



Research Article

L-CARNITINE AND CO-ENZYME Q10 AMELIORATE CIPROFLOXACIN-INDUCED REPRODUCTIVE TOXICITY IN MALE RATS: REGULATION OF INFLAMMATION AND EXPRESSION OF STEROIDOGENIC GENES

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ABSTRACT

This study was conducted to evaluate Ciprofloxacin (CPX) reproductive toxicity in 30 days and the protective effect of L-Carnitine (LC) and/or Co-Enzyme Q10 (Co-Q10) against reproductive toxicity induced by CPX and the molecular changes that related to their effects. Animals were divided into 5 groups (12 rats/group). Group 1, was kept as a control. Group 2, was administered CPX (90 mg/kg/day, p.o) and kept as a positive control. Group 3, was co-administered CPX with LC (94.5 mg/kg/day p.o). Group 4, was co-administered CPX with Co-Q10 (8.1 mg/kg/day p.o). Group 5, was concurrently administered CPX with Co-Q10 + LC orally for 30 days. After thirty days, body and genital sex organ weights (testes, prostate glands, and seminal vesicles) and semen analysis (sperm count, motility and morphology), were assayed. Gene expression of StAR, SR-B1, and 3 β HSD were assayed by using real-time PCR. Hormonal assay (Testosterone, LH, and FSH), biomarkers of inflammatory mediators (TNF- α) and anti-inflammatory mediators (IL-10) were assayed by using ELISA. MDA, GSH, and TAC were investigated by a spectrophotometer. Results: The thirty-day administration of CPX to adult male rats promotes reproductive toxicity in rats by generating oxidative damage. It induces an adverse effect on reproductive organs weights, sperm parameters, reduction of gene coordination (StAR, SR-B1, and 3 β HSD) and reproductive hormones. Also, increases TNF- α and decreases IL-10. Notably, LC and Co-Q10 co-administration overcame all of these side effects. Conclusion: concurrent administration of both LC and Co-Q10 with CPX ameliorating reproductive toxicity induced by CPX in thirty days administration.

Keywords: L-Carnitine, Co-EnzymeQ10, Ciprofloxacin, Male infertility, Steroidogenic acute regulatory protein and Scavenger receptor class.

INTRODUCTION

Infertility is one of the problems of both human and animal society. According to the WHO, 15-20% of couples have experienced some forms of infertility problems. About 40% of these problems are due to male factor¹. Drug treatment and chemotherapy can have a harmful effect on spermatogenesis and sperm normal production². Ciprofloxacin (CPX) is antibiotic which belongs to the family of fluoroquinolones with a very broad spectrum against many microbial pathogens³. It is widely used as an oral synthetic chemotherapeutic antimicrobial agent with broad-spectrum activity against infections caused by both Gram-positive and Gram-negative bacteria⁴. However, there is recent evidence assured that it can directly lower sperm quality, testes weight, and testosterone levels, that are dose and time-dependent⁵. Levo-carnitine (L-carnitine) is a biologically active water-soluble antioxidant molecule⁶. It is present in all mammals localized on the inner mitochondrial membrane and facilitates the transport of long chain fatty acids (LCFAs) through the mitochondrial membrane for utilization in energy production (β -Oxidation)⁷. The major exogenous dietary sources of LC are milk, fish, and meat. It shows a broad range of biological activities including; anti-inflammatory, cardioprotective, gastroprotective, and neuroprotective properties⁸. Furthermore, LC plays an important part in sperm metabolism by providing readily available energy for employ by spermatozoa that positively impacts sperm maturation, motility, and the

spermatogenic process⁹. Co-enzymeQ10 (Co-Q10), a vitamin-like substance, is essential for the body and presents in a small amount in a wide variety of foods. It is a component of the mitochondrial respiratory chain; playing a role in energy metabolism so acting as an antioxidant for cell membranes and lipoproteins¹⁰. Co-Q10 biosynthesis is markedly active in testis, and spermatozoa. Co-Q10 level decreased in seminal plasma and spermatozoa of infertile men¹¹. Moreover, the exogenous administration of Co-Q10 has been reported to improve sperm motility¹². This study was conducted to evaluate CPX reproductive toxicity in 30 days and the protective effects of LC and/or Co-Q10 against reproductive toxicity induced by CPX and the molecular changes that related to their effects.

MATERIAL AND METHODS

Drugs

Ciprofloxacin: Each extended release film coated tablet contains 1164 mg of CPX-HCl equivalent to 1 gram of CPX. Manufactured by Mash for pharmaceutical industries (Mash Premiere)- Bader City - Egypt

L-Carnitine: Each capsule contains 350 mg of LC (as tartrate). Produced by Arab Company for Pharmaceuticals & Medicinal Plants Mepaco-Medifood (Enshas – Sharkeye – Egypt)

Co-Enzyme Q10: Each hard gelatin capsule containing 30 mg of Co- Q10. Produced by Arab Company for Pharmaceuticals & Medicinal Plants Mepaco-Medifood (Enshas- Sharkeye – Egypt).

Animals

Adult male Wistar rats weighing (275 ± 25 g) were obtained from the animal house of the National Organization for Drug Control and Research (NODCAR), Giza, Egypt. They were allowed two weeks for accommodation to the new environment before starting the experiment. The rats were housed at $23 \pm 2^{\circ}$ C and $55 \pm 5\%$ humidity with 12 h light/dark cycle and were given standard rodent chow and drinking water ad libitum. All animal's procedure and the current investigation conform to the standard ethical procedures and policies approved by Ethical Committee for Animal Experimentation at Faculty of Pharmacy, Al-Azhar University and were approved by the Guide for the Care and Use of Laboratory Animals (Code No. 92).

Experimental Design

Induction of Reproductive toxicity

Reproductive toxicity was induced in rats by orally administration of CPX at a dose of (90 mg/kg) once daily for 30 days that equivalent to human recommended dose (1000 mg/kg)¹³.

Experimental group

Rats were divided into 5 groups each the group contained 12 rats and treated as follows:

Group (1) was given distilled water orally and kept as a control.

Group (2) administered only CPX served as positive control.

Group (3) simultaneous administered CPX and LC orally at a dose of (94.5 mg/kg) once daily for 30 days that equivalent to human recommended dose (1050 mg/kg).

Group (4) simultaneous administered CPX and Co-Q10 orally at a dose of (8.1 mg/kg) once daily for 30 days that equivalent to human recommended dose (90 mg/kg).

Group (5) simultaneous administered CPX and both of Co-Q10 and LC orally for 30 days.

Collection and Preparation of Samples

Blood samples

Blood samples were collected from the retro-orbital sinus, under mild ether anesthesia and serum was separated, aliquoted and stored at -20° C till the determination the levels of (testosterone, LH, FSH, TNF- α and IL-10) by enzyme-linked immunosorbent assay (ELISA) and determination the level of TAC by spectrophotometer.

Tissue specimens and semen analysis:

After blood collection, the rats were immediately decapitated. Pairs of testes and epididymides, seminal vesicles (without coagulation and full of secretion) and prostate gland were removed, cleared from adhering tissue, washed in ice-cold 1.15% KCL then blot dried and weighed. The right epididymis was used for estimating sperm count while the left one was used for assessing sperm motility. The right testis was kept in 10% formalin saline for gene expression for (StAR, SR-B1, and 3 β HSD). While the left testis was homogenized in ice-cold 1.15% KCL to make 10% (w/v) homogenate with Glass-Col motor-

driven homogenizer (USA) and the homogenate was used for measuring (MDA& GSH).

METHODS

Body weight: At the end of the experimental period, the body weight of each individual rat was measured.

Reproductive organ indices

Reproductive organs weight

Rats were sacrificed after the last day of treatment and reproductive organs; testes, prostate glands, and seminal vesicles were weighed.

Sperm functions analysis

Sperm count: The pipette of counting erythrocytes by haemocytometer was used. The epididymal content was withdrawn up to the mark 0.1 then the pipette was filled up to the mark 101 by 0.9% sodium citrate solutions. The content of the pipette was mixed and shaken well then a cover slide was placed over the counting chamber and a drop of diluted epididymal content was spread between the haemocytometer chamber and the cover slide. The sperms in five large squares (80 small squares) were counted using the high power objective lens (x400). The total number in five small squares was multiplied by million¹⁴.

Mass motility: A small droplet of epididymal content was added to one drop of 2.9% sodium citrate solution on a clear glass slide then the slide was gently warmed. Several fields were quickly examined under the microscope (x100) and the progressive motility of sperms was estimated as a percentage¹⁴.

Epididymal sperm abnormalities: A drop from the epididymal content of each rat was immediately taken and mixed with an equal drop of Eosin-Nigrosin stain for detection of dead and malformed sperm. The semen was carefully mixed with the stain, then films were examined at random per slide under x 200 and the type (live and dead) and percentage of abnormal sperms¹⁵.

Biochemical analysis

Serum analysis

Hormonal assay for Testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH) was performed using enzyme-linked immunosorbent assay (ELISA). Biochemical analysis of inflammatory and anti-inflammatory marker; tumor necrosis factor alpha (TNF- α) and Interleukin-10 (IL-10) estimated using immunoassay CUSABIO ELISA kit®. Furthermore, the serum level of TAC (Total antioxidant capacity) was determined by Bio-Diagnostic kit.

Tissue Homogenate

The right testis was kept in 10% neutral buffered formalin for Gene expression using real-time PCR (StAR, SR-B1, and 3 β HSD). While the left testis was homogenized in ice-cold 1.15% KCL to make 10% (w/v) homogenate with Glass-Col motor-driven homogenizer (USA) and the homogenate was used for measuring (MDA& GSH).

Gene expression using RT-PCR

Detection of (StAR, SR-B1, and 3 β HSD) gene expression by real-time quantitative reverse transcription PCR: Total RNA was extracted from frozen samples using TRIzol® reagent (Invitrogen, USA) according to a standard protocol. The isolated total RNA was turned into complementary DNA (cDNA) utilizes the Moloney murine leukemia virus (M-MLV) reverse transcriptase (Promega, USA). Real-time PCR was proceeded

using an ABI 7500 Real-Time PCR System (Applied Biosystems, USA) and an SYBR® Green PCR Master Mix (Applied Biosystems) in a final volume of 10 μ L together with the following thermic cycling conditions: 95°C for 10min, followed by 40 cycles of 95°C for 15s and 60°C for 1min¹⁶. The sequences of PCR primer pairs employed for each gene are displayed in (Table 1). Finally, all values were normalized to the β -actin genes as an invariant endogenous control (reference gene).

Statistical analysis

The results were expressed as the mean $\pm$ standard error (SE). Differences between groups were assessed by one-way analysis of variance (ANOVA). Subsequent multiple comparisons between the different groups were analyzed by Tukey (compare all pairs of columns) tests. Data were statistically analyzed using the (GraphPad Prism version 5® (GraphPad Prism software). Values at $P < 0.05$ were considered significant¹⁷.

RESULTS

Effect of different treatment on body and genital organ weights

All weights are shown in (Table 2) administration of CPX caused a significant decrease in body weight by 27.75 % in comparison with the control group. However, administration of LC and Co-Q10 is significantly ameliorated this decreasing in body weight. In addition, CPX induced a significant decrease in the weights of testes (37.93%), prostate gland (50%) and seminal vesicles (44.23%) as compared to the control group. These reductions were significantly improved by co-administration of LC and Co-Q10.

Effect of different treatment on semen analysis

Data of the epididymal sperm motility, sperm count, and viability % are shown in (Table 3), a marked reduction in sperm motility, sperm count and viability% was recorded in CPX treated group (64.64% and 63.43%, 58.12% respectively) when compared with the control group. Co-administration of LC or Co-Q10 with CPX attenuates the decrease in sperm count, motility and improves sperm viability % in comparison to the control group. Moreover, administration of both LC and Co-Q10 with CPX caused the

significant increase in the motility, number, and viability of sperm in compared to the positive group.

Effect of different treatment on StAR, SR-B1 and 3 β HSD

(Figure 1) was shown that the administration of CPX caused a significant decrease in StAR (80%), SR-B1 (81%), and 3 β HSD (83%) relative quantification as compared to the control group. Co-administration of LC or Co-Q10 with CPX attenuates the decrease in StAR, SR-B1, and 3 β HSD incomparable to the positive group. On the other hand, concurrent administration of LC and Co-Q10 with CPX increase StAR, SR-B1 and 3 β HSD relative quantification compared to the positive group.

Effect of different treatment on Testosterone, LH and FSH

The values obtained for serum sex hormones level are shown in (Figure 2). Administration of CPX was associated with a significant reduction in testosterone (70.55%), LH (50%) and FSH (61.90%) as compared to the control rats. Co-administration of LC or Co-Q10 with CPX ameliorates the decrease in testosterone, LH and FSH. On the other hand, concurrent administration of both LC and Co-Q10 with CPX increase testosterone, LH and FSH serum levels but not reaching the values of control rats.

Effect of different treatment on TNF- α and IL-10

The values obtained for TNF- α and IL-10 levels are shown in (Figure 3). Administration of CPX was associated with a significant increase in inflammatory marker (TNF- α) and a significant decrease in anti-inflammatory marker (IL-10) compared to the control group. Co-administration of LC and/or Co-Q10 with CPX improved inflammation as TNF- α level was decreased and IL-10 level was increased incomparably to CPX group.

Oxidative stress markers

The Data represented in (Table 4) were revealed a significant increase in the mean values of MDA and a significant decrease in GSH and TAC activity in CPX treated rats versus the control group. Concurrent administration of CPX with LC and/or Co-Q10 were caused a significant decrease in lipid peroxidation were caused a remarkable increase in the GSH and TAC level compared with the CPX treated rats.

Table 1: Primers Sequences of studied gene

Studied gene	Primer sequence
StAR	Forward primer :5'- GGGCATACTCAACAACCAG -3' Anti – sense :5'- ACCTCCAGTCGGAACACC -3'
SR-B1	Forward primer :5'-ACAGGTCCCAGGGCTCAG-3' Reverse primer:5'-CGTGCGGTTCAAAAGG-3'
3- β HSD	Forward primer :5'- TGTGCCAGCCTTCATCTAC -3' Reverse primer:5'- CTTCTCGGCCATCCTTT-3'

Table 2: Effect of different treatment on body and genital organ weights

Groups	Variables			
	Final body (g)	Testes (g)	Prostate gland (g)	Seminal vesicles (g)
Control	279.2 $\pm$ 6.38	2.61 $\pm$ 0.08	0.44 $\pm$ 0.02	0.52 $\pm$ 0.02
CPX	201.7 $\pm$ 7.03 ^a	1.62 $\pm$ 0.10 ^a	0.22 $\pm$ 0.02 ^a	0.29 $\pm$ 0.02 ^a
CPX + LC	235 $\pm$ 4.83 ^{abc}	2.09 $\pm$ 0.11 ^{abc}	0.34 $\pm$ 0.02 ^{abc}	0.42 $\pm$ 0.02 ^{abc}
CPX + Co-Q10	222.5 $\pm$ 7.042 ^{abc}	1.95 $\pm$ 0.09 ^{ac}	0.32 $\pm$ 0.02 ^{abc}	0.41 $\pm$ 0.01 ^{abc}
CPX + LC + Co-Q10	260.8 $\pm$ 3.27 ^b	2.54 $\pm$ 0.09 ^b	0.43 $\pm$ 0.02 ^b	0.50 $\pm$ 0.02 ^b

The data are presented as mean $\pm$ SE (n=12 rats/group). The symbols **a**: significant difference from control values; **b**: significant difference from CPX values; **c**: significant difference from CPX +LC+ Co-Q10 values. The values at $p < 0.05$ were considered significant

Table 3: Effect of different treatment on semen analysis

Groups	Variables		
	Motility %	Sperm count $\times 10^6/\text{ml}$	Sperm Viability %
Control	85.33 $\pm$ 2.89	82.15 $\pm$ 2.64	85.17 $\pm$ 2.94
CPX	30.17 $\pm$ 2.52 ^a	30.17 $\pm$ 2.52 ^a	35.67 $\pm$ 2.96 ^a
CPX + LC	72.00 $\pm$ 3.65 ^{abc}	67.17 $\pm$ 3.88 ^{abc}	62.83 $\pm$ 4.04 ^{abc}
CPX + Co-Q10	62.5 $\pm$ 3.35 ^{abc}	57.50 $\pm$ 3.79 ^{abc}	57 $\pm$ 4.83 ^{abc}
CPX + LC + Co-Q10	83.83 $\pm$ 2.76 ^b	81.27 $\pm$ 3.37 ^b	78.83 $\pm$ 3.32 ^b

The data are presented as mean $\pm$ SE (n=12 rats/group). The symbols **a**: significant difference from control values; **b**: significant difference from CPX values; **c**: significant difference from CPX +LC+ Co-Q10 values. The values at $p < 0.05$ were considered significant

Table 4: Effect of different treatment on oxidative stress markers

Groups	Variables		
	MDA (nmol/g.tissue)	GSH (mmol/gm)	TAC (mM/L)
Control	3.103 $\pm$ 0.31	1.34 $\pm$ 0.09	2.28 $\pm$ 0.13
CPX	9.09 $\pm$ 0.67 ^a	0.57 $\pm$ 0.04 ^a	0.55 $\pm$ 0.08 ^a
CPX + LC	6.25 $\pm$ 0.32 ^{abc}	0.85 $\pm$ 0.04 ^{abc}	1.34 $\pm$ 0.09 ^{abc}
CPX + Co-Q10	6.71 $\pm$ 0.28 ^{abc}	0.79 $\pm$ 0.04 ^{abc}	1.25 $\pm$ 0.07 ^{abc}
CPX + LC + Co-Q10	4.08 $\pm$ 0.32 ^b	1.15 $\pm$ 0.01 ^b	2.03 $\pm$ 0.09 ^b

The data are presented as mean $\pm$ SE (n=12 rats/group). The symbols **a**: significant difference from control values; **b**: significant difference from CPX values; **c**: significant difference from CPX +LC+ Co-Q10 values. The values at $p < 0.05$ were considered significant

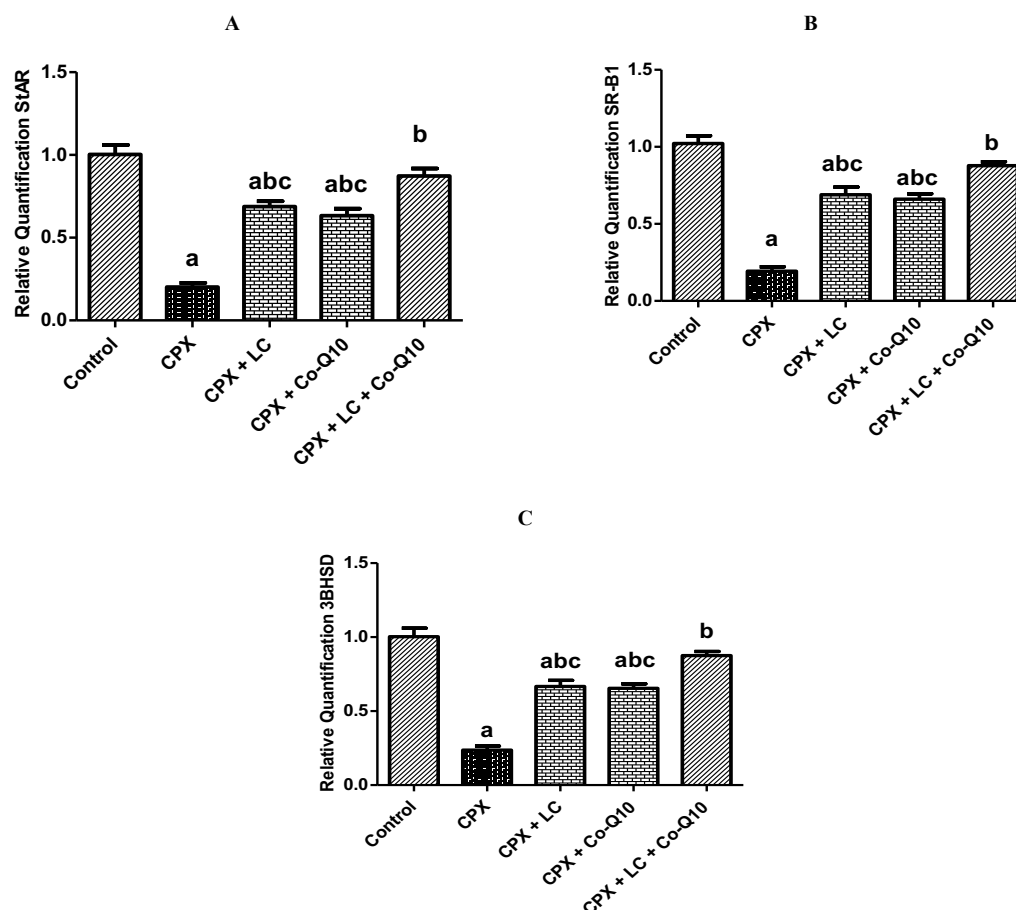


Figure (1): Effect of different treatment on StAR, SR-B1 and 3βHSD

Mean $\pm$ SE of StAR, SR-B1 and 3βHSD in the studied groups: The data are presented as mean $\pm$ SEM (n=12 rats/group). The symbols **a**: significant difference from control values; **b**: significant difference from CPX values; **c**: significant difference from CPX +LC+ Co-Q10 values

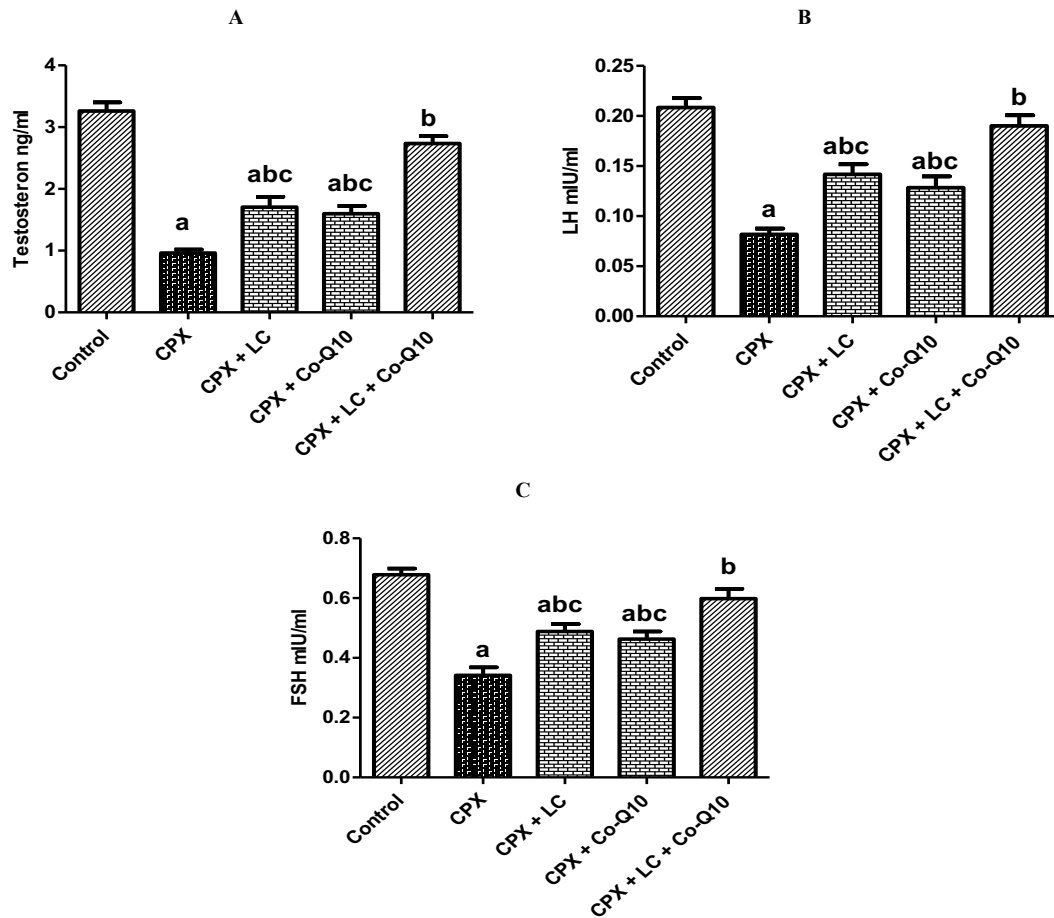


Figure (2): Effect of different treatment on Testosterone, LH and FSH

Mean ± SE of Testosterone, LH and FSH in the studied groups: The data are presented as mean ± SE (n=12 rats/group). The symbols **a**: significant difference from control values; **b**: significant difference from CPX values; **c**: significant difference from CPX +LC + Co-Q10 values

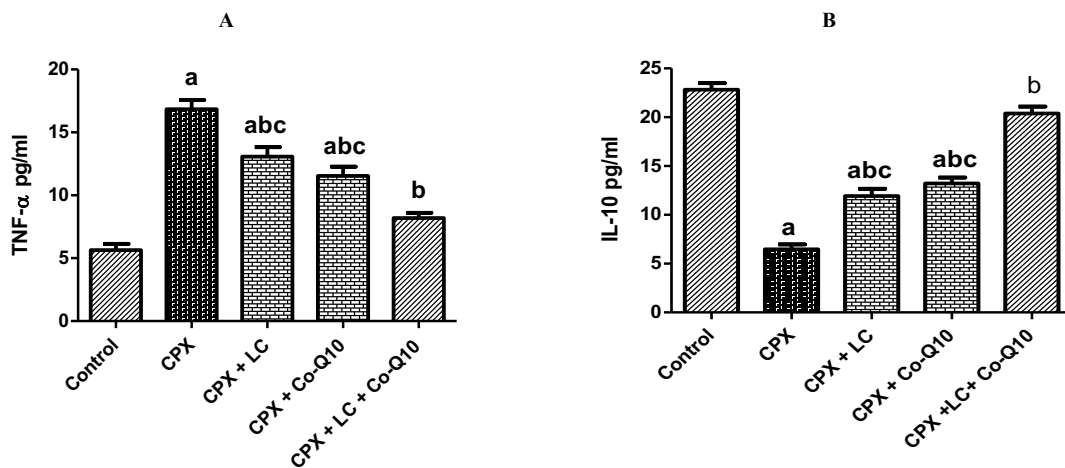


Figure 3: Effect of different treatment on TNF-α and IL-10

Mean ± SE of TNF- α and IL-10 in the studied groups: The data are presented as mean ± SE (n=12 rats/group). The symbols **a**: significant difference from control values; **b**: significant difference from CPX values; **c**: significant difference from CPX +LC + Co-Q10 values

DISCUSSION

Ciprofloxacin is one of the best drugs for the treatment of different bacterial infections¹⁸. However, some reports^{19,20} recorded that the administration of CPX significantly impairs testicular structure and function. In the current study, administration of CPX influence the body weight of the animals and caused a significant decrease in the weights of testes, prostate glands and seminal vesicles comparative to the control group²¹. Further, concurrent administration of LC and Co-Q10 with CPX clearly restored the reproductive organ weights towards normal that may be due to their androgenic activity²². Epididymal sperm count, motility and viability supply a direct measurement of fertility in animals²³. Our results were in accordance with²⁴ who reported that CPX causing decrease in sperm counts and motility in laboratory animals. On the other hand The obtained data are parallel with^{25,26} who reported that LC and Co-Q10 attenuated spermatogenic and testicular damage by returning sperm count, motility and viability towards normal control values. A series of enzymatic reactions are required to synthesize testosterone and estrogen from cholesterol. SR-B1 is a trans membrane protein that mediates selective cholesterol uptake by steroidogenic tissues, including Leydig cells²⁷. StAR transport of cholesterol across the mitochondrial membrane is generally considered the rate-limiting step in steroidogenesis, followed by the conversion of cholesterol to pregnenolone²⁸. Pregnenolone is metabolized into testosterone mainly by 3β -HSD in the smooth endoplasmic reticulum²⁹. Our report is the first that describes the exposure of male rats to CPX for 30 days has important effects on these key steroidogenic testicular genes that causing a decrease in expression of genes involved in cholesterol transport and steroidogenesis with a resultant reduction in testosterone production in the testes. The concurrent treatment of CPX with LC and/or Co-Q10 increase StAR, SR-B1 and 3β HSD relative quantification compared to the positive group. Normal testicular function is dependent on testosterone, FSH and LH which are absolutely required for normal spermatogenesis³⁰. Our results were in accordance with³¹ who recorded that CPX induced a significant decrease in the testosterone, LH and FSH levels associated with degenerative changes in the seminal vesicle. The present study was supported by³² who found that, the levels of FSH and testosterone increased in the LC treated group. Also, ³³ reported that Co-Q10 significantly increased serum testosterone level. The results obtained in this study parallel with³⁴ who reported that Co-Q10 suppressed the production of inflammatory mediators such as TNF- α and the expression of IL-10 was increased significantly. Also, with³⁵ who reported that carnitine therapy reduced levels of pro-inflammatory cytokines as TNF- α , moreover enhancement of IL-10. The present study was supported by²¹ who found that the oxidative stress marker in the rat testes of CPX group resulted in increased MDA levels as well as decreased GSH hormone as the plasma membrane in the sperm contains a high proportion of polyunsaturated fatty acids that are easily susceptible to oxidized lipid peroxide³⁶. The obtained results were parallel with⁸ who reported that LC affects these sperm parameters mainly by increasing the activity of antioxidant enzymes, which is reflected in the increased levels of GSH and TAC. ^{22,28} reported that Co-Q10 reduced MDA level and protected against peroxidative damage.

CONCLUSION

Our study revealed that the thirty-day administration of CPX to adult male rats promotes reproductive toxicity in rats, while LC and Co-Q10 co-administration could effectively prevent the reproductive toxicity induced by CPX on the male reproductive system.

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