longer little and antioxidant acted as a protective (Ahmad *et al*., 2011).

In the present study the total mean of serum aspartate aminotransferase (AST) in different doses of lithium carbonate and L-ascorbic acid showed significantly higher levels compared to the control group. The results agreed with Kielczykowska *et al*., (2014) who reported that lithium carbonate given with antioxidant to rats in the form of water solution by stomach tube for 6 weeks caused increase serum aspartate aminotransferase (AST). The results disagreed with Ahmad *et al*., (2011) who observed that a significant decrease in these enzymes activities in rats receiving lithium. However, the period of the experiment was longer little and antioxidant acted as a protective (Ahmad *et al*., 2011).

In the current study the hepatocyte superoxide dismutase enzyme activity was insignificantly decreased in all different doses of lithium carbonate compared to control group. This result is similar to the findings of Devesh *et al*., (2013) who reported that oral administration of lithium therapy for 21 days decreased the liver SOD .The reduction in SOD and CAT may lead to lower oxidative stress, which is reflected mainly in a decrease in the concentration of cell hydrogen peroxide (Gsell *et al*., 1995). The result was similar to the findings of Kielezykowska *et al*., (2006) who reported the influence of different doses of lithium administration in drinking water decrease the liver SOD activity. Lithium toxicity represents a state of increased oxidative stress, which is mainly based on the evidence of increased lipid peroxidation, or by indirect evidence of reduction reserve, such as SOD and Catalase enzymes, in animal models (Tandon *et al*., 1998).

Table 1. The effect of adding different doses (mg/kg) of lithium carbonate on serum total protein (g/dL) in Wistar albino rats.

Treatment	Months				Overall	*P-value*.
	Zero	1st	2nd	3rd		
A	6.86 ± 0.31^{bB}	6.39 ± 0.24	5.95 ± 0.19^{bdA}	6.45 ± 0.38	6.42 ± 0.15^{B}	0.197^{Ns}
B	7.95 ± 0.25^{adBC}	5.68 ± 0.21^{dACD}	7.00 ± 0.14^{aAB}	7.25 ± 0.69^{B}	6.95 ± 0.21^{AD}	0.000^{**}
C	7.14 ± 0.20^{bdBC}	5.85 ± 0.30^{dAD}	6.14 ± 0.17^{bcaAD}	7.85 ± 0.32^{B}	6.74 ± 0.17^{Ns}	0.000^{**}
D	6.31 ± 0.21^{b}	6.69 ± 0.36^{b}	6.60 ± 0.21^{a}	6.75 ± 0.14	6.56 ± 0.12^{D}	0.546^{Ns}
Overall	7.06 ± 0.15^{BC}	6.10 ± 0.15^{AD}	$6.41\pm.11^{AD}$	7.09 ± 0.21^{BC}		
***P-value*.**	0.001^{**}	0.062^{Ns}	0.000^{**}	0.083^{Ns}		

In the present study the hepatocyte superoxide dismutase enzyme activity was insignificantly decreased among all groups of the experiment compared to group A the control group, and also the hepatocyte superoxide dismutase enzyme activity was insignificantly increased among all groups of the experiment compared to group B, the positive control group. This finding agreed with Vijaimoban *et al*., (2010) who reported that there was a decrease in the activity of SOD in the liver during lithium therapy and an antioxidant as a co administration. The reduced enzyme activity, may lead to perturbation in the antioxidant defense. Following L-ascorbic acid administration, the altered levels of enzymes tended to be normalized because of antioxidative property of L-ascorbic acid. Similar reports indicating the antioxidative properties of L-ascorbic acid have been reported (Sidhu *et al*., 2004, and Sidhu and 2006). Similar study conducted by Ibrahim *et al*., (2015) reported that co-treatment of rats with L-ascorbic acid along lithium therapy results in decline in the activities of SOD and CAT in comparison with lithium therapy alone. The effect of L-ascorbic acid could be returned to the antioxidant properties of L-ascorbic acid as evidence by decreasing levels lipid peroxidation and SOD and CAT activities as in the present study (Ibrahim *et al*., 2015). A similar study conducted by Kielezykowska *et al*., (2015) reported that lithium carbonate therapy caused depletion of CAT and SOD after 6 weeks and MDA was slightly increased the present agree also with Omar *et al*., (2016) reported that co-treatment of rats with antioxidant and lithium treatment resulted in decline in the activity of SOD in comparison with lithium treatment alone. From this L-ascorbic acid acted was able to reduce free radicals to hydrogen peroxide , and also reduced the activity of SOD, this reported by Virgili *et al*., (1999).

Table 2. The effect of adding different doses (mg/kg) levels of lithium carbonate on serum albumin (g/dL) in rats.

Treatment	Months				Overall	*P-value*.
	Zero	1st	2nd	3rd		
A	3.74 ± 0.27^{D}	3.56 ± 0.10^{dD}	3.47 ± 0.06^{D}	2.51 ± 0.12^{bcdABC}	3.32 ± 0.11^{B}	0.000^{**}
B	3.99 ± 0.15^{BD}	3.34 ± 0.13^{A}	3.69 ± 0.11^{D}	3.16 ± 0.18^{aAC}	3.58 ± 0.09^{A}	0.002^{**}
C	3.75 ± 0.19^{B}	3.40 ± 0.13^{dA}	3.55 ± 0.08	3.40 ± 0.24^{a}	3.53 ± 0.08^{AB}	0.466^{Ns}
D	3.73 ± 0.21	2.95 ± 0.16^{ac}	3.40 ± 0.18	3.52 ± 0.32^{a}	3.43 ± 0.12^{AB}	0.112^{Ns}
Overall	3.80 ± 0.10^{B}	3.34 ± 0.07^{A}	3.54 ± 0.05^{AB}	3.12 ± 0.12^{AB}		
P-value.	0.783^{Ns}	0.025^{*}	0.332^{Ns}	0.009^{**}		

In the present study the hepatocyte catalase enzyme activity was significantly (p=0.040) lower in all lithium carbonate treated groups compared to a control group. CAT is the most important peroxidase in detoxifying excess hydrogen peroxide to prevent hydroxyl production (Andrades *et al*., 2005).The results in this study were similar to Devesh *et al*., (2013) who reported that oral administration of lithium therapy for 21 days significantly decreased the liver CAT enzyme. And also similar to Kielezykowska *et al*., (2006) who reported that the influence of different doses of lithium administration in drinking water decreased the liver CAT activity. The study agreed with Vijaimoban *et al*., (2010) who showed a lower activity of CAT in liver during lithium toxicity condition. The result also agreed with Nciri *etal*., (2009) who found lower activity of CAT when used the different doses (20 mg bw and40 mg bw) of lithium in rats for 14 days. The present results again agreed with Tandon *et al*., (1998) who reported that Lithium toxicity represents a state of increased oxidative stress, which is mainly based on the evidence of increased lipid

peroxidation, or by indirect evidence of reduction reserve, such as SOD and Catalase enzymes, in animal models. This reduction in SOD and CAT may lead to lower oxidative stress, which is reflected mainly in a decrease in the concentration of cell hydrogen peroxide (Gsell *et al*., 1995). Lithium carbonate induces the free radicals, which may cause cellular injury, and suppress the antioxidant enzymes, and increase the rate of peroxidation by the liver this is a well-known risk of toxicity caused by lithium carbonate (Sharma and Iqbal 2005 and Nciri *et al*., (2009).

Table 3. The effect of adding different doses (mg/kg) levels of lithium carbonate on serum alanine amino transferase (U/L) in Wistar albino rats.

Treatment	Months				Overall	*P-value.*
	Zero	1st	2nd	3rd		
A	15.35 ± 4.29^{D}	16.87 ± 3.82^{bD}	30.00 ± 2.11^{b}	45.60 ± 9.52^{cdAB}	26.96±3.35B	0.002^{**}
B	27.68 ± 6.52^{dD}	30.21 ± 6.66^{cdD}	36.00 ± 1.63^{aD}	61.30 ± 6.19^{ABC}	38.80 ± 3.46^{A}	0.001^{**}
C	10.92 ± 4.59^{bBD}	14.82 ± 4.82^{bD}	32.00 ± 2.00^{AD}	72.70 ± 10.31^{aAB}	32.61 ± 4.93^{AB}	0.000^{**}
D	9.04 ± 2.40^{bCD}	11.46 ± 2.40^{bCD}	35.00 ± 2.24^{ABD}	73.80 ± 7.23^{aABC}	32.32 ± 4.62^{A}	0.000^{**}
Overall	3.80 ± 0.10^{B}	3.34 ± 0.07^{A}	3.54 ± 0.05^{AB}	3.12 ± 0.12^{AB}		
P-value.	0.783^{Ns}	0.025^{*}	0.332^{Ns}	0.009^{**}		

Table 4. The effect of adding different doses (mg/kg) levels of lithium carbonate on serum aspartate amino transferase (U/L) in Wistar albino rats.

Treatment	Months				Overall	*P-value.*
	Zero	1st	2nd	3rd		
A	54.39 ± 10.44^{c}	57.40±12.15	63.40±9.79	69.00 ± 8.59^{bcd}	61.05 ± 5.04^{CD}	0.757^{Ns}
B	36.26 ± 5.47^{dBCD}	58.47 ± 6.72^{AD}	69.28 ± 4.11^{AD}	90.65 ± 5.39^{aABC}	63.66 ± 4.10^{D}	0.000^{**}
C	34.53 ± 5.43^{adBCD}	63.06 ± 5.39^{ACD}	80.07 ± 3.78^{ABD}	93.33 ± 1.79^{aABC}	67.75 ± 4.09^{AD}	0.000^{**}
D	57.10 ± 4.25^{bcCD}	68.95 ± 4.14^{D}	78.15 ± 5.32^{A}	89.85 ± 3.81^{aAB}	73.51 ± 2.86^{AC}	0.000^{**}
Overall	45.57 ± 3.67^{BC}	61.97 ± 3.78^{AC}	72.73 ± 3.18^{AB}	85.71 ± 3.06^{AB}		
P-value.	0.043^{*}	0.710^{Ns}	0.215^{Ns}	0.012^{*}		

Table 5. The effect of lithium carbonate on hepatocyte antioxidant parameter in rats.

Treatment	Superoxide dismutase (unit/ml)	Malonodialdhyde (µm)	Catalase (unit/ml)
A	15.07±0.39	0.595±0.07	1.66 ± 0.01^{bcd}
B	13.97±0.58	0.660±0.10	1.64±0.02
C	14.15±0.29	0.664±0.10	1.62±0.01
D	14.15±0.22	0.894±0.08	1.52±0.03
Overall	14.33±0.20	0.703±0.05	1.64±0.01
Sig.	0.221^{Ns}	0.119^{Ns}	0.040^{*}

Table 6. Effect of adding different doses (mg/kg) of Li_2Co_3 and L -ascorbic acid on serum total protein (g/dL) in rats.

Treatment	Months				Overall	*P-value.*
	Zero	1st	2nd	3rd		
A	6.64±0.50	$7.78±0.18^{b}$	6.39±1.4	$6.44±0.23^{cde}$	$6.81±0.37^{C}$	0.544^{Ns}
B	6.53±0.85	$6.52±0.31^{a}$	7.08±0.53	$6.33±0.25^{cde}$	$6.62±0.26^{CE}$	0.784^{Ns}
C	7.19±0.49	7.51±0.29	7.43±1.1	$8.83±0.30^{a}$	$7.71±0.32^{AB}$	0.273^{Ns}
D	$6.34±0.35^{BCD}$	$7.64±0.35^{AC}$	$9.02±0.46^{AB}$	$8.13±0.40^{aA}$	$7.90±0.40^{AB}$	0.001^{**}
E	$6.42±0.21^{CD}$	$7.05±0.29^{C}$	$9.23±0.32^{ABD}$	$7.67±0.21^{aAC}$	$7.67±0.23^{B}$	0.000^{**}
Overall	$6.62±0.23^{CD}$	7.30±0.15	$7.83±0.41^{A}$	$7.48±0.20^{A}$		
P-value.	0.804^{Ns}	0.030^{*}	0.112^{Ns}	0.000^{**}		

Table 7. Effect of adding different doses (mg/kg) of Li_2Co_3 and L -ascorbic acid on serum albumin (g/dL) in rats.

Treatment	Months				Overall	*P-value.*
	Zero	1st	2nd	3rd		
A	$3.80±0.44^{D}$	$4.35±0.25^{D}$	$4.64±0.20^{eD}$	$2.42±0.24^{ABC}$	$3.80±0.21^{Ns}$	0.000^{**}
B	$4.24±0.45^{D}$	$4.21±0.22^{D}$	$3.90±0.18^{eD}$	$2.90±0.33^{ABC}$	$3.81±0.18^{Ns}$	0.020^{*}
C	$5.03±0.13^{BD}$	$4.03±0.29^{A}$	$4.63±0.28^{eD}$	$3.45±0.31^{AC}$	$4.30±0.17^{E}$	0.002^{**}
D	$4.03±0.39^{CD}$	$4.06±0.40^{CD}$	$5.05±0.26^{eABD}$	$3.03±0.15^{ABC}$	$4.06±0.20^{E}$	0.002^{**}
E	$4.93±0.39^{CD}$	$4.52±0.26^{CD}$	$1.62±0.53^{abcdABD}$	$2.66±0.12^{ABC}$	$3.43±0.31^{C}$	0.000^{**}
Overall	$4.40±0.18^{D}$	$4.24±0.13^{D}$	$3.97±0.25^{D}$	$2.89±0.11^{ABC}$		
P-value.	0.110^{Ns}	0.740^{Ns}	0.000^{**}	0.062^{Ns}		

Table 8. Effect of adding different doses (mg/kg) of Li_2Co_3 and L -ascorbic acid on serum alanine transferase (U/L) in rats.

Treatment	Months				Overall	*P-value.*
	Zero	1st	2nd	3rd		
A	$25.11±0.77^{de}$	$29.01±1.9^{d}$	36.10±7.9	28.93±2.7	$29.80±2.2^{Ns}$	0.362^{Ns}
B	$22.03±0.32^{deB}$	$37.33±2.9^{cdeA}$	$23.94±2.8^{B}$	$26.77±2.8^{B}$	$27.57±1.6^{Ns}$	0.001^{**}
C	$28.60±2.0^{de}$	$26.85±3.2^{bCD}$	36.08±8.5	$19.31±2.3^{C}$	$27.70±2.5^{Ns}$	0.030^{*}
D	$48.06±5.1^{abceBCD}$	$16.71±2.6^{abA}$	$25.15±3.5^{A}$	$23.63±2.9^{A}$	$28.40±2.9^{Ns}$	0.000^{**}
E	$41.65±2.7^{abcBCD}$	$20.32±1.8^{bA}$	$23.70±2.1^{A}$	$23.53±1.6^{A}$	$27.30±1.9^{Ns}$	0.000^{**}
Overall	$33.09±2.0^{BCD}$	$26.04±1.6^{A}$	$28.99±2.6^{A}$	$24.43±1.2^{A}$		
P-value.	0.000^{**}	0.000^{**}	0.284^{Ns}	0.111^{Ns}		

The hepatocyte catalase enzyme activity was insignificantly increased among all different droups dosed with lithium carbonate and L-ascorbic acid compared to control group. Similar study conducted by (Ibrahim *et al*., 2015) reported that co-treatment of rats with L-ascorbic acid along with lithium therapy results in decline in the activities of CAT in comparison with lithium therapy alone. The effect of L-ascorbic acid could be returned to the antioxidant properties of L-ascorbic acid as evidence by decreasing levels lipid peroxidation and SOD and CAT activities as as response by Ibrahim *et al*., (2015). A similar study conducted by Kielezykowska *et al*.,(2015) who reported that lithium carbonate therapy caused depletion of CAT after 6 weeks obtained results. The reduced enzyme activity, may lead to perturbation in the antioxidant defense. Following L-ascorbic acid administration, the

altered levels of enzymes tended to be normalized because of antioxidative property of L-ascorbic acid. Similar reports indicating the antioxidative properties of L-ascorbic acid have been reported by Sidhu *et al*., (2004) and Sidhu and (2006).

In the present study, hepatocyte malonodialdehyde concentration was insignificantly increased in all groups of rats treated with different doses of lithium carbonate of the experiment compared to a control group. This tendency of increasing the MDA was similar to findings of Devesh *et al*., (2013) who reported that oral administration of lithium therapy for 21 days increased the liver lipid peroxidation. The results also agreed with Tandon *et al*., (1998) who reported that Lithium toxicity represents a state of increased oxidative stress, which is mainly based on the evidence of increased lipid peroxidation, or by indirect evidence of reduction reserve, such as SOD and Catalase enzymes, in animal models. The present study agrees with Vijaimoban *et al*., (2010) who showed that lithium therapaoy can increase liver MDA. The results agreed with (Nciri *et al*., 2009). Who reported that lithium administration for 14 and 28 days resulted in a disturbance of oxidative status in liver cells as evident by the increased of MDA level, a classical index of lipid peroxidation. Several studies have demonstrate altered oxidative stress parameters in the pathophysiology and therapeutics of lithium carbonate including changes in SOD, CAT and lipid peroxide levels (Machado *et al*.,2007, Andreazza *et al*.,2007, Ranjekar *et al*.,2003).

In the present study, the hepatocyte malonodialdehyde concentration was insignificantly decreased in the group received different doses (mg/kg) of lithium carbonate and L -ascorbic acid compared to control group. This result agree with Ibrahim *et al*., (2015) who reported that the effect of L-ascorbic acid could be returned to the antioxidant properties of L-ascorbic acid as evident by the decreasing levels lipid peroxidation concentration. A similar study conducted by Cabre *et al*., (1995) reported that antioxidant supplementation for 12 weeks caused a decreased lipid peroxidation in rats. The anti-oxidant supplementation is involved in destruction of free radicals through L-ascorbic acid which may serve as an efficient antagonist in inhibition lipid peroxidation to stabilize bio membrane (Dhawan and Goel, 1995, Chan *et al*., 1995). The supplementation of the anti-oxidant drugs in lithium therapy with affective disorders may be considered to protect membranous structures from lipid peroxidation (Dubey *et al*., 2013).

Table 9. Effect of adding different doses (mg/kg) of Li_2Co_3 and L -ascorbic acid on serum asparatae transferase (U/L) in rats.

Treatment	Months				Overall	*P-value.*
	Zero	1st	2nd	3rd		
A	22.53 ± 0.95^{BCD}	28.27 ± 1.4^{eA}	29.48 ± 2.0^{cdeA}	28.31 ± 1.2^{cdeA}	27.1 ± 1.2^{BCD}	0.010^{*}
B	23.35 ± 0.89^{BCD}	28.92 ± 1.8^{A}	29.94 ± 2.3^{cdeA}	28.27 ± 1.3^{cdeA}	27.6 ± 0.92^{CD}	0.046^{*}
C	23.99 ± 0.69^{BCD}	36.18 ± 2.9^{ACD}	43.62 ± 1.7^{abAB}	48.26 ± 3.4^{abAB}	38.0 ± 2.1^{AB}	0.000^{**}
D	24.15 ± 0.58^{BCD}	47.33 ± 8.1^{aA}	45.59 ± 2.6^{abA}	53.94 ± 2.6^{abA}	42.8 ± 3.0^{AB}	0.001^{**}
E	24.62 ± 1.0^{BCD}	47.93 ± 7.6^{aA}	51.14 ± 1.6^{abA}	56.33 ± 1.5^{abA}	45.0 ± 2.9^{AB}	0.000^{**}
Overall	23.73 ± 0.38^{BCD}	37.73 ± 2.6^{AD}	39.96 ± 1.7^{AD}	43.02 ± 2.3^{A}		
P-value.	0.468^{Ns}	0.022^{*}	0.000^{**}	0.000^{**}		

Table 10. The effect of lithium carbonate and L -ascorbic acid on hepatocyte antioxidant parameters in albino wistar rats.

Treatment	Superoxide dismutase (ml)	Malonodialdhyde (µm)	Catalase (ml)
A	15.07±0.39	0.595±0.07	1.61±0.01
B	9.88±1.97	0.461±0.06	1.65±0.04
C	10.49±3.02	0.361±0.03	1.65±0.01
D	13.20±0.78	0.476±0.05	1.66±0.02
E	13.95±0.48	0.498±0.05	1.67±0.01
Overall	12.52±0.79	0.478±0.03	1.66±0.04
Sig.	0.161^{Ns}	0.062^{Ns}	0.670^{Ns}

The pathological findings in liver of the current study showed that rats treated with 9 mg lithium carbonate include massive necrosis, congestion of central vein and infiltration of inflammatory cells; Coagulative necrosis was common at 17 and 34 mg lithium carbonate doses. This result supported by Tandon *et al*., (1997)and Klemfus, (1992) reported that Lithium effects have been investigated in the liver revealed many deformities and histological alteration due to lithium treatment .This result supported by Loghin *et al*., (1999) who reported that Chronic lithium treatment can produce significant inflammatory and congestive changes in the liver .This result was similar to Mohammad *et al*., (2011) reported that treated rats with doses of lithium showed significant necrotic changes and degenerative tissue damage in the hepatocytes and central vein. The degenerated cells showed coagulative necrosis. He also reported that the histopathological observations of the liver tissue revealed many deformities and histological alteration due to lithium treatment. A similar study conducted by Devesh *et al*., (2013) reported that lithium treated orally in rats showed slightly degenerative changes as evident in numerous hepatocytes , and the cells were damaged. The morphological examination of liver revealed that cellular architecture was disturbed following lithium treatment. These findings concomitant with the finding of Swann *et al*., (1987). This study agreed also with Sharma and Iqbal (2005) as they reported chronic passive congestion of liver during long term of lithium therapy treated rats. The hepatotoxicity of lithium had been explained on the basis of two independent mechanisms, bio-transformation of lithium in the liver with the formation of toxic metabolites or induction of an allergic hypersensitivity reaction. He was also suggested that similar hepatic changes in laboratory animals could also be observed by dose dependent effect of directly acting therapeutic agents (Whiting, 1999). Both inflammatory and congestive changes had also been reported in liver of lithium treated animal (Shulman, 2010). A similar study performed by Bhat *et al*., (2014) reported that histological changes in the liver of lithium carbonate on long term treated in albino rats causes hepatic degeneration, hepatitis and necrosis and also the cell infiltrated inframammary and congestion of central vein. The author used the same doses used in the present study. A similar study conducted by Sharif *et al*., (2011) showed that adverse effect of withdrawal of chronic lithium therapy on liver of rabbits were found such as cholangitis, central vein congested and lymphocytic infiltration of the liver parenchyma, which is supporting the finding of the present study. They did not report any derangement of the hepatic architecture, but in the present study there was cytoplasmic and nuclear degeneration, followed by necrosis. They also reported development of cholangiocarcinoma in rabbits after 4 weeks of lithium therapy, no such development was observed in the present study,

may be because in the present study therapeutic doses of lithium carbonate were used, whereas Sharif *et al*., (2011) used double the therapeutic dose in their study. The hepatotoxicity of lithium carbonate has been explained on the basis of two independent mechanism: biotransformation of the drug in the liver with the formation of toxic metabolites, and also induction of an allergic hypersensitivity reaction (Kumar *et al*., 1999).The former mechanism seems to be working in this experiment rather than the other one as no allergic infiltrate like eosinophils was observed in liver parenchyma. Similar hepatic changes in laboratory animals could also be observed by dose dependent effect of directly acting therapeutic agents. Both inflammatory and congestive had been reported of lithium animals (Loghin *et al*., 1995).

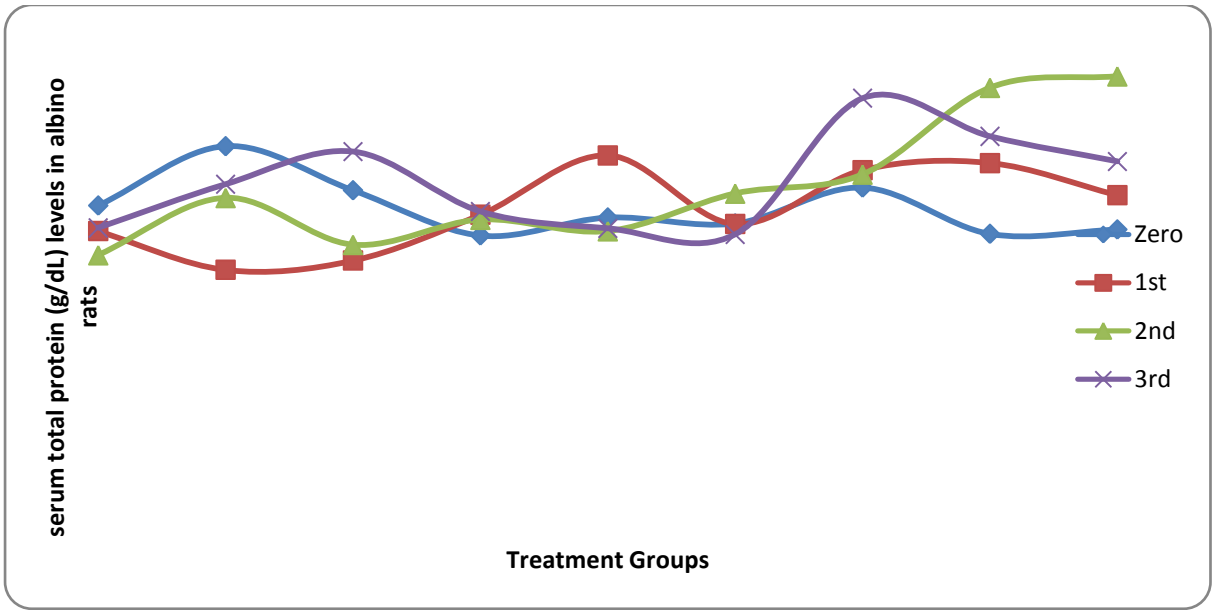


Figure 1. The effects of different doses of lithium carbonate alone or with L- ascorbic acid on serum total protein.

In the present study L-ascorbic acid was co administered with lithium carbonate to the experimental rats, this caused reduced infiltration of inflammatory cells in the different doses of the treatment compared to rats treated only with lithium carbonate. But vacoulations occurred in a dose of 9mg/kg body weight and coagulative necrosis occurred in lithium therapy of doses 17, 34 mg/kg. In the current study the L-ascorbic acid appeared to act as protective agent to the hepatocytes. No available data on the use of L-ascorbic acid and lithium therapy co administration, on liver histopathology only many authors reported that daily oral administration of vitamin C to rats played a pivotal role in maintaining normal tissues, anti-inflammatory and reduced the toxicity of lithium therapy. Antioxidant supplements may include a number of different free radical-fighting compounds. It is thought that antioxidants, such as vitamin C may reduce the damage caused by free radical in the bodies by inhibiting their formation (Frei *et al*., 1989). Form this I recomomded that, from this study it is advised that patients on lithium therapy should be supplied with vitamin C, to reduce the toxicity of lithium carbonate, It is advised that patients on lithium therapy should undergo continuous assessment of serum for markers reflecting condition of liver.

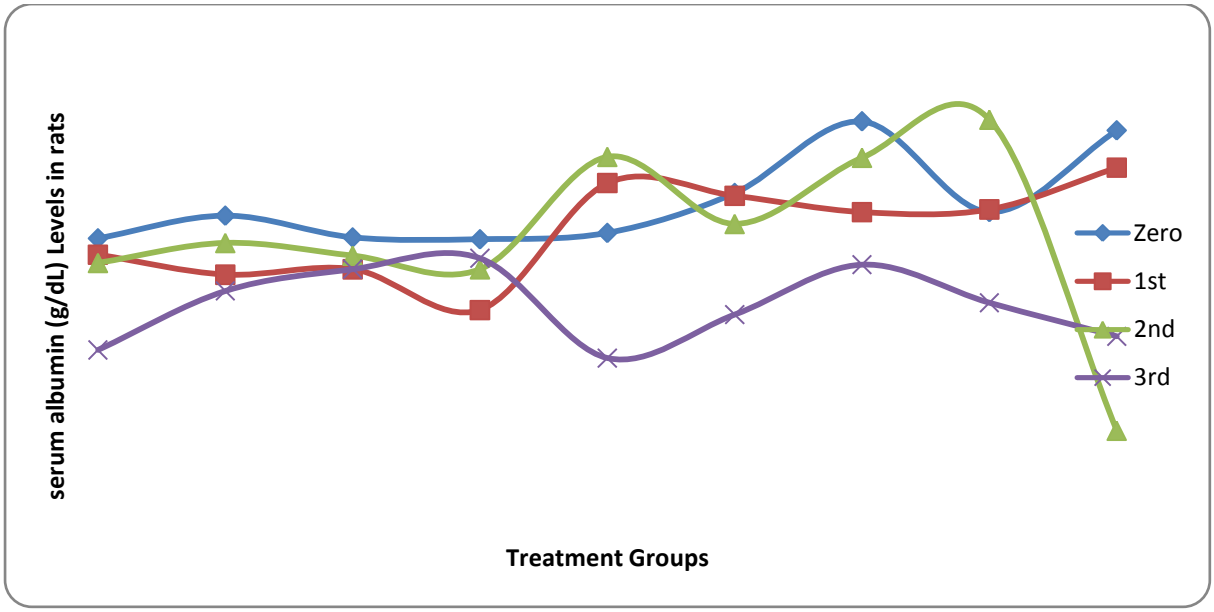


Figure 2. The effects of different doses of lithium carbonate alone or with L- ascorbic acid on serum albumin.

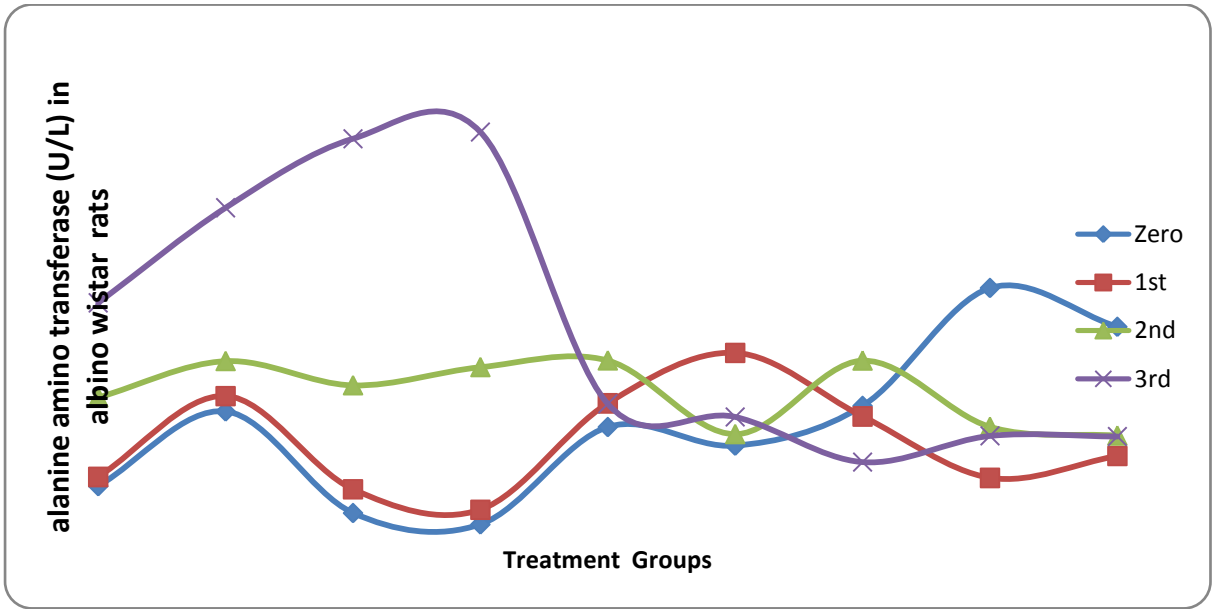


Figure 3. The effects of different doses of lithium carbonate alone or with L- ascorbic acid on serum alanine aminotransferase(ALT).

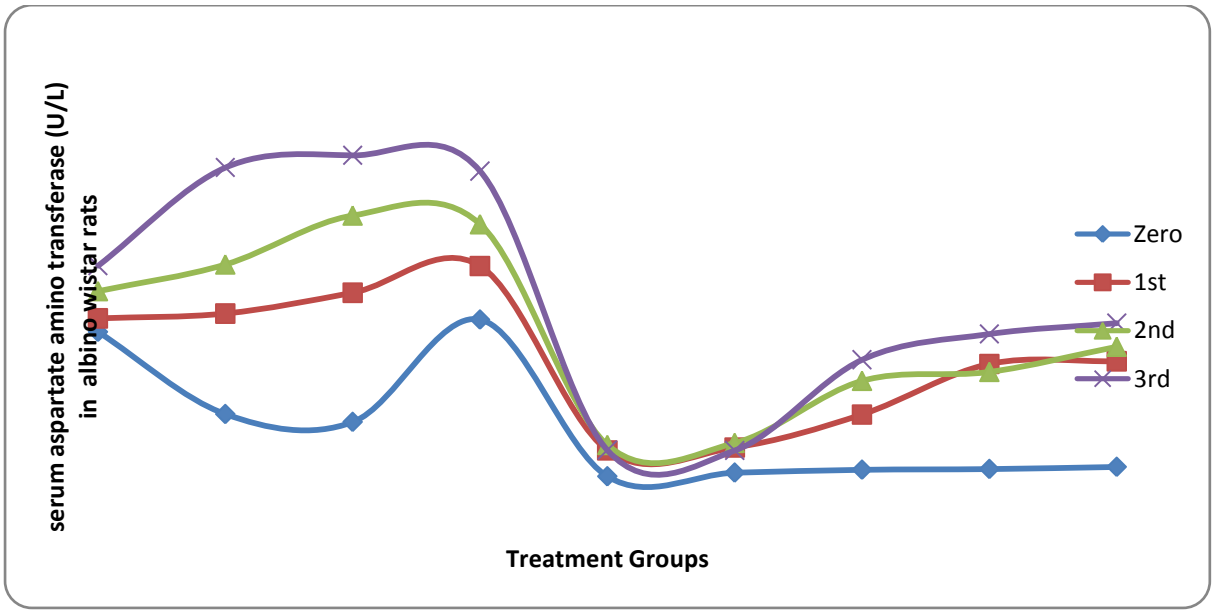


Figure 4. The effects of different doses of lithium carbonate alone or with L- ascorbic acid on serum aspartate aminotransferase (AST).

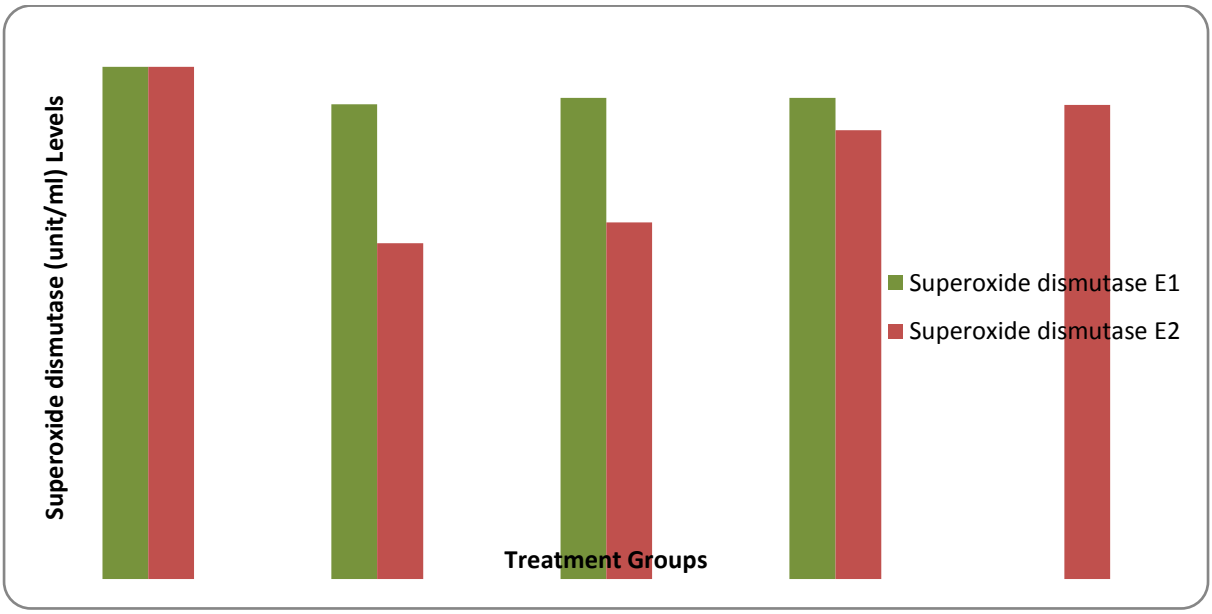


Figure 5. The effects of different doses of lithium carbonate alone or with L- ascorbic acid on hepatocyte superoxide dismutase (SOD).

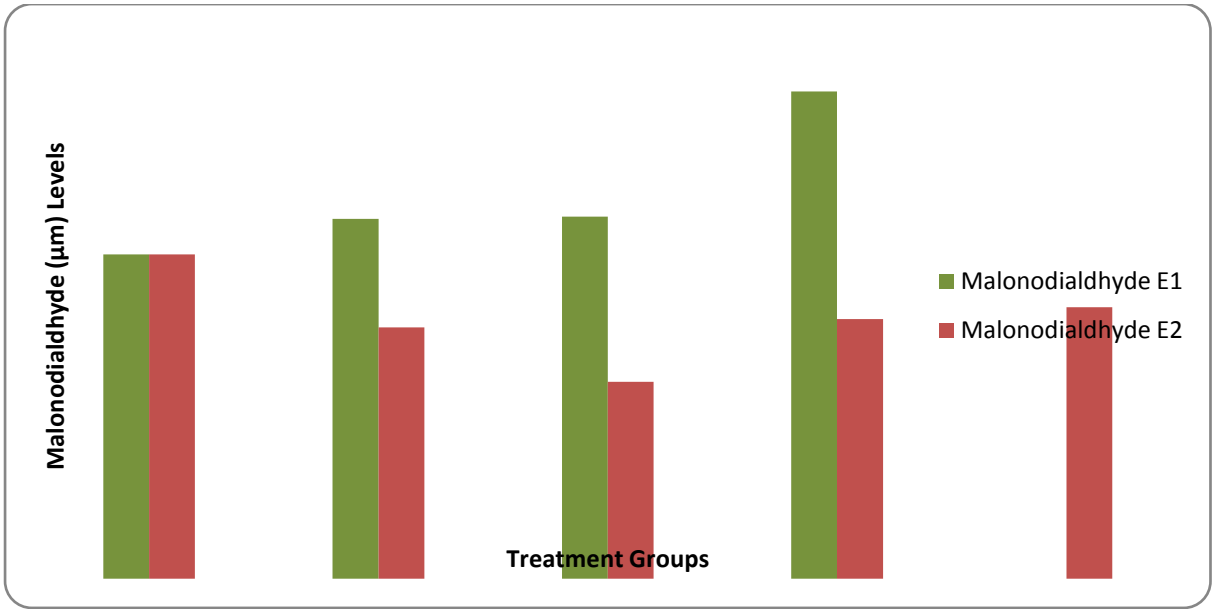


Figure 6. The effects of different doses of lithium carbonate alone or with L- ascorbic acid on hepatocyte malnodialdyde (MDA).

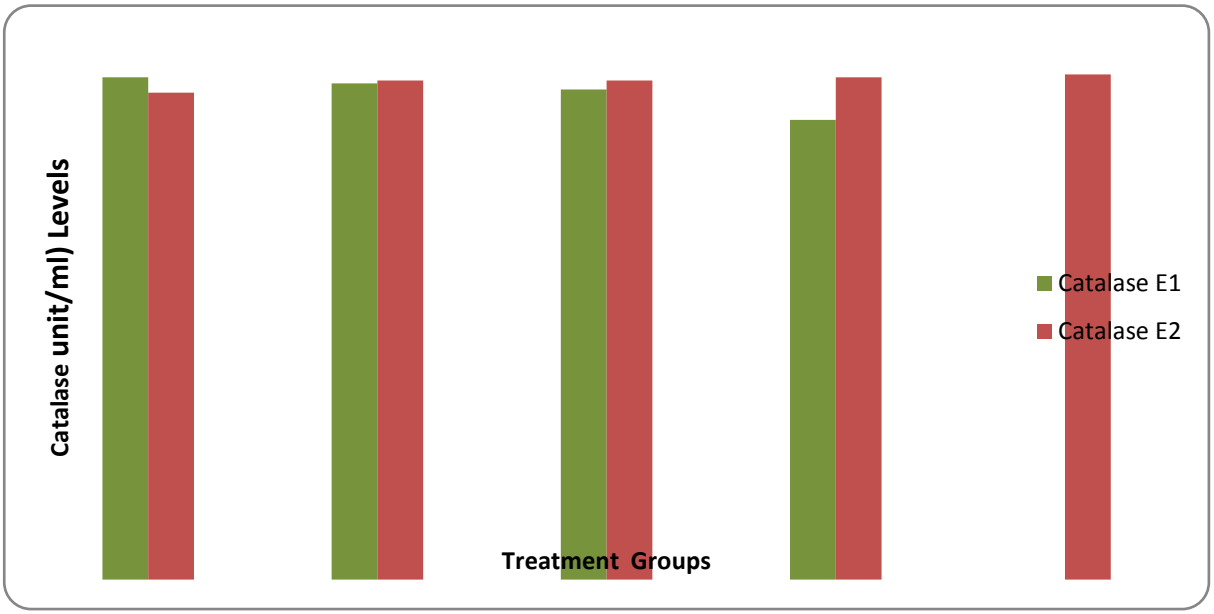


Figure 7. The effects of different doses of lithium carbonate alone or with L- ascorbic acid on hepatocyte catalse (CAT).

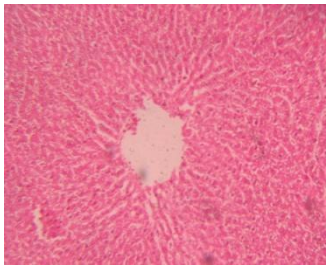


Figure (1): Liver normal hepatic cells in control group (H&E X100)

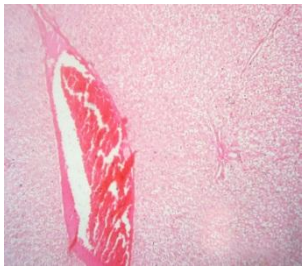


Figure (2): Congestion of central vein, necrosis of hepatocytes in rats treatedwith (9mg/kg) lithium carbonate (H&E X100)

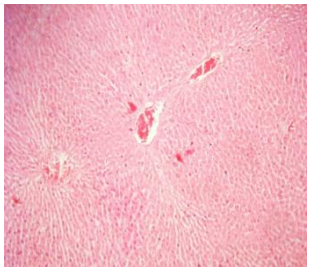


Figure (3): Coagulative necrosis of hepatocytes, congestion of central veinin rats treated with 17mg/kg lithium carbonate (H&E X100)

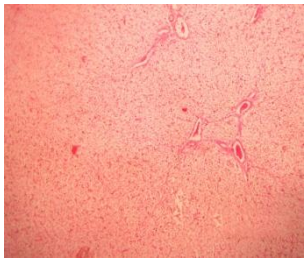


Figure (4): Congestion of central veins and necrosis of hepatocyte in ratstreated with 34mg/ kg lithium carbonate (H&E X100)

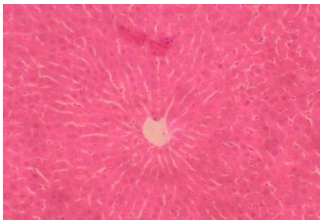


Figure (5): Normal hepatocytes in rats treated with L-ascorbic acid (H& E 100X)

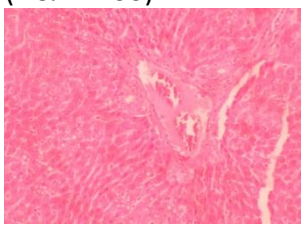
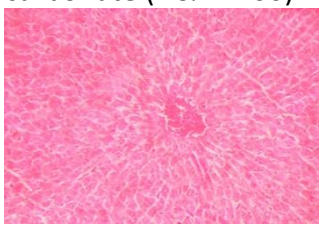
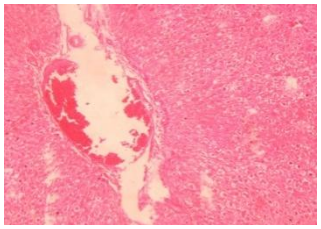


Figure (6): Vacoulations of hepatocytes and congestion of centralvein in rats treated with 9mg of lithium carbonate acid (H& E 100X)



Figure(7): Necrosis of hepatocytes and sever congestion of central vein in rats treated with 17 mg lithium carbonate + L-ascorbic acid(H&E 100X)



Figure(8): Necrosis of hepatocytes and sever congestion of central veins in rats treated with 34mg lithium carbonate +L-ascorbic acid (H&E 100X)

CONCLUSIONS

In conclusion, the present results suggested that lithium carbonate induced hepatic toxicity in rats at physiological and histopathological levels. It has also potentials of inducing adverse effects in rat blood values and oxidative stress in rat liver tissue. Although, the precise mechanism of lithium carbonate toxicity still remains incompletely understood, the clinical use of lithium needs a carful and caution attention. And also, the data from the present study showed that L-ascorbic acid alone or it's the interaction with lithium carbonate is effective in protection against lithium liver toxicity in rats. In addition, L-ascorbic acid is known free radical scavenger. Lithium carbonate exposure caused a histological and biochemical changes mediated by oxidative stress and lithium accumulation but co-treatment with L-ascorbic acid showed clear protect on against lithium toxicity.

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