Received: 07 April 2023, Accepted: 27 May 2023

Original Research

Journal of Advanced Veterinary Research
(2023) Volume 13, Issue 5, 730-736

Ameliorative Effect of L-Carnitine against Hematological and Hepatorenal Alterations Induced by Cefquinome Sulfate in Male Albino Rats

Abd El-Salam F. El-Sawy, Zeynab Kh. El-Maddawy, Mahmoud K. Elsaady, Hawary S. Ibrahim*

Veterinary Pharmacology Department, Faculty of Veterinary Medicine, Alexandria University, Egypt.

***Correspondence**
Corresponding author: Hawary S. Ibrahim
E-mail address: dr.hawary_vetpharma@yahoo.com

Abstract

The present study was conducted to evaluate the ameliorative effect of L-carnitine (LC) against possible deleterious effects of cefquinome sulfate (CS) on hematological, hepatorenal parameters and histopathological changes of some internal organs in male rat's model. Therefore, sixty mature male rats were equally assigned into four groups as following: The control group of rats was administered with two subcutaneous (SC) injections of physiological saline (vehicle of other drugs) (2 ml/kg. b.wt once daily for 5 successive days and 2ml/kg. b.wt once daily for 56 successive days), the second group was injected subcutaneously with LC (200 mg/kg b.wt. once daily for 56 successive days), the third group was administered with SC injection with CS (50 mg/kg. b.wt once daily for 5 successive days) and the fourth group was injected subcutaneously with CS concomitantly with LC by the same doses at the same treatment periods as mentioned in 2nd and 3rd groups. The obtained results showed that administration of CS induced a significant ($P \leq 0.05$) increase in WBCs count and serum levels of alanine amino transferase, alkaline phosphatase and creatinine with significant ($P \leq 0.05$) decrease in PCV value and serum levels of albumin. Moreover, CS induced histopathological changes on liver and kidney tissues. Conversely, administration of LC concomitantly with CS ameliorates all previous hematological, biochemical, and histopathological alterations induced by CS. It could be concluded that CS induces mild to moderate troubles on blood picture, hepato-renal indices and histopathological findings which could be ameliorated by L-carnitine in male albino rats.

KEYWORDS
Cefquinome, L-carnitine, hepatorenal, rats

INTRODUCTION

Antibiotics are primarily used in animals to avoid or treat bacterial infections, such as mastitis, arthritis, infections of the respiratory tract, gastrointestinal disorders and other diseases (Darwish *et al*., 2013).

Numerous widely used antibiotics may affect the metabolic breakdown of other medications or result in cardiovascular or respiratory depression. Instead of being associated with allergic reactions or cytotoxic lesions, these adverse reactions are thought to be caused by the direct effects of antibiotics on certain physiologic processes. Attention should be taken towards these adverse effects (Dancer, 2004).

Cephalosporins are bactericidal antibiotics with a wide range of activity and are derived chemically from 7 aminocephalosporic acid. They are linked to penicillins structurally and functionally because they contain a common β-lactam ring. They consist of a six-membered ring with a connected sulfur atom and a β-lactam ring. (Choma, 2007; Naqvi *et al*., 2011).

Cefquinome Sulfate (CS) is a fourth-generation cephalosporin that was produced only for animal use. It exhibits strong antimicrobial properties against a variety of bacterial species including many Gram-positive bacteria, some Gram-negative bacteria, vibrio, spirochetes and mycoplasma (Coulthurst *et al*., 2005). It is widely used to treat bacterial infections of the respiratory system and the udder in cattle and pig (Zonca *et al*., 2011).

Cephalosporins have a high therapeutic index and a very low incidence of adverse drug reactions. The adverse effects of cephalosporins, except for hypersensitivity, depend on the dose and duration of administration. As, cephalosporins cause agranulocytosis, glomerular and interstitial nephritis, tubular necrosis, hepatitis, and neurotoxicity (Maden *et al*., 2001).

L-carnitine (LC) is a natural compound, described chemically as L-trimethy l-3-hydroxy ammonobutanoate. It is an endogenous co-factor that improves the metabolism of carbohydrate and lowers the accumulation of toxic metabolites inside the cells when subjected to ischemia (Salama *et al*., 2012).

L-carnitine is essential for the transportation of long-chain fatty acids from the cytosol to the mitochondria so they can start the oxidation cycle (Brass, 2000; Rani and Panneerselvam, 2001). It acts primarily as an efficient dietary supplement and has antioxidant properties (Brass, 2000).

Many previous studies focused on the effects of different cephalosporins on hemato-biochemical status, few of them who use antioxidant drugs such as LC to ameliorate their side and/or adverse effects. The novelty of such study is to evaluate the

ISSN: 2090-6277/2090-6269/

possible troubles of CS on hematological, biochemical parameters and histopathological picture with possible role of LC in restoring these possible deleterious effects in male albino rats was evaluated.

MATERIALS AND METHODS

Drugs and reagents

Cefquinome sulfate (Cobactan)® injection was obtained from MSD animal house, USA. L-carnitine (L-carnitine) ® ampule is provided by Arab Company for Pharmaceuticals and Medicinal Plants (Mepaco-Medifood), Egypt. all the diagnostic assay kits for hepatic and renal function tests were obtained from Bio-diagnostic Company, Egypt.

Experimental design

Animals and management

Sixty healthy mature male albino rats (with a weight of 180±10 g and about 150 days old) were purchased from Medical Research Institute of Alexandria University, Egypt. Rats were housed in separate plastic cages (6-8 rat/cage) with soft wood chips for bedding under unique conditions (23±2ºC, 55% RH, and 12-h light/dark cycle) and had regular food and water ad libitum. The animals were acclimatized for 2 weeks prior to the commencement of study to ensure normal growth and behavior.

Approval to use animals in research and teaching has been obtained from the institutional animal care and use committee (IACUC) Alexandria University (5/2022/128). The rats were equally divided into 4 groups as following:

Group1 (control): Rats were injected subcutaneously with two doses of physiological saline (2ml/kg. b.wt once daily for 5 successive days with 2ml/kg. b.wt once daily for 56 successive days)

Group 2 (LC group): Rats were injected subcutaneously with LC (200 mg/kg b.wt). (Kopple *et al*., 2002) once daily for 56 successive days.

Group 3 (CS group): Rats were injected subcutaneously with CS (50 mg/kg. b.wt). (Vasseur *et al*., 2014) once daily for 5 successive days.

Group 4 (CS plus LC): Rats were injected subcutaneously with CS (50 mg/kg. b.wt once daily for 5 successive days) concomitantly with subcutaneous injection of LC (200 mg/kg b.wt. once daily for 56 successive days).

At the 2nd week, 1 month and 2 months from the beginning of drug administration, 5 rats from each group were euthanized and blood samples and body organs samples (liver and kidney) were collected for further analysis.

Blood sampling

Blood samples were collected from the retro-orbital vein from the eye of the rat by using heparinized micro-hematocrit tubes under light ether anesthesia before being euthanized by cervical dislocation. Two blood samples were collected from each animal. The first blood sample was collected on EDTA for hematological studies. The second blood sample was collected without anticoagulant in clean test tubes, left for 2 hours at room temperature in slope position to clot, and then centrifuged at 3000 r.p.m for 15 minutes to separate serum. Clear serum samples were stored at -20ºC until used for biochemical analysis.

Hematological studies

The hematological parameters were measured automatically by using Mindray® BC-2800 Auto Hematology Analyzer with three-part differentiation of WBC according to Buttarello and Plebani (2008).

Biochemical studies

The biochemical parameters were measured colorimetrically according to Reitman and Frankel (1957) for serum ALT and AST activities, Belfield and Goldberg (1971) for serum ALP activity, Doumas *et al.* (1971) for serum total protein and albumin levels, Coles (1974) for serum globulin level, Coulomb and Farreau (1963) for serum urea level and Bartels *et al.* (1972) for serum creatinine level.

Histopathological studies

The kidney and small fresh specimen from liver were collected and rapidly fixed in formalin solution 10%. The fixed specimens were processed using conventional paraffin-embedding techniques. Paraffin blocks were cut by microtome into 5 microns thick sections and stain with Hematoxylin and Eosin (H&E) for light microscopic examination according to the method described by Harries (1989).

Statistical analysis

The obtained data were analyzed by using one-way analysis of variance using SPSS, version 25. Means were compared by Tukey,s test was performed to evaluate variations between groups when a significant difference was detected. The significant effect was set up at P≤0.05. Data were presented as mean ± standard errors (SE) (Steel and Torrie, 1980).

RESULTS

Hematological findings

Results revealed that CS administration in male albino rats induced a significant (p≤0.05) reduction in PCV % with a significant (p≤0.05) increase in WBCs count at the 4th week of the experiment as compared with control group of rats. While co-administration of LC with CS induced a significant (p≤0.05) increase in PCV % as compared with rats administered CS alone. Moreover, male rats administered with LC alone showed a significant (p≤0.05) increase in Hb concentration at the 2nd week and RBCs count at the 8th week of the experiment as compared with control group of rats. Conversely, there were insignificant changes in all hematological parameters in all other experimental periods and in other groups of rats as compared with control group of rats (Table 1).

Biochemical findings

Effect on serum hepatic enzymes

The results in Table 2 showed that the activity of serum ALT and ALP significantly (P ≤ 0.05) increased in CS-administered rats as compared with control rats at the 2nd and 4th week respectively. While co-administration of LC with CS results in a significant (p≤0.05) decrease in serum ALT and ALP level as compared with rats administered CS alone. Conversely, there were insignificant changes in serum activity of ALT and ALP in all other experimental

periods and in other groups as compared with control group of rats. Moreover, there was insignificant change in serum AST levels in all groups all over the experimental periods as compared with control group of rats.

Effect on serum proteins

The results in Table 3 showed that there was a significant ($P \leq 0.05$) decrease in serum albumin level at the 4th week of the experiment in CS-administered rats as compared with control group of rats. While, co-administration of LC with CS results in a significant ($P \leq 0.05$) increase in serum albumin level as compared with rats administered CS alone. Moreover, rats administered LC alone showed a significant ($P \leq 0.05$) increase in total protein and albumin levels at the 2nd week and in globulin level at the 2nd and 4th week of the experiment. Conversely, there were insignificant

Table 1. Effect of administration of L-carnitine (LC) and cefquinome sulfate (CS) on hematological parameters in mature male rats (n.= 5) at different periods.

Parameter	Period	Control	L-carnitine	Cefquinome	LC+CS
Hb (g/dl)	2 wk.	12.12 ± 0.39^{b}	13.34 ± 0.18^{a}	12.44 ± 0.26^{ab}	13.20 ± 0.29^{ab}
	4 wk.	13.14 ± 0.30^{a}	13.92 ± 0.19^{a}	12.76 ± 0.26^{a}	13.46 ± 0.43^{a}
	8 wk.	13.16 ± 0.09^{a}	13.14 ± 0.13^{a}	13.30 ± 0.14^{a}	13.16 ± 0.34^{a}
PCV (%)	2 wk.	44.20 ± 0.58^{a}	43.94 ± 0.46^{a}	41.42 ± 0.97^{a}	44.18 ± 0.84^{a}
	4 wk.	42.62 ± 0.47^{a}	42.78 ± 0.49^{a}	39.00 ± 0.78^{b}	40.50 ± 0.93^{ab}
	8 wk.	42.62 ± 0.50^{a}	45.00 ± 0.80^{a}	44.80 ± 0.57^{a}	44.54 ± 0.85^{a}
RBCs count (10^{6}/µl)	2 wk.	7.34 ± 0.17^{a}	7.17 ± 0.03^{a}	7.14 ± 0.16^{a}	7.11 ± 0.32^{a}
	4 wk.	7.27 ± 0.09^{a}	7.40 ± 0.19^{a}	6.95 ± 0.07^{a}	7.29 ± 0.18^{a}
	8 wk.	7.53 ± 0.02^{b}	7.74 ± 0.07^{a}	7.68 ± 0.03^{ab}	7.65 ± 0.03^{ab}
Total WBCs count (10^{3}/µl)	2 wk.	8.08 ± 0.79^{ab}	5.90 ± 0.34^{b}	9.14 ± 0.56^{a}	6.78 ± 0.64^{ab}
	4 wk.	5.48 ± 0.19^{bc}	4.52 ± 0.15^{c}	7.40 ± 0.44^{a}	5.62 ± 0.16^{b}
	8 wk.	9.58 ± 0.42^{a}	9.42 ± 0.23^{a}	10.96 ± 0.93^{a}	8.48 ± 0.81^{a}

Values are expressed as Means ± S.E. *Means carrying different letters within the same raw are significantly different ($p \leq 0.05$).

Table 2. Effect of administration of L-carnitine (LC) and cefquinome sulfate (CS) on serum liver enzymes activities in mature male rats (n.= 5) at different periods.

Parameter	Period	Control	L-carnitine	Cefquinome	LC+CS
ALT (U/L)	2 wk.	36.00 ± 1.30^{c}	31.00 ± 1.18^{c}	81.80 ± 2.46^{a}	58.60 ± 1.33^{b}
	4 wk.	54.20 ± 3.12^{b}	61.20 ± 1.11^{b}	86.00 ± 5.04^{a}	81.40 ± 0.81^{a}
	8 wk.	36.00 ± 1.41^{a}	37.20 ± 1.85^{a}	40.00 ± 1.95^{a}	34.00 ± 0.71^{a}
AST (U/L)	2 wk.	273.30 ± 3.35^{a}	263.85 ± 3.09^{a}	261.6 ± 4.31^{a}	275.20 ± 4.05^{a}
	4 wk.	238.20 ± 2.08^{a}	248.40 ± 2.66^{a}	244.00 ± 2.92^{a}	244.00± 3.15^{a}
	8 wk.	208.00 ± 3.65^{a}	194.00 ± 2.35^{a}	196.20 ± 4.52^{a}	199.00 ± 3.79^{a}
ALP (U/L)	2 wk.	227.40 ± 8.16^{a}	233.00 ± 3.39^{a}	225.40 ± 4.31^{a}	217.00 ± 3.90^{a}
	4 wk.	180.20 ± 5.20^{b}	155.00 ± 3.49^{b}	225.80 ± 9.92^{a}	159.60 ± 9.89^{b}
	8 wk.	145.00 ± 4.90^{a}	128.00 ± 3.63^{a}	127.80 ± 3.14^{a}	142.00 ± 5.63^{a}

Values are expressed as Means ± S.E. *Means carrying different letters within the same raw are significantly different ($p \leq 0.05$).

Table 3. Effect of administration of L-carnitine (LC) and cefquinome sulfate (CS) on serum protein levels in mature male rats (n.= 5) at different periods.

Parameter	Period	Control	L-carnitine	Cefquinome	LC+CS
Total protein (g./dl.)	2 wk.	6.52 ± 0.09^{c}	7.24 ± 0.05^{a}	6.60 ± 0.03^{bc}	6.76 ± 0.02^{b}
	4 wk.	6.60 ± 0.09^{ab}	7.02 ± 0.10^{ab}	6.02 ± 0.46^{b}	7.06 ± 0.11^{a}
	8 wk.	6.70 ± 0.03^{a}	6.68 ± 0.16^{a}	6.60 ± 0.09^{a}	6.47 ± 0.14^{a}
Albumin (g./dl.)	2 wk.	3.22 ± 0.12^{b}	3.54 ± 0.05^{a}	3.10 ± 0.03^{b}	3.22 ± 0.04^{b}
	4 wk.	3.51 ± 0.05^{a}	3.38 ± 0.09^{ab}	3.14 ± 0.02^{c}	3.24 ± 0.05^{bc}
	8 wk.	2.95 ± 0.05^{a}	3.10 ± 0.10^{a}	3.18 ± 0.11^{a}	3.02 ± 0.12^{a}
Globulin (g./dl.)	2 wk.	3.30 ± 0.08^{b}	3.70 ± 0.09^{a}	3.50 ± 0.05^{ab}	3.54 ± 0.05^{ab}
	4 wk.	3.09 ± 0.12^{b}	3.64 ± 0.09^{a}	2.88 ± 0.18^{b}	3.82 ± 0.09^{a}
	8 wk.	3.75 ± 0.07^{a}	3.58 ± 0.12^{a}	3.42 ± 0.09^{a}	3.45 ± 0.08^{a}

Values are expressed as Means ± S.E. *Means carrying different letters within the same raw are significantly different ($p \leq 0.05$).

Table 4. Effect of administration of L-carnitine (LC) and cefquinome sulfate (CS) on serum urea and creatinine levels in mature male rats (n.= 5) at different periods.

Parameter	Period	Control	L-carnitine	Cefquinome	LC+CS
Urea (mg/dl)	2 wk.	39.60 ± 1.36^{a}	40.80 ± 1.43^{a}	42.40 ± 1.21^{a}	39.40 ± 1.29^{a}
	4 wk.	37.80 ± 1.07^{a}	37.00 ± 1.05^{a}	34.20 ± 1.39^{a}	35.60 ± 1.29^{a}
	8 wk.	37.80 ± 0.58^{ab}	39.00 ± 1.00^{a}	39.00 ± 0.45^{a}	35.40 ± 1.03^{b}
Creatinine (mg/dl)	2 wk.	0.77 ± 0.05^{a}	0.75 ± 0.03^{a}	0.68 ± 0.03^{a}	0.73 ± 0.02^{a}
	4 wk.	0.93 ± 0.07^{c}	1.13 ± 0.10^{bc}	1.28 ± 0.03^{ab}	1.41 ± 0.02^{a}
	8 wk.	0.79 ± 0.02^{b}	0.80 ± 0.05^{b}	1.10 ± 0.04^{a}	0.74 ± 0.06^{b}

Values are expressed as Means ± S.E. *Means carrying different letters within the same raw are significantly different ($p \leq 0.05$).

changes in serum proteins levels in all other experimental periods and in other groups as compared with control group of rats.

Effect on renal parameters

The obtained results showed that there was a significant ($P \leq 0.05$) increase in serum creatinine level at the 4th and 8th week of the experiment in CS-administered male rats as compared with control rats. While co-administration of LC with CS results induced a significant ($P \leq 0.05$) reduction in serum creatinine level as compared with rats administered CS alone. Conversely, there were insignificant changes in serum creatinine level in all other experimental periods and in other groups of rats as compared with control group of rats. Also, the serum level of urea remains unchanged in all groups all over the experimental periods as compared with control group of rats (Table 4).

Histopathological findings

Histopathological effects on hepatic tissue

Liver section of the control male rats showed normal histological structure of central vein and hepatocytes in the 2nd, 4th and 8th weeks of the study (Fig.1A). Similar histological structures were seen in male rats administered with LC in the 2nd, 4th and 8th weeks of the study (Fig.1B). Liver section of CS- administered male rats showed congestion of portal vein and intense inflammatory cell infiltration in portal area in the 2nd weeks of the study (Fig. 1C). In the 4th week of the study, fatty degeneration of hepatocytes was noticed (Fig. 1E). On the 8th week of the study, focal hepatic necrosis was noticed (Fig. 1G). However, liver section of male rats co-administered with CS concomitantly with LC showed mild inflammatory cell infiltration in portal area with relatively normal hepatocytes on the 2nd week of the study (Fig. 1D). On the 4th and 8th week of the study, normal portal area with relatively normal hepatocytes was observed (Fig. 1F & 1H).

Histopathological effects on renal tissue

Kidney section of the control male rats showed normal histological structure of glomeruli and renal tubules on the 2nd, 4th and 8th week of the study (Fig. 2A). Similar histological structures were seen in male rats administered with LC on the 2nd, 4th and 8th week of the study (Fig. 2B). Kidney section of CS-administered male rats showed congestion of blood vessel and necrotic glomeruli on the 2nd week of the study (Fig. 2C). On the 4th week of the study, interstitial nephritis with inflammatory cell infiltration around glomeruli was noticed (Fig. 2E). On the 8th week of the study, interstitial peri-glomerular inflammatory cell infiltration with remnant of tubular epithelium in the lumen of renal tubes was noticed (Fig. 2G). While kidney section of male rats co-administered with CS concomitantly with LC showed mild conges-

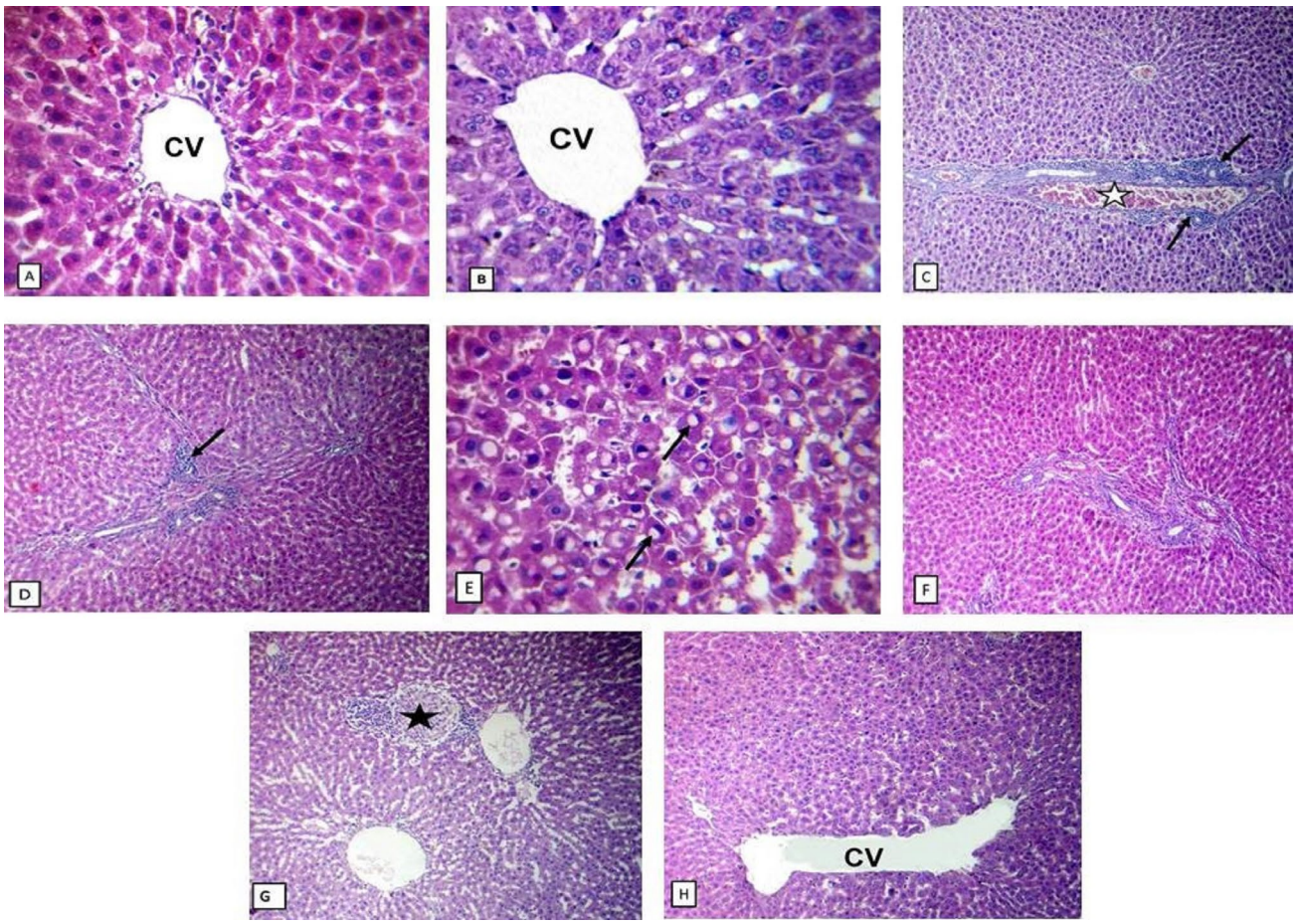

Fig. 1. Photomicrograph of a rat liver sections stained by H&E: (A): male rat of control group at the 2nd week. Note: normal histological structure of central vein (CV) and hepatocytes. (B): male rat administered with LC at 2nd week. Note: normal histological structure of central vein (CV) and hepatocytes. (C): male rat administered with CS at the 2nd week. Note: congestion of portal vein (white star) and intense inflammatory cell infiltration in portal area (arrows). (D): male rat administered with CS concomitantly with LC at the 2nd week. Note: mild inflammatory cell infiltration in portal area (arrow) with relatively normal hepatocytes. (E): male rat administered with CS at the 4th week. Note: fatty degeneration of hepatocytes (arrows). (F): male rat administered with CS concomitantly with LC at the 4th week. Note: normal portal area with relatively normal hepatocytes. (G): male rat administered with CS at the 8th week. Note: focal hepatic necrosis (black star). (H): male rat administered with CS concomitantly with LC at the 8th week. Note: normal central vein (CV) with relatively normal hepatocytes. (Magnification : A, B, and E = X 400. C, D, F, G and H = X.160).

tion of blood vessel with relatively normal glomeruli and renal tubules on the 2nd and 4th week of the study (Fig. 2D & 2F). On the 8th week of the study, normal histological structure of glomeruli and renal tubules was noticed (Fig. 2H).

DISCUSSION

The present study showed that there was a significant reduction in PCV values in rats administered with CS at the 4th week of the experiment as compared with control group of rats. The obtained results are compatible with other previous studies, For instance, reduction of PCV value in buffalo calves (Mangal and Sharma, 2015) and in diarrheic calves after treatment with CS (El-Sayed *et al*., 2018). The reduction in PCV could be attributed to the numerical reduction in total erythrocytes count in this period of study. The production of the erythropoietin hormone is one of the most significant variables taken into account in decrease of total erythrocytic count (Edwards *et al*., 1987). Reduction in total erythrocytic count could be due to lowering synthesis of red blood cells in bone marrow (Mandal *et al*., 1986) or decreasing biosynthesis of heme in bone marrow (Khan *et al*., 2009) or as a result of higher rate of degradation (Mangal and Sharma, 2015).

Our results showed that injection of LC concomitantly with CS induced a significant increase in PCV value compared with CS-administered rats. The obtained results are agree with El-Maddawy (2014) who noticed treatment of rats with L-carnitine improved a significant reduction in Hb concentration, PCV% and RBCs count in male rats treated with gentamicin. She interpreted these results by the antioxidant properties of L-carnitine that enhanced hematopoiesis. Also, we agree with Picardal (2017) who mentioned that treatment of broiler with L-carnitine improve hematological indices via improvement of stability and integrity of the RBCs membrane by helping in the regulation of membrane's phospholipids exposed to oxidative stress or damage.

Moreover, results showed a significant increase in WBCs count in CS-administered rats at the 4th week of the study. Several literature studies have showed CS increase WBCs count. For example, in buffalo calves (Kishanrao, 2016) in coliform mastitic cows treated with CS (Shams, 2017) and in diarrheic calves (El-Sayed *et al*., 2018). Results may be attributed to the anti-allergic reactions of the body that CS stimulated as interpreted by Mshelia and Madusolumuo (2021) who indicate that ceftriaxone (of the same chemical class of CS) stimulated the anti-allergic and anti-parasitic infectious responses of the body.

Acute hepatotoxicity or mild hepatocellular damage usually associated with an increase of liver enzymes such as AST, ALT, and ALP which are among the markers for liver function and integrity (Ahmed *et al*., 2008). The obtained results showed that there was a significant increase in serum ALT level at the 2nd and 4th week and serum ALP level at the 4th week in CS-administered rats which are reversible alterations to normal levels on the 8th week of the study. These findings are agree with Fekety (1990) who reported that CS caused a transient elevation in serum ALT level. Also, Shams (2017) mentioned that there was a statistically significant increase in serum ALT and serum ALP levels in CS-treated cows. Moreover, El-Sayed *et al*. (2018) reported a significant elevation in ALP level in diarrheic calves. The obtained results may be attributed to degenerative changes of the hepatocytes induced by cephalosporins as noticed by El-Maddawy and Bogzil (2015) who

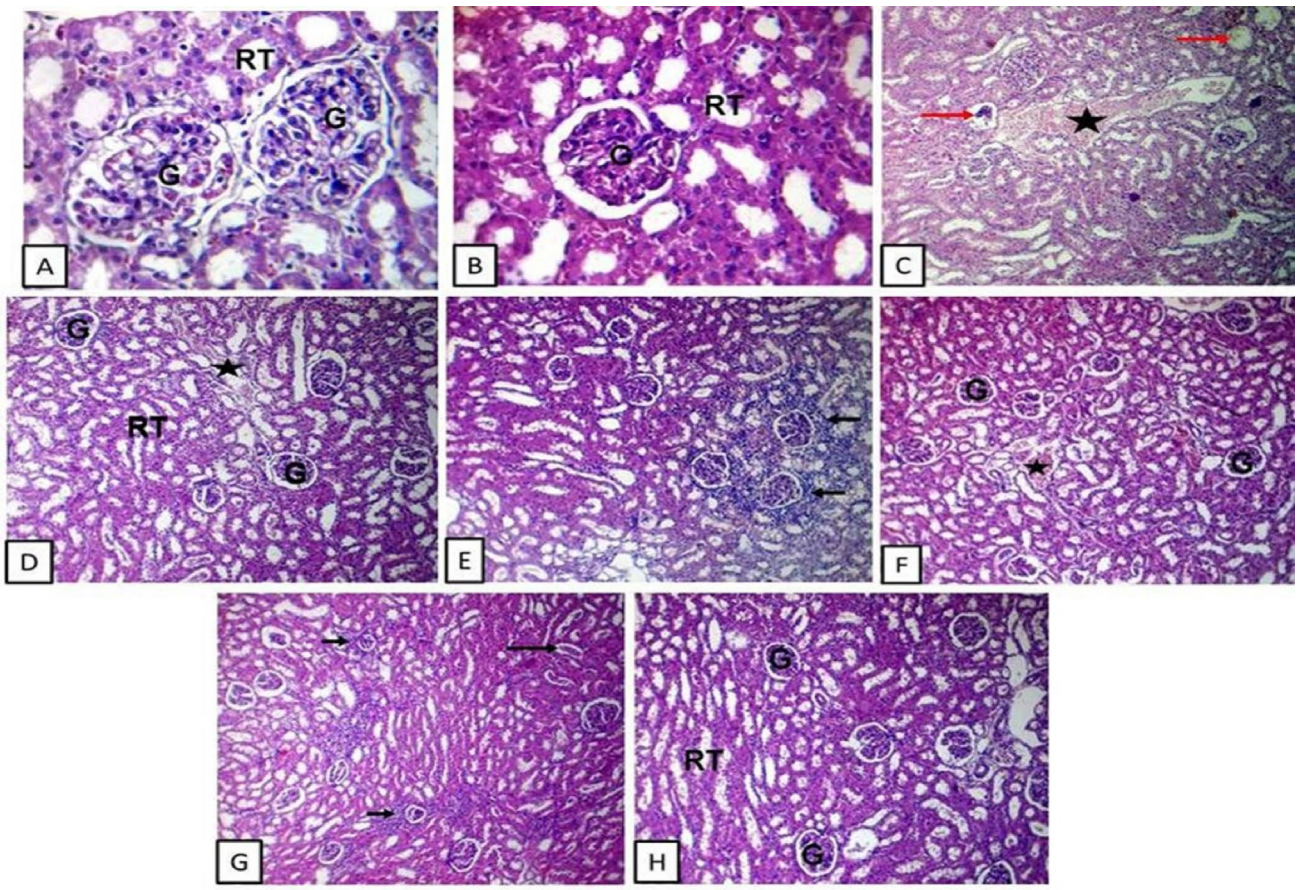

Fig. 2. Photomicrograph of rat kidney sections stained by H&E: (A): male rat of control group at the 2nd week. Note: normal histological structure of glomeruli (G) and renal tubules (RT). (B): male rat administered with L-carnitine at the 2nd week. Note: normal histological structure of glomeruli (G) and renal tubules (RT). (C): male rat administered with CS at the 2nd week. Note: congestion of blood vessel (black star) and necrotic glomeruli (red arrows). (D): male rat administered with CS concomitantly with LC at the 2nd week. Note: mild congestion of blood vessel (black star) with relatively normal glomeruli (G) and renal tubules (RT). (E): male rat administered with CS at the 4th week. Note: interstitial nephritis with inflammatory cell infiltration around glomeruli (black arrows). (F): male rat administered with CS concomitantly with LC at the 4th week. Note: mild congestion of blood vessel (black star) with relatively normal glomeruli (G) and renal tubules. (G): male rat administered with CS at the 8th week. Note: interstitial peri-glomerular inflammatory cell infiltration (short black arrows) with remnant of tubular epithelium in the lumen of renal tubes (long black arrow). (H): male rat administered with CS concomitantly with LC at the 8th week. Note: normal histological structure of glomeruli (G) and renal tubules (RT). (Magnification, A and B = X.400. C, D, E, F, G and H = X.160).

noticed that male rats receiving cefotaxime sodium showed a significant rise in serum ALT, AST, and ALP levels.

Administration of LC concomitantly with CS induced a significant decrease in serum ALT and ALP level as compared with CS-administered rats. The results are agreed with previous literatures as improvement of serum ALT and AST levels after administration of LC in individuals with liver diseases (Pirmadah *et al.* , 2020) and in patients with chronic liver diseases treated with LC (Oh *et al*., 2022). These results could be attributed to the scavenging mechanism of LC and its protective action against the free radicals by exerting the anti-oxidative properties (Gülcin, 2006 ; Augustyniak and Skrzydlewska, 2009).

Regarding to results of serum protein after CS administration, a significant decrease in serum albumin level at the 4th week of the experiment was recorded. The significant decrease in serum albumin level was also recorded by El-Sayed *et al*. (2018) in diarrheic calves and by El-Maddawy and Bogzil (2015) in male rats receiving cefotaxime sodium. The obtained results may be attributed to degenerative changes of the hepatocytes affecting serum albumin synthesis.

All alterations in hepatic function tests were supported by our histopathological findings in hepatic tissue of CS-administered rats. As, there was congestion of portal vein and intense inflammatory cell infiltration in portal area. Also, fatty degeneration of hepatocytes and focal hepatic necrosis were reported.

Conversely, administration of LC concomitantly with CS induced a significant increase in serum albumin level. These findings are compatible with Cakir and Yalcin (2007) and Abbasnezhad *et al*. (2019), who demonstrated that LC significantly enhanced serum albumin concentrations in broiler chicks and in patients with hepatic encephalopathy respectively. These results are supported by hepatic histopathological findings of male rats administered with CS concomitantly with LC. As, there was normal portal area with relatively normal hepatocytes.

Regarding to renal indices, there was a significant increase in serum creatinine level at the 4th and 8th week in CS-administered rats. This agrees with Mangal and Sharma (2015) who showed that the administration of CS in buffalo calves induced a significant increase in the serum level of creatinine. These outcomes may be related to the detrimental effects of CS on renal tissue that confirmed by our histopathological findings including congestion of blood vessel with necrotic glomeruli in addition to interstitial nephritis with inflammatory cell infiltration around glomeruli. Also, there was remnant of tubular epithelium in the lumen of renal tubes.

These results were reversed by administration of LC concomitantly with CS. The obtained results are compatible with results of Chen *et al*. (2021) in nephrotoxic mice and results of Salama *et al*. (2022) in nephrotoxic rats. Both studies indicated improvement in renal functions post LC administration. LC improved renal function tests because it significantly diminished nephrotoxicity indices and repaired the histopathological troubles (Tufekci *et al*., 2009). This is confirmed by our histopathological results of the kidney of rats administered with LC concomitantly with CS. As, there was relatively normal histological structure of glomeruli and renal tubules.

CONCLUSION

Administration of cefquinome sulfate produce some mild to moderate deleterious effects on hematological and biochemical parameters and induce histopathological alterations. While concomitant administration of LC with CS able to ameliorate these induced effects in male albino rats. Therefore, the present study recommended the use of LC together with CS when it is necessary to repeat its administration in veterinary practice.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Abbasnezhad, A., Choghakhori, R., Kashkooli, S., Alipour, M., Asbaghi, O., Mohammadi, R., 2019. Effect of L-carnitine on liver enzymes and biochemical factors in hepatic encephalopathy: A systematic review and meta-analysis. Journal of Gastroenterology and Hepatology 34, 2062-2070.

Ahmed, M.B., Hasona, N.A.S., Selemain, H.A.H., 2008. Protective effects of extract from dates (*Phoenix dactylifera* L.) and ascorbic acid on thioacetamide-induced hepatotoxicity in rats.

Augustyniak, A., Skrzydlewska, E., 2009. L-Carnitine in the lipid and protein protection against ethanol-induced oxidative stress. Alcohol 43, 217-223.

Bartels, H., Böhmer, M., Heierli, C., 1972. Serum creatinine determination without protein precipitation. Clinica Chimica Acta 37, 193-197.

Belfield, A., Goldberg, D., 1971. Colorimetric determination of alkaline phosphatase activity. Enzyme 12, 561-568.

Brass, E.P., 2000. Supplemental carnitine and exercise. The American Journal of Clinical Nutrition 72, 618S-623S.

Buttarello, M., Plebani, M., 2008. Automated blood cell counts: state of the art. American Journal of Clinical Pathology 130, 104-116.

Cakir, S., Yalcin, S., 2007. Effects of L-carnitine supplementation in diets with low or normal energy level on growth performance and carcass traits in broilers. Revue de Médecine Vétérinaire 158, 291-296.

Chen, Y.C., Cheng, C.Y., Liu, C.T., Sue, Y.M., Chen, T.H., Hsu, Y.H., Huang, N.J., Chen, C.H., 2021. Combined protective effects of oligo-fucoidan, fucoxanthin, and L-carnitine on the kidneys of chronic kidney disease mice. European Journal of Pharmacology 892, 173708.

Choma, I.M., 2007. TLC Separation of cephalosporins: searching for better selectivity. Journal of Liquid Chromatography and Related Technologies 30, 2231-2244.

Coles, E.H., 1974. Veterinary Clinical Pathology. WB Saunders.

Coulomb, J.J., Farreau, L., 1963. A new simple semi-micro method for colourimeteric determination of urea. Clin. Chem. 9, 102.

Coulthurst, S.J., Barnard, A.M., Salmond, G.P., 2005. Regulation and biosynthesis of carbapenem antibiotics in bacteria. Nature Reviews Microbiology 3, 295-306.

Dancer, S.J., 2004. How antibiotics can make us sick: the less obvious adverse effects of antimicrobial chemotherapy. The Lancet Infectious Diseases 4, 611-619.

Darwish, W.S., Eldaly, E.A., El-Abbasy, M.T., Ikenaka, Y., Nakayama, S., Ishizuka, M., 2013. Antibiotic residues in food: the African scenario. Japanese Journal of Veterinary Research 61, S13-S22.

Doumas, B.T., Watson, W.A., Biggs, H.G., 1971. Albumin standards and the measurement of serum albumin with bromcresol green. Clinica ChEmica Acta 31, 87-96.

Edwards, R., Millburn, P., Hutson, D., 1987. The toxicity and metabolism of the pyrethroids cis-and trans-cypermethrin in rainbow trout, Salmo gairdneri. Xenobiotica 17, 1175-1193.

El-Maddawy, Z.K., 2014. Modulation of gentamicin-induced testicular and brain damage in rats. Global Journal of Pharmacology 8, 284-293.

El-Maddawy, Z.K., Bogzil, A.H., 2015. Adverse effects of cefotaxime sodium in comparison with ceftiofur sodium in male rats. International Journal of Pharmacy and Life Sciences 6, 4291-4303.

El-Sayed, M., El-Diasty, M., Waheed, D., 2018. Effect of cefquinome in treatment of diarrhea in calves. Mansoura Veterinary Medical Journal 19, 401-412.

Fekety, F.R., 1990. Safety of parenteral third-generation cephalosporins. The American Journal of Medicine 88, S38-S44.

Gülcin, İ., 2006. Antioxidant and antiradical activities of L-carnitine. Life sciences 78, 803-811.

Harries, M., 1989. Some studies on parasitic gastroenteritis in sheep. In: Oxford Univ. Press, New York, Toronto.

Khan, A., Faridi, H.A., Ali, M., Khan, M.Z., Siddique, M., Hussain, I., Ahmad, M., 2009. Effects of cypermethrin on some clinico-hemato-biochemical and pathological parameters in male dwarf goats (*Capra hircus*). Experimental and Toxicologic Pathology 61, 151-160.

Kishanrao, P. M., 2016. Cefquinome concentration in various biological fluids in buffaloes and its comparative pharmacokinetics in buffalo calf, Buffalo and goats. A Thesis for the degree of Doctor of Philosophy in Vet. Pharmacology and toxicology. India university.

Kopple, J.D., Ding, H., Letoha, A., Ivanyi, B., Qing, D.P.Y., Dux, L., Wang, H.Y., Sonkodi, S., 2002. l-carnitine ameliorates gentamicin-induced renal injury in rats. Nephrology Dialysis Transplantation 17, 2122-2131.

Maden, M., Traş, B., Baş, A., Elmas, M., Yazar, E., Birdane, F., 2001. Pharmacology: Investigation of biochemical and haematological side-effects of cefquinome in healthy dogs. Veterinary Quarterly 23,

32-34.
Mandal, A., Chakraborty, S., Lahiri, P., 1986. Hematological changes produced by lindane (γ-HCH) in six species of birds. Toxicology 40, 103-111.
Mangal, M., Sharma, S.K., 2015. Effect of repeated administration of cefquinome on biochemical and hematological parameters in buffalo calves. Toxicology International 22, 110.
Mshelia, P.A., Madusolumuo, M.A., 2021. Effects of ceftriaxone on the hematology and lipid profile values in rats. International Journal of Animal and Livestock Production Research 5, 10-25.
Naqvi, I., Saleemi, A., Naveed, S., 2011. Cefixime: a drug as efficient corrosion inhibitor for mild steel in acidic media. Electrochemical and thermodynamic studies. Int. J. Electrochem. Sci. 6, 146-161.
Oh, H., Park, C.H., Jun, D.W., 2022. Impact of l-Carnitine Supplementation on Liver Enzyme Normalization in Patients with Chronic Liver Disease: A Meta-Analysis of Randomized Trials. Journal of Personalized Medicine 12, 1053.
Picardal, J.P., 2017. Influence of L-carnitine on blood values of broiler chickens exposed to 16l: 8d and 8l: 16d photoperiod regimes. International Journal of Biosciences 11, 421-434.
Pirmadah, F., Ramezani-Jolfaie, N., Mohammadi, M., Talenezhad, N., Clark, C.C., Salehi-Abargouei, A., 2020. Does L-carnitine supplementation affect serum levels of enzymes mainly produced by liver? A systematic review and meta-analysis of randomized controlled clinical trials. European Journal of Nutrition 59, 1767-1783.
Rani, P.J.A., Panneerselvam, C., 2001. Carnitine as a free radical scavenger in aging. Experimental Gerontology 36, 1713-1726.
Reitman, S., Frankel, S., 1957. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. American Journal of Clinical Pathology 28, 56-63.
Salama, A.A., Mostafa, R.E., Elgohary, R., 2022. Effect of L-carnitine on potassium dichromate-induced nephrotoxicity in rats: modulation of PI3K/AKT signaling pathway. Research in Pharmaceutical Sciences 17, 153.
Salama, A.F., Kasem, S.M., Tousson, E., Elsisy, M.K., 2012. Protective role of L-carnitine and vitamin E on the kidney of atherosclerotic rats. Biomedicine and Aging Pathology 2, 212-215.
Shams, M.M.I., 2017. Use of some antibiotics and anti- inflammatory in control of mastits in cattle. A Thesis for master degree of Vet. Med. Sciences. Pharmacology Department. Mansoura University, Egypt.
Steel, R.G.D., Torrie, J.H., 1980. Principles and Procedures of Statistics, a Biometrical Approach. McGraw-Hill Kogakusha, Ltd.
Tufekci, O., Gunes, D., Özoğul, C., Kolatan, E., Altun, Z., Yılmaz, O., Aktaş, S., Erbayraktar, Z., Kırkım, G., Mutafoğlu, K., 2009. Evaluation of the effect of acetyl L-carnitine on experimental cisplatin nephrotoxicity. Chemotherapy 55, 451-459.
Vasseur, M.V., Laurentie, M., Rolland, J.-G., Perrin-Guyomard, A., Henri, J., Ferran, A.A., Toutain, P.-L., Bousquet-Mélou, A., 2014. Low or high doses of cefquinome targeting low or high bacterial inocula cure Klebsiella pneumoniae lung infections but differentially impact the levels of antibiotic resistance in fecal flora. Antimicrobial Agents and Chemotherapy 58, 1744-1748.
Zonca, A., Gallo, M., Locatelli, C., Carli, S., Moroni, P., Villa, R., Cagnardi, P., 2011. Cefquinome sulfate behavior after intramammary administration in healthy and infected cows. Journal of Dairy Science 94, 3455-3461.