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RESEARCH ARTICLE

Effect of Curcumin and Ginger on Adverse Effects of Levofloxacin in Male Rats

Hosny A. Ibrahim[1], Shimaa A.I. Abdallah[2] and Esraa M.A. El-Gazzar[1*]
[1]Pharmacology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Egypt
[2]Physiology Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Egypt
***Corresponding author: Esraa Maghawry Abd-Allah El-Gazzar**
Email: esraamaghawry2021@gmail.com

Abstract

Fluoroquinolones are more likely than any other antibacterial drug classes to cause serious side effects. The purpose of this study is to assess the protective effects of vitamin E, curcumin, and ginger in male rats against the side effects of levofloxacin (LFX).Ninety male Wistar rats were placed into six groups, each of 15 animals. Groups 1 and 2 received distilled water or olive oil and kept as normal controls, while groups 3-6 received LFX [10 mg/kg body weight (BW)] alone or in combination with vitamin E (100 mg/kg BW.), curcumin (200 mg/kg BW.) or ginger (200 mg/kg BW.), respectively. All medications were administered orally via gavage once a day for 5 successive days. Samples of blood were collected at zero day , 7th and 14th day post-treatments for biochemical analysis, while liver and kidney tissues were dissected and subjected to antioxidants estimation. Levofloxacin administration caused hepatic and renal damage evidenced by significant increase in serum liver enzymes, urea (76.43±3.70, 72.67±0.47, 75.00±6.42), creatinine (2.48±0.01, 2.48±0.01, 2.50±0.01), total cholesterol (166.67±6.81, 174.00±4.04, 176.00±2.88), triglycerides (269.67±5.84, 289.33±4.91, 249.67±1.86), and low density lipoprotein- cholesterol (LDL- C) (243.00±7.09, 213.67±5.03, 226.33±5.45) levels. Meanwhile, significant decline in serum levels of high density lipoprotein- cholesterol (HDL- C) (20.00±1.11, 23.33±3.38, 20.10±1.53), total protein (5.77±0.03, 5.97±0.09, 5.87±0.09), albumin (3.45±0.03, 3.60±0.06, 3.57±0.09) and A/G ratio (1.49±0.02, 1.51±0.05, 1.55±0.09) were determined in relation to normal control at zero, 7th and 14th day post-treatments, respectively in a time dependent manner. The superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities in the liver (1.50±0.13, 1.67±0.18, 1.60±0.15; 2.02±0.38, 2.81±0.25, 3.30±0.37) and kidney (24.97±1.04, 21.33±1.33, 26.33±1.71; 3.15±0.14, 2.13±0.36, 2.44±0.28) tissues were significantly decreased in all levofloxacin- exposed rats compared to control values in the liver (3.00±0.11, 3.33±3.13, 3.33±0.16 for SOD; 19.76±0.03, 19.18±0.05, 18.42±0.13 for GPx) and kidney (71.33 ± 2.60, 67.67±0.88, 66.00±1.73 for SOD; 8.32±0.08, 8.30±0.04, 7.81±0.06 for GPx). However, the hepatic and renal malondialdehyde (MDA) concentrations (74.51±0.69, 80.97±0.41, 95.88±0.52; 66.58±0.14, 65.09±0.12, 65.23±0.14) were significantly increased compared to the control (11.82±0.01, 11.82±0.001, 11.11±0.03; 30.88±0.03, 33.20±0.03, 32.83±0.04).Co-administration of LFX with vitamin E, curcumin or ginger attenuated the elevated liver enzymes, renal damage biomarkers, lipogram and hepato-renal MDA, with elevation of tissues antioxidants. From this study, biochemical results indicated that levofloxacin induced hepato-renal alterations in rats over time, and that curcumin or ginger medications may be more effective when used prophylactically rather than curatively.

Key words: Levofloxacin, Vitamin E, Curcumin, Ginger, Liver Enzymes, Antioxidants.

***Corresponding author e-mail: (yasmin-ali.ams@o6u.edu.eg). Medical laboratory Department, Faculty of Applied Medical Science, 6thOctober University, 12511, Giza, Egypt.**

Introduction

Levofloxacin (LFX), a fluoroquinolone antibiotic of the 3rd-generation, is commonly used in respiratory and urinary tract infections, prostatitis and orchitis [1]. LFX has a strong antibacterial action alongside both Gram-positive and Gram-negative bacteria. [2].When compared to other fluoroquinolones, LFX has a substantially higher efficacy in treating typhoid fever. It's commonly used to treat infections like pneumonia, sinusitis, and genitourinary infections [3]. LFX's bactericidal activity is primarily achieved by its interaction with the enzyme DNA gyrase, which inhibits DNA replication and transcription, preventing bacteria from dividing [4]. In general, LFX toxicity in the liver causes the generation of free radicals, the destruction of mitochondria, and lipid peroxidation of membranes or alterations in redox status of glutathione [5]. Fluoroquinolones have been linked to allergic interstitial nephritis, acute tubular necrosis, acute renal failure, and crystalluria. The majority of these reactions are linked to the antibiotics ciprofloxacin, norfloxacin, ofloxacin, and LFX [6, 7].

Plant-derived phytochemicals are used to treat a wide range of human illnesses. According to the World Health Organization (WHO), around 75% of the global population, particularly in developing countries, believe and rely on herbal remedies for the prevention and treatment of a variety of ailments. About 10% of the population relies on herbal medicine for the treatment or prevention of digestive disturbances [8].

Curcumin, a polyphenolic compound, is a natural bioactive constituent isolated from the rhizome of *Curcuma longa* Linn. contains antioxidant characteristics as well as anti-inflammatory, anticancer, immune-enhancing, antitumor, and hepatoprotective activities [9]. Curcumin protects against peroxidative damage by acting as a free radical scavenger. Curcumin's efficacy in pretreatment against hazardous substances is enhanced by these features [10]. It has been found to be an effective free radical scavenger in the fight against oxidative stress in a variety of tissues, and its hepatoprotective effects have been reported in various liver damage studies [11].

Ginger (*Zingiber officinale*) is a well-known *Zingiberaceae* family plant that is one of the most extensively used spices in the world and one of the top five antioxidant foods [12]. Ginger has several beneficial effects in hyperglycemia and hyperlipidemia [13], antioxidant and hepatoprotective [14], with anti-obesity and hypocholesterolemic effects in human [15] and experimental animals [16]. Gingerols were considered an important active ingredient in ginger. The compound 6‑gingerol appears to be responsible for its characteristic taste. The analyzed chemical compositions of aqueous extracts of ginger root contain polyphenols, Vitamin C, B, β‑carotene, flavonoids, and tannins [12].

Vitamin E, as a conventional antioxidant, has been shown to protect the liver from a variety of pollutants [14]. It is a well-known free radical scavenger that protects essential cellular structures from oxidative injury caused by oxygen free radicals and lipid peroxidation reactive products [17].Various antioxidants, such as vitamin C, vitamin E, and selenium, were effectively added to the diet, reducing oxidative stress *in vivo* and in animal products [3, 18, 19].

Therefore, the current investigation was designed to ascertain the beneficial effects of curcumin and ginger supplement on LFX- induced liver and kidney damage, with relationship to vitamin E as a good example.

Material and Methods

Drug, plants and doses preparation

1. Levofloxacin tablets (500 mg/tablet) were supplied by Sanofi Avents Company, Cairo, Egypt. They were dissolved in distilled water then given orally to individual rats at the therapeutic dose [10 mg/kg body weight (BW)] [3].

2. Vitamin E capsules (1000 mg vitamin E/capsule) were obtained from Pharco

Pharmaceutical Industries CO., Alex., Egypt. The capsules were expurgated open and deflated in a clean container. To make a suspension containing a dosage of vitamin E (100 mg/kg BW.), it was dissolved in 10 mL olive oil [20].

3. Curcumin powder was procured from Pharco Pharmaceutical Industries CO., Alex., Egypt and emulsified in 10 mL olive oil and administered orally at a dose of 200 mg/kg BW [21].

4. Ginger powder was bought from Pharco Pharmaceutical Industries CO., Alex., Egypt, dissolved in 10 mL olive oil and supplemented by oral route at a dose of 200 mg/kg BW. [22].

Animals and experimental design

Ninety healthy adult male Wistar rats with mean body weight of 150±10g were obtained from the Laboratory Animal Housing, Faculty of Veterinary Medicine, Zagazig University, Egypt. The rats were kept in specially constructed metal cages under immaculate hygienic conditions and fed a balanced diet with unlimited access to water. All animals were kept for one week before starting the experiments for adaptation.

The rats were arbitrarily divided into equal six groups: negative control groups take either distilled water (DW; 0.2 mL/kg BW) or olive oil (0.2 mL/kg BW.) as a vehicle. The positive control group received LFX (10 mg/kg b.wt.), while the treated groups received LFX + Vit. E (100 mg/kg BW), LFX + curcumin (200 mg/kg BW.) or LFX + ginger (200 mg/kg BW).

All administrations were supplemented orally by gavage once a day for 5 successive days. This study's methodology complied with the ethical criteria for the Care and Use of Laboratory Animals in Scientific Investigations established by the Animal Welfare and Research Ethics Committee of the Faculty of Veterinary Medicine at Zagazig University in Egypt.

Sampling

At zero day, 7th and 14th day post-treatments, blood samples (n = 4/ group) were collected from median canthus of overnight fasted rats and were put in test tubes (sterile, labeled and without anticoagulant). Sera were separated out by centrifugation to be used for biochemical analysis.

Tissue specimens: Pieces of hepatic and renal tissues (n = 4/ group) were removed, then weighed (0.5 g), washed out with ice-cold saline to remove the blood and homogenized in cold 50 mM phosphate buffer. Tissue homogenate was centrifuged to remove the debris. Finally, the pellets were discarded and the supernatants were collected to determine the antioxidants status and lipid peroxidation level.

Biochemical and antioxidant studies

Serum was used to determine alanine aminotransferase (ALT) and aspartate aminotransferase (AST) , ALP , total proteins , albumin , urea , creatinine , cholesterol , triglycerides , high density lipoprotein-cholesterol (HDL- C) , and low density lipoprotein- cholesterol (LDL- C) [23-32] concentrations according to the instructions of the diagnostic kits purchased from Biodiagnostic Co., Cairo, Egypt. Serum level of globulins was estimated by deducting the value of albumin from total proteins, while albumin/ globulins ratio (A/G) was determined by dividing the values of albumin on those of globulins [33]. Furthermore, hepatic and renal superoxide dismutase (SOD) [34], glutathione peroxidase (GPx) [35], and malondialdehyde (MDA) [36] levels were detected in the tissue samples.

Statistical analysis

The SPSS software was used to analyze the data in this study. At $P < 0.05$, one way ANOVA is significant [37]. The differences among the groups were intended by Tukey's Post-hoc Test and the maximum value was characterized by the letter (a).

Results and discussion

As shown in Table 1, the serum ALT, AST and ALP activities were significantly increased in LFX- treated male rats (group 3) at all experimental periods compared to the control group. The increase in liver enzyme activities indicates liver damage in the LFX-

treated rats, as fluoroquinolones are known to display hepatotoxic effect [3]. The key indicators used to diagnose liver damage are intracellular enzymes (ALT, AST). Because of the loss of structural integrity and impaired liver function, serum levels of these enzymes could be altered following a liver injury [38]. In mammalian cells, ALP is a crucial enzyme. ALP is a good biochemical indicator of bile flow into the small intestine and liver dysfunction [39]. Although the exact mechanism of fluoroquinolone-induced liver damage is uncertain, several reports suggest that it is caused by an immunoallergic reaction [40]. Due to the oxidative stress and depletion of hepatic antioxidant reserves, LFX induced liver damage [3].A similar increase in liver enzymes induced by LFX has been reported in humans [41, 42], rats [3, 43- 45], mice [1], and or in white leg horn layer birds [46]**.** However, vitamin E, curcumin or ginger therapy significantly reduced liver enzyme activities as compared with LFX group, accordingly providing proof that these medicaments can guard against LFX -induced liver damage. We found that rats treated with LFX and vitamin E showed better improvement and better recovery in liver damage induced-marker changes than rats exposed to LFX and curcumin or ginger. Curcumin possesses free radical scavenging activity that protects against peroxidative damage and also the hydrogen donor capacity, which is accompanied with phenolic and methoxy groups. These properties interestingly increase the efficiency of curcumin in pretreatment against toxic compounds [11].Gingerols, the major components of ginger, have anti-inflammatory and hepatoprotective properties against several toxic compounds [11, 13,16]. There are about eight naturally occurring tocopherols with vitamin E activity, among these, α- tocopherol is considered to be the most important α-tocopherol that possesses hepatoprotective property against various toxicity in male and female rats [14, 17, 18]. The components of vitamin E, curcumin or ginger may stabilize hepatocytes plasma membrane or preserve the structural integrity of hepatocellular membrane and prevent transmission of enzymes to the extracellular fluid as reported by the previous reports [1, 46]. Similar results were previously obtained and confirmed our findings [47-50].

Regarding proteinogram (Table 2), serum total proteins, albumin and A/G ratio levels displayed a statistical *(P* <0.01) diminution (5.77±0.03, 5.97±0.09, 5.87±0.09; 3.45±0.03, 3.60±0.06, 3.57±0.09; 1.49±0.02, 1.51±0.05, 1.55±0.09) in LFX-exposed rats, meanwhile serum globulin was significantly increased (2.32±0.01, 2.37±0.07, 2.30±0.12) compared with the control group (7.60±0.21, 7.87±0.09, 7.49±0.09 for total proteins; 5.80±0.06, 5.93±0.03, 5.60±0.06 for albumin; 1.80±0.20, 1.93±0.09, 1.89±0.09 for globulin; 3.28±0.22, 3.07±0.09, 2.96±0.10 for A/G) at zero, 7th and 14th day post- treatments, respectively.

Table (1): Effect of oral administration of vitamin E, curcumin or ginger on serum liver enzymes of levofloxacin treated male rats for five successive days (Mean ± SE) (n=4).

Groups	**Days post-treatment**	**Liver enzymes**		
		ALT (U/L)	**AST (U/L)**	**ALP (U/l)**
Group 1 (Control)	Zero day	13.00±2.11^{d}	14.33±6.64^{d}	72.67±6.74^{d}
	7th day	12.00±1.15^{d}	13.00±1.15^{d}	71.67±3.84^{d}
	14th day	13.00±1.15^{d}	14.33±1.45^{d}	72.00±6.43^{d}
Group 2 (Olive oil)	Zero day	13.00±4.04^{d}	14.33±3.53^{d}	71.33±9.8^{d}
	7th day	12.67±0.88^{d}	15.33±2.60^{d}	72.33±9.45^{d}

	14th day	13.00±1.73 d	15.33±3.93 d	71.00±9.84 d
Group 3 (Levofloxacin)	Zero day	76.67±0.88a	59.00±3.50 a	147.00±13.31 a
	7th day	71.58±1.45 a	66.33±2.33 a	151.33±15.03 a
	14th day	70.93±6.36 a	55.33±2.33 a	153.67±12.19 a
Group 4 (Vit. E + levofloxacin)	Zero day	45.33±4.26 c	34.33±13.96 c	95.00±8.59 c
	7th day	42.67±1.45c	32.97±2.03 c	94.00±8.55 c
	14th day	40.67±2.40 c	34.00±10.82 c	95.33±6.51 c
Group 5 (Curcumin+ levofloxacin)	Zero day	57.67±8.19 b	37.67±23.14 b	112.67±11.64 b
	7th day	58.67±2.33 b	39.33±3.18 b	115.33±9.13 b
	14thday	59.00±2.08 b	37.95±2.40 b	111.00±9.16 b
Group 6 (Ginger+ levofloxacin)	Zero day	54.33±5.21b	35.67±16.19bc	115.00±14.55 b
	7th day	56.00±1.15 b	36.40±5.57bc	114.33±18.61 b
	14th day	55.33±2.73 b	36.00±2.31bc	116.67±16.90 b

Means within the same column having different alphabetical superscript letters are significantly different at P <0.05. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase.

Table (2): Effect of oral administration of vitamin E, curcumin or ginger on proteinogram of levofloxacin treated male rats for five successive days (Mean ± SE) (n=4).

Groups	**Days post-treatment**	**Proteinogram**			
		Total protein (g/dL)	**Albumin (g/dL)**	**Globulin (g/dL)**	**A/G**
	Zero day	7.60±0.21 a	5.80±0.06 a	1.80±0.20 b	3.28±0.22 a
Gp. 1 (Control)	7th day	7.87±0.09 a	5.93±0.03 a	1.93±0.09 b	3.07±0.09 a
	14th day	7.49±0.09 a	5.60±0.06 a	1.89±0.09 b	2.96±0.10 a
	Zero day	7.20±0.32 a	5.50±0.31a	1.70±0.15 b	3.23±0.30 a
Gp. 2 (Olive oil)	7th day	7.40±0.06 a	5.50±0.15 a	1.90±0.21b	2.89±0.27a
	14th day	7.03±0.09 a	5.10±0.06 a	1.93±0.03 b	2.64±0.02 a
	Zero day	5.77±0.03 c	3.45±0.03 c	2.32±0.01 a	1.49±0.02 b
Gp. 3 (Levofloxacin)	7th day	5.97±0.09 c	3.60±0.06 c	2.37±0.07 a	1.51±0.05 b
	14th day	5.87±0.09 c	3.57±0.09 c	2.30±0.12 a	1.55±0.09 b
	Zero day	6.75±0.23ab	4.32±0.03ab	2.43±0.20 a	1.77±0.28 c
Gp. 4 (Vit. E+ levofloxacin)	7th day	6.80±0.06ab	4.35±0.06ab	2.45±0.06 a	1.78±0.08 c
	14th day	6.87±0.09ab	4.47±0.03ab	2.40±0.12 a	1.86±0.10 c
	Zero day	6.63±0.27ab	4.03±0.13 b	2.60±0.21 a	1.55±0.24 c
Gp. 5 (Curcumin+ levofloxacin)	7th day	6.83±0.15ab	4.00±0.06 b	2.83±0.19 a	1.43±0.10 b
	14thday	6.87±0.09ab	4.27±0.03ab	2.60±0.10 a	1.65±0.07 c
	Zero day	6.87±0.15ab	4.40±0.15ab	2.47±0.18 a	1.78±0.30 c
Gp. 6 (Ginger+ levofloxacin)	7th day	6.67±0.07ab	4.34±0.06ab	2.33±0.03 a	1.86±0.22 c
	14th day	6.47±0.12b	4.23±0.09ab	2.24±0.03 a	1.88±0.02 c

Means within the same column having different alphabetical superscript letters are significantly different at P < 0.05.

A/G: albumin/globulin ratio

The levels of total proteins and albumins are imperative indicators of damaged hepatocyte or their normal functions [51]. The hypoproteinemia and hypoalbuminemia evident in the present study may be attributed to liver damage and nephrotoxic effect induced by LFX resulting in severe reduction in protein synthesis by liver and also increases protein loss in urine by the kidney [52]. Our results were in agreement with other investigations [53]**.**The obtained hyperglobulinemia is associated with liver damage induced by fluoroquinolones [54] or may be secondary to hypoalbuminemia or as autoantibodies against diseased liver cells [33].

Co-supplementation of vitamin E, curcumin or ginger with LFX ameliorates the abovementioned aberrations caused by LFX toxicity; this supports the hepatorenal protective, antioxidant, and anti-inflammatory properties of vitamin E, curcumin or ginger on the liver and kidney parameters [48, 55-58].

As presented in Table 3, serum urea and creatinine used as biomarkers for kidney function evaluation were expressively (P < 0.001) augmented (76.43±3.70, 72.67±0.47, 75.00±6.42; 2.48±0.01, 2.48±0.01, 2.50±0.01) at zero, 7^{th} and 14^{th} day, respectively post- treatment with LFX indicating their toxic effect on the kidneys. Our data are consistent with previous studies after administration of LFX, ciprofloxacin, norfloxacin and other fluoroquinolones [52-55]. However, administration of LFX in combination with vitamin E, curcumin or ginger's has significantly (P < 0.01) reduced the urea (38.90±5.27, 46.03±4.13, 58.00±1.07; 50.27±2.84, 53.40±0.81, 55.53±6.14; 53.73±11.02, 46.33±0.74, 49.63±0.71) and creatinine (0.95±0.01, 0.93±0.01, 0.94±0.02; 0.80±0.02, 0.91±0.01, 0.93±0.01; 0.92±0.03, 0.90±0.01, 0.90±0.01) levels at zero, 7^{th} and 14^{th} day, respectively post- treatments in comparison with the rats' administered LFX alone (76.43±3.70, 72.67±0.47, 75.00±6.42; 2.48±0.01, 2.48±0.01, 2.50±0.01). Our findings were in harmony with earlier reports [56- 61]. These results contribute antioxidant activity of vitamin E, curcumin or ginger, which inhibits the generation of free radicals in the body, neutralizes and scavenges them, and chelates prooxidant transition metals such as iron [14, 20, 45, 62, 63]. Similarly, El-Batsh *et al.* [64] reported that the Reno-protective effect of curcumin may be owing to their antioxidant properties as they significantly decreased serum level of malondialdehyde (MDA) and significantly increased renal tissue level of gluthathione (GSH) in treated rats compared with adenine group. Furthermore, ginger may protect against cisplatin-induced hepato-renal damage, since there was a substantial improvement in liver and kidney functions with lower ALT, AST, ALP, urea, and creatinine levels when compared to the cisplatin group [65]. Administration of *Z. officinale* (250 and 500 mg/kg, per Os) with or without vitamin E ameliorated nephrotoxicity produced by cisplatin in mice [59].

Lipid profile showed the highest significant (P < 0.01) increase in serum total cholesterol (166.67±6.81, 174.00±4.04, 176.00±2.88), triglycerides (269.67±5.84, 289.33±4.91, 249.67±1.86) and LDL-C (243.00±7.09, 213.67±5.03, 226.33±5.45) levels, whereas serum HDL revealed a significant (P< 0.01) decrease (20.00±1.11, 23.33±3.38, 20.10±1.53) in rats orally treated with LFX for five successive days matched with the control group (97.33±8.88, 86.67±3.28, 90.33±5.76 for total cholesterol ; 172.00±5.56, 171.00±4.53, 172.67±2.03 for triglycerides; 38.67±2.78, 34.00±2.08, 33.00±1.15 for LDL- C, 63.02±3.20, 60.00±1.15, 61.33±1.45 for HDL- C) at all experimental periods (Table 4). These findings indicate that LFX exposure is associated with perturbations in lipid homeostasis in organs, lipoproteins, plasma and erythrocytes [65] or disorders in the metabolism of lipid and lipoproteins [38]. Our results were in synchronization with

those previously obtained reports [3, 20]. Co-supplementation of vitamin E, curcumin or ginger with LFX significantly improved serum lipid profile, as revealed by marked decrease in cholesterol (97.33±3.93, 86.67±2.60, 81.67±3.93 for Vit. E+LFX; 102.67±2.03, 91.33±6.49, 82.00±3.61 for curcumin+ LFX; 102.00±7.64, 99.00±2.31, 85.67±1.76 for ginger + LFX) triglycerides (198.67±7.45, 185.00±2.65, 161.67±1.20; 198.67±7.86, 191.00±8.08, 182.33±7.87; 174.00±5.36, 169.00±1.53, 188.00±2.65) and LDL-C levels (137.67±1.33, 120.67±1.88, 126.33±2.19; 142.00±1.15, 121.67±2.85, 125.00±2.00; 145.67±2.32, 123.67±1.88, 119.67±1.79) and upsurge in HDL-C (50.67±3.71, 49.67±1.76, 53.33±1.76; 51.67±1.67, 50.00±4.73, 47.00±1.15; 52.00±5.77, 49.83±0.88, 55.33±2.40) level at zero, 7th and 14th day, respectively post-treatments matched with LFX-treated group, these caring properties may be attributed to the antioxidant effects as evident by attenuating lipid peroxidation marker, MDA levels, and increasing renal SOD activity [66, 67]. These results are nearly similar to earlier studies [47, 68- 71]. Vitamin E can help to prevent cholesterol-related endothelial damage, as well as functional impairment caused by ROS [72]. Curcumin's hypocholesterolemic influence can be linked to its stimulatory effect on the hepatic cholesterol-7-hydroxylase enzyme, which regulates cholesterol catabolism, or decrease cholesterol absorption [73]. Ginger's hypolipidemic effect was caused by a diminution in cholesterol synthesis and superior hepatic uptake of circulating LDL-C, or by increased LDL-C receptor activation, resulting in better LDL-C elimination and lower cholesterol levels [74]. Moreover, the hypocholesterolemic effect of ginger because it stimulates hepatic enzyme cholesterol-7-alpha hydroxylase activity, which excites the transformation of cholesterol to bile acids, an important pathway for cholesterol removal from the body [75]. On contrary, other studies indicated that the supplementation with ginger significantly increased HDL-C levels and found no detrimental effect of triglycerides, cholesterol and LDL- C in overweight and obese humans [76].

Table (4): Effect of oral administration of vitamin E, curcumin or ginger on lipogram of levofloxacin treated male rats for five successive days (Mean ± SE) (n=4).

Groups	Days post-treatment	Lipogram			
		Total cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)
Gp. 1 (Control)	Zero day	97.33±8.88 ^{b}	172.00±5.56 ^{c}	63.02±3.20 ^{a}	38.67±2.78 ^{d}
	7th day	86.67±3.28 ^{b}	171.00±4.53 ^{c}	60.00±1.15 ^{a}	34.00±2.08 ^{d}
	14th day	90.33±5.76 ^{b}	172.67±2.03 ^{c}	61.33±1.45 ^{a}	33.00±1.15 ^{d}
Gp. 2 (Olive oil)	Zero day	92.00±7.90 ^{b}	168.00±5.51 ^{c}	62.33±2.98 ^{a}	38.67±2.89 ^{d}
	7th day	89.67±4.76 ^{b}	167.67±6.29 ^{c}	62.67±1.20 ^{a}	34.00±1.15 ^{d}
	14th day	89.00±4.04 ^{b}	169.67±2.40 ^{c}	62.67±3.28 ^{a}	36.67±1.86 ^{d}
Gp. 3 (Levofloxacin)	Zero day	166.67±6.81 ^{a}	269.67±5.84 ^{a}	20.00±1.11 ^{c}	243.00±7.09 ^{a}
	7th day	174.00±4.04 ^{a}	289.33±4.91 ^{a}	23.33±3.38 ^{c}	213.67±5.03 ^{a}
	14th day	176.00±2.88 ^{a}	249.67±1.86 ^{a}	20.10±1.53 ^{c}	226.33±5.45 ^{a}
Gp. 4 (Vit. E + levofloxacin)	Zero day	97.33±3.93 ^{b}	198.67±7.45 ^{b}	50.67±3.71 ^{b}	137.67±1.33 ^{b}
	7th day	86.67±2.60 ^{b}	185.00±2.65 ^{b}	49.67±1.76 ^{b}	120.67±1.88 ^{c}

	14th day	81.67±3.93 c	161.67±1.20 c	53.33±1.76 b	126.33±2.19bc
	Zero day	102.67±2.03 b	198.67±7.86 b	51.67±1.67 b	142.00±1.15bc
Gp. 5 (Curcumin+ levofloxacin)	7th day	91.33±6.49 b	191.00±8.08 b	50.00±4.73 b	121.67±2.85 c
	14thday	82.00±3.61c	182.33±7.87 b	47.00±1.15 b	125.00±2.00bc
	Zero day	102.00±7.64 b	174.00±5.36 c	52.00±5.77 b	145.67±2.32 b
Gp. 6 (Ginger+ levofloxacin)	7th day	99.00±2.31 b	169.00±1.53 c	49.83±0.88 b	123.67±1.88 c
	14th day	85.67±1.76bc	188.00±2.65 bc	55.33±2.40ab	119.67±1.79 c

Means within the same column having different alphabetical superscript letters are significantly different at $P < 0.05$.

HDL-C: high density lipoprotein- cholesterol; LDL-C: low density lipoprotein-cholesterol.

Table (5): Effect of oral administration of vitamin E, curcumin or ginger on the hepatic antioxidants/ oxidant status of levofloxacin treated male rats for five successive days (Mean ± SE) (n=4).

Groups	**Days post-treatment**	**Hepatic antioxidants/ oxidant status**		
		SOD (U/mg)	**GPx (U/mg)**	**MDA (UmoL/gm)**
	Zero day	3.00±0.11 a	19.76±0.03 a	11.82±0.01 e
Gp. 1 (Control)	7th day	3.33±3.13 a	19.18±0.05 a	11.82±0.001 e
	14th day	3.33±0.16 a	18.42±0.13 a	11.11±0.03 e
	Zero day	3.00±0.13 a	19.69±0.01 a	11.21±0.04 e
Gp. 2 (Olive oil)	7th day	3.67±0.13 a	18.85±0.02 a	11.92±0.03 e
	14th day	3.33±0.15 a	18.88±0.01 a	12.12±0.04 e
	Zero day	1.50±0.13 c	2.02±0.38 d	74.51±0.69 a
Gp. 3 (Levofloxacin)	7th day	1.67±0.18 c	2.81±0.25 d	80.97±0.41 a
	14th day	1.60±0.15 c	3.30±0.37 d	95.88±0.52 a
	Zero day	2.55±0.08ab	16.61±0.99 b	25.84±0.26 c
Gp. 4 (Vit. E + levofloxacin)	7th day	2.53±0.04ab	19.52±0.60 a	21.62±0.27 d
	14th day	2.67±0.01ab	18.02±0.82 a	29.40±1.05bc
	Zero day	2.67±0.03ab	17.21±0.59 b	20.83±0.06 d
Gp. 5 (Curcumin+ levofloxacin)	7th day	2.00±0.04 bc	14.01±0.39 c	27.8±0.26 c
	14th day	2.84±0.09ab	17.40±0.44 b	30.78±0.06bc
	Zero day	2.00±0.01bc	15.02±0.87 c	26.75±1.03 c
Gp. 6 (Ginger+ levofloxacin)	7th day	2.67±0.03ab	17.56±0.40 b	34.78±0.33 b
	14th day	2.77±0.01ab	15.83±0.42bc	32.06±0.25 b

Means within the same column having different alphabetical superscript letters are significantly different at $P<0.05$.

SOD: superoxide dismutase; GPx: glutathione peroxidase, MDA: malondialdehyde.

As demonstrated in Tables 5 and 6, the aptitude of LFX to generate oxidative stress has been demonstrated by a significant decline in SOD and GPx activities in liver

(1.50±0.13, 1.67±0.18, 1.60±0.15; 2.02±0.38, 2.81±0.25, 3.30±0.37) and kidney (24.97±1.04, 21.33±1.33, 26.33±1.71; 3.15±0.14, 2.13±0.36, 2.44±0.28) tissues of rats compared to the control values in the liver (3.00±0.11, 3.33±3.13, 3.33±0.16 for SOD; 19.76±0.03, 19.18±0.05, 18.42±0.13 for GPx) and kidney (71.33 ± 2.60, 67.67±0.88, 66.00±1.73 for SOD; 8.32±0.08, 8.30±0.04, 7.81±0.06 for GPx) at the end of zero, 7th and 14thday, respectively post-treatments. However, the MDA concentrations were significantly increased in the liver (74.51±0.69, 80.97±0.41, 95.88±0.52) and kidney (66.58±0.14, 65.09±0.12, 65.23±0.14) tissues compared to control levels compared to control values of MDA concentrations in the liver (11.82±0.01, 11.82±0.001, 11.11±0.03) and kidney (30.88±0.03, 33.20±0.03, 32.83±0.04) at the end of zero, 7th and 14thday, respectively post- treatments. Levofloxacin has been publicized to produce ROS in phagocytic cells [60]. Increased ROS production causes a depletion of one or more antioxidants, which can be used as an indicator of oxidative stress [77].

Table (6): Effect of oral administration of vitamin E, curcumin or ginger on the renal antioxidants/ oxidant status of levofloxacin (10 mg/kg b.wt.) treated male rats for five successive days (Mean ± SE) (n=4).

Groups	**Days post-treatment**	**Renal antioxidants/ oxidant status**		
		SOD (U/mg)	**GPx (U/mg)**	**MDA (UmoL/gm)**
Gp. 1 (Control)	Zero day	71.33 ± 2.60 ^{a}	8.32±0.08 ^{a}	30.88±0.03 ^{b}
	7th day	67.67±0.88 ^{a}	8.30±0.04 ^{a}	33.20±0.03 ^{b}
	14th day	66.00±1.73 ^{a}	7.81±0.06 ^{a}	32.83±0.04 ^{b}
Gp. 2 (Olive oil)	Zero day	68.67±0.57 ^{a}	7.35±0.33 ^{a}	31.92±0.14 ^{b}
	7th day	72.33±0.88 ^{a}	8.72±0.12 ^{a}	31.43±0.03 ^{b}
	14th day	71.67±2.03 ^{a}	7.77±0.06 ^{a}	31.17±0.16 ^{b}
Gp. 3 (Levofloxacin)	Zero day	24.97±1.04 ^{d}	3.15±0.14 ^{c}	66.58±0.14 ^{a}
	7th day	21.33±1.33 ^{d}	2.13±0.36 ^{c}	65.09±0.12 ^{a}
	14th day	26.33±1.71 ^{d}	2.44±0.28 ^{c}	65.23±0.14 ^{a}
Gp. 4 (Vit. E + levofloxacin)	Zero day	65.33±1.61^{ab}	9.05±0.43 ^{a}	32.65±0.15 ^{b}
	7th day	65.33±1.33^{ab}	8.69±1.31 ^{a}	32.83±0.08 ^{b}
	14th day	58.00±1.53 ^{b}	9.19±0.05^{a}	33.24±0.16 ^{b}
Gp. 5 (Curcumin+ levofloxacin)	Zero day	60.67±1.55 ^{b}	7.79±0.76^{ab}	31.01±0.19 ^{b}
	7th day	52.67±0.17 ^{b}	7.25±0.46 ^{b}	32.52±0.20 ^{b}
	14th day	48.00±0.53 ^{c}	8.79±0.28 ^{a}	31.36±0.25 ^{b}
Gp. 6 (Ginger+ levofloxacin)	Zero day	44.33±0.53 ^{c}	8.37±0.54 ^{a}	33.49±0.13 ^{b}
	7th day	44.67±0.67 ^{c}	9.18±0.33 ^{a}	31.89±0.18 ^{b}
	14th day	59.00±0.69 ^{b}	9.20±1.04 ^{a}	33.37±0.17 ^{b}

Means within the same column having different alphabetical superscript letters are significantly different at $P<0.05$.

SOD: superoxide dismutase; GPx: glutathione peroxidase, MDA: malondialdehyde.

This findings are consistent with earlier reports proving the same results in brain of male rats received ciprofloxacin or

levofloxacin [78], in liver homogenate of rats received ciprofloxacin and levofloxacin [22, 79], in the liver of male Wistar rats received levofloxacin at different doses (5, 10 and 20mg/kg/ BW) for 7days [3], and in kidney tissues of male Wistar rats ordered ciprofloxacin (100 mg/kg/day, intraperitoneally) for eight consecutive days [57]. Also, administration of LFX (40 mg/kg BW.) daily for two weeks showed a reduction in catalase, SOD and GSH as well as rise in MDA levels in liver tissue of rats [44]. Concurrent oral supplementation of vitamin E, curcumin and ginger with LFX repaired the oxidant/antioxidant balance as reflected by significant increase of SOD in liver (2.55±0.08, 2.53±0.04, 2.67±0.01 for Vit. E+LFX; 2.67±0.03, 2.00±0.04, 2.84±0.09 for curcumin+ LFX; 2.00±0.01, 2.67±0.03, 2.77±0.01 for ginger+ LFX) and kidney (65.33±1.61, 65.33±1.33, 58.00±1.53; 60.67±1.55, 52.67±0.17, 48.00±0.53; 44.33±0.53, 44.67±0.67, 59.00±0.69), GPx in liver (2.02±0.38, 2.81±0.25, 3.30±0.37; 16.61±0.99, 19.52±0.60, 18.02±0.82; 17.21±0.59, 14.01±0.39, 17.40±0.44; 15.02±0.87, 17.56±0.40, 15.83±0.42) and kidney (9.05±0.43, 8.69±1.31, 9.19±0.05; 7.79±0.76, 7.25±0.46, 8.79±0.28; 8.37±0.54, 9.18±0.33, 9.20±1.04) enzymes and reduction of lipid peroxidation (32.65±0.15, 32.83±0.08, 33.24±0.16; 31.01±0.19, 32.52±0.20, 31.36±0.25; 33.49±0.13, 31.89±0.18, 33.37±0.17) in the liver and kidney comparatively with LFX - cured rats alone. Such result values were returned in close to normal values of control especially SOD enzyme. The positive effects of vitamin E, or plants are linked to its antioxidant qualities, which play a vital role in hepato-renal protective mechanisms by removing free radicals and enhancing the activity of the natural antioxidant defense system **[**19, 49, 59]. Our results and interpretations are in agreement with aforementioned reports [14, 46, 50,]. In addition, Hashem et al. [80] revealed good amelioration in the hepatic MDA and catalase levels after treatment of paracetamol- induced hepatic damage in rats with *Zingiber Officinale* and *Moringa oleifera* extracts. Damiano *et al.* [81] showed that the treatment with curcumin, used alone or in association with ochratoxin A, revealed a significant reversion of the activities of CAT, SOD, and GPx and MDA levels, inhibiting effects of oxidative stress induced by ochratoxin A in rats.

Conclusion

This study prominently exhibited that curcumin and ginger display significant protective effects in the liver and kidney injury induced by levofloxacin, in comparison with vitamin E as a standard antioxidant. This protective effect is concomitant with a significant reduction of elevated liver enzymes, renal damage biomarkers, lipogram and MDA level, associated with improvements in the proteinogram and antioxidants levels in the experimental rats. In addition, the findings proved that vitamin E had a better hepatoprotective impact than curcumin or ginger in levofloxacin-induced liver damage, despite that both vitamin E and herbs (curcumin and ginger) had nearly similar alleviative effects on other biochemical investigations.

Conflict of interest

The authors have no conflict of interest to declare.

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الملخص العربى

تأثيرالكركمين والزنجبيل على الأثارالضارة لليفوفلوكساسين في ذكورالجرذان

حسني عبدالفضيل ابراهيم[1] ،شيماء أحمد ابراهيم عبدالله[2]،اسراء مغاورى عبدالله الجزار[3]
3,1 قسم الفارماكولوجيا البيطرية- كلية الطب البيطري- جامعة الزقازيق-
2 قسم الفسيولوجيا - كلية الطب البيطري- جامعة الزقازيق

الهدف من هذه الدراسة هو تقييم ومقارنة التأثيرات الوقائية لفيتامين E والكركمين والزنجبيل ضد الآثار الضارة لليفوفلوكساسين في ذكور الجرذان. تم تقسيم عدد تسعين من ذكورالجرذان إلى ست مجموعات (15 جرذا لكل مجموعة). تلقت المجموعتان 1 و 2 الماء المقطر أو زيت الزيتون لاستخدامهما كمجموعات ضابطة، بينما تلقت المجموعات 3 - 6 الليفوفلوكساسين بجرعة 10 مجم / كجم من وزن الجسم فقط أو بالاشتراك مع فيتامين هـ (100 مجم / كجم من وزن الجسم) ، الكركمين (200 مجم / كجم من وزن الجسم) أو الزنجبيل (200 مجم / كجم من وزن الجسم) على التوالي. تم إعطاء جميع الأدوية عن طريق الفم مرة واحدة في اليوم لمدة 5 أيام متتالية وفي اليوم صفر واليوم السابع والرابع عشر بعد العلاج ، تم جمع عينات الدم للتحليل الكيميائي الحيوي ، بينما تم تشريح أنسجة الكبد والكلى وإخضاعها لتقدير مضادات الأكسدة.
تسبب تناول اليفوفلوكساسين في تلف الكبد والكلى ، كما يتضح من الزيادة الكبيرة في إنزيمات الكبد في الدم ، واليوريا (76.43±3.70, 72.67±0.47, 75.00±6.42) ، والكرياتينين (2.48±0.01, 2.48±0.01, 2.50±0.01)، والكوليسترول الكلي (166.67±6.81, 174.00±4.04, 176.00±2.88) ، والدهون الثلاثية (269.67±5.84, 289.33±4.91, 249.67±1.86) ، ومستويات LDL(243.00±7.09, 213.67±5.03, 226.33±5.45) ، مع انخفاض كبير في مستويات HDL (5.77±0.03, 20.00±1.11, 23.33±3.38, 20.10±1.53) في الدم ، والبروتين الكلي (5.87±0.09, 5.97±0.09، والألبومين (3.45±0.03, 3.60±0.06, 3.57±0.09) ، ونسبة الألبومين / الجلوبيولين (A / G) (1.49±0.02, 1.51±0.05, 1.55±0.09) مقارنة بالمجموعات الضابطة في اليوم صفر والسابع والرابع عشر من العلاجات. علاوة على ذلك فقد لوحظ انخفاض فى نشاط كل من انزيم السوبراكسيد ديسميوتيز (SOD) والجلوتاثيون بيروكسيديز (GPx) في أنسجة الكبد(1.50±0.13, 1.67±0.18, 1.60±0.15; 2.02±0.38, 2.81±0.25, 3.30±0.37) والكلى (24.97±1.04, 21.33±1.33, 26.33±1.71; 3.15±0.14, 2.13±0.36, 2.44±0.28)بشكل كبير في جميع الجرذان المعرضة لليفوفلوكساسين مقارنةً للمجموعات الضابطة فى الكبد (3.00±0.11, 3.33±3.13, 3.33±0.16 for SOD; 19.76±0.03, 19.18±0.05, 18.42±0.13for GPx) والكلى (71.33 ± 2.60, 67.67±0.88, 66.00±1.73 for SOD; 8.32±0.08, 8.30±0.04, 7.81±0.06 for GPx). ومع ذلك ، تم زيادة تركيز المالونديهيد (MDA)فى أنسجة الكبد والكلى بشكل كبير.
التناول المشترك لـليفوفلوكساسين مع فيتامين هـ أو الكركمين أو الزنجبيل يقلل من مستوى إنزيمات الكبد المرتفعة ، المؤشرات الحيوية الكلوية الضار بالدم، مع زيادة مضادات الأكسدة في الأنسجة.

وقد تبين من هذه الدراسة الأثار الضارة التي سببها الليفوفلوكساسين على كل من الكبد والكلى في الجرذان بمرور الوقت ، وأن الاستخدام المتزامن لكل من الكركمين أوالزنجبيل مع الليفوفلوكساسين أدى الى تحسن مؤشرات التلف الناتجة من استخدام الليفوفلوكساسين منفردا.