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Protective effect of l-carnitine on oxidative stress in the liver of acute hepatotoxicity male rats after cytarabine chemotherapy

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Abstract---Hepatotoxicity is a common clinical manifestation associated with a wide range of anticancer therapies. Because of the inherent toxicity of anticancer therapies, oncologists must maintain a broad understanding of their effects on the body, including the liver. Therefore, the study was conducted to examine the effects of two doses of L-carnitine on damaged liver as a result of giving cytarabine. Twenty-four male rats were used in the experiment. The rats were divided into four groups, each with six rats. The first group injected normal saline intraperitoneally and set as control group (G1), the second group injected cytarabine 25 mg/kg/bw intraperitoneally and set as (G2), the third injected cytarabine 25 mg/kg/bw and 50 mg/kg/bw L-carnitine intraperitoneally and set as (G3), the fourth injected cytarabine 25 mg/kg/bw and 300 mg/kg/bw L-carnitine intraperitoneally and set as (G4).

Intraperitoneally and set as(G4), the study showed that use of L-carnitine reduced the harmful effect of cytarabine in the body when compared to the group that was injected only with cytarabine at level of (p-value <0.05). ALT show a significant increase in G2 when compared to other groups the mean value was (104±7.697, 134.66±13.08, 105.66±5.89, 94.33±3.5) for groups: control, cytarabine, 50mg/kg/bw & 300mg/kg/bw of L-carnitine respectively; ACE show a significant increase in G2 when compared to other groups the mean value was (2.3±0.99, 5.77±0.96, 3.86±0.7, 3.23±0.87) for groups control, cytarabine and 50 mg/kg/bw & 300mg/kg/bw of L-carnitine respectively; SOD show a significant decrease in G2 when compared to other groups, the main value was (51.74± 5.60, 40.26±5.53, 55.34±10.84, 61.34±6.76) for groups: control, cytarabine and 50mg/kg/bw & 300mg /kg/bw of L-carnitine respectively; and CAT show a significant decrease in G2 when compared to other groups, the main value was (92.23±16.09, 63.04±25.88, 112.33±32.83, 119±15.12) for groups: control, cytarabine and 50mg /kg/bw & 300mg/kg/bw of L-carnitine respectively.

Keywords---Hepatotoxicity, L-carnitine, Cytarabine, Liver enzyme, Antioxidants.

Introduction

The liver serves many metabolic functions. It has enormous regenerative capacity. The liver is an important target of the toxicity of drugs, xenobiotics, and oxidative stress. The liver plays a key role in the metabolism of a variety of drugs and toxins and thus is especially susceptible to damage induced by drugs including cytotoxic chemotherapy regimens (1).

Hepatotoxicity represents a common clinical manifestation that is associated with a variety of anticancer therapies. The inherent toxicity of anticancer therapies requires oncologists to maintain a broad awareness of their effects on the body, including the liver (2). As a result, proper monitoring and strategies such as discontinuation or dose-modification of pharmacologic agents is commonly required when hepatotoxicity occurs (3). Oncologists and hepatologists must collaborate closely to monitor patients for hepatotoxicity and take appropriate action to prevent long-term liver damage as new, specialized cancer medicines are developed (4).

Treatment with anticancer drugs can have harmful effects, and the toxicity can lead to a worsened condition quality of life and survival time. Cytarabine is one of the most potent cytotoxic drugs used in the treatment of acute leukemia. Cytarabine is an antimetabolite chemotherapy drug that is primarily used to treat cancers of white blood cells (WBCs), such as non-Hodgkin lymphoma, acute myeloid leukemia, acute lymphocytic leukemia, and chronic myelogenous leukemia (5). Its actions are unique to the cell cycle's S-phase. It causes extensive chromosomal destruction causing chromatid aberrations. As a result, quickly dividing cells that require DNA replication, mitosis is the most commonly

affected (6). Cytarabine causes the generation of reactive oxygen species (ROS), depletion levels, and inhibition of antioxidant enzyme activity in liver tissues. However, it is known that cytarabine is metabolized in the human liver to a significant degree, and high doses of the drug induce hepatotoxicity.

L-carnitine is synthesized endogenously in the liver, the kidney, and the brain from the essential amino acids lysine and methionine (7,8) or ingested via animal-based food products (9). Its name comes from the Latin *carnus*, meaning meat, because the compound is extracted from meat (10, 11). L-carnitine plays an important role in energy metabolism (12). It transfers long-chain fatty acids to cell mitochondria for oxidation, which produces energy needed by the body, it also transports harmful substances out of the organelle, preventing them from accumulating in the cell (13). L-carnitine may provide cell membranes protection against oxidative stress, given its pivotal role in fatty acid oxidation and energy metabolism (9). L-carnitine has the potential to protect these cellular events in several manners including decreasing the production of reactive oxygen species at different points and maintaining mitochondrial functions (14).

Synthetic drugs used to treat cancer are not only expensive, but also have a complicated mode of administration and a number of side effects. L-carnitine plays important roles in reducing the cytotoxic effects of free fatty acids by forming acyl-carnitine and promoting beta-oxidation (8, 15), leading to alleviation of cell damage.

Materials and Methods

Twenty-four (24) male white albino rat were used in this experiment and their ages between (12-14) weeks and they were (260-300) gm per body weight and the animals were placed in good condition in special plastic cages and provided the animals with the appropriate conditions in terms of temperature around (30 ±5 °C) and ventilation and the light system was 12 hrs. per day.

The experiment lasted about during 28 days the rats were administration as the following groups, which include first group (G1): six male rats were given normal saline (daily, intraperitoneally injection) and served as the control. Second group (G2): six male rats were given single dose of cytarabine (25 mg/kg/bw) intraperitoneally injection. Third group (G3): six male rats were given single dose of cytarabine (25 mg/kg/bw) intraperitoneally and L-Carnitine (50 mg/kg/bw) for intraperitoneally injection for 4 weeks. Fourth group (G4): six male rats were given a dose of cytarabine (25 mg/kg/bw) intraperitoneally and L-Carnitine (300 mg/kg/bw) for intraperitoneally injection for 4 weeks. Blood samples were collected from all rats, and samples were coded to avoid the possibility of bias. Experimental animals (rats) get anaesthetized by putting them in covered jar include cotton rinsed with chloroform to be sedated for the next step which is blood via cardiac puncture in sterile syringes by needle prick in the heart draining 5ml of blood carefully, then separation of the blood collected into 1 ml the rest of the blood drained into two separated parts; about 2ml set in gel tube it is left about half hour at room temperature for properly agglutinated, then it would be separated at centrifuge at 3000 rpm for fifteen minutes to get the serum apart in Eppendorf tube, samples are hold in freezer at -20 °C.

Parameters of study

- 1- Antioxidant indices assessment of catalase (CAT) according to (16) and super oxide dismutase (SOD) according to (17)
- 2- Level of malondialdehyde (MDA) assay method of (18) on spectrophotometer.
- 3- Enzymes measurement angiotensin converting enzyme (ACE), according to (19); gamma-glutamyl transferase (GGT) according to (20); aspartate transaminase (AST) and alanine transaminase (ALT) according to (21).

Statistical Analysis

Statistical analysis of the results was conducted according to SPSS (2016) version 24.00 where one way (ANOVA) was used to assess the significance of changes between the groups' results. The data were expressed as Mean Standard Errors (SE) and P-value ≤ 0.05 was considered as statistically significant, LSD test was carried out to test the significant levels among means of treatments (22).

Results

Effect of cytarabine+ 50 & 300 mg/kg/bw L-carnitine on serum liver enzyme in adult male rats:

1. Effect of cytarabine+ 50 & 300 mg/kg/bw L-carnitine on serum ALT of adult male rats:

The main value of serum ALT show a significant increase ($p \leq 0.05$) in G2 group when compared with G1, G3 and G4 groups. While there is no significant ($p \geq 0.05$) difference between G1 and G3 groups. On the other hand, G4 show a significant ($p \leq 0.05$) decrease when compared to the other groups. The main value of serum ALT was (104 ± 7.697 , 134.66 ± 13.08 , 105.66 ± 5.89 , 94.33 ± 3.5) for groups control, cytarabine+ 50 & 300 mg/kg/bw L-carnitine respectively (LSD=7.997), figure (1).

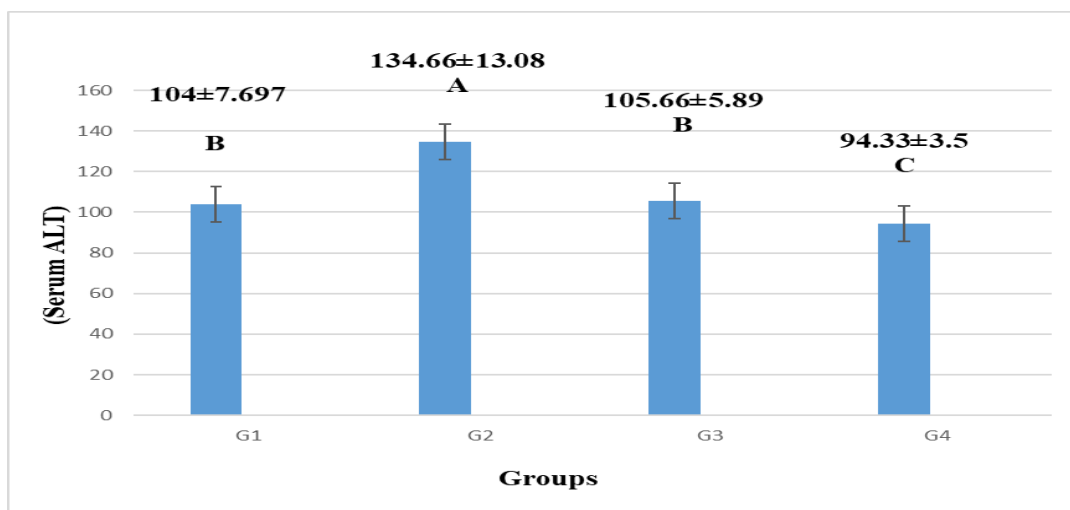


Figure (1): Effect of cytarabine+ 50 & 300 mg/kg/bw L-carnitine on serum ALT

2. Effect of cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum AST in adult male rats:

The main value of serum AST show a significant increase ($p \leq 0.05$) in G2 group when compared with G1, G3 and G4 groups. While there is no significant ($p \geq 0.05$) between G3 and G4 groups. also G1 show a significant decrease ($p \leq 0.05$) when compared to G2 and G3. While it shows no significant ($p \geq 0.05$) difference when compared to G4. The main value of AST was (39 ± 7.29 , 52 ± 3.87 , 45.33 ± 3.16 , 42 ± 2.44) for groups control, cytarabine + 50 & 300 mg/kg/bw L-carnitine respectively (LSD=4.406), figure (2).

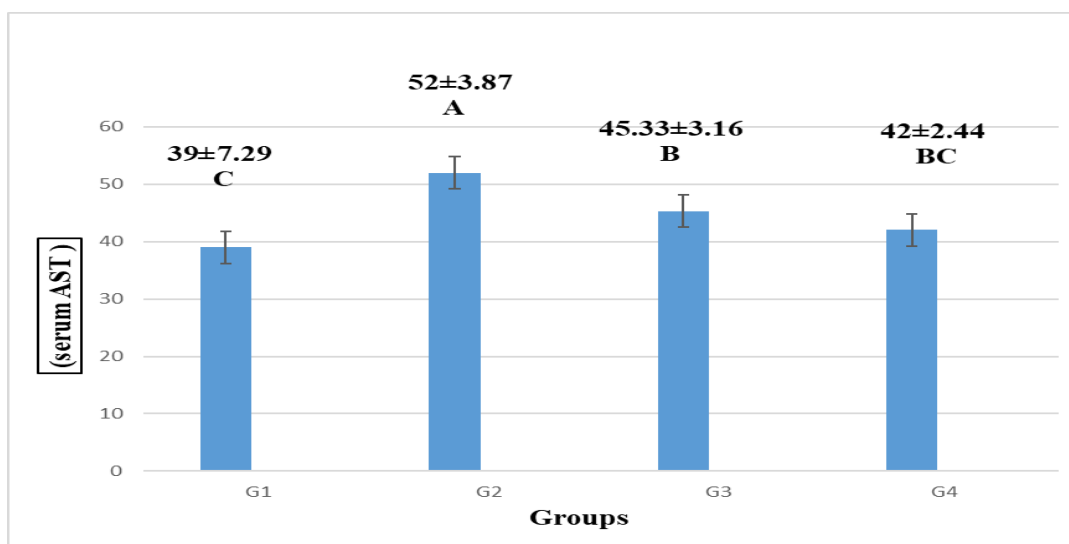


Figure (2): Effect of cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum AST

3. Effect of cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum GGT of adult male rats:

The main value of serum GGT show a significant increase ($p \leq 0.05$) in G2 group when compared with G1, G3 and G4 groups. While there is no significant ($p \geq 0.05$) difference between G1, G3, G4 groups. The main value of GGT was (2.66 ± 0.72 , 5.6 ± 1.79 , 3.66 ± 1.80 , 3 ± 1.93) for groups control, cytarabine + 50 & 300 mg/kg/bw L-carnitine respectively (LSD=1.939), figure (3).

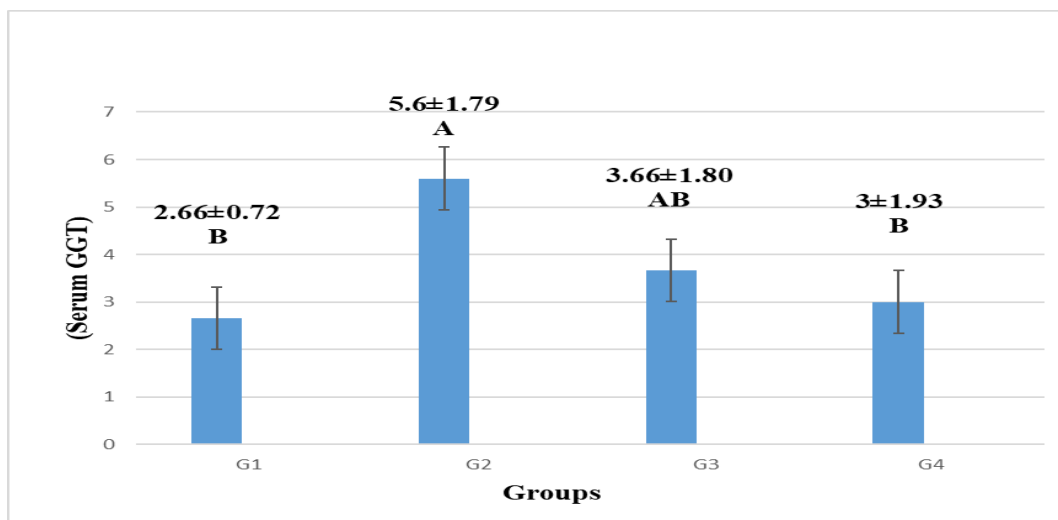
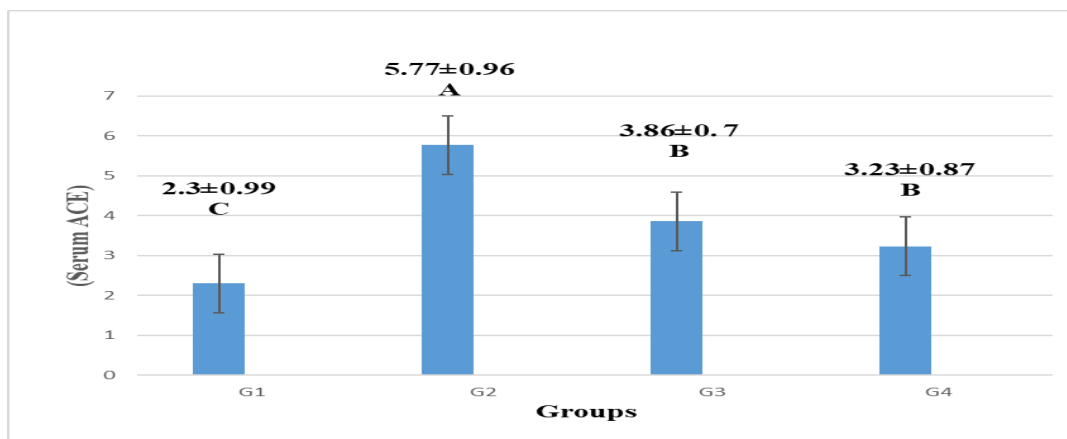


Figure (3): Effect of cytarabine + 50 & 300mg/kg/bw L-carnitine on serum GGT

4. Effect of cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum ACE of adult male rats:

The main value of serum ACE show a significant increase ($p \leq 0.05$) in G2 group when compared with G1, G3 and G4 groups. While there is no significant ($p \geq 0.05$) between G3, G4 groups. Also there is a significant ($p \leq 0.05$) decrease in G1 group when compared to the others groups. The main value of ACE was (2.3 ± 0.99 , 5.77 ± 0.96 , 3.86 ± 0.7 , 3.23 ± 0.87) for groups control, cytarabine + 50 & 300 mg/kg/bw L-carnitine respectively (LSD=0.857), figure (4).

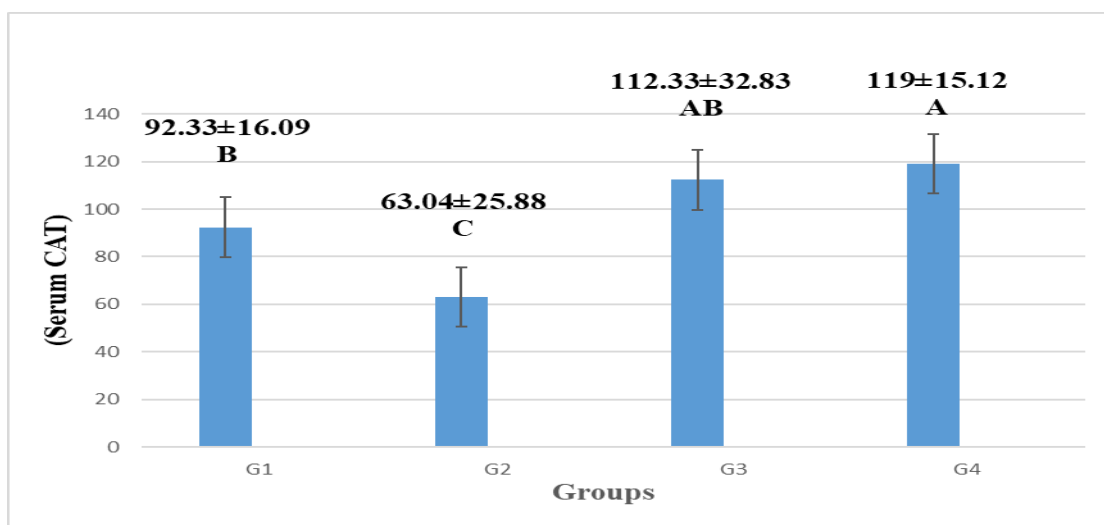


Cytarabine + 50 & 300mg/kg/bw L-carnitine on serum ACE **Figure (4):** Effect of

Effect of cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum anti-oxidant of adult male rats:

1. Effect of cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum catalase (CAT) of adult male rats:

The main value of serum CAT show a significant ($p \leq 0.05$) increases in G4 group when compared with G1 and G2 groups. While there is no significant ($p \geq 0.05$) difference between G4 and G3 groups. While there is a significant increase ($p \leq 0.05$) in G1 Group when compared to G2. The main value of CAT was (92.23 ± 16.09 , 63.04 ± 25.88 , 112.33 ± 32.83 , 119 ± 15.12) for groups control, cytarabine + 50 & 300 mg/kg/bw L-carnitine respectively (LSD=21.770), figure (5).



cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum CAT **Figure (5):** Effect of

2. Effect of cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum superoxide dismutase (SOD) of adult male rats:

The main value of serum SOD show a significant ($p \leq 0.05$) increases in G4 group when compared with G1 and G2 groups. While there is no significant ($p \geq 0.05$) difference between G4 and G3 groups. On the other hand, G1 show a significant ($p \leq 0.05$) increases when compared to G2. The main value of SOD was (51.74 ± 5.60 , 40.26 ± 5.53 , 55.34 ± 10.84 , 61.34 ± 6.76) for groups control, cytarabine + 50 & 300 mg/kg/bw L-carnitine respectively (LSD=7.405), figure (6).

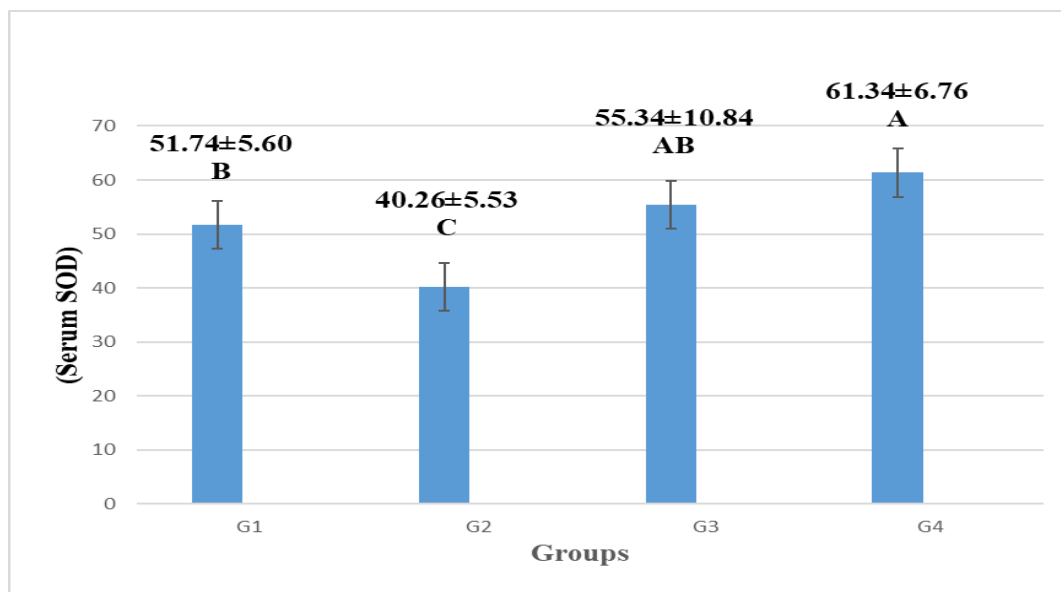


Figure (6): Effect of cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum SOD

Effect of cytarabine + 50% & 300% L-carnitine on serum level of malondialdehyde (MDA) of adult male rats:

The main value of serum MDA show a significant increase ($p \leq 0.05$) in G2 group when compared with G1 and G4 groups. While there is no significant ($p \geq 0.05$) difference between G2 and G3 groups. On the other hand, there is no significant ($p \geq 0.05$) between G1, G4 groups. The main value of serum MDA was (2.41 ± 1.016 , 4.80 ± 1.74 , 4.73 ± 1.91 , 2.46 ± 0.81) for groups control, cytarabine + 50 & 300 mg/kg/bw L-carnitine respectively (LSD=1.484), figure (7).

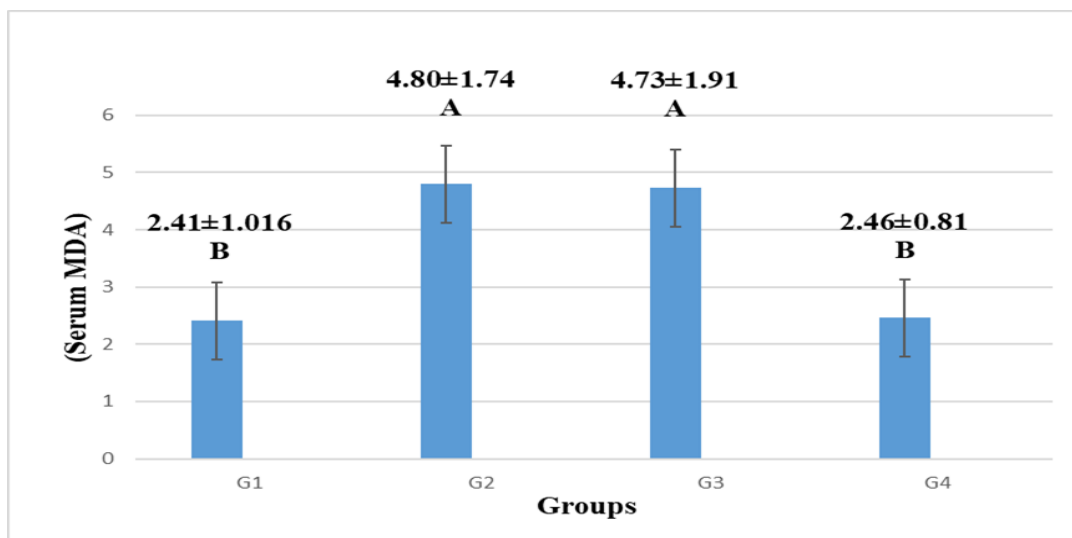


Figure (7): Effect of cytarabine + 50 & 300 mg/kg/bw L-carnitine on serum MDA

Discussion

In the current study, higher significant differences in cytarabine, treated group as compared with other groups, after intraperitoneal administration of cytarabine, showed significant increase in serum liver enzymes activities ALT, AST, GGT, ACE, and the level of MDA. The results were consistent with those obtained by (23), obtained a similar result when they reported that acute leukemia complicated by hyperbilirubinemia due to high dose cytosine arabinoside therapy. Another similar result was obtained by (24) who, reported that cytosine arabinoside induced liver damage. This data agreement with (25) who, found the liver enzymes (ALT, AST, GGT, and alkaline phosphatase) were elevated denotes a hepatocellular disease.

Enzyme, generates reactive oxygen species such as superoxide radical and these various oxidants can promote toxicity by protein oxidation and enzyme inactivation and by damage to cell membranes via lipid peroxidation and production of reactive lipid aldehydes, such as malondialdehyde and 4-hydroxynonenal.

The result contradicted the findings of (26), who discovered hepatic dysfunction and jaundice following high-dose cytosine arabinoside. (27) obtained a similar result when they investigated low-dose cytarabine-induced hepatic and renal dysfunction in a patient with myelodysplastic syndrome, who investigated the side effects of high-dose arabinoside cytosine administration to children with acute myelogenous leukemia. (28) confirmed these results, discovering that serious liver damage and pathological changes in the liver were able to alleviate: For starters, the number of white blood cells in the peripheral blood was significantly lower, and there were fewer transplanted K562 leukemia cells.

Hepatotoxicity is one of the most prevalent medical disorders. The process of lipid peroxidation is closely related to hepatotoxicity, which causes cell death primarily due to oxidative stress, which is caused by an alteration in the intracellular pro-oxidant to antioxidant ratio in favor of pro-oxidants (29). Lipid peroxy radicals cause increased cell membrane permeability, decreased cell membrane fluidity, membrane protein inactivation, and mitochondrial membrane polarity loss.

In the present study, the level of liver MDA in the cytarabine treated group was significantly higher compared with their levels in the controls. Increased MDA levels indicated that lipid peroxidation, mediated by ROS, was an important contributing factor in the development of cytarabine-mediated tissue damage.

Further, the rats treated with Ara-C have shown a dose-dependent and significant reduction in CAT and SOD. The placental GSH, SOD, GPx, CAT levels and increase in MDA levels as compared to control rats, was addressed by (30) in a recent study.

The result of the effect of L-carnitine was a decrease in the plasma concentration of intracellular serum enzymes (ALT, AST, GGT, ACE) and MDA when compared to that in the animals of the control with cytarabine-induced acute drug damage (31).

And this agreement with study showed that D-gal increase serum MDA level as result of oxidative stress which is manifested by significant increase in lipid peroxidation and reduce in GSH, SOD and CAT. MDA is evidence of lipid peroxidation it is final products of polyunsaturated fatty acids peroxidation in the cells. An increase in free radicals causes overproduction of MDA (32).

When cellular antioxidant defense systems are insufficient to keep ROS levels below a dangerous threshold, oxidative stress ensues. This can be caused by excessive ROS generation, antioxidant defense failure, or both. (33). Studies suggest that L-carnitine may play an important role in oxidative/ antioxidant balance and has an antiperoxidative effect on several tissues (34,35). Previous research has shown that L-carnitine has a key role in the oxidative/antioxidative balance as well as the transport of long-chain fatty acids into mitochondria in biological systems (36; 37).

However, the effects of L-carnitine on certain antioxidant enzymes that detoxify H₂O₂ in water, such as GPX, CAT, and MPO, have been independently observed in a few studies (34,38). (34) investigated the effects of 500 mg/kg (IP) L-carnitine on cisplatin-induced oxidative damage in rat liver and kidney tissues. Their findings revealed that L-carnitine produced considerable protective action in the liver and kidney by lowering MDA levels and increasing GPX activity, implying that this molecule has an antioxidant effect. (38) investigated the effects of L-carnitine at a dose of 500 mg/kg (IP) on the oxidant/antioxidant status in acetic acid-induced colitis, finding that L-carnitine administration to the acetic acid-treated rats significantly reduced MDA levels and MPO activity, while CAT activity increased in colon tissue. Unlike Cetinkaya's findings, two separate dosages of given L-carnitine significantly increased MPO activity in liver tissue in our study.

Furthermore, treating hyperthyroid rats for 10 days with both low-dose (100 mg/kg) and high-dose (500 mg/kg) L-carnitine resulted in a significant increase in antioxidant enzyme activities in the liver tissue as compared to levels in the second group of rats. The high-dose L-carnitine group (Hyper+LC500) had higher L-carnitine-induced increases in MPO, GPX, and CAT activities than the low-dose group (Hyper+LC100), but the differences between the groups were not statistically significant (13).

(39) found that pretreatment with L-carnitine (100 mg/kg, IP) increased tissue catalase activity and protected the gastric mucosa from ischemia-reperfusion injury by decreasing lipid peroxidation via its lipid peroxidation-decreasing activity, which protected the gastric mucosa from ischemia-reperfusion injury. However, pretreatment with L-carnitine significantly prevented cytarabine-induced lipid peroxidation in the liver tissues, implicating an antioxidant effect from this molecule. This was probably due to less damage having occurred from oxygen free radicals.

Reactive oxygen species readily attack the polyunsaturated fatty acids of the fatty acid membrane, initiating a self-propagating chain reaction. The destruction of membrane lipids and the end-products of such lipid peroxidation reactions are especially dangerous for the viability of cells, even tissues. Enzymatic (catalase, superoxide dismutase), since lipid peroxidation is a self-propagating chain-

reaction, the initial oxidation of only a few lipid molecules can result in significant tissue damage (40,41).

Drug-induced liver injury may manifest a cumulative effect, where in earlier harm may compound to cause impaired drug metabolism and increased toxicity. The hepatotoxicity of many drugs, dysfunction of these vital cell organelles results in impairment of energy metabolism and an intracellular oxidant stress with excessive formation of reactive oxygen species and peroxynitrite. As a result, proper monitoring and strategies such as discontinuation or dose-modification of pharmacologic agents is commonly required when hepatotoxicity occurs. For example, research exploring the mechanism of methotrexate related hepatotoxicity identified the activation of inflammatory path-ways and cytokines, upregulation of pro-apoptotic mediators, and reactive oxygen species (ROS) formation as contributing factors to liver damage (2).

Conclusion

According to the study, cytarabine reduces liver activity and causes liver damage, and L-carnitine works to reduce cytarabine damage, with L-carnitine 300 mg/kg/bw working better than L-carnitine 50 mg/kg/bw.

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