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RESEARCH ARTICLE

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Investigation of the effects of three different generations of fluoroquinolone derivatives on antioxidant and immunotoxic enzyme levels in different rat tissues

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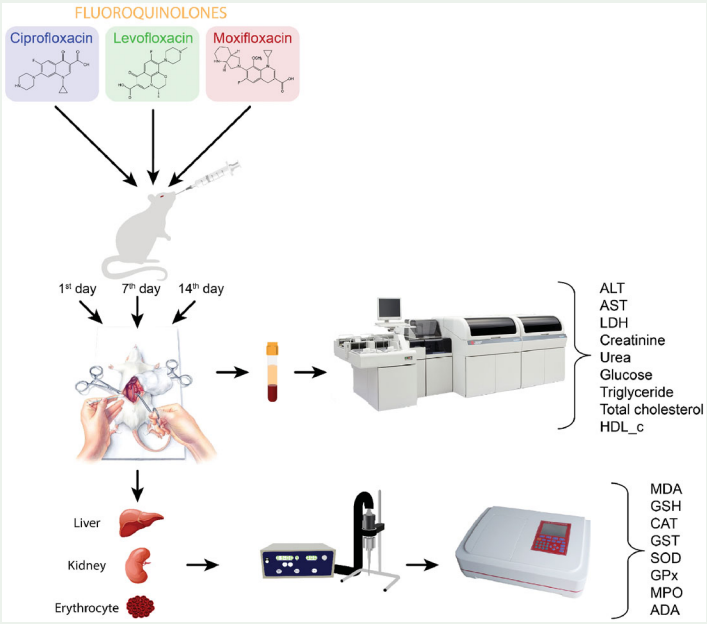
ABSTRACT

Fluoroquinolones (FQs) are synthetic and broad-spectrum antimicrobial drugs derived from nalidixic acid. FQs are used against SARS-CoV-2 in our country, and for the treatment of some urinary tract diseases, gastrointestinal diseases, respiratory tract diseases, sexually transmitted diseases, and dermatological diseases. The present study investigated the effect of 1-,7-,14-day treatments of three different FQ derivatives; ciprofloxacin (CIP) 80 mg/kg/day, levofloxacin (LVX) 40 mg/kg/day, and moxifloxacin (MXF) 40 mg/kg/day, on biochemical parameters, lipid peroxidation, antioxidant enzymes, and immunotoxicity. 72 *Wistar albino* male rats were distributed to four groups including 18 rats in each group and were sacrificed on three different time points. The 14-day treatment of MXF significantly reduced the levels of aspartate aminotransferase (AST), glucose, reduced glutathione (GSH), malondialdehyde (MDA), catalase (CAT), myeloperoxidase (MPO), adenosine deaminase (ADA), and glutathione peroxidase (GPx). Furthermore, 14-day treatment of LVX increased liver [GSH, MPO, ADA, superoxide dismutase (SOD)], and GSH (erythrocyte) levels; whereas it significantly reduced the levels of AST, TG (triglycerides) and associated parameters levels in all the tissues (MDA), erythrocytes, and liver (MPO, CAT, SOD, GPx). After 14-day treatment of CIP; the erythrocyte levels of GSH, MPO, GPx, and CAT significantly decreased; whereas the levels of glucose, creatinine, MPO (liver), and GST (kidney and erythrocyte) significantly increased. It has been concluded that FQ derivatives used in this experiment did not display any correlation in terms of the efficacies in the different time points and tissues. Thus, it is recommended to use such FQ derivatives considering the duration of use and target tissue.



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Introduction

Fluoroquinolones (FQs) are synthetic derivatives of nalidixic acid with a bactericidal action against both gram-positive and gram-negative pathogens (Dönmez *et al.* 2018). FQs prevent DNA replication by targeting DNA gyrase and topoisomerase IV in bacteria (Gibson *et al.* 2018). Classification of FQs is made by considering their antimicrobial spectrum and clinical indications. Drugs in each group are similar in their antimicrobial activity. In each successive generation, a new and important group of pathogens is added, while also covering the previous generation (Ezelarab *et al.* 2018). FQs are generally classified into four generations according to their activity and spectrum (Mimouni *et al.* 2019). Although many FQs have been developed so far, moxifloxacin (MXF), ciprofloxacin (CIP), gemifloxacin, levofloxacin (LVX), delafloxacin, and ofloxacin have been approved by the U.S. Food and Drug Administration (FDA). Fluoroquinolones are used in the treatment of urinary tract infections, prostatitis, respiratory tract infections, prosthetic joint infections, intra-abdominal infections, skin and skin structure infections, osteomyelitis, and sexually transmitted diseases (Kim and Hooper 2014, Richards *et al.* 2019). In addition, ciprofloxacin, levofloxacin, and moxifloxacin are used against the SARS-CoV-2 threat due to their potential antiviral effects (Karampela and Dalamaga 2020, Scroggs *et al.* 2021).

The shifting of the balance between oxidants/antioxidants in favor of oxidants is called oxidative stress (Birben *et al.* 2012). Oxidative stress is caused by releasing of reactive oxygen species (ROS) due to the toxic effects of drugs (Hosohata 2016; Yew *et al.* 2018). ROS can be divided into two groups as radicals and non-radicals according to their state of electrons (Chowdhury and Saikia 2020). While free radicals form superoxide ($O_2^{-\bullet}$), hydroxyl ($HO^{\bullet}$), hydroperoxyl ($HOO^{\bullet}$), peroxyl ($ROO^{\bullet}$), and alkoxyl ($RO^{\bullet}$) radicals; non-radicals form hydrogen peroxide (H_2O_2), hypochlorous acid (HClO), ozone (O_3), and singlet oxygen ($^1O_2$) (Bratovcic 2020). Various metabolic diseases can occur together with oxidative stress as a result of the presence of endogenous and exogenous ROS in the body (Dogan *et al.* 2018).

In addition, FQs are used to form an oxidative stress generation model (Ilgin *et al.* 2015, Elbe *et al.* 2016). Although the exact mechanism of this is not fully understood, it is known that FQs induce the formation of $^1O_2$ and $O_2^{-\bullet}$as a result of phototoxicity, which is a side effect of FQs (Goswami *et al.* 2006). It is also reported that FQs modulate the oxidative metabolism of leukocytes and stimulate the production of ROS in neutrophils (Talla and Veerareddy 2011). In oxidative stress studies on FQs, these appear to have both oxidant and antioxidant effects. CP, a broad-spectrum antibiotic, is a second-generation fluoroquinolone derivative (Batiha *et al.* 2020). It inhibits bacterial DNA gyrase IV and stabilizes the DNA-topoisomerase-drug complex, resulting in bactericidal and bacteriostatic effects. It has been approved by the FDA to be used in the treatment of urinary tract infections, sexually transmitted infections (gonorrhea and chancroid), skin, bone and joint infections, prostatitis, typhoid fever, gastrointestinal infections, lower respiratory tract infections, anthrax, plague, and salmonellosis (Thai *et al.* 2020). LVX, a second-generation fluoroquinolone derivative, is the first optically active fluoroquinolone (Hara and Honjo 2019), and is a drug that accumulates especially in the cell cytoplasm (Zimmermann *et al.* 2016). It is known to bind to plasma proteins at a rate of 38% (Anderson and Perry 2008). MF is a fourth-generation synthetic fluoroquinolone derivative approved by the FDA for use in the treatment of various diseases (Reddy *et al.* 2010). It is used in the treatment of acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, acute bacterial sinusitis, skin infections, and conjunctivitis (Szabó *et al.* 2018). It has been reported in previous studies that FQs (CIP, LVX, and MXF) increase and decrease the MDA and GSH levels (Fatai *et al.* 2013, Ilgin *et al.* 2015, Kovalenko *et al.* 2019). In general, it has been reported that they also show similar effects on antioxidant enzymes (CAT, GST, SOD, and GPx activities) (Khan *et al.* 2017, Dogan *et al.* 2019, Kovalenko *et al.* 2019, Abdelrahman *et al.* 2020, Dawood *et al.* 2020, Farid and Hegazy 2020).

ADA (EC 3.5.4.4) and MPO (EC 1.11.2.2) are biological markers of immunotoxicity in vertebrates (Doğan *et al.* 2020). While ADA protects lymphocytes from the toxic effects of adenosine, deoxyadenosine triphosphate (dATP), and deoxyadenosine diphosphate (dADP), which lead to decreased immune functions in lymphocytes; MPO plays an important role in killing phagocyted bacteria (Doğan and Çelik 2020). Studies have shown that FQ treatment reduces the MPO and ADA activities of infected groups (Yazar *et al.* 2010, Dwivedi *et al.* 2010, Chandira *et al.* 2013, Rayaman *et al.* 2015, Gupta *et al.* 2018).

Biochemical and lipid profile parameters that leak into the blood, in which there are concentration changes as a result of the damage caused by oxidative stress, provide information about the damage. In studies conducted with FQs, it has been reported in general that there are fluctuant results observed in ALT, AST, LDH, Creatinine, Urea, Glu, TRIGs, CHOL) and HDL_c levels (Fatai *et al.* 2013, Olayinka *et al.* 2015, Ara *et al.* 2020, Igbayilola *et al.* 2020).

In this study, the effects of oral administration of three different FQ derivatives (CIP, LVX, and MXF) for different three time points on various antioxidants enzyme levels, reduced glutathione (GSH), Malondialdehyde (MDA) and some biochemical parameters, were investigated extensively.

Materials and methods

Chemicals and reagents

All chemicals and reagents were obtained by Sigma Chemical Co. (St. Louis, MO, USA) and the kits for the antioxidant enzyme analyses were supplied by Randox Laboratories Ltd.

Animals

In this experimental study, seventy-two male *Wistar albino* rats, 2–3 months old and weighing 150–300 g, obtained from Van YüzüncüY ı l University Experimental Animal Unit, were used. Ethical committee number was provided by the Experimental Animal Research Center, Van Yuzuncu Yil

University (Van, Turkey) (2020/10–13). The rats were fed *ad libitum* (as desired) in standard plastic containers at 25 ± 2 °C, in a 12 hours light/12 hours dark light period. All experimental procedure was conducted according to the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Science and published by the National Institutes of Health.

Drugs and treatment

All pharmaceutical dosages administered were obtained from local pharmacies. Tablet forms of CIP, LVX, and MXF (80 mg/kg/day, 40 mg/kg/day, and 40 mg/kg/day, respectively) were first suspended in 1 ml distilled water, and then administered as gavage to rats. (Rawi *et al.* 2011, Afolabi and Oyewo 2014, Huang *et al.* 2016).

Experimental design

The experimental animals were randomly divided into four groups with eighteen animals in each group. These groups were sacrificed in three different time periods after 1, 7, and 14 days of treatment.

(I) *Control group (n = 18):* Animals were fed *ad libitum* with standard feed and water for the indicated times, as well as distilled water by gavage daily. Six of the animals were sacrificed 1 day after the experiment, six of them 7 days after the experiment, and the remaining 14 days after the experiment.

(II) *CIP treated group (n = 18):* The animals were fed *ad libitum* with standard feed and water for the specified periods, as well as 80 mg/kg CIP gavage daily. Six of the animals were sacrificed 1 day after the application, six of them 7 days after the application, and the rest 14 days after the application.

(III) *LVX treated group (n = 18):* The animals were fed *ad libitum* with standard feed and water for the specified periods, as well as 40 mg/kg LVX gavage daily. Six of the animals were sacrificed 1 day after the application, six of them 7 days after the application, and the rest 14 days after the application.

(IV) *MXF treated group (n = 18):* The animals were fed *ad libitum* with standard feed and water for the specified periods, as well as 40 mg/kg MXF gavage daily. Six of the animals were sacrificed 1 day after the application, six of them 7 days after the application, and the rest 14 days after the application.

Determination of biochemical parameters

Serum biochemical parameters ALT, AST, LDH, Creatinine, Urea, Glu, TRIGs, CHOL and HDL_c

were measured using an auto-analyzer (ARCHITECT 16,200, Abbott Park, IL 60,064, USA), and Abbott biochemistry kits (USA).

Determination of MDA and GSH levels

Malondialdehyde, one of the peroxidation products formed as a result of the reaction of fatty acids with free radicals, was read spectrophotometrically at 532 nm according to the principle of transforming into the pink-colored form with thiobarbituric acid (Buege and Aust 1978). GSH levels were determined using the method described by Beutler (1963) based on spectrophotometric measurement at 412 nm wavelength of the yellow color formed by the reaction of the sulfhydryl groups of GSH in the supernatant with DTNB.

Determination of the antioxidant enzymes

SOD activity was measured at 505 nm according to McCord and Fridovich's methods by calculating the percentage of inhibition of red formazan dye formation (McCord and Fridovich 1969). GPx catalyzes the oxidation of GSH by cumene hydroperoxide. Enzyme activity was determined by monitoring the change in absorbance at 340 nm (Paglia and Valentine 1967). GST activity was based on measuring the absorbance changes at 340 nm due to the formation of the GSH-CDNB complex (Guthenberg and Mannervik 1981). CAT activity as described by Beutler (1984) was observed by measuring the absorption reduction due to H_2O_2 consumption at 230 nm.

Determination of the immunotoxic enzymes

ADA enzyme activity was assayed by the method described by Giusti (1974). The blue-colored mixture formed in proportion to the ammonia concentration released by using adenosine was read at 640 nm. Measurement of MPO enzyme activity was conducted by using the method developed by Bradley et al. (1982). This method is based on the reduction of H_2O_2 oxidized by MPO with O-dianisidine hydrochloride and measuring the absorbance of this reduced product at 460 nm.

Statistical analysis

Statistical analysis was conducted with SPSS (version 13) software. Repeated measures ANOVA was used to evaluate the significance between groups and times. Following the analysis of variance, Duncan's multiple comparison test was used to identify different groups. The raw values obtained from all the analyses were presented as the mean ± standard deviation of the groups. Statistical significance level in calculations was taken as ($p < 0.05$).

Results

The effect of three different FQ derivatives on biochemical parameters

As shown in Table 1, the urea level of the drug groups on the 1st day was observed to significantly increase compared to the control group ($p < 0.05$). ALT, AST (CIP and

Table 1. Time dependent changes in the effect of three different fluoroquinolone derivatives on rat serum biochemical parameters.

		Days		
Parameter	Groups	1st Day	7th Day	14th Day
ALT (U/L)	Control	39.17 ± 3.97^{Aa}	36.33 ± 3.72^{Aa}	39.00 ± 2.65^{Aa}
	CIP (80 mg/kg/day)	43.33 ± 3.72^{Aa}	46.67 ± 6.74^{Ab}	46.17 ± 6.62^{Ab}
	LVX (40 mg/kg/day)	40.00 ± 6.45^{Aa}	39.83 ± 3.82^{Aa}	44.00 ± 4.34^{Aab}
	MXF (40 mg/kg/day)	46.17 ± 7.41^{Aa}	47.83 ± 4.79^{Ab}	42.83 ± 4.02^{Aab}
AST (U/L)	Control	100.80 ± 10.76^{Aa}	99.60 ± 11.99^{Aa}	97.80 ± 7.22^{Aa}
	CIP (80 mg/kg/day)	105.83 ± 10.98^{Aa}	111.17 ± 10.42^{Aab}	111.33 ± 10.88^{Aa}
	LVX (40 mg/kg/day)	113.80 ± 8.52^{Aa}	99.17 ± 9.95^{Ba}	94.33 ± 3.83^{Ba}
	MXF (40 mg/kg/day)	117.83 ± 17.29^{Aa}	119.67 ± 20.28^{Ab}	105.67 ± 19.63^{Aa}
LDH (U/L)	Control	1292.33 ± 167.17^{Aa}	1269.17 ± 208.74^{Aa}	1185.00 ± 269.83^{Aa}
	CIP (80 mg/kg/day)	1495.67 ± 392.87^{Aa}	1310.17 ± 341.96^{Aa}	1490.50 ± 372.30^{Aa}
	LVX (40 mg/kg/day)	1596.33 ± 510.88^{Aa}	1245.67 ± 147.01^{Aa}	1288.67 ± 135.30^{Aa}
	MXF (40 mg/kg/day)	1145.83 ± 244.63^{Aa}	833.667 ± 15.64^{Bb}	996.33 ± 233.46^{Aa}
Glucose (mg/dL)	Control	185.83 ± 23.73^{Aa}	212.33 ± 32.40^{Aa}	201.20 ± 40.45^{Aa}
	CIP (80 mg/kg/day)	179.50 ± 17.24^{Aa}	246.33 ± 51.60^{Ba}	212.83 ± 29.10^{Ba}
	LVX (40 mg/kg/day)	202.50 ± 42.92^{Aa}	206.17 ± 30.60^{Aa}	235.33 ± 43.79^{Ba}
	MXF (40 mg/kg/day)	267.00 ± 89.21^{ABa}	324.00 ± 34.60^{Ab}	206.33 ± 46.13^{Ba}
Creatinine (mg/dL)	Control	0.48 ± 0.01^{Aa}	0.51 ± 0.03^{Aa}	0.51 ± 0.03^{Aa}
	CIP (80 mg/kg/day)	0.46 ± 0.02^{Aa}	0.51 ± 0.04^{Ba}	0.51 ± 0.03^{Ba}
	LVX (40 mg/kg/day)	0.47 ± 0.02^{Aa}	0.47 ± 0.02^{Aa}	0.52 ± 0.02^{Ba}
	MXF (40 mg/kg/day)	0.51 ± 0.07^{Aa}	0.52 ± 0.08^{Aa}	0.51 ± 0.04^{Aa}
Urea (mg/dL)	Control	55.83 ± 6.62^{Aa}	55.50 ± 6.03^{Aa}	56.40 ± 10.76^{Aa}
	CIP (80 mg/kg/day)	40.33 ± 5.13^{Ac}	41.33 ± 6.77^{Ab}	48.50 ± 4.81^{Aa}
	LVX (40 mg/kg/day)	50.00 ± 3.74^{Aab}	39.83 ± 1.84^{Bb}	47.17 ± 5.88^{Aa}
	MXF (40 mg/kg/day)	44.50 ± 3.94^{Abc}	45.33 ± 3.67^{Ab}	46.17 ± 5.00^{Aa}

Groups with different lower case letters (a, b, c) showed meaningful differences within at the same time point (the same column) ($p < 0.05$).
Groups with different capital letters (A, B, C) showed significant time-dependent changes within each drug experiments (the same row) ($p < 0.05$).
CIP: siprofloxacin; LVX: levofloxacin; MXF: moxifloxacin; ALT:alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase.

Table 2. Time dependent changes in the effect of three different fluoroquinolone derivatives on rat serum lipid profile parameters.

		Days		
Parameters	Groups	1st Day	7th Day	14th Day
Triglyceride (mg/dL)	Control	52.17 ± 13.32^{Aa}	52.33 ± 7.40^{Aa}	57.25 ± 2.22^{Aa}
	CIP (80 mg/kg/day)	47.83 ± 11.55^{Aa}	61.00 ± 17.91^{Aa}	64.50 ± 20.61^{Aa}
	LVX (40 mg/kg/day)	60.00 ± 14.39^{Aa}	55.83 ± 9.50^{ABa}	49.50 ± 14.56^{Ba}
	MXF (40 mg/kg/day)	58.83 ± 15.92^{Aa}	42.33 ± 7.26^{Aa}	45.50 ± 6.60^{Aa}
Cholesterol (mg/dL)	Control	45.67 ± 5.24^{Aa}	50.33 ± 3.50^{Aa}	53.00 ± 5.62^{Aa}
	CIP (80 mg/kg/day)	55.00 ± 7.46^{Aa}	55.33 ± 5.20^{Aa}	47.50 ± 5.89^{Aa}
	LVX (40 mg/kg/day)	50.00 ± 4.98^{Aa}	55.17 ± 4.58^{Aa}	53.17 ± 6.37^{Aa}
	MXF (40 mg/kg/day)	48.33 ± 5.99^{Aa}	50.50 ± 5.32^{Aa}	53.17 ± 5.78^{Aa}
HDL_c (mg/dL)	Control	31.58 ± 2.97^{Aa}	33.95 ± 2.79^{Aa}	33.60 ± 3.08^{Aa}
	CIP (80 mg/kg/day)	35.92 ± 4.78^{Aa}	36.37 ± 3.45^{Aa}	30.92 ± 3.29^{Aa}
	LVX (40 mg/kg/day)	33.72 ± 3.58^{Aa}	36.33 ± 3.69^{Aa}	34.93 ± 3.75^{Aa}
	MXF (40 mg/kg/day)	31.37 ± 4.31^{Aa}	34.58 ± 3.54^{Aa}	35.35 ± 3.42^{Aa}

Groups with different lower case letters (a, b, c) showed meaningful differences within at the same time point (the same column) ($p < 0.05$).
Groups with different capital letters (A, B, C) showed significant time-dependent changes within each drug experiments (the same row) ($p < 0.05$).
CIP: ciprofloxacin; LVX: levofloxacin; MXF: moxifloxacin.

MXF), glucose (MXF), and urea (all drug groups) levels were observed to significantly increase compared to the control group at the 7th day time-point. ALT levels were significantly increased in all drug groups as compared to the control group at the 14th day time-point.

The parameters at 3 different time points are given in Table 1. The AST level of LVX group at days 7 and 14, LDH level of MXF group at day 7, and creatinine levels of CIP group on days 7 and 14 increased significantly compared to the 1st day, while CIP and MXF groups' glucose levels on the 14th day, and LVX group urea on the 7th day levels were significantly decreased compared to the 1st day.

The effect of three different FQ derivatives on lipid profile parameters

As seen in Table 2, there was no difference between the parameters in the groups at three different time points; although, the triglyceride level of the LVX group on the 14th day was found to be significantly lower than the 1st day.

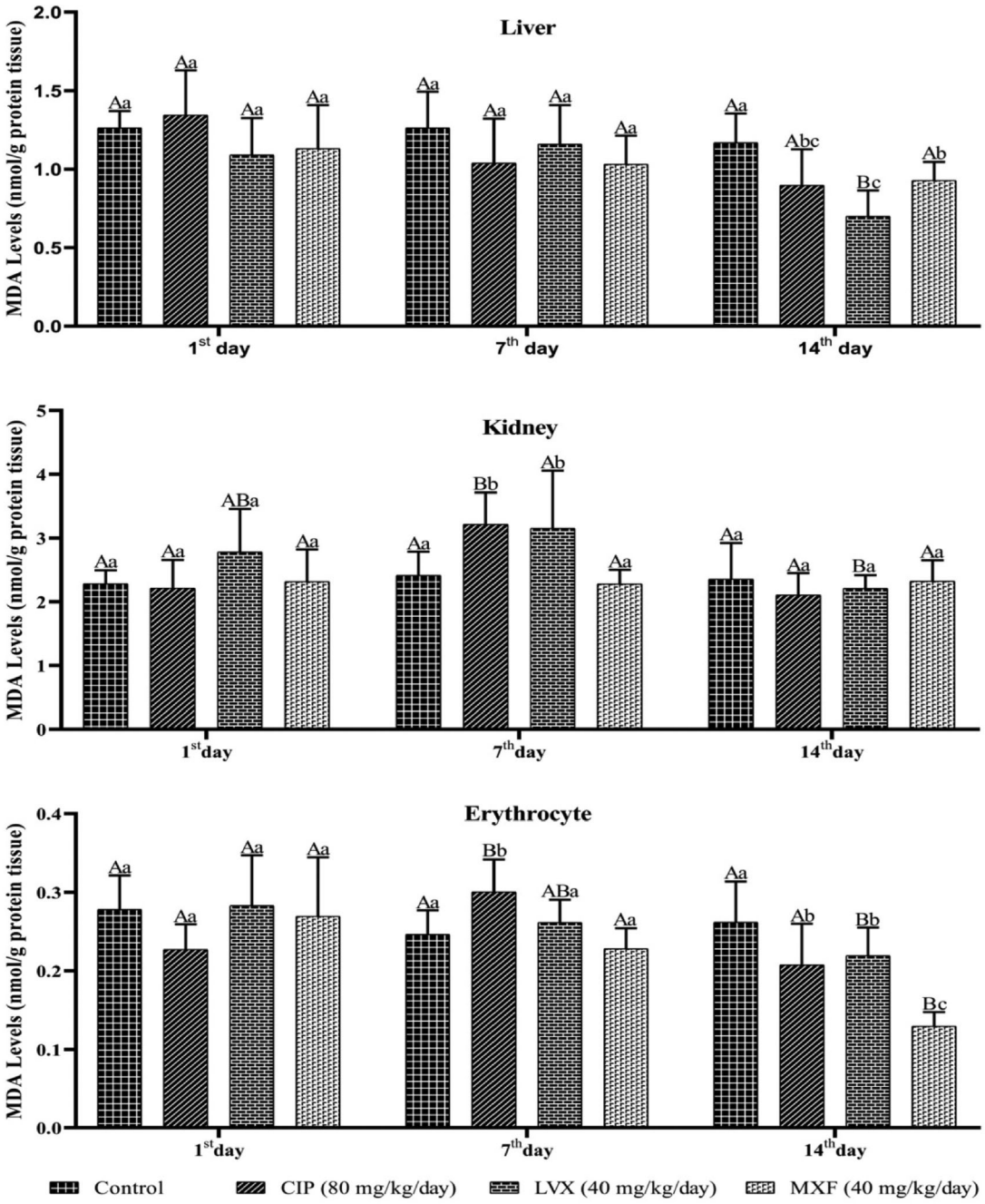

Figure 1. Time dependent changes in the effect of three different fluoroquinolone derivatives on MDA levels in rat tissues. Groups with different lower case letters (a, b, c) showed meaningful differences within at the same time point ($p < 0.05$). Groups with different capital letters (A, B, C) showed significant time-dependent changes within each drug experiments ($p < 0.05$). CIP: ciprofloxacin; LVX: levofloxacin; MXF: moxifloxacin; MDA: malondialdehyde.

The effect of three different FQ derivatives on the MDA and GSH levels

As seen in Figure 1, The MDA contents of the liver and erythrocyte treatment groups on the 14th day showed a significant decrease compared to the control group; while the MDA levels of the kidney tissue in the CIP and LVX groups on the 7th day showed a significant increase compared to the control and MXF groups. In the difference between the times, the MDA level of the liver LVX group on the 14th day showed a significant decrease compared to the 1st and 7th days; while on the 7th day, the MDA levels in the kidney and erythrocyte CIP group showed a significant increase compared to the 1st and the 14th days. Also, the MDA level on the 14th day kidney tissue in the LVX group compared to 7th day, as well as the erythrocyte MDA level for the LVX and MFX groups, decreased significantly compared to both the 1st and 7th days (excluding day 7 for LVX).

As shown in Figure 2, on the 7th day, GSH levels in the kidney tissue CIP and LVX groups showed a significant increase compared to the control and MFX groups, while the erythrocyte GSH levels of all the treatment groups on the 14th day showed a significant decrease compared to the

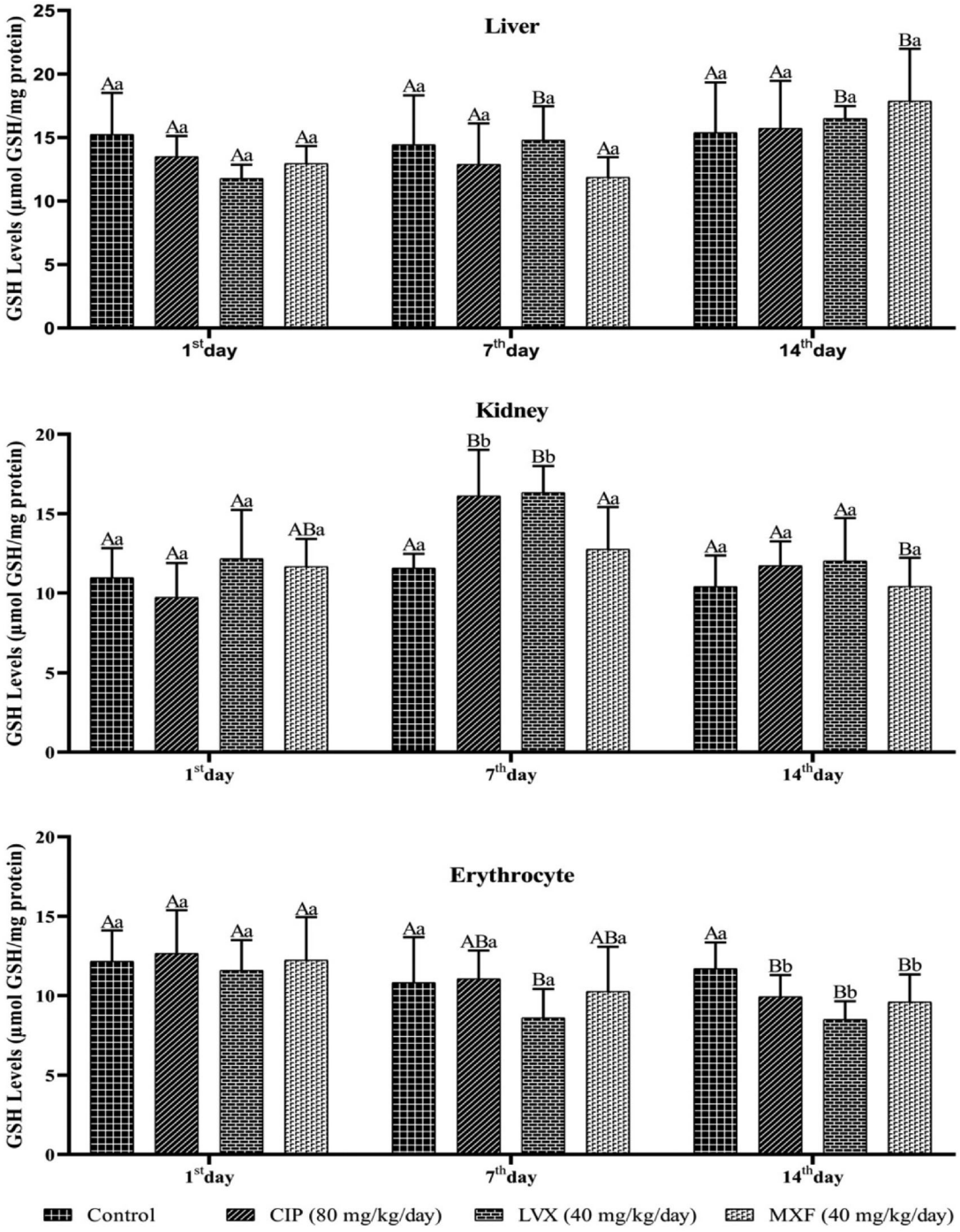

Figure 2. Time dependent changes in the effect of three different fluoroquinolone derivatives on GSH levels in rat tissues. Groups with different lower case letters (a, b, c) showed meaningful differences within at the same time point ($p < 0.05$). Groups with different capital letters (A, B, C) showed significant time-dependent changes within each drug experiments ($p < 0.05$). CIP: ciprofloxacin; LVX: levofloxacin; MXF: moxifloxacin; GSH: glutathione.

control group. For the CIP group, kidney tissue GSH levels showed a significant increase on the 7th day compared to the 1st and the 14th days. For the LVX group, Liver, and kidney tissue GSH levels showed a significant increase on days 7 and 14 (excluding kidney tissue) compared to day 1, while GSH levels in erythrocyte tissue (LVX group) were found to be significantly lower. The GSH level of the liver tissue for the MFX group on the 14th day as compared to the other days; kidney tissue GSH level in the MFX group in 14 days compared to 7 days, and GSH level in erythrocyte MFX group in 14 days as compared to day 1 were found to be significant.

The effect of three different FQ derivatives on antioxidant enzymes

A comparison of the values of liver, kidney, and erythrocyte GPx enzyme levels is presented in detail in Table 3. In the liver and erythrocyte tissue, the GPx enzyme levels after the application of CIP, LVX and, MXF generally decreased from

Table 3. Time dependent changes in the effect of three different fluoroquinolone derivatives on rat liver and kidney tissues and erythrocyte antioxidant enzyme activities.

			Days		
Enzyme	Tissues	Groups	1st Day	7th Day	14th Day
GPx (U/g Protein)	Liver	Control	20.91 ± 4.11^{Aa}	21.33 ± 5.16^{Aab}	22.09 ± 4.49^{Aa}
		CIP (80 mg/kg/day)	29.85 ± 7.82^{Ab}	26.22 ± 8.39^{Ac}	20.21 ± 4.84^{Aab}
		LVX (40 mg/kg/day)	33.40 ± 9.85^{Ab}	29.19 ± 5.47^{Ac}	16.58 ± 3.49^{Bbc}
		MXF (40 mg/kg/day)	33.31 ± 5.18^{Ab}	17.27 ± 5.21^{Bb}	13.26 ± 2.47^{Bc}
	Kidney	Control	65.19 ± 8.77^{Aa}	68.48 ± 9.69^{Aa}	67.04 ± 5.96^{Aa}
		CIP (80 mg/kg/day)	51.55 ± 8.62^{Aa}	78.65 ± 14.61^{Ba}	56.74 ± 6.05^{Aa}
		LVX (40 mg/kg/day)	59.21 ± 14.79^{Aa}	81.11 ± 12.05^{Ba}	62.35 ± 11.50^{Aa}
		MXF (40 mg/kg/day)	62.55 ± 9.76^{Aa}	49.39 ± 4.58^{Bb}	58.87 ± 12.27^{ABa}
	Erythrocyte	Control	3.18 ± 0.61^{Aa}	3.69 ± 0.67^{Aab}	3.64 ± 0.48^{Aa}
		CIP (80 mg/kg/day)	3.81 ± 0.94^{ABab}	4.63 ± 1.11^{Aa}	3.14 ± 0.39^{Bab}
		LVX (40 mg/kg/day)	4.94 ± 1.40^{Ab}	2.90 ± 0.34^{Bb}	3.14 ± 1.01^{ABab}
		MXF (40 mg/kg/day)	4.63 ± 0.71^{Ab}	3.74 ± 0.72^{Bab}	2.70 ± 0.54^{Cb}
GST (nmol/g Protein)	Liver	Control	8.60 ± 1.09^{Aa}	7.66 ± 2.16^{Aa}	8.05 ± 1.98^{Aa}
		CIP (80 mg/kg/day)	6.58 ± 1.63^{Aa}	6.24 ± 1.45^{Aab}	5.97 ± 1.88^{Ab}
		LVX (40 mg/kg/day)	6.43 ± 1.76^{Aa}	4.85 ± 1.46^{ABbc}	3.28 ± 0.87^{Bc}
		MXF (40 mg/kg/day)	7.92 ± 2.30^{Aa}	3.302 ± 0.94^{Bc}	3.44 ± 1.10^{Bc}
	Kidney	Control	7.59 ± 0.52^{Aa}	9.33 ± 2.34^{Aab}	8.16 ± 1.06^{Aa}
		CIP (80 mg/kg/day)	6.53 ± 1.55^{Aa}	11.20 ± 2.19^{Cac}	8.70 ± 1.07^{Ba}
		LVX (40 mg/kg/day)	8.73 ± 2.05^{Aa}	11.94 ± 1.02^{Bc}	8.43 ± 1.60^{Aa}
		MXF (40 mg/kg/day)	7.23 ± 2.05^{Aa}	8.40 ± 1.43^{Ab}	7.394 ± 1.20^{Aa}
	Erythrocyte	Control	0.22 ± 0.08^{Aa}	0.26 ± 0.07^{Aa}	0.26 ± 0.03^{Aab}
		CIP (80 mg/kg/day)	0.17 ± 0.03^{Aa}	0.31 ± 0.09^{Ba}	0.31 ± 0.06^{Bb}
		LVX (40 mg/kg/day)	0.23 ± 0.03^{Aa}	0.30 ± 0.07^{ABa}	0.31 ± 0.06^{Bb}
		MXF (40 mg/kg/day)	0.23 ± 0.03^{Aa}	0.33 ± 0.04^{Ba}	0.21 ± 0.05^{Aa}
CAT (nmol/g Protein)	Liver	Control	0.52 ± 0.08^{Aa}	0.48 ± 0.13^{Aab}	0.50 ± 0.09^{Aa}
		CIP (80 mg/kg/day)	0.57 ± 0.16^{ABa}	0.62 ± 0.18^{Aa}	0.48 ± 0.14^{Ba}
		LVX (40 mg/kg/day)	0.32 ± 0.16^{Aab}	0.28 ± 0.09^{Ac}	0.41 ± 0.14^{Aa}
		MXF (40 mg/kg/day)	0.28 ± 0.08^{Ab}	0.33 ± 0.08^{Abc}	0.26 ± 0.09^{Aa}
	Kidney	Control	2.89 ± 0.40^{Aa}	2.59 ± 0.70^{Aa}	2.56 ± 0.31^{Aa}
		CIP (80 mg/kg/day)	1.53 ± 0.53^{ABbc}	1.54 ± 0.29^{Ab}	1.15 ± 0.34^{Bb}
		LVX (40 mg/kg/day)	1.73 ± 0.35^{Ab}	1.49 ± 0.34^{Ab}	1.21 ± 0.35^{Ab}
		MXF (40 mg/kg/day)	1.11 ± 0.35^{Ac}	1.20 ± 0.29^{Ab}	1.34 ± 0.32^{Ab}
	Erythrocyte	Control	3.04 ± 0.30^{Aa}	2.72 ± 0.42^{Aa}	2.70 ± 0.26^{Aa}
		CIP (80 mg/kg/day)	2.98 ± 0.68^{Aa}	2.27 ± 0.72^{ABa}	1.91 ± 0.64^{Bb}
		LVX (40 mg/kg/day)	3.80 ± 0.64^{Ab}	1.93 ± 0.45^{Ba}	2.10 ± 0.60^{Bab}
		MXF (40 mg/kg/day)	2.21 ± 0.22^{Ac}	2.38 ± 0.45^{Aa}	1.70 ± 0.47^{Bb}
SOD (U/g Protein)	Liver	Control	85.33 ± 10.87^{Aa}	85.11 ± 14.39^{Aa}	88.40 ± 16.27^{Aa}
		CIP (80 mg/kg/day)	76.08 ± 12.33^{Aab}	77.31 ± 17.78^{Aa}	90.10 ± 16.32^{Aa}
		LVX (40 mg/kg/day)	66.82 ± 10.94^{Ab}	78.93 ± 18.40^{ABa}	88.64 ± 6.42^{Ba}
		MXF (40 mg/kg/day)	82.82 ± 8.98^{Aa}	71.26 ± 10.51^{Aa}	91.41 ± 19.84^{Aa}
	Kidney	Control	89.65 ± 14.21^{Aa}	91.69 ± 13.23^{Aa}	89.43 ± 8.83^{Aa}
		CIP (80 mg/kg/day)	77.44 ± 17.03^{Aa}	122.00 ± 20.39^{Bb}	85.24 ± 5.22^{Aa}
		LVX (40 mg/kg/day)	98.41 ± 17.77^{Aa}	125.25 ± 14.50^{Bb}	90.06 ± 11.21^{Aa}
		MXF (40 mg/kg/day)	91.24 ± 13.35^{Aa}	86.75 ± 19.05^{Aa}	77.20 ± 15.02^{Aa}
	Erythrocyte	Control	14.01 ± 1.65^{Aa}	14.70 ± 1.81^{Aa}	15.21 ± 1.13^{Aa}
		CIP (80 mg/kg/day)	14.33 ± 3.00^{Aa}	14.95 ± 1.10^{Aa}	13.99 ± 1.42^{Aab}
		LVX (40 mg/kg/day)	16.88 ± 3.37^{Aa}	12.65 ± 1.29^{Bb}	13.34 ± 1.34^{Bb}
		MXF (40 mg/kg/day)	15.38 ± 2.41^{Aa}	13.46 ± 0.81^{Aab}	11.17 ± 1.46^{Bc}

Groups with different lower case letters (a, b, c) showed meaningful differences within at the same time point (the same column) ($p < 0.05$).
Groups with different capital letters (A, B, C) showed significant time-dependent changes within each drug experiments (the same row) ($p < 0.05$).
CIP: ciprofloxacin; LVX: levofloxacin; MXF: moxifloxacin; GPx: glutathione peroxidase; GST: glutathione-S-transferase; CAT: catalase; SOD: superoxide dismutase.

1 day to 14 days compared to the control group (except for a slight increase in LVX application on day 14 for erythrocyte), whereas there was no statistically significant difference in the kidney tissue. Similarly, GPx activity in LVX and MXF groups decreased due to the time increase in liver and erythrocytes; however, kidney tissue's GPx level was found to be significantly increased in drug applied groups (except for MXF) for day 7 measurements as compared to other measurements conducted for other tissues on day 7.

Detailed data on liver, kidney, and erythrocyte GST enzyme activity are given in Table 3. There was no statistically significant difference in liver, kidney, and erythrocyte GST enzyme activity at day 1, while the GST activities of all drug groups of the liver tissue were observed to decrease compared to the control group on the 7th and 14th day. In addition, GST activities of the kidney (7th day) and erythrocyte (14th day), it was observed that the CIP and LVX drug groups showed a significant increase compared to the control and MXF groups. Liver GST activity on day 7, and LVX and MXF groups on day 14, showed a significant decrease compared to day 1. The CIP and LVX groups showed a significant increase in renal GST activity on the 7th day

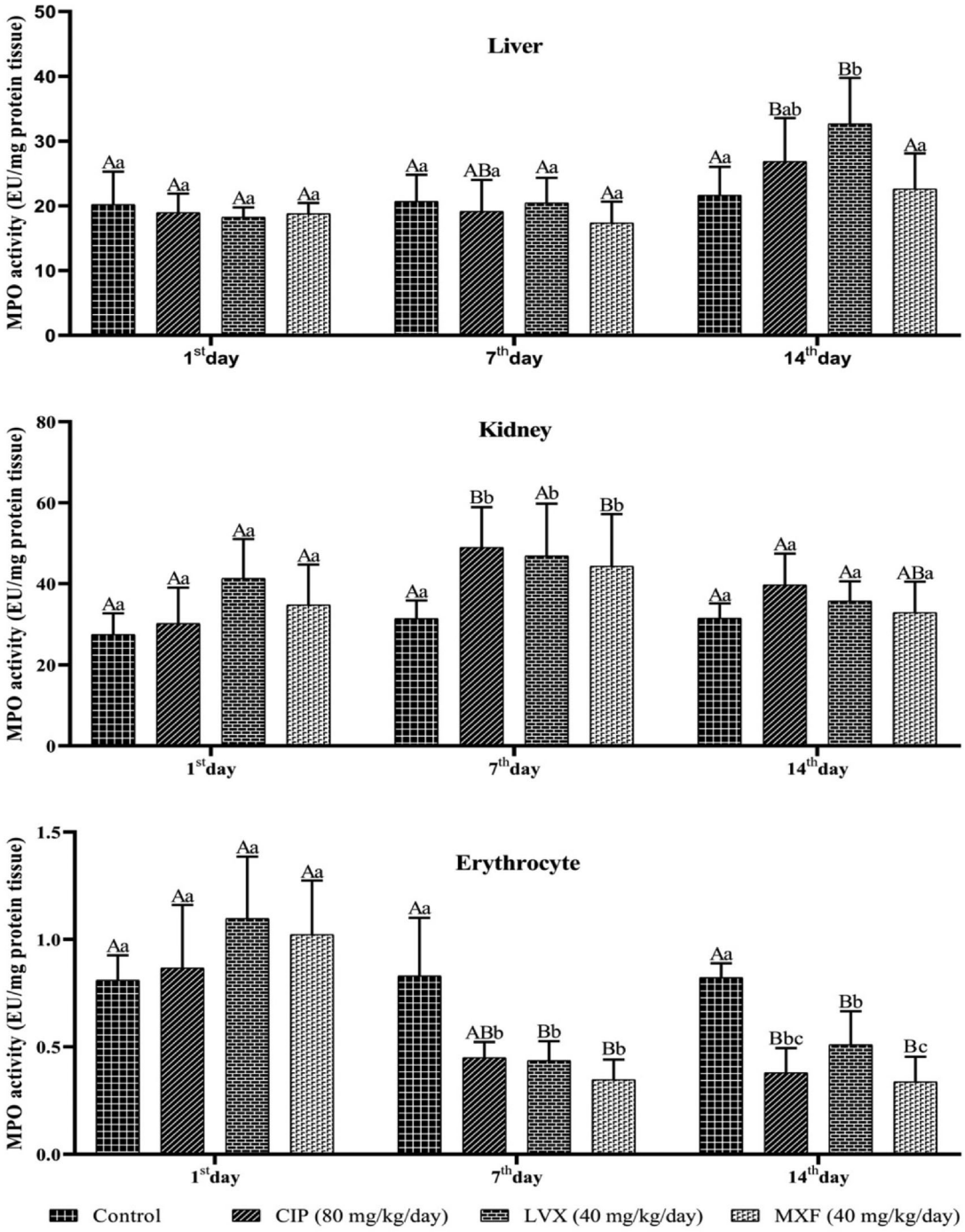

Figure 3. Time dependent changes in the effect of three different fluoroquinolone derivatives on MPO levels in rat tissues. Groups with different lower case letters (a, b, c) showed meaningful differences within at the same time point ($p < 0.05$). Groups with different capital letters (A, B, C) showed significant time-dependent changes within each drug experiments ($p < 0.05$). CIP: ciprofloxacin; LVX: levofloxacin; MXF: moxifloxacin; MPO: myeloperoxidase.

compared to the day 1 and day 7 time-points. In general, all drug group erythrocyte GST activities at days 7 and 14 increased significantly compared to the results recorded on day 1.

Liver, kidney, and erythrocyte CAT activities are provided in Table 3. Generally, the CAT activity of the 14 days CIP group was found to be significantly lower in all the tissues compared to the other time points. Also, CAT activities of erythrocyte LVX and MXF groups on day 14 were significantly decreased compared to days 1 and 7 (excluding the MXF group). In the comparison within the group, liver (day 1 and day 7) and kidney (all time points) CAT activities were found to be significantly lower in all drug groups as compared to the control group. In addition, for erythrocyte, the CAT activities in the drug groups at the time points on day 1 (excluding the CIP group) and day 14 were found to be significantly decreased compared to the control group.

The activities of the SOD enzyme in tissues are given in Table 3. Liver LVX group SOD activity showed a significant increase on day 14 compared to day 1, and kidney CIP and LVX SOD activity on day 7 compared to day 1 and day 14. Furthermore, the 7th and 14th day erythrocyte LVX

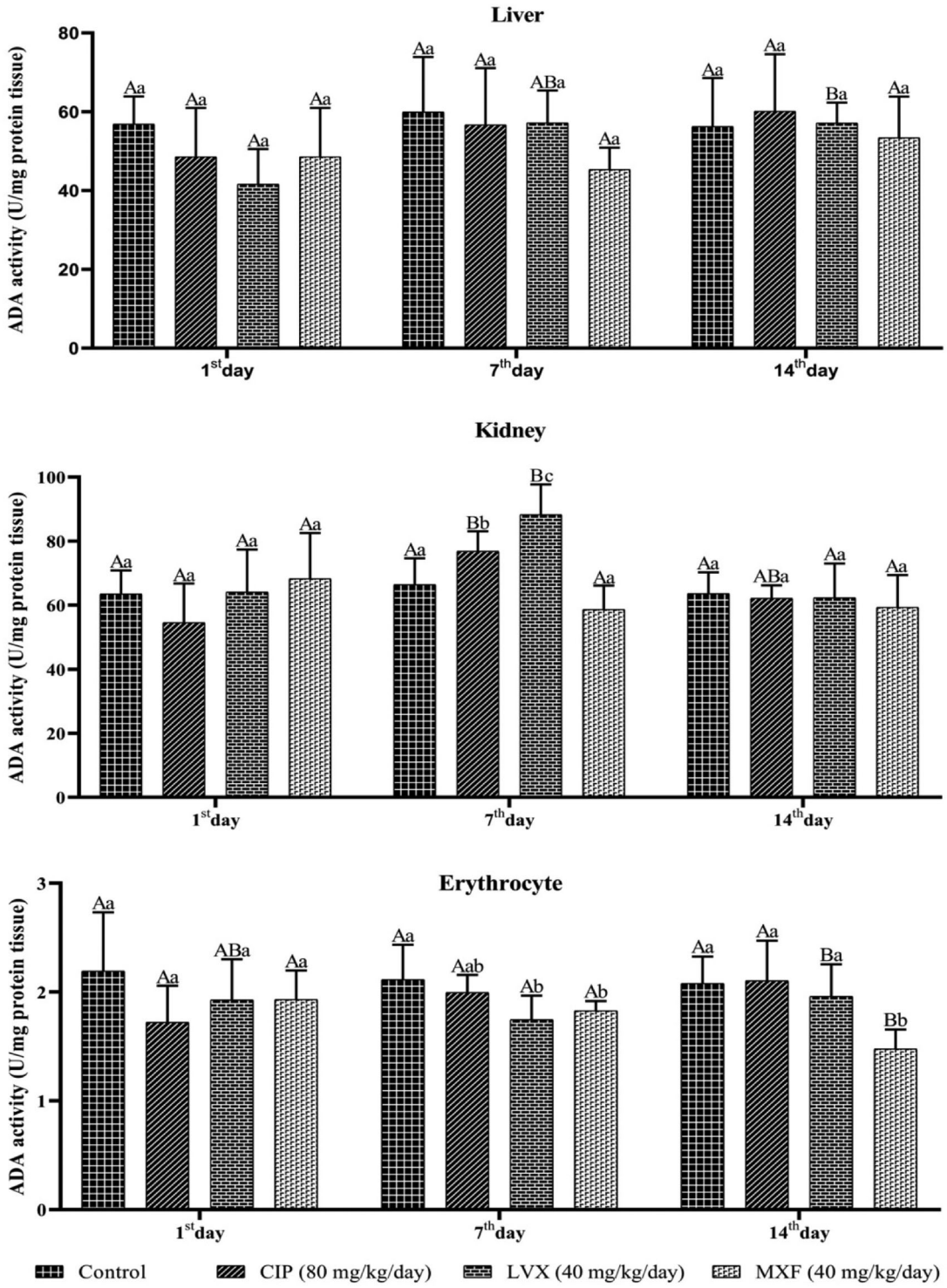

Figure 4. Time dependent changes in the effect of three different fluoroquinolone derivatives on ADA levels in rat tissues. Groups with different lower case letters (a, b, c) showed meaningful differences within at the same time point ($p < 0.05$). Groups with different capital letters (A, B, C) showed significant time-dependent changes within each drug experiments ($p < 0.05$). CIP: ciprofloxacin; LVX: levofloxacin; MXF: moxifloxacin; ADA: adenosine deaminase.

group SOD activities were significantly decreased compared to the 1st day, as well as the 14th day MXF group compared to the 1st and 7th days. The first-day liver SOD activities for the CIP and LVX groups decreased compared to the control and MXF groups; while on the 7th day, kidney tissue's CIP and LVX group SOD activities were found to be significantly increased compared to the control and MXF groups. On the 7th day, the erythrocyte MXF and LVX group SOD activities decreased compared to the control and CIP groups, while the SOD activities of all drug groups on the 14th day were found to be significantly decreased compared to the control group.

The effect of three different FQ derivatives on the MPO activity

Information on the MPO enzyme activity is shown in Figure 3. MPO activity for the CIP and LVX groups on day 14 in liver tissue compared to other time points; as well as the kidney tissue for the CIP and MXF groups on the 7th day showed a significant increase compared to the other two time points. However, the erythrocyte drug groups on the 7th and 14th day showed a significant decrease compared to the 1st day. The liver tissue's CIP and LVX groups MPO activity on the 14th day showed a significant increase compared to the other groups; and on the 7th day, the kidney tissue drug groups showed a significant increase compared to the control group. Furthermore, unlike on the 7th and 14th day, the erythrocyte drug groups showed a significant decrease compared to the control group.

The effect of three different FQ derivatives on the ADA activity

The levels of the ADA enzyme in tissues are given in Figure 4. On the 14th-day, liver LVX group ADA level was found to be significantly increased compared to the 1st day. ADA levels in the 7th-day kidney CIP and LVX groups were found to be significantly increased compared to the other time points, while the erythrocyte MXF group found a significant decrease compared to the other time points. On the other hand, in the comparison within the group, ADA levels of the kidney CIP and LVX groups increased significantly compared to the control and MXF groups. In addition, the 7th day LVX and MXF groups and the 14th day MXF group were found to be significantly lower than the other groups.

Discussion

FQs and their derivatives have been widely used in the treatment of various diseases such as urinary tract diseases, gastrointestinal diseases, respiratory diseases, sexually transmitted diseases, and skin diseases, due to their broad-spectrum antimicrobial effects (Durand *et al.* 2019, Pham *et al.* 2019). In addition, some FQ derivatives have been used as an adjunct to the treatment of pneumonia associated with the coronavirus disease (COVID-19) due to its potential antiviral activity, immunomodulatory properties, and favorable pharmacokinetic profiles against SARS-CoV-2 (Beović *et al.* 2020, Karampela and Dalamaga 2020). In this study, the possible effects of oxidant/antioxidant and anti-immunotoxic effects of three different generations of FQ derivatives at three different time points were investigated on rat liver, kidney and blood samples in detail.

FQ derivatives have been reported in an *in vivo* study that FQs may cause different effects on the biochemical and antioxidant enzyme levels (Dawood *et al.* 2020). It was stated in various studies that even fluctuations in parameters may differ from tissue to tissue depending on the route of administration, doseand the duration of the use of FQ drug types. (Rawi *et al.* 2011, Fatai *et al.* 2013, Hemieda *et al.* 2019). The damage to cells and cell organelles causes enzymes such as AST, ALT, LDH, creatinine, etc. to leak from the cell membrane into the circulation.

In general, in our study, by contributing to tissue damage at certain times of application of the CIP drug, the serum ALT level of the CIP drug administration group increased compared to the control group on the 7th and 14th days; while the urea levels of all drugs groups decreased on the 1st and 7th days compared to the control group. Treatment with CIP increases the release of ROS, which contributes to its overall bactericidal effect (Radovanovic *et al.* 2018). In another study, it was reported that the CIP (100 mg/kg) administration on rats for 28 days decreased blood serum glucose levels, but increased urea, creatinine, ALT, and AST levels compared to the control group (Srinivasu 2017). As seen in Table 1, the MXF drug group increased ALT, AST, and glucose levels on the 7th day compared to the control group. In a study supporting our findings, it was reported that three different doses of MXF (4, 8 and16 mg/kg, respectively) for 7 days increased ALT and AST levels compared to the control group (Ore and Olayinka 2015). As seen in Table 2, there was no statistically significant difference in the lipid profile parameters of the studied FQs drugs during the 14-day application; but at the end of the 14th day, it was seen that the LVX group triglyceride level caused a significant decrease compared to the 1st day. In literature reviews on LVX, it was observed that the short-term LVX administration increased the triglyceride levels (Olayinka *et al.* 2015), while the long-term LVX treatment caused a decrease in the triglyceride levels (Sawayama *et al.* 2007). Furthermore, LVX drug group decreased the levels of AST (7 and 14 days), urea (7 days), and triglycerides (14 days) compared to the first day; while glucose (14 days) and creatinine (14 days) were increased by the first day.

In various studies on FQ derivatives, it has been observed that such drugs cause different effects on MDA and GSH levels (El-Metwaly *et al.* 2019, Kovalenko *et al.* 2019). In the present study, it was observed that three different time points of three different FQ derivative drugs (CIP, LVX, and MXF) caused different fluctuations in both the duration and tissue as well as drug groups A study by Olayinka *et al.* (2015) reported that in rats that were administered with different doses of LVX (5 mg/kg, 10 mg/kg, and 20 mg/kg) for 7 days, LVX treatment groups showed a significant increase in liver MDA content, while the GSH level decreased significantly when compared to the control group. In the present study, LVX significantly decreased MDA level on the 14th days when compared to the control group. At the end of the administration of LVX (0.0516 mg/kg, i.v) once a day for three weeks to rats with osteomyelitis, the serum MDA levels decreased compared to the control group, while GSH levels increased (Dwivedi *et al.* 2010). In the rats administered with three different doses (5 mg/kg, 10 mg/kg, and 20 mg/kg, orally) of CIP drug, 5 mg/kg and 10 mg/kg doses MDA and GSH levels were lower in the control group; while in the 20 mg/kg dose, it was determined that MDA level increased compared to the control group (Igbayilola *et al.* 2020). At the end of the 7-day treatment with MXF (10 mg/kg, IP), it was observed that in rats that had lung damage caused by hydrochloric acid, the mesenchymal stem cell inflammation, oxidative stress,

apoptosis, and MDA levels were prevented/reduced as compared to the control group. (El-Metwaly *et al.* 2019). In the present study, CIP significantly increased lipid peroxidation on the 7th days in erythrocyte and kidney.

There are important *in vivo* antioxidant enzymes (CAT, SOD, GPx, and GST) that scavenge and eliminate the effects of free radicals caused by oxidative stress in living organisms. In our study, FQs have caused fluctuations in the antioxidant enzyme activities of the drug groups compared to the control group, both on a tissue and time basis. The reason for this fluctuation is probably due to the adaptation period of the oxidative stress caused by drugs and the different physiological properties of the tissues.

It was determined that GPx, CAT, and SOD enzyme activities were decreased compared to the control group after 21 days of administration of ciprofloxacin (20 mg/kg/twice daily dose) in rats with fetal liver damage caused by ciprofloxacin (Dogan *et al.* 2017). In the study where the effects of three different doses of CIP (50, 100,150 mg/kg) on rat liver, lung, and kidney GST activity at 2, 4, and 6 hours were investigated, it was observed that the liver GST activity of the CIP administered groups decreased depending on the dose and time increase, compared to the control group. It was also determined that while the lung tissue GST activity decreased at the 4th hour, it caused an increase at the 6th hour, and finally, the kidney tissue's GST activity increased at the 6th hour (Dawood *et al.* 2020).

In the study conducted by Rawi et al., 2011, they reported that there were fluctuations in some parameter levels in the rat brain regions, but there was a significant decrease in the cortex MDA, SOD, GPx, and GSH levels, when the CIP and LVX groups were compared with the control group due to the increase in the treatment time. In another study, it was reported that LVX (40 mg/kg) administration for 7 and 14 days caused a significant increase in the liver MDA level compared to the control group (Afolabi and Oyewo 2014). In another study investigating the protective role of curcumin, glucosamine and vitamin C on LVX-induced oxidative stress, they reported that the zero and 14th day LVX (10 mg/kg i.p) treatment groups showed a significant increase in the MDA levels and a significant decrease in CAT and GPx activities when compared to the control group (Abd Elfadil *et al.* 2019). Rats treated with 4, 8, and 16 mg/kg MF doses, respectively, according to their body weight for 7 days, showed significant increases in MDA, urea, creatinine, ALT, AST, total cholesterol, HDL_c and triglyceride levels compared to the control group; while there was a significant decrease in the SOD and CAT enzyme activities and GSH levels (Ore and Olayinka 2015). In another study, it was determined that MF (7.2 mg/kg, oral) given to rats for 1, 7, 14 and 21 days caused a decrease in the CAT, SOD, and GPx activities, as well as a significant increase in the MDA levels compared to the control group (Abdelrahman *et al.* 2020).

Conclusions

As a conclusion, FQ derivatives used in this experiment did not display any correlation in terms of the efficacies in the different time points and tissues. LVX on the 14th day suppressed lipid peroxidation in all tissues when compared to control group and different time points. MPO activities of FQ derivatives in erythrocytes were significantly decreased compared to the control group on 7th and 14th days. Furthermore, there were fluctuations in other parameters in terms of antioxidant activity, GSH, biochemical parameters and ADA. Thus, it is recommended to use such FQ derivatives considering the duration of use and target tissue.

Disclosure statement

The authors declare that they have no conflict of interest.

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