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# AMELIORATIVE EFFECT OF VITAMIN E AGAINST SOME ADVERSE EFFECTS OF LEVOFLOXACIN IN MALE RATS

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## ABSTRACT

The present study was designed to investigate the possible protective effect of vitamin E against some adverse effects of levofloxacin in male rats. This experiment was done on twenty five male rats, four months old apparently healthy weighing 200±10g, divided randomly into 5 equal groups (5 rats in each). 1st group rats received 0.2ml/kg b.wt. distalled water orally (control group), 2nd group rats received 0.2ml/kg b.wt. olive oil orally. 3rd group rats received vitamin E 100mg/kg b.wt. orally. 4th group rats received levofloxacin 10mg/kg b.wt. orally. 5th group rats received vitamin E 100mg/kg b.wt. orally and levofloxacin 10mg/kg b.wt. orally. Treatment duration was 14 successive days for all groups. Levofloxacin evoked a significant decrease in total erythrocytic count, hemoglobin content (Hb), packed cell volume percent (PCV), platelets count (PLT), total leukocytic count (TLC), differential leukocytic count (lymphocytes, neutrophils and monocytes), high density lipoprotein (HDL), superoxide dismutase (SOD) and catalase (CAT) levels beside an elevation in liver enzymes activities (AST, ALT, ALP), total cholesterol (TC) , triglycerides (TG), low density lipoprotein (LDL), very low density lipoprotein (VLDL), urea level, malondialdehyde (MDA), tumor necrosis factor-alpha (TNF-α) level coupled with non-significant effect on MCV, MCHC, serum total protein, albumin, globulin levels, A/G ratio and serum creatinine level. Concurrent administration of vitamin E with levofloxacin produced a significant increase in total erythrocytic count, (Hb), **(**PCV), (PLT), (TLC), differential leukocytic count (lymphocytes, neutrophils and monocytes), (HDL), (SOD) and (CAT) levels coupled with a significant decrease in liver enzymes activities (AST, ALT, ALP), (TC), (TG), (LDL), (VLDL), urea level, MDA, TNF-α level beside non-significant variations of MCV, MCHC, serum total protein, albumin, globulin levels, A/G ratio and serum creatinine level. In the light of the present investigation it could be concluded that administration of levofloxacin induced adverse effects in blood picture, liver enzymes, protein profile and oxidant/antioxidant status. Vitamin E induced ameliorations in some adverse effects of levofloxacin via its antioxidant effect.

***Key Words:*** Adverse effects, levofloxacin, rats, vitamin E.

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# INTRODUCTION

Levofloxacin is purely synthetic third-generation flouroquinolones antibiotic. It has a bactericidal activity against wide range of gram positive (G+ve) and gram negative (G-ve) bacteria (Al-Soufi and Al-Rekabi, 2019).

Nausea, diarrhea and vomiting were the most common side effects noted during therapy with levofloxacin (0.8% to 6.8%). Its central nervous system-related adverse drug reactions may range from mild (headache, dizziness, tiredness or sleepiness) to severe (psychotic reactions, hallucination, depression and seizures). Several in vitro and in vivo animal studies revealed that floroquinolones induced oxidative stress by producing reactive oxygen species (ROS) (Wolfson and Hooper 1991, Christ and Esch 1994). Antioxidants can inhibit or delay the oxidation of susceptible cells and prevent oxidative stress (Rice-Evan *et al.,* 1996).

Antioxidants are used as dietary supplements in maintaining health and preventing diseases such as cancer and coronary heart disease. A dietary antioxidant is a substance that significantly decrease the harmful effects of ROS and nitrogen molecules, which disrupt normal physiological functions at the cellular level in animals and humans. Superoxide dismutase (SOD) has a high catalytic effect, and it is present in high concentrations in all tissues protecting cells against oxygyn molecular O2 under normal condition (Morikawa *et al.,* 2000).

The present investigations were carried out to investigate the protective effect of vitamin E on the adverse effects of levofloxacin through studying hematological picture, liver functions, kidney functions, antioxidants/oxidant status and TNF-α.

# MATERIALS AND METHODS

## Materials

**a. Drugs :**

**1- Levofloxacin (Tavanic)** obtained from (Sanofi Avents Company) received in a dose of (10mg/kg b.wt.) once daily (Ebenzer *et al.*, 2015).

**2- Vitamin E (Vitamin E)** obtained from (Pharco Pharmaceuticals Company Egypt), each capsule contain 1000mg vitamin E. Capsules of vitamin E were cut open and emptied in clean container. Olive oil was added to prepare a suspension containing dose of the vitamin E in 0.1 ml/each rat (Zdunczyk *et al.*, 2002).

Vitamin E dose: 100 mg/kg b.wt. orally once daily as standard antioxidant calculated according to Ambali *et al.* (2011).

**b. Experimental animals :**

A total number of twenty five apparently healthy adult male albino rats (weighing 200±10g) were obtained from the Laboratory Animal House, Faculty of Veterinary Medicine, Zagazig University, Egypt. Rats were acclimatized for two weeks before starting of experiment. The animals were housed in metaly cages under optimal conditions. They were fed on standered diet and water *ad-libitum* during the investigation. The care and welfare of the Animal use Research Ethics Committee of Faculty of Veterinary Medicine, Zagazig University, Egypt.

## Methods

**a. Experimental design :**

Rats were randomly a located in to five equal groups (5 rat in each). The first two groups were kept as control groups, 1st group rats received distalled water and kept without any treatment. 2nd group rats received olive oil (0.2ml/kg b.wt. orally). 3rd group received vitamin E (100mg/kg b.wt. orally). 4th group rats received levofloxacin (10mg/kg b.wt. orally) dissolved in distalled water. 5th group rats received vitamin E (100mg/kg b. wt. orally) dissolved in olive oil and levofloxacin (10mg/kg b.wt. orally) dissolved in distalled water. Treatment duration was 14 successive days for all groups.

**b. Sampling :**

At the end of experiment, two blood samples from each rats were collected from orbital plexus by using heparinized microhematocrite tube under light ether anathesia.

The first blood sample was collected with anticoagulant as EDTA for hematological studies to determine erythrogram and leukogram.

The second blood sample was collected without anticoagulant to obtain clear serum for biochemical

analysis. Serum were analyzed for estimation of AST, ALT (Reitman and Frankel *et al.,* 1957) and ALP (Kind and King *et al.,* 1954), serum total protein (Doumas *et al.,* 1981), serum albumin (Bauer *et al.,* 1982). Serum globulin was determined by substraction albumin level from the level of total proteins according (Kapale *et al.,* 2008), serum cholesterol (White *et al.,* 1970), triglyceride (Wahlefeld and bergmeyer *et al.,* 1974), low density lipoprotein and high density lipoprotein (Burstein and Scholnick *et al.,* 1973), urea (Artiss *et al.,* 1981), creatinine levels (Nishikimi *et al.,* 1972), superoxide dismutase (Nishikimi *et al.,* 1972), catalase (Sinha *et al.,* 1972), malondialdehyde (Nielsen *et al.,* 1997), tumor necrosis factor-α (TNF-α) (Corti *et al.,* 1992).

**Statistical analysis:**

The obtained data were analyzed by using SPSS program version 16 according to Tambane and Dunlop *et al.* (2000).

# RESULTS

**1. Haematological results :**

**a. Erythrogram :**

The current study indicated that administration of levofloxacin significantly decreased Red blood cells (RBCs) count, Hemoglubin (Hb) conc., Packed cell volume (Pcv) % and Platelets (Plt) count when compared with control group. Oral administration of vitamin E 2 hours before levofloxacin produced a significant increase in RBCs count, Hb conc., Pcv % and Plt count when compared with levofloxacin group (Table 1).

**Table 1:** Effect of vitamin E (100 mg/kg b.wt. orally) on erythrogram of levofloxacin (10 mg/kg b.wt. orally) treated male rats for 14 successive days.

| Groups | Erythrogram | | | | | |
|---|---|---|---|---|---|---|
| | **RBCs ($X10^6$ /ul)** | **Hb (g/dl)** | **PCV (%)** | **MCV (fl)** | **MCHC (pg)** | **PLT ($X10^3$ /ul)** |
| **Control** | $8.07^a \pm 0.12$ | $18.10^a \pm 0.31$ | $56.66^a \pm 1.20$ | $70.23^a \pm 0.69$ | $23.41^a \pm 0.35$ | $336.00^d \pm 8.19$ |
| **Olive oil** | $8.00^a \pm 0.03$ | $15.56^a \pm 0.34$ | $54.66^a \pm 1.20$ | $68.32^a \pm 1.20$ | $28.47^a \pm 0.39$ | $331.00^d \pm 15.09$ |
| **Vitamin E** | $8.11^a \pm 0.06$ | $17.40^a \pm 0.27$ | $57.81^a \pm 1.26$ | $71.00^a \pm 0.87$ | $27.90^a \pm 0.35$ | $341.20^d \pm 14.50$ |
| **Levofloxacin** | $4.91^d \pm 0.05$ | $9.67^d \pm 0.36$ | $34.75^d \pm 1.11$ | $70.68^a \pm 1.56$ | $27.98^a \pm 0.57$ | $418.75^a \pm 10.63$ |
| **Vitamin E+ Levofloxacin** | $6.89^b \pm 0.04$ | $13.62^b \pm 0.17$ | $46.50^b \pm 1.65$ | $67.49^a \pm 1.15$ | $24.31^a \pm 0.59$ | $362.50^c \pm 10.91$ |

(Mean ± S.E) (n = 5)

Means within the same column carrying different superscript letters are significantly different at $P \leq 0.05$

**b. Leukogram :**

The present study revealed that levofloxacin elicited a significant increase in WBCs, lymphocytes, neutrophils and monocytes counts when compared with control group. Administration of vitamin E 2 hours before levofloxacin in male rats displayed a significant decrease in WBCs, lymphocytes, neutrophils and monocytes in comparison with levofloxacin group (Table 2).

**Table 2:** Effect of vitamin E (100 mg/kg b.wt. orally) on leukogram of levofloxacin (10 mg/kg b.wt. orally) treated male rats for 14 successive days.

| Groups | Leukogram | | | | |
|---|---|---|---|---|---|
| | **WBCs ($X10^3$ ul)** | **Lymphocytes ($X10^3$ /ul)** | **Neutrophils ( $X10^3$ /ul)** | **Eosinophils ( $X10^3$ /ul)** | **Monocytes ( $X10^3$ /ul)** |
| **Control** | $11.08^d \pm 0.24$ | $8.59^c \pm 0.24$ | $1.34^d \pm 0.05$ | $0.44^a \pm 0.018$ | $0.72^d \pm 0.02$ |
| **Olive oil** | $11.01^d \pm 0.03$ | $8.51^c \pm 0.49$ | $1.35^d \pm 0.03$ | $0.44^a \pm 0.03$ | $0.71^d \pm 0.03$ |
| **Vitamin E** | $11.50^d \pm 0.22$ | $8.67^c \pm 0.46$ | $1.38^d \pm 0.04$ | $0.45^a \pm 0.17$ | $0.75^d \pm 0.04$ |
| **Levofloxacin** | $18.49^a \pm 0.59$ | $11.89^a \pm 0.48$ | $4.44^a \pm 0.20$ | $0.42^a \pm 0.07$ | $1.75^a \pm 0.09$ |
| **Vitamin E+ Levofloxacin** | $13.33^c \pm 0.45$ | $4.47^b \pm 0.39$ | $2.51^c \pm 0.22$ | $0.44^a \pm 0.03$ | $0.92^c \pm 0.01$ |

(Mean ± S.E) (n = 5)

Means within the same column carrying different superscript letters are significantly different at $P \leq 0.05$

**2.Liver functions :**

**a. Liver enzymes :**

The present investigation indicated that administration of levofloxacin in male rats displayed a significant increase in ALT, AST and ALP activities when compared with control group while administration of vitamin E 2 hours before levofloxacin displayed a significant decrease in ALT, AST and ALP activities in comparison with levofloxacin group (Table 3).

**Table 3:** Effect of vitamin E (100 mg/kg b.wt. orally) on liver enzymes of activities of levofloxacin (10 mg/kg b.wt. orally) treated male rats.

| Groups | Liver enzymes | | |
|---|---|---|---|
| | ALT(U/L) | AST(U/L) | ALP(U/L) |
| **Control** | $13.67^{d} \pm 1.20$ | $14.67^{d} \pm 0.88$ | $72.10^{d} \pm 0.05$ |
| **Olive oil** | $13.00^{d} \pm 1.54$ | $14.00^{d} \pm 1.73$ | $71.87^{d} \pm 1.47$ |
| **Vitamin E** | $14.01^{d} \pm 1.45$ | $14.59^{d} \pm 1.55$ | $73.00^{d} \pm 1.08$ |
| **Levofloxacin** | $69.25^{a} \pm 2.14$ | $57.50^{a} \pm 1.55$ | $147.22^{a} \pm 2.25$ |
| **Vitamin E+ Levofloxacin** | $40.00^{c} \pm 1.29$ | $34.50^{c} \pm 2.63$ | $99.95^{c} \pm 1.8268$ |

(Mean ± S.E) (n = 5)

Means within the same column carrying different superscript letters are significantly different at $P \leq 0.05$

**b. Protein profile :**

Oral administration of levofloxacin in male rats produced a significant decrease in total protein, albumin, globulin and albumin/ globulin ratio. Oral administration of vitamin E 2 hours before levofloxacin elicited a significant increase in total protin and albumin levels in comparison with levofloxacin group (Table 4).

**Table 4:** Effect of vitamin E (100 mg/kg b.wt. orally) on protein profile of levofloxacin (10 mg/kg b.wt. orally) treated male rats for 14 successive days.

| Groups | Protein profile | | | |
|---|---|---|---|---|
| | Total Protein ( mg/dl ) | Albumin ( mg/dl ) | Globulin ( mg/dl ) | A/G ratio ( mg/dl ) |
| **Control** | $7.30^{a} \pm 0.11$ | $5.15^{a} \pm 0.06$ | $2.15^{a} \pm 0.09$ | $2.39^{ab} \pm 0.12$ |
| **Olive oil** | $7.18^{a} \pm 0.09$ | $5.19^{a} \pm 0.16$ | $1.99^{a} \pm 0.25$ | $2.72^{a} \pm 0.47$ |
| **Vitamin E** | $7.64^{a} \pm 0.12$ | $5.22^{a} \pm 0.14$ | $2.17^{a} \pm 0.17$ | $2.61^{a} \pm 0.29$ |
| **Levofloxacin** | $5.19^{d} \pm 0.09$ | $2.97^{d} \pm 0.11$ | $2.23^{a} \pm 0.11$ | $1.34^{c} \pm 0.11$ |
| **Vitamin E+ Levofloxacin** | $6.36^{b} \pm 0.07$ | $4.19^{b} \pm 0.05$ | $2.16^{a} \pm 0.09$ | $1.96^{bc} \pm 0.11$ |

(Mean ± S.E) (n = 5)

Means within the same column carrying different superscript letters are significantly different at $P \leq 0.05$

**c. Lipid profile :**

The current study revealed that oral administration of levofloxacin in male rats elicited a significant increase in total cholesterol, triglycerides, LDL and VLDL levels with a significant decrease in HDL levels when compared with control group. Oral administration of vitamin E 2 hours before levofloxacin evoked a significant decrease in total cholesterol, triglyceride, LDL and VLDL with a significant increase in HDL levels in comparison with levofloxacin group (Table 5).

**Table 5:** Effect of vitamin E (100 mg/kg b.wt. orally) on lipid profile of levofloxacin (10 mg/kg b.wt. orally) treated male rats for 14 successive days.

| Groups | Lipid profile | | | | |
|---|---|---|---|---|---|
| | Total cholesterol (mg/dl) | Triglycerides (mg/dl) | HDL (mg/dl) | LDL (mg/dl) | VLDL (mg/dl) |
| **Control** | $92.00^{d} \pm 1.53$ | $146.33^{d} \pm 4.05$ | $68.33^{a} \pm 4.91$ | $54.21^{d} \pm 4.81$ | $29.27^{d} \pm 0.82$ |
| **Olive oil** | $93.00^{d} \pm 2.08$ | $147.00^{d} \pm 2.65$ | $66.67^{a} \pm 3.76$ | $56.91^{d} \pm 5.37$ | $24.40^{d} \pm 0.53$ |
| **Vitamin E** | $92.50^{d} \pm 1.99$ | $151.00^{d} \pm 3.05$ | $67.61^{a} \pm 4.21$ | $57.80^{d} \pm 4.70$ | $28.60^{d} \pm 0.55$ |
| **Levofloxacin** | $193.75^{c} \pm 1.49$ | $259.25^{a} \pm 3.22$ | $23.500^{d} \pm 1.443$ | $239.90^{a} \pm 1.27$ | $51.85^{a} \pm 0.64$ |
| **Vitamin E+ Levofloxacin** | $139.25^{a} \pm 2.29$ | $199.50^{c} \pm 4.41$ | $45.500^{b} \pm 1.5545$ | $142.65^{c} \pm 2.75$ | $39.90^{c} \pm 0.88$ |

(Mean ± S.E) (n = 5)

Means within the same column carrying different superscript letters are significantly different at $P \leq 0.05$

**3. Kidney functions :**

Oral administration of levofloxacin in male rats produced a significant increase in urea and creatinine levels when compared with control group. The current study revealed that oral administration of vitamin E 2 hours before levofloxacin in male rats displayed a significant decrease in urea and creatinne levels when compared with levofloxacin group (Table 6).

**Table 6:** Effect of vitamin E (100 mg/kg b.wt. orally) on kidney functions of levofloxacin (10 mg/kg b.wt. orally) treated male rats for 14 successive days.

| Groups | Kidney functions | |
|---|---|---|
| | Urea (mg/l) | Creatinine (mg/l) |
| **Control** | $27.47^{d} \pm 0.99$ | $0.79^{d} \pm 0.03$ |
| **Olive oil** | $27.33^{d} \pm 0.49$ | $0.79^{d} \pm 0.02$ |
| **Vitamin E** | $28.21^{d} \pm 0.65$ | $0.79^{d} \pm 0.04$ |
| **Levofloxacin** | $72.75^{a} \pm 1.15$ | $2.03^{a} \pm 0.05$ |
| **Vitamin E+ Levofloxacin** | $39.85^{c} \pm 1.27$ | $1.01^{c} \pm 0.04$ |

(Mean ± S.E) (n = 5)

Means within the same column carrying different superscript letters are significantly different at $P \leq 0.05$

**4. Oxidant/Antioxidant status :**

The current investigation illusterated that oral administration of levofloxacin in male rats produced a significant increase in MDA conc. with a significant decrease in CAT and SOD activities when compared with control group. Oral administration of vitamin E 2 hours before levofloxacin displayed a significant decrease in MDA conc. With a significant increase in CAT and SOD activities in comparison with levofloxacin group (Table 7).

**Table 7:** Effect of vitamin E (100 mg/kg b.wt. orally) on oxidant/antioxidant status of levofloxacin (10 mg/kg b.wt. orally) treated male rats for 14 successive days.

| Groups | Oxidant/antioxidant status | | |
|---|---|---|---|
| | MDA (mol/ml) | CAT (u/l) | SOD (u/ml) |
| **Control** | $11.47^{d} \pm 0.49$ | $501.32^{a} \pm 9.43$ | $3.84^{a} \pm 0.08$ |
| **Olive oil** | $12.43^{d} \pm 0.33$ | $506.25^{a} \pm 7.29$ | $3.82^{a} \pm 0.08$ |
| **Vitamin E** | $12.78^{d} \pm 0.37$ | $508.30^{a} \pm 6.88$ | $3.76^{a} \pm 0.07$ |
| **Levofloxacin** | $73.75^{a} \pm 1.59$ | $311.09^{c} \pm 4.08$ | $1.01^{d} \pm 0.04$ |
| **Vitamin E+ Levofloxacin** | $35.93^{c} \pm 1.83$ | $410.75^{b} \pm 6.79$ | $1.48^{b} \pm 0.03$ |

(Mean ± S.E) (n = 5)

Means within the same column carrying different superscript letters are significantly different at $P \leq 0.05$

**5. Tumor necrosis factor-α :**

The present investigation indicated that levofloxacin produced a significant increase in TNF-α in comparison with control group. Oral administration of vitamin E 2 hours before levofloxacin elicited a significant decrease in TNF-α when compared with levofloxacin group (Table 8).

**Table 8:** Effect of vitamin E (100 mg/kg b.wt. orally) on TNF-α of levofloxacin (10 mg/kg b.wt. orally) treated male rats for 14 successive days.

| Groups | TNF-α ( pg/ml ) |
|---|---|
| **Control** | $19.23^{d} \pm 0.90$ |
| **Olive oil** | $20.03^{d} \pm 0.55$ |
| **Vitamin E** | $19.77^{d} \pm 0.88$ |
| **Levofloxacin** | $90.80^{b} \pm 1.45$ |
| **Vitamin E+ Levofloxacin** | $51.30^{c} \pm 1.01$ |

(Mean ± S.E) (n = 5)

Means within the same column carrying different superscript letters are significantly different at $P \leq 0.05$

## DISCUSSION

Levofloxacin is a third generation flouroquinolone antibiotic. It has a broad spectrum activity against (G+ve) and (G-ve) bacteria, as well as certain other pathogens such as Mycoplasma, Chlamydia, Legionella and Mycobacteria species. Levofloxacin is significantly more active against bacterial pathogens than R-(+)-ofloxacin (Talla and Veerareddy, 2011; Neda Riahifard *et al.,* 2017).

Antioxidants are used as dietary supplements in maintaining health and preventing diseases such as cancer and coronary heart disease. A dietary antioxidant is a substance that significantly decreases the harmful effects of ROS and nitrogen molecules, which disrupt normal physiological functions at the cellular level in animals and humans. SOD has a high catalytic effect, and it is present in high concentrations in all tissues protecting cells against O2 under normal condition (Morikawa *et al.,* 2000).

The present investigations were carried out to investigate the protective effect of vitamin E on some adverse effects of levofloxacin through studying hematological picture, liver functions, kidney functions, antioxidants/oxidant status and TNF-α.

The current study revealed that oral administration of levofloxacin for 14 successive days produced a significant decrease in RBCs count, Hb content and PCV% with a significant increase in PLT count in comparison with control group.

This finding could be attributed to suppressive effect of flouroqinolones on growth and differentiation of hematopoietic cells like erythroid precursors (Axel and Itamar, 2003). These obtained data are in agreement with Kim *et al.* (2003) as the authors reported that total leukocytic count significantly elevated after administration of levofloxacin in rats. Similar finding was recorded by Oh *et al.* (2003) and Oridupa *et al.* (2013) as they reported that levofloxacin caused a reduction in total erythrocytic count, Hb content and PCV% beside a significant increase in TLC count.

This finding is in accordance with these of Samah *et al.* (2014) who recorded that daily levofloxacin administration in rabbits for 4 weeks showed insignificant decrease in erythroctic count, Hb content, PCV% and a significant increase in total leukocytic count at the end of the 1st and 4th weeks post drug administration. These results are in accordance with that obtained by Amer and El-Said (1997) as the authors reported that the use of another floroqinolone (danofloxacin) to rats induced a significant decrease in Hb content and increase in leukocytic count. Our results supported by results recorded by Amer and El-Shaieb (1998) who found that administration of another flouroqinolone (enrofloxacin) to rabbits revealed a significant decrease in erythrocytic count, Hb content and PCV%. Similar observations were recorded by Tohamy (2017) who reported that oral administration of levofloxacin 7.5 mg/kg

bwt. in male rats displayed a significant decrease in total erythrocytic count, Hb content and PCV % with increase in TLC count and PLT count.

In this study, it has been shown that oral administration of vitamin E in male rats treated with levofloxacin for 14 successive days produced a significant increase in RBCs count, Hb content, and PCV % and a significant decrease in PLT count in comparison with levofloxacin group.

The improvement in erythrogram may be due to the positive effect for the role of vitamin E on the hematological parameter which improved blood parameters or increase in PCV% and Hb content (Ihsan and Gelawesh 2012). This change in hematological parameters may be due to vitamin E led to increase the number of colony forming units of erythroid precursors, preventing the oxidation of polyunsaturated fatty acids in erythrocytic membrane, thus inhibiting the premature erythrocyte lysis, enhancing erythropoiesis and decreasing the premature erythrocyte hemolysis by reducing the fragility of erythrocytes. Thus, vitamin E may improve the post-supplemental Hb content and PCV% levels (Jilani and Iqbal, 2011).

The obtained results was supported by Khaled (2013) who mentioned that vitamin E induced a significant increase in erythrogram.

Ukpanukpong *et al.* (2013) stated that vitamins E have ameliorating effects against toxic effect of another quinolone (pefloxacin) in rats, including insignificant increase in erythrocytic count, Hb content, PCV% and leukocytic count.

The recorded results agree with findings of Tohamy (2017) who reported that oral administration of vitamin E with levofloxacin for 10 successive days in rats resulted in a significant increase in total erythroctic count, Hb content and PCV% and insignificant decrease in TLC count on 1$^{st}$ and 10$^{th}$ day post drug administration and returned to nearly normal levels on 20$^{th}$ day post administration. Also, co-administration of levofloxacin with vitamin E displayed insignificant increase in total erythrocytic count, hemoglobin content, PCV% and TLC count.

The current study revealed that oral administration of levofloxacin produced a significant increase in ALT, AST and ALP activities. Serum AST and ALT are reliable marker enzymes of liver function and integrity (Naik and Panda 2007). Previous studies have shown that high levels of AST, ALT and ALP in serum or plasma are usually indicative of liver injury in humans and animals (Yabubu *et al.,* 2003). Where as the lower levels of these enzymes could indicate a degree of liver protection (Manna *et al.*, 1996).

Our finding clearly confirmed by those obtained by Ebenzer *et al.* (2015) as the previous authors reported a significant increase in serum liver enzymes activities in rats received levofloxacin (10mg/kg). The elevation in the activity of these enzymes by levofloxacin may be as a result of their release in response to tissue damage during routine normal destruction of liver cells by the drug (Macafarlane *et al.,* 2000). Our results are fit with Kim *et al.* (2003) who observed that elevation in AST in rats administered levofloxacin. Similar observations were recorded by Tohamy (2017) who mentioned that oral administration of levofloxacin in dose of (7.5mg/kg) in rats displayed a significant increase in liver enzymes (AST, ALT and ALP) levels on 1$^{st}$ and 10$^{th}$ days post drug administration and return to the nearly to normal levels on 20$^{th}$ day post administration when compared with the control rats.

The current study indicated that co-administration of vitamin E with levofloxacin decreased ALT, AST and ALP activities in comparison with levofloxacin group.

The obtained results in this research is similar to those recorded by George and Degoke (2011) who found that vitamin E displayed a reduction in liver enzymes (AST, ALT and ALP) in albino rats. The obtained results are in agreement with El Maghraby, Somia and Hamdy (2012) who found that vitamin E induced insignificant increase in the liver enzyme activities of liver. Moreover, Mehmet and Mustafa (1999) mentioned that vitamin E induced insignificant reduction in liver enzymes.

Similar data were observed with Tohamy (2017) who mentioned that oral administration of vitamin E with levofloxacin decreased ALT, AST and ALP activities in male rats.

The recorded results in this investigation agree with Farid and Hegazy (2019) who mentioned that levofloxacin (40mg/kg b.wt. daily for 2 weeks) in rats produced displayed hepatic dysfunctions (increase AST and ALT activities).

In this experiment, oral administration of levofloxacin resulted in a significant decrease in total protein, albumin and albumin/globulin ratio levels.

Total protein and albumin are the most sensitive biomarkars directly implicated in the extent of hepatic damage and toxicity (Stockham and Scott 2002).

Our obtained results co-ordinate with Tohamy (2017) who mentioned that rats received levofloxacin (7.5mg/kg bwt.) and vitamin E (50mg/kg bwt.) produced non-significant changes in total protein, albumin and albumin/globulin ratio.

The present investigation revealed that oral administration of levofloxacin produced a significant increase in TC, TG, LDL and VLDL with a significant decrease in HDL in comparison with control group.

The current study revealed that co-administration of vitamin E with levofloxacin produce a significant decrease in TC, TG, LDL and VLDL levels with a significant increase in HDL level when compared with levofloxacin group.

Both urea and creatinine are metabolic waste products that are freely filtered by the glomeruli of the kidneys (Johnson, 2011) so serum urea and creatinine concentrations are commonly used to screen for renal function (Ferguson and Waikar, 2012). The current study revealed that oral administration of levofloxacin produced a significant increase in urea and creatinine levels. The increase in serum creatinine and urea might be attributed to the decreased GFR or might be secondary due to the increase of the reactive of species (Noori and Mahboob 2010).

Co-administration of vitamin E with levofloxacin displayed a significant decrease in urea and creatinine levels in comparison with levofloxacin group.

The obtained results are in agreement with the results obtained by Mouton and Holder (2006) who reported that elevation of the serum levels of urea and creatinine post levofloxacin administration is an indication of abnormal renal function. These results may be due to norfloxacin induced mild interstitial nephritis and decreased renal function (Rashmi *et al.*, 2012).

Another explanation for increase urea and creatinine levels post administration of levofloxacin come from Afolabi and Oyewo (2014) who stated that levofloxacin have been reported to generate ROS which may result in oxidative stress and cellular damage to the liver and kidney. The same result also obtained by George and Degoke (2011) who mentioned that rats fed diet containing vitamin E showed reduction in urea and creatinine levels. This finding is in accordance with the finding of Hamza and El-Shennawy (2009) as they stated that the male albino rats received vitamin E induced insignificant decrease in serum creatinine and urea levels. The recorded results are supported by Karabulut *et al.* (2008) who mentioned that vitamin E induced a decrease in urea and creatinine levels in rats.

Oral administration of levofloxacin elicited a significant increase in MDA concentrations with a significant decrease in catalase and SOD enzymes activities. Co-administration of vitamin E with levofloxacin induced a significant decrease in MDA concentrations with a significant increase in CAT and SOD enzyme activities when compared with levofloxacin group.

In this regard, vitamin E supplementation increased antioxidant recycling and improved synergistic antioxidant effect (Makimura *et al.*, 1993). The improvement recorded in the activities antioxidant enzymes (SOD and CAT) induced by vitamin E when compared with control rats could be attributed to the well established antioxidant potential of vitamin E (Helen *et al.*, 2000). Vitamin E prevents oxidative damage by interrupting the propagation of the oxidation of polyunsaturated fatty acids (Aldana *et al.*, 2001). Vitamin E inhibits lipid peroxidation of cellular and intracellular membrane structures (Fadlaallah, Manal *et al.*, 2007).

Moreover, vitamin E cooperate in the defense against oxidative strees upon cells by detoxifying and inhibiting the formation of lipid hydroperoxides (Saito *et al.,* 2003). Also, vitamin E are not only effective against oxidative damage alone, but also have a synergistic effect when used in combination (Bartfay *et al.,* 1998). Administration of vitamin E for 8 weeks elevated antioxidant enzymes (SOD and CAT) activities in rats (Mekinova *et al.,* 1995). Vitamin E prevents oxidative damage to sensitive membrane lipids by destroying hydroperoxide formation, acting in conjunction with selenium, and protects cellular membranes and lipid containing organelles from peroxidative damage by oxidative stress (Gupta *et al.,* 2010).

The observed data in this study co-ordinate with Farid and Hegazy (2019) who reported that levofloxacin (40mg/kg b.wt. daily for 2 weeks) in rats displayed oxidative stress represented by reduction in antioxidant enzymes (CAT and SOD) with an increase in MDA concentrations.

Oral administration of levofloxacin produced a significant increase in TNF-α. The increase in TNF-α may be attributed to co-administration of vitamin E with levofloxacin significantly decreased TNF-α level.

The present investigation indicated that levofloxacin administration in rats produced a significant increase in TNF-α in comparison with control group.

Levofloxacin significantly increased the expression of TNF-α when compared to normal rats (Bode *et al.,* 2015).

Tumor necrosis factor-alpha rapidly migrates into the injured tissue following vasodilatation in atrial to suppress further cell death, invigorate stem cells and stimulate epithelial proliferation (Kuraishy *et al.,* 2011).

Fischer and Marier (2015) found a strong relation between cytokines production including TNF-α and oxidative stress in rats. This study may explain the significant reduction in TNF-α levels in groups which were treated with vitamin E one hour before levofloxacin in comparison with levofloxacin, they had powerful antioxidant properties which strongly counteracted any adverse effect produced by oxidative stress such as elevation of TNF-α levels in levofloxacin group. Vitamin E significantly decreased serum TNF-α level in comparison with vancomycin group in the study of Blesa *et al.* (2003) and attributed that to its direct antioxidant effect, additionally it can protect indirectly via decreasing neutrophil recruitment.

## CONCLUSION

It could be concluded that levofloxacin may result in oxidative stress and cellular damage to the liver and kidney. Levofloxacin induced biochemical disturbances and altered oxidative stress and vitamin E restored liver and kidney functions biomarkers and re-esablished the antioxidant/oxidant condition.

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## التأثير التحسيني لفيتامين هـ ضد بعض الأثار الجانبية لليفوفلوكساسين في ذكور الجرزان

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أجريت هذه الدراسة لكشف النقاب عن الدور الوقائي المحتمل لفيتامين هـ ضد الأثار الجانبية لليفوفلوكساسين في ذكور الجرزان . في هذه التجربة تم تقسيم ٢٠ من الجرزان البيضاء إلي خمسة مجموعات متساوية خمسة جرزان في كل مجموعة أعطيت المجموعة المجموعة الأولي ماء مقطر عن طريق الفم ٢مللیلتر /كجم من وزن الجسم الحي ,أعطيت المجموعة الثانية زيت الزيتون عن طريق الفم ٢مللیلتر /كجم من وزن الجسم الحي ,أعطيت المجموعة الثالثة فيتامين هـ عن طريق الفم ١٠٠مجم/كجم من وزن الجسم الحي , أعطيت المجموعة الرابعة الليفوفلوكساسين عن طريق الفم بجرعة ١٠ مجم/كجم من وزن الجسم الحي ,أعطيت المجموعة الخامسة فيتامين هـ عن طريق الفم ١٠٠مجم/كجم من وزن الجسم الحي و الليفوفلوكساسين عن طريق الفم١٠مجم/كجم من وزن الجسم الحي. مدة العلاج كانت ١٤ يوم متتالية في جميع المجموعات .إعطاء الليفوفلوكساسين في الجرزان أحدث نقص معنوي في عدد كرات الدم الحمراء ,الهيموجلوبين ,معبأة حجم الخلية ,عدد الصفائح الدموية ,عدد كرات الدم البيضاء ,الليبوبروتين عالي الكثافة ,أنزيم السوبر أوكسيد ديسميوتيز ,إنزيم الكتاليز وحدوث إرتفاع في إنزيمات الكبد الأسبرتيت أمينوترانسفيريز ,ألانين أمينوترانسفيريز والألكالين فوسفاتيز والكوليستيرول الكلي ,التراي جليسريد ,الليبوبروتين منخفض الكثافة ,الليبوبروتين منخفض الكثافة جدا ,اليوريا ,المالون داي ألدهيد ,عامل التنخر ألفا . إعطاء فيتامين هـ مع الليفوفلوكساسين أحدث زيادة معنوية في عدد كرات الدم الحمراء ,الهيموجلوبين ,معبأة حجم الخلية ,عددالصفائح الدموية ,عدد كرات الدم البيضاء ,الليبوبروتين عالي الكثافة , إنزيم السوبر أوكسيد ديسميوتيز و إنزيم الكتاليز مع نقص معنوي في إنزيمات الكبد الأسبرتيت أمينوترانسفيريز ,ألانين أمينوترانسفيريز ,الألكالين فوسفاتيز والكوليستيرول الكلي ,التراي جليسريد ,الليبوبروتين منخفض الكثافة ,الليبوبروتين منخفض الكثافة جدا ,اليوريا ,المالون داي ألدهيد ,عامل التنخر ألفا . إعطاء فيتامين هـ أحدث تحسن في الأثار الجانبية لليفوفلوكساسين عن طريق أثارهم المضادة للأكسدة .