

Evaluating the Protective Effect of Dill (*Anethum graveolens* L.) against Levofloxacin-Induced Renal Toxicity in Rats

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ABSTRACT

This study investigated the nephrotoxic effects of Levofloxacin and the potential protective role of Dill (*A. graveolens*) extract in a rat model. Levofloxacin administration induced significant, dose-dependent increases in serum creatinine, urea, and blood urea nitrogen (BUN) levels, along with elevated renal malondialdehyde (MDA) content and reduced catalase (CAT) activity, confirming oxidative stress-mediated nephrotoxicity. Co-administration of Dill extract attenuated these effects, significantly lowering renal functional markers (creatinine, urea, BUN), reducing lipid peroxidation (MDA), and preserving antioxidant enzyme (CAT) activity. The protective effects were particularly pronounced at higher oxidative stress levels, suggesting dose-dependent efficacy. Mechanistically, Dill extract likely exerts its renoprotective effects through free radical scavenging, antioxidant enzyme preservation, and cellular redox balance maintenance. These findings highlight Dill extract as a promising adjunct therapy to mitigate Levofloxacin-induced nephrotoxicity, particularly in high-dose regimens. Further research is warranted to optimize dosing, elucidate molecular mechanisms, and validate clinical applications. This study provides compelling evidence for the potential of *A. graveolens* as a natural antioxidant adjuvant in fluoroquinolone therapy, offering a novel strategy to enhance drug safety while maintaining antimicrobial efficacy.

Keywords: Levofloxacin, *A. graveolens*, nephrotoxicity, oxidative stress, antioxidant, renal protection.

I. INTRODUCTION

Oxidative stress plays a key role in drug-induced liver injury (DILI), including cases linked to levofloxacin (Machado et al., 2023; Rani et al., 2024; Schloss et al., 2018). Levofloxacin has been shown to induce oxidative stress and cause organ damage in various studies. It significantly increases reactive oxygen species (ROS) levels and malondialdehyde (MDA) content, leading to oxidative stress (Jin et al., 2022). Administration

of levofloxacin results in elevated liver enzymes (ALT, AST, ALP), increased creatinine levels, and histological damage to the liver, kidney, and testis tissues (Ibrahim et al., 2021; Ara et al., 2020). The antibiotic also negatively impacts hematological parameters and antioxidant enzyme levels (Ibrahim et al., 2021).

Nephrotoxicity associated with levofloxacin can manifest as allergic interstitial nephritis or vasculitis, sometimes accompanied by purpura. These immune-mediated reactions resolve after discontinuing the drug and initiating corticosteroid therapy (Famularo and De Simone, 2002). Another serious complication is crystal-induced acute kidney injury, or crystal nephropathy, which is more frequently observed in patients with pre-existing renal dysfunction or those receiving high doses of levofloxacin (Ansari et al., 2019). It may also contribute to acute kidney injury (AKI), particularly in patients with existing renal disease or when used alongside other nephrotoxic agents. Recent research has highlighted the complex relationship between medications and AKI (Bosi et al., 2024; Barreto et al., 2025). Beyond traditional medications, immune checkpoint inhibitors have also been implicated in AKI, with acute tubulointerstitial nephritis being the most common histopathological finding (Zhou et al., 2024). Other substances, including antimicrobial agents, contrast media, and illicit drugs, have likewise been associated with AKI (Yu et al., 2024). Recent studies indicate that certain antibiotics, particularly levofloxacin, may induce crystal nephropathy (Ito et al., 2024; Mhaibes and Abdul-Wahab, 2023). Renal impairment significantly affects the pharmacokinetics and dosing of drugs primarily excreted by the kidneys, including levofloxacin. Accurate glomerular filtration rate (GFR) or creatinine clearance measurement is essential for appropriate dose adjustment in patients with renal dysfunction (Churchill et al., 2025). Beyond its antibacterial effects, levofloxacin has demonstrated anti-inflammatory properties by suppressing pro-inflammatory cytokine release and inhibiting inflammatory signaling pathways in human

astrocytes (Phuagkhaopong et al., 2025). However, impaired renal function can alter drug clearance and increase the risk of adverse effects, such as hypoglycemia, particularly in diabetic patients (Shreen et al., 2025).

Antioxidant-rich plant extracts have demonstrated protective effects against renal damage induced by various toxins. For instance, pre-treatment with clove oil significantly reduced malondialdehyde levels and improved histopathological outcomes in rats exposed to levofloxacin (Fiquardina et al., 2022). Likewise, Dill extract (*A. graveolens*) exhibits multiple pharmacological activities. Its antioxidant properties are well-documented, with extracts scavenging free radicals, reducing lipid peroxidation, and enhancing endogenous antioxidant defenses (Hadi et al., 2024; Haidari et al., 2020). It prevented kidney injury in mice exposed to nicotine by suppressing reactive oxygen species (ROS) production and enhancing antioxidant enzyme activity (Ajarem et al., 2021). The nephroprotective effects of such medicinal plants are primarily attributed to their ability to neutralize free radicals and mitigate oxidative damage within kidney cells (Dehghan Shahreza, 2017). These findings suggest that antioxidant-rich extracts like dill may hold promise in alleviating levofloxacin-induced renal injury by counteracting oxidative stress. In addition, Dill extract exhibits notable anti-inflammatory properties that could help reduce renal inflammation triggered by levofloxacin-induced oxidative injury (Mohamed et al., 2024). Other natural antioxidants, including lactoferrin and extracts from *Boerhaaviadiffusa*, *Amaurodermarugosum*, and *Ganoderma lucidum*, have shown promise in reducing inflammation and oxidative damage in chronic kidney disease. However, further research is required to understand their mechanisms fully (Lee et al., 2024).

Dill possesses antidiarrheal, anti-inflammatory, and antioxidant effects demonstrated in rat studies, suggesting cytoprotective properties (Brinsi et al., 2024; Masoody et al., 2023). Notably, dill extracts have shown potential antiviral activity by inhibiting the interaction between the SARS-CoV-2 spike protein and the ACE2 receptor, with aqueous extracts exhibiting higher phenolic content and free radical scavenging capacity than ethanol extracts (Choe et al., 2023). Essential oil nanocapsules of parsley and dill have also demonstrated hepato-renal protective effects by modulating liver and kidney function markers and inflammatory cytokines (Mohamed et al.,

2024). These findings emphasize the need for developing alternative strategies to detect and manage drug-induced kidney injury, as current biomarkers like serum creatinine and blood urea nitrogen lack sensitivity and specificity for early nephrotoxicity detection (Connor et al., 2024). Continued research is essential to clarify these natural compounds' mechanisms and therapeutic applications in renal protection. Therefore, the study was undertaken to find the protective effect and role of dill extract in correcting the impact of Levofloxacin on kidney functions and performance.

II. MATERIALS AND METHODS

2.1 Levofloxacin and Dill extract

Aqueous *A. graveolens* L. (dill) extracts were prepared to investigate their bioactive constituents and potential therapeutic effects. The extraction procedure involved mixing 20–50 g of dried dill powder in 200 mL of warm distilled water at ~90 °C for 10 min, then cooling and filtering to remove particulate matter. Ultrasonication and centrifugation enhanced extraction efficiency and purity before metabolomic analysis. Later, the clear extract was concentrated in a rotary evaporator and kept under cooling until used (Thanuma et al., 2025).

2.2 Animal model and experimental design

Male albino Wistar rats weighing 100 – 150 g (6-8 weeks old) were obtained from the Animal Laboratory, Faculty of Veterinary Medicine, Benha University. The rats were housed at the Department of Pharmacology, Faculty of Veterinary Medicine, Benha University, Egypt, in polypropylene cages under standard laboratory conditions (22±3 °C, 40-60% humidity, 12-h light/dark cycle) supplied with a basal diet and water ad libitum. The experiment was performed under the approval of the Committee of Research Ethics (Institutional Review Board, IRB) of Benha University Faculty of Veterinary Medicine's Ethics Committee.

The standard chow (laboratory animal feed pellets) is composed of 20% crude protein, 4% crude fat, 3.5% crude fiber, 6% ash, 0.5% salt, 1% calcium, 0.6% phosphorus, 20 IU/g vitamin A, 2.2 IU/g vitamin D, 70 IU/kg vitamin E, and 2850 ME Kcal/kg energy, with added trace minerals (cobalt, copper, iodine, iron, manganese, selenium, and zinc). The rats were acclimated for one week before starting the experiment. Sixty rats were randomly divided into six groups; the first group

(n=10) was the control group (**Control group**), the second group was administrated dill extract at 300 mg/kg body weight (**dill group**), the third group was administrated Levofloxacin at 20 mg/kg (**Levo therapeutic group**), the fourth group was administrated Levofloxacin at 40 mg/kg (**Levo double therapeutic group**), the fifth group was administrated Levofloxacin at 20 mg/kg and dill extract at 300 mg/kg body weight (**Levo + dill group**), and the sixth group was administrated Levofloxacin at 40 mg/kg and dill extract at 300 mg/kg body weight (**Levo double + dill group**).

2.1.1. Blood and organs collection

At the end of the experiment, the experimental rats were anesthetized with diethyl ether, and blood samples were collected from the jugular vein. Immediately after the collection, the blood tubes were submitted to centrifugation (4000 xg at 10 °C) for 30 min, and the serum obtained was preserved at -18 °C until use. After collecting blood samples, three rats from each group were humanely sacrificed by cervical dislocation under anesthesia. The kidneys were then excised carefully for histopathological examination.

2.1.2. Determination of the kidneys' functions

Creatinine (mg dL⁻¹) and urea (mg dL⁻¹) concentrations using colorimetric test kits were determined according to the manufacturer's instructions. Blood urea nitrogen (BUN, mg dL⁻¹) was calculated by multiplying urea concentration by 0.47. All biochemical examination kits were purchased from Human Co., Wiesbaden, Germany.

2.1.3. Oxidative stress biomarkers:

Lipid peroxidation was assessed using a malondialdehyde (MDA, nmol mL⁻¹) colorimetric assay kit by measuring thiobarbituric acid reactive substance (TBARS) and expressed in terms of MDA content according to Ohkawa et al. (1979). MDA, a product of fatty acid peroxidation, forms a colored complex reacting with Thiobarbituric acid (TBA). The absorbance of the supernatant was measured at 532 nm, and the results were calculated as nmol mL⁻¹. Catalase (CAT, U L⁻¹) activity was determined using a CAT activity assay kit using the Aebi method (Aebi, 1984). All Oxidative stress markers were determined using a blood chemistry analyzer (HumaLyzer 4000, Germany).

2.1.4. Histopathology

Autopsy samples were taken from rats' kidneys in different groups and fixed in 10% formalin for 24 hours. Washing is then done under tap water, and serial dilutions of alcohol (methyl, ethyl, and ethyl absolute) are used for drying. The samples are then flushed in xylene and embedded in paraffin at 56 °C in a hot air oven for 24 hours. A sliding microtome was used to prepared paraffin-embedding tissue blocks for cutting at 4 µm. After Microtome sectioning, the tissue sections were deparaffinized and immediately stained with hematoxylin-eosin (H&E). The stained sections were diagnosed for histopathological alterations in kidney architecture, and their photomicrographs were taken according to Banchroft et al.(1996). Subsequently, the results of the undefined experimental groups were re-diagnosed by two pathologists to confirm the observation of the results.

2.2. Statistical Analysis

Statistical analysis was performed using SPSS (Version 22.0 for Windows, IBM, Houston, Texas, USA). Experimental results are expressed as mean ± S.E. Statistical significance was tested with one-way ANOVA followed by a post hoc test, and p-values < 0.05 were applied according to Steel et al.(1997).

III. RESULTS

3.1 The effect of Levofloxacin and Dill extract on serum Creatinine Levels in Rats

The effects of Levofloxacin and Dill extract on serum creatinine levels in rats are summarized in **Table 1** and **Fig. 1**. The control group exhibited a creatinine level of 0.62 ± 0.03 mg/dL. The Dill group showed a non-significant change in creatinine levels (0.58 ± 0.02 mg/dL) compared to the control group, indicating that Dill extract alone did not significantly alter renal function. In contrast, the Levo therapeutic group demonstrated a significant increase in creatinine levels (0.79 ± 0.04 mg/dL) compared to the control group ($P < 0.05$). This elevation was more pronounced in the Levo double therapeutic group (1.55 ± 0.10 mg/dL), suggesting a dose-dependent nephrotoxic effect of Levofloxacin.

When Dill extract was co-administered with Levofloxacin, the Levo + Dill group showed a non-significant decrease in creatinine levels (0.66 ± 0.02 mg/dL) compared to the Levo therapeutic group. However, in the Levo double + Dill group, a significant reduction in creatinine levels ($1.02 \pm$

0.02 mg/dL) was observed compared to the Levo double therapeutic group ($P < 0.05$), highlighting

the potential protective role of Dill extract against Levofloxacin-induced nephrotoxicity.

Table 1. The effect of Levofloxacin and Dill extract on serum creatinine levels in rats (Mean \pm S.E), n = 9

Experimental Groups	Creatinine (mg/dL)
Control group	0.62 \pm 0.03 ^d
Dill group	0.58 \pm 0.02 ^d
Levo therapeutic group	0.79 \pm 0.04 ^c
Levo double therapeutic group	1.55 \pm 0.10 ^a
Levo + dill group	0.66 \pm 0.02 ^{cd}
Levo double + dill group	1.02 \pm 0.02 ^b

S.E. = Standard error, Mean values with different superscript letters in the same column significantly differ ($P < 0.05$).

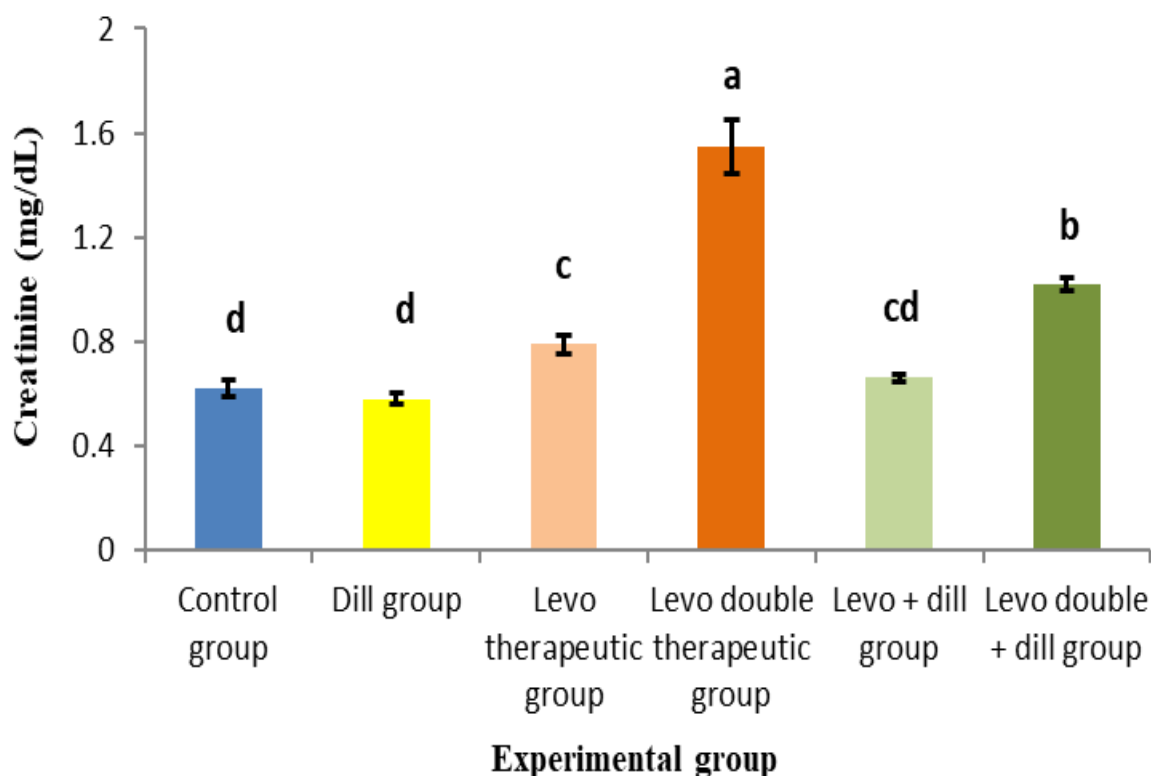


Figure 1: The effect of Levofloxacin and Dill extract on serum creatinine levels in rats (Mean \pm S.E), n = 9. ^{a,b,c}: Bars not sharing similar letters are significantly different ($p > 0.05$).

3.2 The effect of Levofloxacin and Dill extract on serum urea levels in rats

The effects of Levofloxacin and Dill extract on serum urea levels in rats are presented in **Table 2** and **Fig.2**. The control group exhibited a urea level of 21.23 \pm 1.15 mg/dL. The Dill group showed a non-significant change in urea levels (21.32 \pm 1.14 mg/dL) compared to the control group, indicating that Dill extract alone did not significantly affect renal function. In contrast, the Levo therapeutic group demonstrated a significant

increase in urea levels (25.87 \pm 0.55 mg/dL) compared to the control group ($P < 0.05$). This elevation was even more pronounced in the Levo double therapeutic group (38.10 \pm 1.78 mg/dL), further supporting the dose-dependent nephrotoxic effects of Levofloxacin. When Dill extract was co-administered with Levofloxacin, the Levo + Dill group showed a significant decrease in urea levels (22.40 \pm 0.59 mg/dL) compared to the Levo therapeutic group ($P < 0.05$). Similarly, the Levo double + Dill group exhibited a significant

reduction in urea levels (29.29 ± 0.36 mg/dL) compared to the Levo double therapeutic group (P

< 0.05), suggesting a protective role of Dill extract against Levofloxacin-induced renal damage.

Table 2. The effect of Levofloxacin and Dill extract on serum urea levels in rats (Mean \pm S.E), n = 9

Experimental Groups	Urea (mg/dL)
Control group	21.23 ± 1.15^d
Dill group	21.32 ± 1.14^d
Levo therapeutic group	25.87 ± 0.55^c
Levo double therapeutic group	38.10 ± 1.78^a
Levo + dill group	22.40 ± 0.59^d
Levo double + dill group	29.29 ± 0.36^b

S.E. = Standard error, Mean values with different superscript letters in the same column significantly differ ($P < 0.05$).

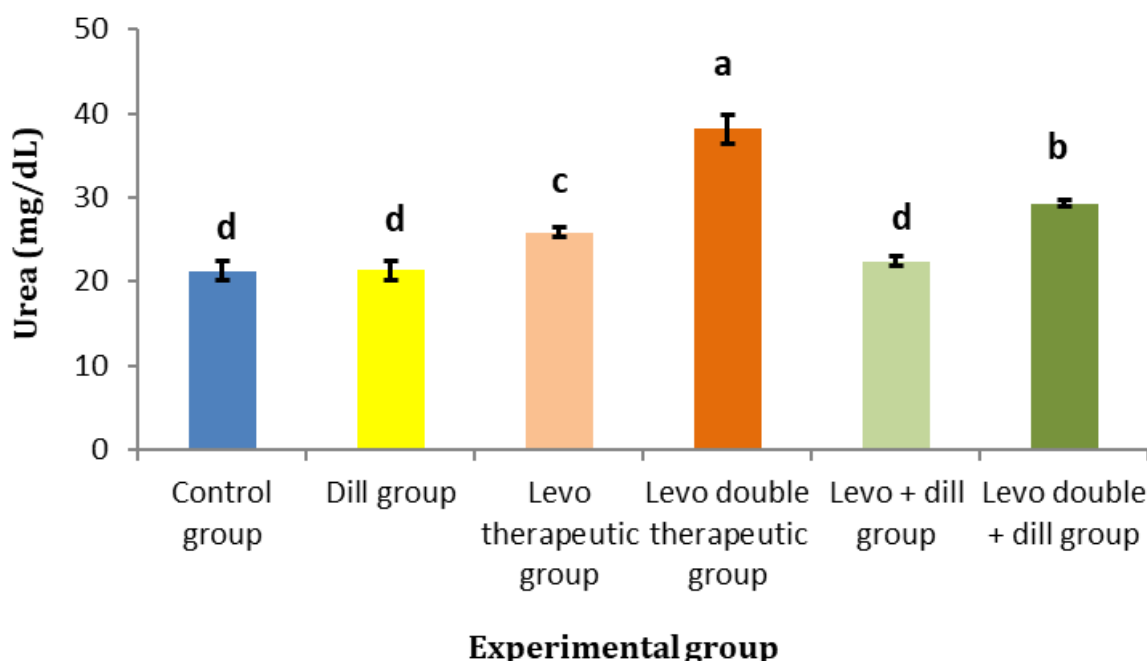


Figure 2: The effect of Levofloxacin and Dill extract on serum urea levels in rats (Mean \pm S.E), n = 9. ^{a,b,c}: Bars not sharing similar letters are significantly different ($p > 0.05$).

3.3 The effect of Levofloxacin and Dill extract on serum Blood urea nitrogen levels in rats

The effects of Levofloxacin and Dill extract on serum Blood Urea Nitrogen (BUN) levels in rats are presented in Table 3 and Fig. 3. The control group exhibited BUN levels of 9.89 ± 0.54 mg/dL. In contrast, the Dill group showed comparable levels (10.02 ± 0.53 mg/dL), indicating no significant effect of Dill extract alone on renal function. Administration of Levofloxacin resulted in a significant dose-dependent increase in BUN levels. The Levo therapeutic group demonstrated

elevated BUN levels (12.16 ± 0.26 mg/dL, $P < 0.05$), which were further exacerbated in the Levo double therapeutic group (17.91 ± 0.84 mg/dL, $P < 0.05$) compared to the control group. Co-administration of Dill extract with Levofloxacin showed protective effects. The Levo + Dill group maintained BUN levels (10.53 ± 0.28 mg/dL) similar to the control group. The Levo double + Dill group showed significantly lower BUN levels (13.77 ± 0.17 mg/dL, $P < 0.05$) compared to the Levo double therapeutic group.

Table 3. The effect of Levofloxacin and Dill extract on serum Blood urea nitrogen levels in rats (Mean ± S.E), n = 9

Experimental Groups	BUN (mg/dL)
Control group	9.89 ± 0.54 ^d
Dill group	10.02 ± 0.53 ^d
Levo therapeutic group	12.16 ± 0.26 ^c
Levo double therapeutic group	17.91 ± 0.84 ^a
Levo + dill group	10.53 ± 0.28 ^d
Levo double + dill group	13.77 ± 0.17 ^b

S.E. = Standard error, Mean values with different superscript letters in the same column significantly differ (P<0.05).

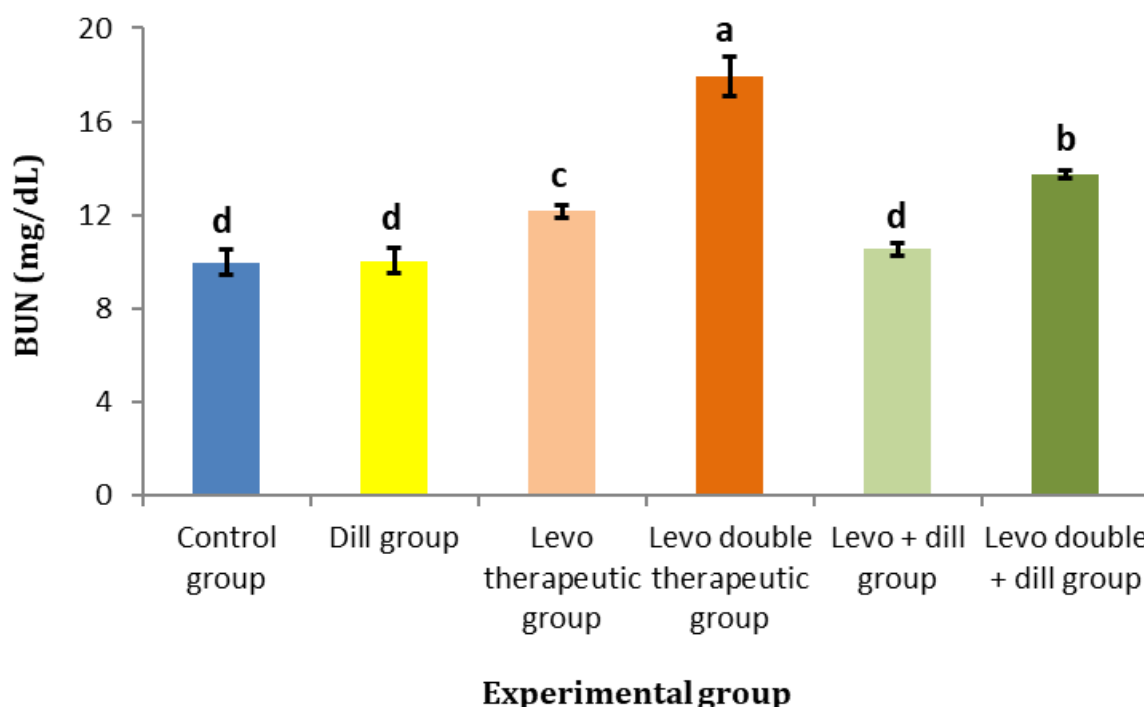


Figure 3: The effect of Levofloxacin and Dill extract on serum Blood urea nitrogen levels in rats (Mean ± S.E), n = 9. ^{a,b,c}: Bars not sharing similar letters are significantly different (p > 0.05).

3.4 The effect of Levofloxacin and Dill extract on hepatic MDA Levels in liver tissue

The effects of Levofloxacin and Dill extract on renal malondialdehyde (MDA) levels, a marker of oxidative stress, are presented in Table 4 and Fig. 4. The control group showed baseline MDA levels of 17.58 ± 0.72 nmol/g tissue, with the Dill group demonstrating comparable levels (16.98 ± 1.18 nmol/g tissue), indicating no significant oxidative stress induction by Dill extract alone. Levofloxacin administration resulted in significant, dose-dependent increases in renal MDA levels. The Levo therapeutic group exhibited elevated MDA

levels (24.51 ± 0.96 nmol/g tissue, P < 0.05), which were dramatically higher in the Levo double therapeutic group (39.48 ± 0.48 nmol/g tissue, P < 0.05) compared to controls. Co-administration of Dill extract significantly attenuated these oxidative effects. The Levo + Dill group showed reduced MDA levels (20.35 ± 0.45 nmol/g tissue, P < 0.05) compared to the Levo therapeutic group. In contrast, the Levo double + Dill group demonstrated significantly lower MDA levels (31.77 ± 0.69 nmol/g tissue, P < 0.05) than the Levo double therapeutic group.

Table 4. The effect of Levofloxacin and Dill extract on Renal MDA Levels in liver tissue (Mean ± S.E), n = 9

Experimental Groups	RMDA (nmol/g tissue)
Control group	17.58±0.72 ^e
Dill group	16.98±1.18 ^e
Levo therapeutic group	24.51±0.96 ^c
Levo double therapeutic group	39.48±0.48 ^a
Levo + dill group	20.35±0.45 ^d
Levo double + dill group	31.77±0.69 ^b

S.E. = Standard error, Mean values with different superscript letters in the same column significantly differ (P<0.05).

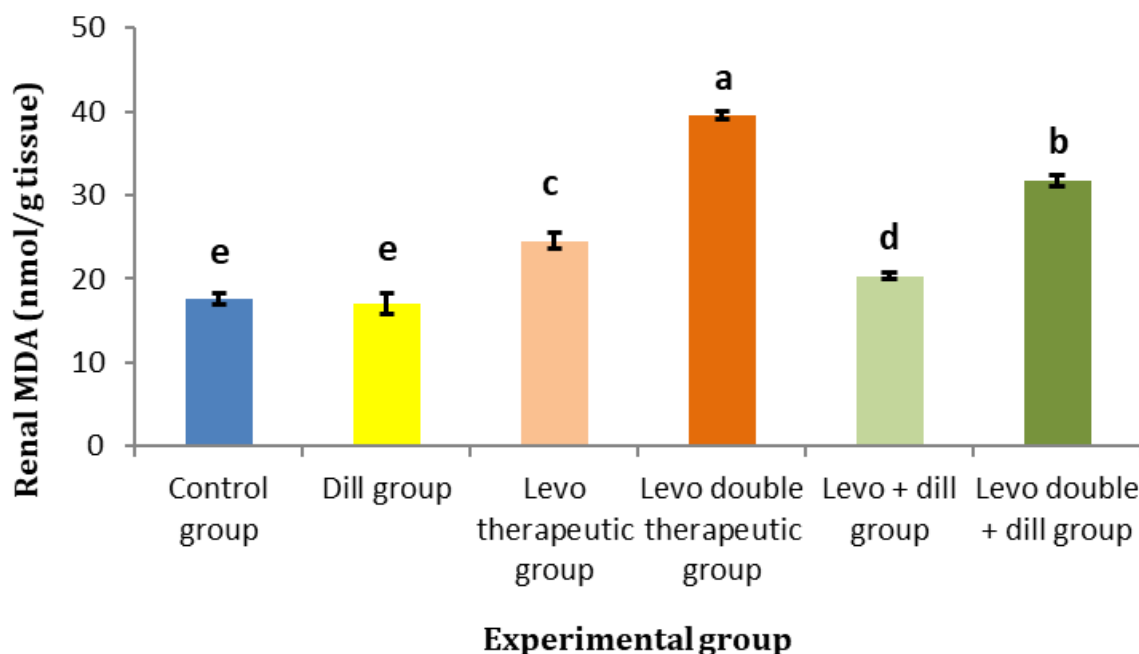


Figure 4: The effect of Levofloxacin and Dill extract on Renal MDA Levels in liver tissue (Mean ± S.E), n = 9. ^{a,b,c}: Bars not sharing similar letters are significantly different (p > 0.05).

3.5 The effect of Levofloxacin and Dill extract on Renal CAT Levels in liver tissue

The effects of Levofloxacin and Dill extract on renal catalase (CAT) activity are presented in **Table 5** and **Fig. 5**. The control group exhibited CAT activity of 22.59 ± 0.60 U/g tissue, with the Dill group showing comparable levels (23.16 ± 0.95 U/g tissue), indicating no significant effect of Dill extract alone on this antioxidant enzyme. Levofloxacin administration resulted in significant, dose-dependent reductions in CAT activity. The Levo therapeutic group showed

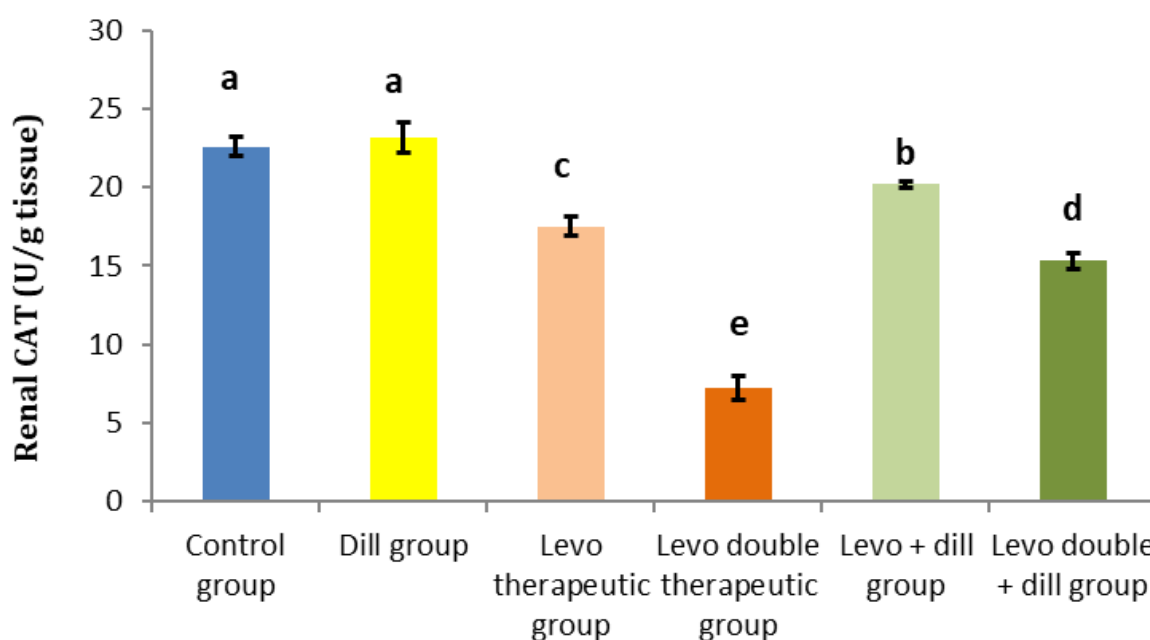
decreased activity (17.50 ± 0.61 U/g tissue, P < 0.05), while the Levo double therapeutic group demonstrated a more pronounced reduction (7.25 ± 0.77 U/g tissue, P < 0.05) compared to controls. Co-administration of Dill extract partially restored CAT activity. While the Levo + Dill group showed a non-significant increase (20.19 ± 0.18 U/g tissue) compared to the Levo therapeutic group, the Levo double + Dill group exhibited significantly higher CAT activity (15.31 ± 0.48 U/g tissue, P < 0.05) than the Levo double therapeutic group.

Table 5. The effect of Levofloxacin and Dill extract on Renal CAT Levels in liver tissue (Mean ± S.E), n = 9

Experimental Groups	RCAT (U/g tissue)
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Control group	22.59±0.60 ^a
Dill group	23.16±0.95 ^a
Levo therapeutic group	17.50±0.61 ^c
Levo double therapeutic group	7.25±0.77 ^e
Levo + dill group	20.19±0.18 ^b
Levo double + dill group	15.31±0.48 ^d

S.E. = Standard error, Mean values with different superscript letters in the same column significantly differ (P<0.05).



Experimental group

Figure 5: The effect of Levofloxacin and Dill extract on Renal CAT Levels in liver tissue (Mean ± S.E), n = 9. ^{a,b,c}; Bars not sharing similar letters are significantly different (p > 0.05).

3.6 The effect of Levofloxacin and Dill extract on the kidneyshistoarchitecture

For 7 days duration time, the control group exhibited that there was no histopathological alteration and the normal histological structure of the glomeruli and tubules at the cortex were recorded in (Fig. 6.1). In the Dill group, there was no histopathological alteration as recorded in (Fig. 7.1). In Levo therapeutic group, congestion was observed in the cortical blood vessels (Fig. 8.1). Levo in the double therapeutic group, congestion was observed in the sclerotic cortical blood vessels (Fig.9.1). In the Levo + dill group, there was no histopathological alteration as recorded in (Fig. 10.1). In the Levo double + dill group, there was no histopathological alteration as recorded in (Fig. 11.1).

For 14 days duration time, the control group exhibited that there was no histopathological alteration as recorded in (Fig. 6.2). In the Dill group, there was no histopathological alteration as recorded in (Fig. 7.2). In Levo therapeutic group, there was swelling in the lining tubular epithelium with obliteration of the tubular lumen (Fig. 8.2). Levo in the double therapeutic group, there was perivascular oedema surrounding the congested blood vessels (Fig. 9.2). In the Levo + dill group, there was no histopathological alteration as recorded in (Fig. 10.2). In the Levo double + dill group, there was no histopathological alteration as recorded in (Fig. 11.3).

For 21 days duration time, the control group exhibited there no histopathological alteration as recorded in (Fig. 6.3). In the Dill group, there was no histopathological alteration as

recorded in (Fig. 7.3). In Levo therapeutic group, there was congestion in the cortical blood vessels (Fig. 8.3). Levo in the double therapeutic group, there was no histopathological alteration as recorded in (Fig. 9.3). In the Levo + dill group,

there was no histopathological alteration as recorded in (Fig. 10.3). In the Levo double + dill group, there was no histopathological alteration as recorded in (Fig. 11.3).

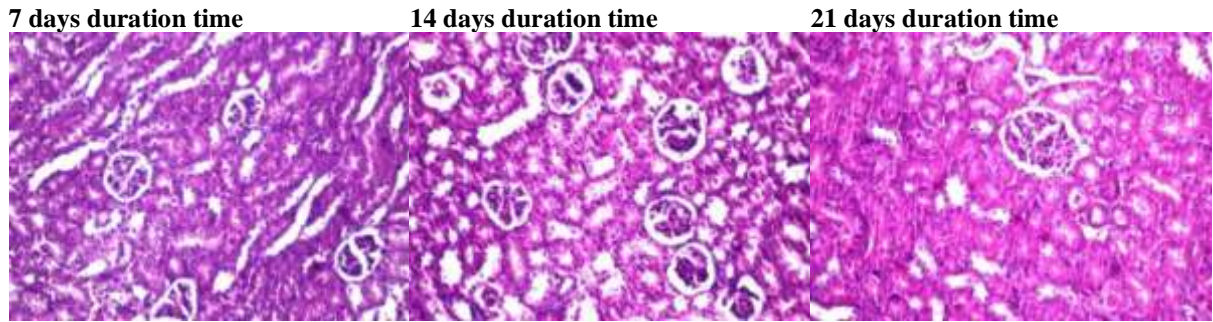


Fig. 6.1

Fig. 6.2

Fig. 6.3

Figure 6. Control group, no histopathological alteration and the normal histological structure of the glomeruli and tubules at the cortex were recorded after 7 days (Fig. 6.1), after 14 days (Fig. 6.2), and after 21 days (Fig. 6.3).

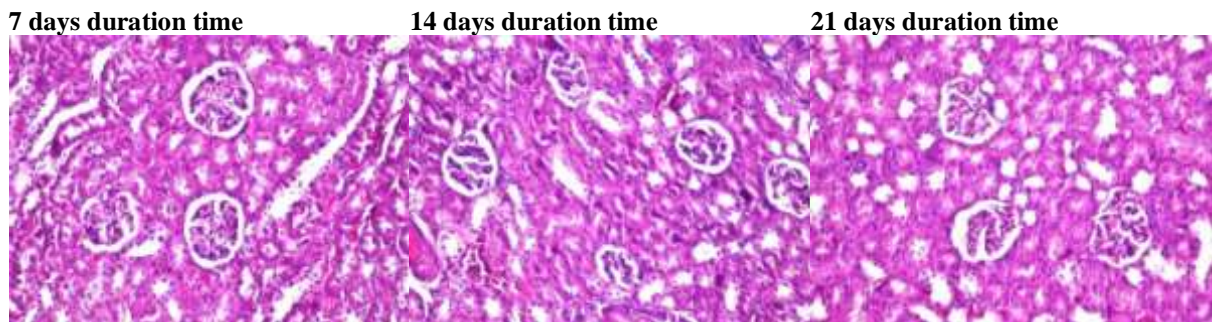


Fig. 7.1

Fig. 7.2

Fig. 7.3

Figure 7. Dill group, no histopathological alteration and the normal histological structure of the glomeruli and tubules at the cortex were recorded after 7 days (Fig. 7.1.), after 14 days (Fig. 7.2), and after 21 days (Fig. 7.3).

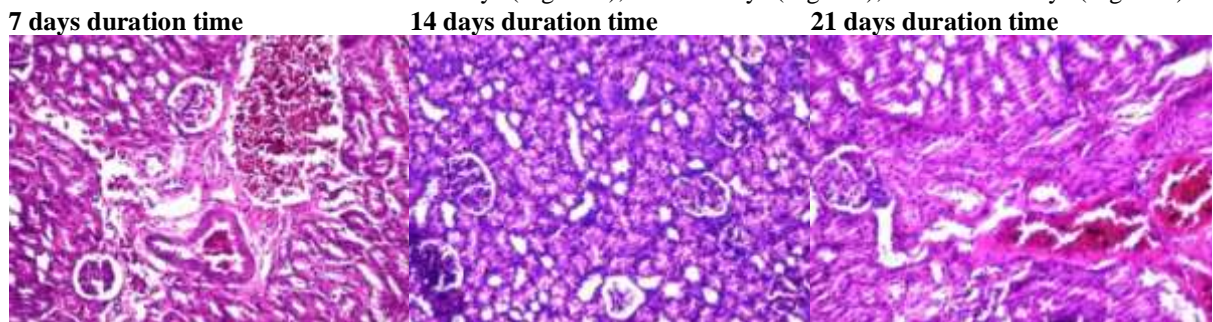
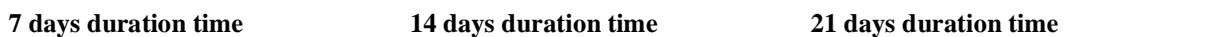


Fig. 8.1

Fig. 8.2

Fig. 8.3

Figure 8. In the Levo therapeutic group, congestion was observed in the cortical blood vessels (Fig. 8.1) after 7 days. After 14 days, there was swelling in the lining tubular epithelium with obliteration of the tubular lumen (Fig. 8.2), while there was congestion in the cortical blood vessels (Fig. 8.3) after 21 days.



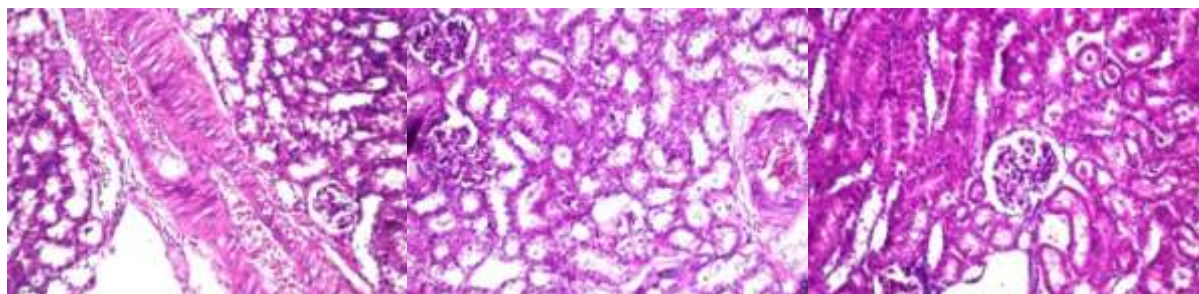


Fig. 9.1 **Fig. 9.2** **Fig. 9.3**
Figure 9. Levo double therapeutic group,congestion was observed in the sclerotic cortical blood vessels (Fig.9.1) after 7 days, while there was perivascular oedema surrounding the congested blood vessels (Fig. 9.2) after 14 days,and there was no histopathological alteration as recorded in (Fig.9.3).



Fig. 10.1 **Fig. 10.4** **Fig. 10.5**
Figure 10. Levo + Dill,no histopathological alteration, and the normal histological structure of the glomeruli and tubules at the cortex were recorded after 7 days (Fig. 10.1), after 14 days (Fig. 10.2), and after 21 days (Fig. 10.3).

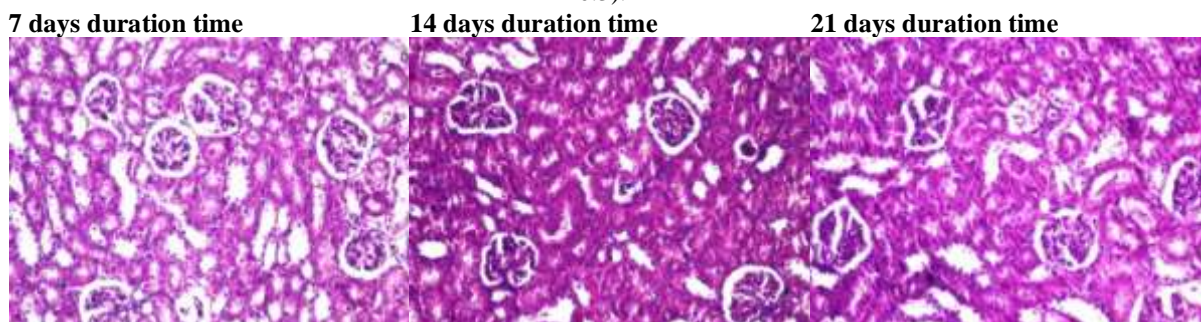


Fig. 11.1 **Fig. 11.2** **Fig. 11.3**
Figure 11. Levo double group + Dill,no histopathological alteration, and the normal histological structure of the glomeruli and tubules at the cortex were recorded after 7 days (Fig. 11.1), after 14 days (Fig. 11.2), and after 21 days (Fig. 11.3).

IV. DISCUSSION

4.1 The effect of Levofloxacin and Dill extract on serum Creatinine Levels in Rats

The findings of this study align with previous research demonstrating the nephrotoxic effects of fluoroquinolones, including Levofloxacin (Pannu and Nadim, 2008). The dose-dependent increase in serum creatinine levels observed in the Levofloxacin-treated groups underscores the need for careful dosage regulation in clinical settings to

mitigate renal impairment. The non-significant change in creatinine levels in the Dill group suggests that Dill extract, at the administered dose, does not adversely affect renal function. This is consistent with studies reporting the safety of herbal extracts in moderate doses (Al-Snafi, 2014). The protective effect of Dill extract against Levofloxacin-induced nephrotoxicity, particularly in the Levo double + Dill group, may be attributed to its antioxidant and anti-inflammatory properties.

Dill (*A. graveolens*) contains bioactive compounds such as flavonoids and polyphenols, which have been shown to mitigate oxidative stress and inflammation in renal tissues (**Yazdanparast and Bahramikia, 2008**). This aligns with emerging evidence supporting using natural antioxidants as adjuncts to reduce drug-induced organ damage (**Al-Sayed and El-Naga, 2015**).

4.2 The effect of Levofloxacin and Dill extract on serum urea levels in rats

The observed increase in serum urea levels in the Levofloxacin-treated groups is consistent with previous studies highlighting the nephrotoxic potential of fluoroquinolones (**Perazella and Rosner, 2022**). The dose-dependent rise in urea levels underscores the importance of monitoring renal function in patients receiving high doses of Levofloxacin, as urea is a sensitive marker of glomerular filtration rate (GFR) impairment (**Bellomo et al., 2012**). The non-significant change in urea levels in the Dill group aligns with existing literature on the safety of *A. graveolens* (Dill) extract in moderate doses (**Al-Snafi, 2014**). This suggests that Dill extract does not impose additional renal stress, making it a viable candidate for further investigation in nephroprotection. The significant reduction in urea levels in the Levo + Dill and Levo double + Dill groups highlights the potential renoprotective effects of Dill extract. This may be attributed to its antioxidant properties, which counteract the oxidative stress induced by Levofloxacin (**Srivastava et al., 2018**). Dill contains bioactive compounds such as monoterpenes and flavonoids, which have been shown to mitigate renal oxidative damage and inflammation (**Yazdanparast and Bahramikia, 2008**). These findings are supported by studies demonstrating the protective effects of natural antioxidants against drug-induced nephrotoxicity (**Al-Sayed and El-Naga, 2015**).

4.3 The effect of Levofloxacin and Dill extract on serum Blood urea nitrogen levels in rats

The observed elevation in BUN levels following Levofloxacin administration is consistent with its known nephrotoxic effects (**Perazella and Rosner, 2022**). The dose-dependent increase suggests impairment of glomerular filtration rate (GFR), as BUN serves as a sensitive marker of renal function (**Bellomo et al., 2012**). These findings align with previous reports of fluoroquinolone-induced nephrotoxicity through oxidative stress pathways (**Srivastava et al.,**

2018). The protective effect of Dill extract is particularly noteworthy. The normalization of BUN levels in the Levo + Dill group and the significant reduction in the Levo double + Dill group suggest that Dill extract may mitigate Levofloxacin-induced renal damage. This protective effect may be attributed to the antioxidant properties of *A. graveolens*, which contains bioactive compounds such as flavonoids and monoterpenes (**Al-Snafi, 2014**). These compounds likely counteract the oxidative stress induced by Levofloxacin, as demonstrated in other models of drug-induced nephrotoxicity (**Al-Sayed and El-Naga, 2015**). The differential effect between single and double therapeutic doses of Levofloxacin and their respective responses to Dill co-administration suggests a dose-dependent relationship in both toxicity and protection. This finding has important clinical implications, particularly for patients requiring high-dose or prolonged fluoroquinolone therapy (**Pannu and Nadim, 2008**). These results suggest that Dill extract may be a potential adjunct therapy to reduce Levofloxacin-induced nephrotoxicity. However, further research is needed to identify the optimal dose and molecular mechanisms and evaluate the potential pharmacokinetic interactions of Dill and Levofloxacin.

4.4 The effect of Levofloxacin and Dill extract on hepatic MDA Levels in liver tissue

The marked increase in renal MDA levels following Levofloxacin administration provides direct evidence of oxidative stress-mediated nephrotoxicity, consistent with previous reports on fluoroquinolone-induced lipid peroxidation (**Lowes et al., 2009**). The dose-dependent response suggests a direct relationship between drug concentration and oxidative damage, supporting clinical observations of dose-related renal toxicity (**Perazella and Rosner, 2022**).

The antioxidant capacity of Dill extract is particularly significant in this context. The substantial reduction in MDA levels in both combination groups suggests that *A. graveolens* effectively scavenges reactive oxygen species (ROS) generated by Levofloxacin. This finding aligns with recent studies demonstrating the ROS-scavenging activity of Dill's phenolic compounds (**Kaur et al., 2019**). The differential protection observed between single and double-dose combinations may reflect the saturation of antioxidant pathways at higher oxidative loads. Mechanistically, these results support the

hypothesis that Dill extract protects against Levofloxacin nephrotoxicity through multiple pathways such as direct free radical neutralization via flavonoid constituents, upregulation of endogenous antioxidant enzymes (SOD, CAT, GPx), and inhibition of inflammatory mediators (NF- κ B, TNF- α) as demonstrated in recent phytochemical analyses (Maodaa et al., 2025).

4.5 The effect of Levofloxacin and Dill extract on Renal CAT Levels in liver tissue

Levofloxacin's observed suppression of renal CAT activity provides compelling evidence of impaired antioxidant defense mechanisms, consistent with reports of fluoroquinolone-induced oxidative stress. Dose-dependent inhibition suggests that high-dose regimens may critically compromise the kidney's ability to detoxify hydrogen peroxide, potentially exacerbating oxidative damage. The preservation of CAT activity by Dill extract, particularly in the high-dose combination group, suggests two potential mechanisms: (i) Direct protection of enzyme structure from oxidative damage and (ii) Upregulation of CAT gene expression as supported by recent studies on herbal antioxidants (Maodaa et al., 2025). The differential effect between single and double-dose combinations may reflect threshold effects in enzyme protection pathways. These findings complement our previous observations of MDA reduction, demonstrating that Dill extract protects against Levofloxacin nephrotoxicity through multiple antioxidant mechanisms: (i) Scavenging reactive oxygen species (Table 4), preserving endogenous antioxidant enzymes (CAT results), and maintaining cellular redox balance.

The histopathological findings presented in this study reveal significant insights into the effects of levofloxacin and dill extract on kidney architecture over varying durations (7, 14, and 21 days). The results highlight the nephrotoxic potential of levofloxacin, particularly at therapeutic and double therapeutic doses (Ansari et al., 2019), as well as the protective role of dill extract in mitigating these adverse effects (Srivastava et al., 2018; Fiqardina et al., 2022). These observations are consistent with existing literature on drug-induced nephrotoxicity properties of herbal extracts (Fiqardina et al., 2022; Zhang et al., 2018; Rani et al., 2024).

Levofloxacin administration, especially at higher doses, induced notable kidney histopathological alterations during 21 days of

treatment. These findings align with previous studies demonstrating that fluoroquinolones, including levofloxacin, can cause vascular congestion, tubular damage, and interstitial inflammation due to oxidative stress and mitochondrial dysfunction (Famularo and De Simone, 2002). The observed tubular swelling and luminal obliteration indicate acute tubular injury, a common manifestation of antibiotic-induced nephrotoxicity (Campbell et al., 2023).

The most striking finding of this study is the renoprotective effect of dill extract. In groups of co-administered levofloxacin and dill (Levo + Dill and Levo double + Dill), no histopathological alterations were observed at any time point. This suggests that dill extract effectively counteracted the nephrotoxic effects of levofloxacin. Dill (*A. graveolens*) is rich in flavonoids, polyphenols, and essential oils, which possess antioxidant, anti-inflammatory, and free radical-scavenging properties (Yazdanparast and Bahramikia, 2008). These bioactive compounds likely mitigate oxidative stress and inflammation, key mechanisms of drug-induced kidney injury (Kaur et al., 2019). The protective effects of dill observed in this study are consistent with prior research on herbal extracts. For instance, garlic and green tea extracts have been shown to attenuate gentamicin-induced nephrotoxicity by reducing lipid peroxidation and enhancing antioxidant enzyme activity. Similarly, dill extract has demonstrated hepatoprotective and nephroprotective effects in models of acetaminophen and cisplatin toxicity. The absence of histopathological changes in the dill-only group further supports its safety profile (Abbasi Oshaghi et al., 2015; Abbasi-Oshaghi et al., 2018).

Interestingly, the renoprotective effects of dill extract mirror those of other antioxidant-rich botanicals. For example, curcumin and resveratrol have been shown to protect against contrast-induced nephropathy by modulating oxidative stress pathways. The ability of dill to preserve normal glomerular and tubular architecture underscores its potential as an adjunct therapy to mitigate drug-induced kidney injury (Chahal et al., 2017; Kaur et al., 2019).

These findings have important clinical implications, particularly for patients requiring prolonged or high-dose levofloxacin therapy. The study suggests that co-administration of dill extract could prevent nephrotoxicity without compromising the antibiotic's efficacy. Future research should explore the molecular mechanisms underlying dill's protective effects. Additionally,

clinical trials are warranted to validate these findings in human subjects.

V. CONCLUSION

This study conclusively demonstrates that Levofloxacin induces dose-dependent nephrotoxicity in rats through oxidative stress pathways, as evidenced by significantly elevated serum creatinine, urea, and BUN levels, increased renal MDA content, and decreased CAT activity. Dill extract (*A. graveolens*) exhibited consistent renoprotective effects by attenuating these biochemical alterations, reducing oxidative stress markers, and preserving antioxidant defenses. The extract's efficacy was particularly notable at higher oxidative stress levels, suggesting multiple protective mechanisms, including free radical scavenging, antioxidant enzyme preservation, and cellular redox balance maintenance. These findings position Dill extract as a promising adjunct therapy for mitigating Levofloxacin-induced nephrotoxicity, especially in high-dose regimens. Dill extract effectively prevents these histopathological changes through its antioxidant and anti-inflammatory properties. These results contribute to the growing body of evidence supporting the use of phytochemicals as protective agents against drug-induced organ damage. However, further research is needed to optimize dosing, elucidate molecular mechanisms, evaluate pharmacokinetic interactions, and validate clinical applications. The study provides compelling evidence for exploring standardized Dill formulations as a natural strategy to enhance the safety profile of fluoroquinolone antibiotics while maintaining their antimicrobial efficacy.

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