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Research Article

Adverse effect of graded Ciprofloxacin oral intake in male Sprague-Dawley rats

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Keywords:
Ciprofloxacin, lipid profile, oxidative stress, liver, renal function, cardiovascular system

ABSTRACT

Background: Ciprofloxacin (CF) is a very popular antibiotics used for therapeutic prospects. This study was investigated to determine the effect of graded CF oral intake on lipid profile, hepato-reno, antioxidant and cardiovascular functions in Sprague-Dawley rats. **Methods**: Male Sprague-Dawley rats (120-150g) were grouped into 4 equal groups. Group A; control, received 1 ml of normal saline/100g bw, group B, C and D received CF orally at 5, 10 and 20mg/kg respectively. After 7days daily treatments, blood sample was collected via retro-orbital puncture to obtain serum sample for the determination of cholesterol (CHOL), triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL). Urea, creatinine, aspartate amino transferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) were investigated. Superoxide dismutase (SOD), reduced glutathione (GSH), catalase (CAT), malonaldehyde (MDA), blood pressure (BP) and heart rate (HR) were measured via femoral cannulation under anesthesia using urethane and 1% α-chloralose. **Results**: There was a significant decrease ($p<0.05$) in CHOL in group C while TG, LDL, urea significantly reduced in groups B and C and significantly increased in group D ($p<0.05$). Creatinine, ALT and ALP upregulated in group D ($p<0.05$) while AST downregulated in groups C and D. GSH and CAT downregulated in groups B, C and D while SOD reduced significantly ($p<0.05$) in groups B and D. MDA downregulated in groups B and C and upregulated ($p<0.05$) in group D ($p<0.05$). BP and HR significantly increased in groups B, C and D compared with control ($P<0.05$). **Conclusion:** This study showed that oral CF intake at 5mg/kg and 10mg/kg had no adverse effect on lipid profile, hepato-reno and antioxidant functions. However, CF at 20mg/kg may predispose to dyslipidaemia, hepato-reno dysfunction and increased oxidative stress. CF at 20mg/kg may exert a deleterious effect cardiovascular function.

INTRODUCTION

Antibiotics are substances derived from microorganisms that inhibits or destroy the growth of other micro-organisms and are used to treat infections caused by organisms that are sensitive to them, usually bacterial or fungi (Douglas et al., 2016). They alter the normal microbial content in specific region of the body such as lungs, bladder and intestine by destroying one or more groups of harmless or beneficial organisms, which may result in infection due to over growth of resistance organisms (Plumb, 2005). These side effects are most likely to occur with broad-spectrum antibiotics that exert their effect against a wide variety of organisms (Douglas et al., 2016).

Fluoroquinolones are anti-microbial agents, with broad spectrum of bacterial activity against both Gram-positive and Gram-negative bacterial (Oliphant and Green, 2002; Shenoy et al., 2011). They are bacterial agents that exert their bactericidal action by inhibiting the action of bacterial enzymes DNA gyrase, a type II topoisomerase and topoisomerase IV, thereby, preventing cell division (Laurence and Parker, 2008). They are effective against urinary, gastrointestinal, skin, respiratory, bone and joint infections (Blondeau, 1999) and are the most commonly prescribed class of antibiotics, being utilized widely in the treatment of

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respiratory, urinary tract, gastrointestinal and abdominal infections (Gootz et al., 1990; Kumar et al., 2011). Fluoroquinolones are well tolerated in patients but their uses have been associated with some adverse effects, including gastrointestinal discomfort, cutaneous reactions e.g. phototoxicity, juvenile joint toxicity and adverse central nervous system (CNS) effects (Nau et al., 2010; Ftai et al., 2013).

Ciprofloxacin is a bactericidal agent that has good activity against many gram-negative bacilli and cocci, including most species and strains of Pseudomonas aeruginosa, Klebesiella spp., E. coli, Enterobacter, Campylobacter, Shigella, Salmonella, Aeromonas, Haemophilis, Proteus, Yersinia, Serratia and Vibrio spp (Plumb, 2005) and also active against Bordetella bronchisepta, Brucella spp., Chlamydia spp. and Mycoplasma spp (Plumb, 2005). It has been shown to have good bioavailability after oral administration, excellent tissue penetration and it is considered relatively safety (Ball and Tillotson, 1995; Papich, 1998). For these reasons, it is used in a variety of human clinical infections (Such and Lorber,1995), particularly urinary tract infections where it is used at a dose of 10 mg/ kg/ day for about 1 to 12 weeks.

In the current practices of anti-infective therapy, it has been shown to be very popular fluoroquinolone used for therapeutic prospects. In recent years, over 20 million outpatient prescriptions were written for ci profloxacin. In USA, ciprofloxacin is the 35th most commonly used drug, and the 5th most commonly prescribed antibiotics (Gyawale et al., 2009). The available clinical evidence suggests the potential enhanced efficacy of this drug for the treatment of various communities acquired and nosocomial infections, e.g. urinary, biliary, respiratory, skin and neuronal pathogens (John and Weigelt, 2007) and onsequent to the broad-spectrum, flouroquinolones were associated with a variety of adverse effects (Dollery, 1999).

Studies on the safety of fluoroquinolones are relatively scarce though there are few reports on toxicity of Ciprofloxacin (Abd-Allaah et al., 2000; Baykal et al., 2005; Demir et al., 2007; Pfister et al., 2007; Khaki et al., 2008). These studies needed to be investigated further. Hence, the study was designed to investigate the effect of graded dose of oral Ciprofloxacin intake on lipid profile, hepato-reno function, oxidative balance and cardiovascular responses in Sprague-Dawley rats.

MATERIALS AND METHODS

Drugs

Drug (Ciprofloxacin 500mg/Tablet) was obtained from a Pharmacy store in Idi-Araba, Lagos Nigeria.

Animals

Healthy male Sprague-Dawley rats weighing between 120-150 grams were obtained from the animal house of Physiology department, College of Medicine, University of Lagos. They were acclimatized for two weeks before the experiment. They were each fed with standard rodent chow and water ad libitum. The experimental procedures adopted were in accordance with the provisions of the Experimentation Ethics Committee on Animals Use of the College of Medicine of the University of Lagos, Lagos State and the United States National Academy of Sciences Guide for the Care and Use of Laboratory Animals (2011).

Dosage preparation

Twenty-four healthy Sprague-Dawley rats were grouped into four groups of equal rats and treated as follows and administered doses were calculated equivalent of human therapeutic dose (FDA, 2002). The stock solution was 25%(w/v)

Control group received 1ml of normal saline per 100g/bw

Group B received 5mg/kg at 1ml/100g resultant solution (low dose)

Group C received 10mg/kg at 1ml/100g resultant solution (normal dose);

Group D received 20mg/kg at 1ml/100g resultant solution (high dose).

Collection of blood sample

Five (5ml) of blood sample was taken by retro-orbital puncture using heparinized capillary tube into the plain bottles and allowed to clot for 1 hour at 4◦c. It was then centrifuged at 3,000 rpm for 10 minutes. The serum samples were obtained and stored at -20◦c until assayed (Morakinyo et al., 2018)

Blood lipids

Serum lipid levels of triglyceride (TG), cholesterol (CHOL), low density lipoprotein (LDL) and high density lipoprotein (HDL) after treatment were determined by automatic biochemistry analyzer (Mindray BS-120, Chema Diagnostica, Italy) using diagnostic kits for each, purchased from BioSystems® (S.A Costa Brava of Barcelona, Spain).

Liver and kidney functions

Albumin (ALB), alkaline phosphatase (ALP), alkaline amino transferase (ALT), aspartate amino transferase (AST) and albumin were determined using serum samples by an automated analyzer (Mindray BS-120, Chema Diagnostica, Italy). The same machine was equally used for the determination of urea and creatinine.

Antioxidant studies

Determination of superoxide dismutase (SOD) activity

Briefly; SOD activity was measured by the inhibition autoxidative capacity of pyrogallol. The SOD activity was evaluated using a spectrophotometer at 420 nm. A calibration curve was constructed using SOD as standard. A 50% inhibition of autoxidation of pyrogallol was defined as one SOD unit (DinizVilela et al., 2016)

Determination of reduced glutathione (GSH) activity

The protein content of the serum samples was initially precipitated by metaphosphoric acid (MPA) at the ratio of 1:1. The samples were centrifuged at 3000rpm for 10 minutes. The supernatant was collected and mixed with sodium phosphate buffer (0.1M, pH 7.4), containing EDTA (5mM) and ortho-phthaldialdehyde (1 mg/mL in methanol). The mixture was incubated in the dark at room temperature for 15 min and fluorescence was measured at 350 nm (excitation) and 420 nm (emission). A standard curve of GSH (0.001–0.1 mM) was used for linear regression (DinizVilela et al., 2016)

Determination of catalase (CAT) activity

Briefly, serum sample (1ml) was mixed with 49 ml of distilled water to give a 1 in 50 dilution of the sample. The assay mixture contained 4ml of H_2O_2 solution (800 µmoles) and 5ml of Phosphate buffer in a 10ml flat bottom flask. 1ml of properly diluted enzymes preparation was rapidly mixed with the reaction mixture by a gentle swirling motion. The reaction was run at room temperature. A 1ml portion of the reaction mixture was blown into 2ml of dichromate acetic acid reagent at 60s intervals**.** Catalase (CAT) activity was determined by measuring the exponential disappearance of H_2O_2 at 240nm and expressed in units/mg of protein (Aebi, 1984).

Determination of malonaldehyde (MDA) activity

Briefly, the most abundant individual aldehyde resulting from lipid peroxidation breakdown in biological systems and this is based on its interaction with thiobarbituric acid (TBA) to form pink complex with absorption at 535nm. Absorbance was read using Microlab 300 recording spectrophotometer (UV 160) in all measurements (Uchiyama and Mihara, 1978).

Cardiovascular analysis

Anesthesia

After 7 days of daily treatment, solution of 25%(w/v) urethane and 1% alpha chloralose were administered as an aesthesia via intraperitoneal route (i.p) to the rats at a dose of 5ml/kg body weight (Oloyo et al., 2019

Blood pressure and Heart Rates Measurement

Blood Pressure and Heart Rate (HR) were determined via cannulation of carotid artery (Oloyo et al., 2011) with polyethylene cannula, connected to 1% heparinized normal saline with a 3-way channel connector. The cannulated artery was secured tightly with thread and connected to Power lab pressure transducer (model SP844, Physiological Pressure Transducer, AD Instrument (Power Lab-4/24T) which was in turn attached through MLACH11 Grass adapter cable to a computerized data acquisition system with Labscribe software. Heart rates were determined by counting the number of arterial pulses at sampling frequency of sample of 5/s. The Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) were obtained directly from the tracing as the peak and the base of the arterial pulses respectively. Mean Arterial Pressure (MAP) was determined from the following formula:1/3(SBP-DBP) + DBP. (Gobel et al., 1978).

Statistical analysis

All results are presented as the mean standard error of mean±(SEM). Statistical analyses were conducted using Graph Pad Prism Software (GraphPad, Inc., La Jolla, CA, USA). Data analyses were performed by one-way analysis of variance (ANOVA) with post hoc Tukey's multiple comparison test. Statistical significance was set at $p < 0.05$.

RESULTS

Effect of graded dose of Ciprofloxacin on serum levels of TG, LDL, HDL and CHOL

There was a significant decrease ($p<0.05$) in TG levels in groups B (0.65±0.03), C (0.60±0.03) with a significant increase in group D (0.10±0.04) compared with control ($p<0.05$), groups B (0.65±0.03), and C (0.60±0.03). LDL showed a significant decrease ($p<0.05$) in groups B (0.83±0.03) and C (0.82±0.04) and significant increase in group D (1.11±0.01) compared with control (1.00±0.01) groups B (0.83±0.03) and C (0.82±0.04). However, there was no significant difference in HDL levels in groups B (1.18±0.06), C (1.05±0.06), and D (1.26±0.04) compared with control ($p>0.05$). The result also showed a decrease in CHOL level in group B (2.53±0.06) and D (2.51±0.07) but not significant ($p>0.05$) compared with control, however, a significant decreased was observed in group C (2.22±0.08) compared with control (2.76±0.09) and group B (2.53±0.06) (Table 1).

Effect of graded dose of Ciprofloxacin on serum levels of urea and creatinine

The urea level was significantly decrease ($p<0.05$) in groups B (6.63±0.12) and C (6.16±0.14) with a

significant increase p<0.05) in group D (7.78±0.12) compared with control, B (6.63±0.12) and C (6.16±0.14) (Figure 1). Figure 2 revealed a significant increase (p<0.05) in creatinine level in group D (80.33±1.98) compared with control (64.50±2.28), B (73.33±3.08) and C (73.40±3.34) (p<0.05)

Effect of graded dose of Ciprofloxacin on serum levels Albumin, AST, ALT and ALP

There was no significance difference (p>0.05) in albumin (ALB) levels in groups B (33.50±1.20), C (32.80±0.96) and D (35.83±0.54) compared with control, however, ALB level significantly elevated (p<0.05) in group D (35.83±0.54) compared with group C (32.80±0.96). The results also showed a significant decrease (p<0.05) in AST level in groups B (96.83±1.31) and C (96.20±1.88) and significant increase in group D (109.67±1.04) compared control (105.00±1.33), B (96.83±1.31) and C (96.20±1.88). There was a significant increase (p<0.05) in ALT level in group D (46.66±1.0) compared with control (39.16±1.10), B (41.50±0.61) and C (46.66±1.0). A significant increase (p<0.05) was observed in ALP level in group D (43.00±1.77) compared with control (35.33±2.76), B (31.66±2.65) and C (31.40±2.58) (Table 2).

Effect of graded dose of Ciprofloxacin on serum activity of GSH, SOD, CAT and MDA level

Results from antioxidant assay showed a significant decrease(p<0.05) in GSH activity in groups B (0.77±0.04) and D (0.92±0.03) compared with control (1.11±0.03) and a significant increase (p<0.05) in group D (0.92±0.03) compared with group B (0.77±0.04) with a significant decrease (p<0.05) compared with group C (1.08±0.02) (Figure 3a)

A significant decrease (P<0.05) was observed in SOD activity groups B (4.80±0.06), C (5.25±0.07) and D (5.00±0.05) compared with control (5.80±0.09) and significantly increased (P<0.05) in group C compared with group B (p<0.05) (Figure 3b).

Figure 3c showed a significant decrease (P<0.05) in CAT activity groups B (23.01±1.04), D compared with control (31.07±1.05) and significantly decreased (P<0.05) in group D, compared (26.03±1.00) with group C (31.13±1.02).

Ciprofloxacin produced a significant decrease (p<0.05) in MDA level in groups B (1.56±0.02) and C (1.35±0.01) with a significant increase (p<0.05) in group D compared with control (p<0.05). Also, MDA level significantly elevated (p<0.05) in group D (2.01±0.02) compared with group B (1.56±0.02) and C (1.35±0.01) (Figure 4).

T**able 1:** Serum levels of TG, CHOL, HDL and LDL in rats treated with graded dose of Ciprofloxacin

Parameters (mmol/l)	**Control**	**Group B**	**Group C**	**Group D**
TG	0.86±0.02	0.65±0.03*	0.60±0.03*	0.10±0.04^{*a1}
CHOL	2.76±0.09	2.53±0.06	2.22±0.08^{*a}	2.51±0.07
HDL	1.18±0.06	1.05±0.06	1.20±0.08	1.26±0.04
LDL	1.00±0.01	0.83±0.03*	0.82±0.04*	1.11±0.01^{*a1}

Values represent Mean ± SEM. **n=6.** Significant ($^{\#}$p<0.05 vs. group A, ^{a}p<0.05 vs group B, ^{1}p<0.05 vs. group C)

Effect of graded dose of Ciprofloxacin on cardiovascular parameters

The cardiovascular analysis shows a significant decrease (P<0.05) in SBP in group C (115.41±8.75) with a significant increase in group D (129.11±9.96) compared with control (103.05±4.75) and group B (105.87±5.81)

The results also showed a significant increase (P<0.05) in DBP in groups, B (76.22±3.08) C (84.42±3.49) and D (96.74±3.00) with a significant increase (P<0.05) in group D (96.74±3.00) compared with control, groups B and C (P<0.05). A significant decrease (p<0.05) in PP was observed in groups B (,29.64±2.63), C (30.98±2.28) and D (32.36±2.86) compared with control.

Effect of graded dose of Ciprofloxacin on cardiovascular parameters

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Table2: Serum levels of ALB, AST, ALT and ALP in rats treated with graded dose of Ciprofloxacin

Parameters	Control	Group B	Group C	Group D
ALB (g/L)	34.66±0.71	33.50±1.20	32.80±0.96	35.83±0.54[1]
AST (IU)	105.00±1.33	96.83±1.31 *	96.20±1.88 *	109.67±1.04[*a1]
ALT (IU)	39.16±1.10	41.50±0.61	42.40±1.12	46.66±1.0[*a1]
ALP (IU)	35.33±2.76	31.66±2.65	31.40±2.58	43.00±1.77[*a1]

Values represent Mean ± SEM. **n=6**Significant ([#]p<0.05 vs. group A, [a]p<0.05 vs group B, [1]p<0.05 vs. group C) **Figure 4:** Serum MDA level in rats treated with graded Ciprofloxacin. Values represent Mean ± SEM. n=6 Significant ([#]p<0.05 vs. group A, [a]p<0.05 vs group B, [1]p<0.05 vs. group C)

(105.87±5.81). The results also showed a significant increase (P<0.05) in DBP in groups, B (76.22±3.08) C (84.42±3.49) and D (96.74±3.00) with a significant increase (P<0.05) in group D (96.74±3.00) compared with control, groups B and C (P<0.05). A significant decrease (p<0.05) in PP was observed in groups B (,29.64±2.63), C (30.98±2.28) and D (32.36±2.86) compared with control.

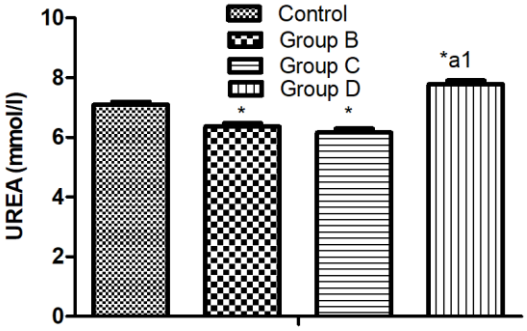

Fig. 1: Serum level of urea in rats treated with graded Ciprofloxacin. Values represent Mean ± SEM**. n=6;** Significant ([#]p<0.05 vs. control, [a]p<0.05 vs group B, [1]p<0.05 vs. group C)

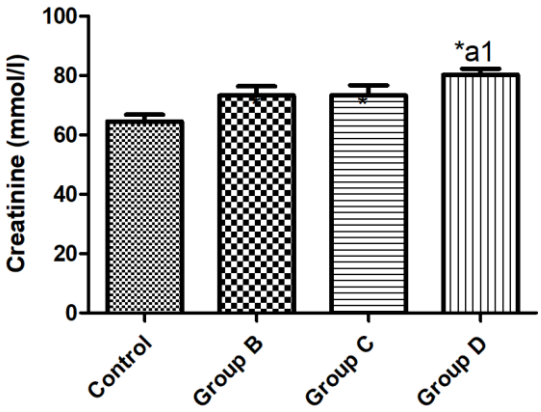

Fig. 2: Serum level of creatinine in rats treated with graded Ciprofloxacin. Values represent Mean ± SEM. n=6. Significant ([#]p<0.05 vs. control, [a]p<0.05 vs group B, [1]p<0.05 vs. group C)

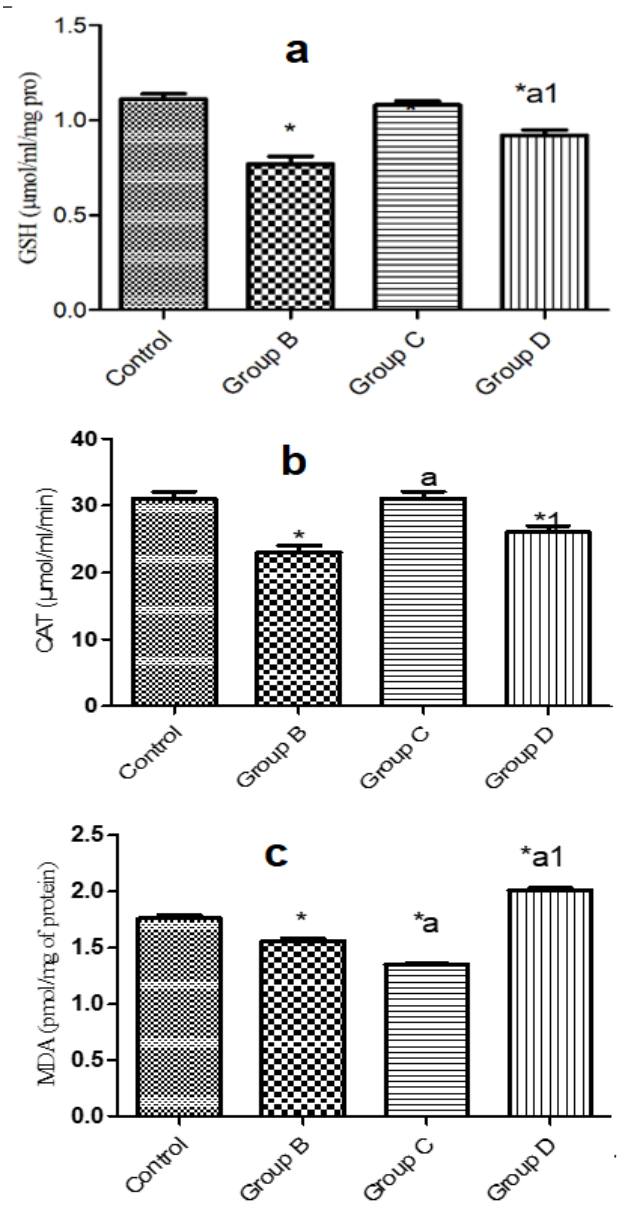

Fig. 3: Serum levels of GSH (a), superoxide dismutase, SOD (b) and Catalase, Cat. (c) in rats treated with graded ciprofloxacin. Values represent Means ± SEM. n=6. Significant ([#]p<0.05 vs. group A, [a]p<0.05 vs group B, [1]p<0.05 vs. group C)

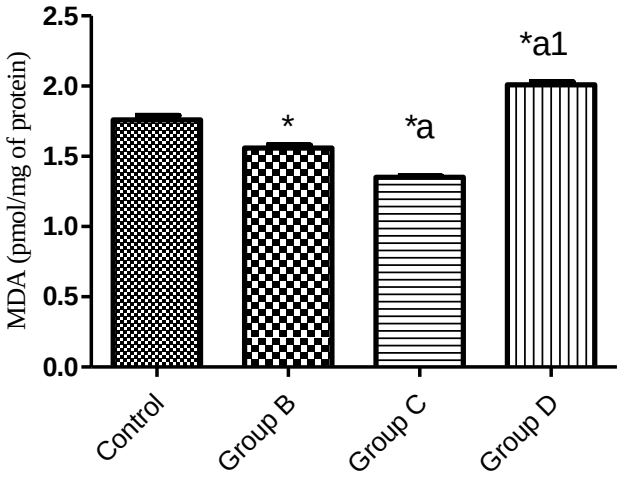

Fig. 4: Serum MDA level in rats treated with graded Ciprofloxacin. Values represent Mean ± SEM. n=6. Significant (#p<0.05 vs. group A, ap<0.05 vs group B, 1p<0.05 vs. group C).

DISCUSSION

Ciprofloxacin inhibits an enzyme called DNA gyrase that is an essential component of the mechanism that posse's genetic information onto daughter cell during division. The use of ciprofloxacin products for medical benefits has played an important role and it is a second-generation fluoroquinolines. It was primarily eliminated by renal exaction; however, the drug was also metabolized and partially cleared through the intestine. It is an antibiotic that can treat a number of infections (Fush et al., 1994).

Though, results for the present study show no risk of lipid disorders in the groups administered with 10 and 15mg/kg bw, however, 20mg/kg dose gave rise to elevated triglyceride and elevated low density lipoprotein as there was a significant decrease in TG and LDL. Elevated triglyceride and elevated low density lipoprotein are well known risk factors for dyslipidaemia and development of arthrosclerosis. Previous study by Fatai et al., (2013) had earlier reported heart diseases and blood vessel disorder in rats treated with Ciprofloxacin.

The significant increase in urea and creatinine in the group treated with 20mg/kg bw is suggestive of kidney disorder or damage. This is an agreement the previous study which reported that over dose of ciprofloxacin can lead to acute renal toxicity and death (Fatai et al., 2013). The liver is a major metabolic organ and plays a key role in lipid metabolism. Depending on species it is, more or less, the hub of fatty acid synthesis and lipid circulation through lipoprotein synthesis (Mguyen et al., 2008). Eventually, the accumulation of lipid droplets results in hepatic steaosis, which may develop as a consequence of multiple dysfunctions such as alterations in β-oxidation, very low density lipoprotein secretion, and pathways involved in the synthesis of fatty acids (Mguyen et al., 2008).

The present study demonstrated a significant elevation of AST, ALT and ALP at 20mg/kg bw suggestive of liver damage. This agrees with previous study by (Orman et al., 2001; Fatai et al., 2013). It was observed that ciprofloxacin induced liver injury marked with elevated liver enzymes (AST, ALT and ALP). Elevated ALP is associated with cholestatic disorder, intrahepatic and extrahepatic obstruction to bile flow (Freidman et al., 1997) while elevated ALT is associated with toxic hepatitis, chronic hepatitis and Cholestatic hepatitis (1999) and Hirsch, (2009)

Bhagirat et al., (2008) and Hirsch, (2009) demonstrated that ciprofloxacin induced hepatotoxicity in most patient treated with over doses is characterized by elevated levels of AST, ALT and ALP. Halliwell and Gutteridge, (1999) and Hirsch, (2009) also reported that ciprofloxacin induced hepatic failure, hepatitis, cholestatic jaundice and acute liver injury marked by elevated level of liver enzymes due to the fact that Ciprofloxacin has a potential hepatotoxic agent. This sis in agreement with the present study as Ciprofloxacin at 20mg/kg bw produced marked elevation of AST, ALT and ALP.

Oxidative stress results when the antioxidant system is overwhelmed by the generation of excess reactive oxygen species (ROS) (Halliwell and Gutteridge, 1999). These reactive species like superoxide radical anion (O^{-}_{2}), hydrogen peroxide (H_2O_2) and hydroxyl radicals (HO^{-}) cause severe damage to macromolecules, tissues and organs through the process of lipid peroxidation (LPO), protein modification and DNA strand breaks (Sun and Chen, 1998; Zaidi and Banu, 2004). Oxidative stress resulting from the generation of these free radicals is known to contribute immensely to several pathological conditions like aging, cancer, cardiovascular disorder, neurodegenerative diseases among others (Halliwell and Gutteridge, 1999; Abuja and Albertini, 2001).

The present findings revealed a significant decrease in GSH, SOD and CAT in the rats challenged with 20mg/kg bw of graded Ciprofloxacin balance with concomitant increase in MDA's lipid peroxidation suggestive of decreased oxidative balance. Lipid

peroxidation is a significant determinant of the degree of free radical generation with MDA being one of the products, as well as, an important marker of the process of the oxidative stress (Halliwell and Gutterridge, 1994; Chaudiere and Ferrari-Iliou, 1999). Fluoroquinolones are known to display hepatotoxic effect (Clark et al., 2001). The studies of (Dhamidharka et al., 1996; Pouzauaud et al., 2006) reported that the generation of reactive oxygen species by fluoroquinolones resulted in cellular damage to liver and kidney. Other researchers have reported the induction of reactive oxygen species (ROS) by fluoroquinolones, as well as, some other antibiotics (Altınordulu and Eraslan, 2009; Páez et al., 2011). Fluoroquinolones as well as some other antibiotics have been demonstrated cause to oxidation of macromolecules in some bacteria, resulting in increased lipid peroxidation (Páez et al., 2011).

Results from the cardiovascular analysis demonstrated Elevated SBP as observed in groups C and D; DBP was elevated in all the experimental groups (B, C, D). PP reduced in groups B, C and D while MABP increased in group B but significantly increased in groups C and D. However, HR increased only in group D. Elevated blood pressure is critical index of cardiovascular disorder. Abnormal changes observed in the cardiovascular parameters may be associated with elevated levels of triglyceride and low density lipoprotein. Serum triglyceride levels have been shown to be an independent risk factor for coronary heart disease and are strongly determined by low-density lipoprotein (LDL) composition, which can be specifically modified by dietary lipid source (Jain *et al*., 2010). Results from this finding agrees with previous investigations by Saracoglu, (2009) and Cholongitas et al., (2009) which reported that over dose of Ciprofloxacin is associated with cardio toxicity.

In conclusion, findings from this study suggests that Ciprofloxacin administration at 5mg/kg and 10mg/kg had no adverse effect on lipid profile, hepato-reno functions and antioxidant status. However, at 20mg/kg, Ciprofloxacin resulted to dyslipidaemia, hepato-reno dysfunction and increased oxidative radical and predisposes to cardiovascular dysfunction. Due to the potential adverse effect of Ciprofloxacin and greater danger it may portend at 20mg/kg bw, care should be taken to avoid possible metabolic and cardiovascular disorders during its therapeutic use.

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