

PROTECTIVE EFFECTS OF *ECHINACEA PURPUREA* AND VITAMIN E AGAINST LINEZOLID-INDUCED RENAL DAMAGE IN RATS

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ABSTRACT

The antibiotic linezolid (LNZ) works well against vancomycin-resistant Enterococci and Gram-positive bacteria. Although thrombocytopenia is the most common adverse hematological impact caused by LNZ, pancytopenia is an uncommon complication that can have detrimental consequences on the kidneys. The existing study was planned to inspect the protective effect of *E. purpurea* and vitamin E against LNZ-induced renal damage in rats. This research was conducted on 35 male rats, two months old, seemingly healthy, weighing 150-200 g, alienated haphazardly into 7 equal groups. The 1st group of rats received 0.5 ml/200 g/day of distilled water (control group), the 2nd group received Tween 80 (0.5 ml/200 g/day), the 3rd group received LNZ (54 mg/kg b.wt), the 4th group was given Vit E (90 mg/kg b.wt), the 5th group received immulant (15.75 mg/kg b.wt), and the 6th and 7th groups received Vit E + LNZ and immulant + LNZ, respectively, at the same doses. Treatments were administered orally for 14 succeeding days for all groups. LNZ exposure evoked significant leukopenia, lymphopenia, neutropenia, and monocytopenia in rats' blood, compared with the controls. This suppression of linezolid was partially improved by vitamin E (gp. 6) or immulant treatments. LZN increased creatinine, urea, pH, and MDA levels in the serum, while serum Ca, SOD, CAT, and GPx levels significantly dwindled compared to the control group. Pathologically, the kidney of rats treated with LNZ exhibited cloudy tubular epithelial swelling and hydropic degeneration, dilated collecting tubules and ducts, and intratubular hyaline and cellular casts, in addition to high caspase expression in renal tissues compared with other treated groups. Co-administration of vitamin E or immulant with LNZ alleviated nearly all adverse side effects caused by LNZ exposure, compared with LNZ-treated rats. Furthermore, the co-administration of vitamin E or an immulant significantly enhanced both the kidney's histological structure and the immunohistochemistry of caspase 3 expression. In conclusion, vitamin E or an immulant showed encouraging renoprotective, anti-inflammatory, antioxidant, and ameliorative effects against linezolid-induced renal damage.

Keywords: Linezolid, immulant, rats, creatinine, calcium, antioxidants.

INTRODUCTION

More than 800 million individuals worldwide suffer from kidney dysfunction,

which affects more than 10% of the population (Kovesdy, 2022). Its incidence is increasing as a result of environmental causes, aging populations, and the development of chronic diseases. With rising mortality and disease burden, kidney dysfunction is acknowledged by the World Health Organization (WHO) as a major

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worldwide health concern (Zhang *et al.*, 2023).

Linezolid (LZD), the first synthetic oxazolidinone antimicrobial drug, inhibits bacterial protein production by binding to rRNA, giving it strong antibacterial efficacy against Gram-positive bacteria (Hashemian *et al.*, 2018; Kendir-Demirkol *et al.*, 2023; Zou *et al.*, 2024).

Rats given LNZ exhibited a substantial increase in lipid peroxidation indicators like MDA and developed liver damage from free radicals (Vivekanandan *et al.*, 2018). LZD is also associated with ocular and peripheral neuropathy, thrombocyte-penia, anemia, hyperlactatemia, nausea, diarrhea, migraines, and other adverse symptoms (Hashemian *et al.*, 2018; Wang *et al.*, 2019).

Due to increased knowledge of immune system modulation and the need to achieve the fundamental objectives of disease hindrance, the immunomodulating effects of natural elements have been the subject of significant and intense research in recent years (Hashem *et al.*, 2020).

Echinacea purpurea is a perennial medicinal herb with important immunomodulatory and anti-inflammatory properties (Puchalski *et al.*, 2025). Other studies showed that *E. purpurea* has been used in the prevention and treatment of different pathological conditions (Jukić *et al.*, 2015; Gu *et al.*, 2023). Alkylamides present in *Echinacea* have also shown antiviral, antibacterial, antioxidant, and anti-osteoporotic action, according to a recent assessment of the plant's biological activities, albeit the precise processes underlying these effects remain unknown (Burlou-Nagy *et al.*, 2022). Additionally, in vitro research has demonstrated that alkylamides have important immunomodulatory and anti-inflammatory qualities due to their modulation of monocytes and macrophages, reduction of

NO, and inhibition of IL-2, lipopolysaccharide-induced TNF- α , COX-1, and, to a lesser extent, COX-2 (Manayi *et al.*, 2015; Nagoor Meeran *et al.*, 2021; Vieira *et al.*, 2022). Additionally, past research demonstrated that *E. purpurea* has adaptive immunomodulating qualities in vivo by raising the anti-inflammatory cytokine IL-10 and diminishing TNF- α and IL-1 β inflammatory cytokines (Kolev *et al.*, 2022; Gancitano *et al.*, 2024). However, if consumed in large quantities or over an extended time, *E. purpurea* may cause renal dysfunction (Rezaie *et al.*, 2013). Numerous works have also displayed an upsurge in blood urea, nitrogen, and creatinine levels after APAP overdose (Esposito *et al.*, 2007; Hindaw and Hendawy, 2019). These results may serve as markers of nephrotoxicity. Echinacea-based preparations have been shown to have antioxidant and free radical scavenging properties (Agnew *et al.*, 2005; Masteikova *et al.*, 2007; Bayramoglu *et al.*, 2011).

Vitamin E is a small molecule antioxidant that is lipid-soluble and a member of the tocopherol antioxidant family. The strongest form of vitamin E can neutralize RNS, such as peroxynitrite, NO₂, and NO (Hammad *et al.*, 2023). Because of its peroxy radical scavenging action, vitamin E prevents the production of free radicals and might effectively reduce lipid peroxidation, which causes oxidative stress in biological systems (Tahmasebi *et al.*, 2015).

According to recent studies, using vitamin E enhanced renal tubular regeneration and decreased biochemical deficits (creatinine, urea, MDA, SOD, and GSH) (Darwish *et al.*, 2017; Ghilissi *et al.*, 2018; Eid *et al.*, 2020). Furthermore, vitamin E administration, either by itself or in conjunction with other antioxidant agents, may improve oxidative stress biomarkers like serum urea, creatinine, and malondialdehyde levels, while also increasing the renal antioxidants such as

GSTs, renal CAT, and SOD (Hakiminia *et al.*, 2019). Vitamin E is suggested as a preventive agent for kidney injuries that go together with ROS, such as happens with acute kidney injury owing to nephrotoxic drugs (Liu *et al.*, 2015; Zhao *et al.*, 2019; Badr *et al.*, 2022).

Therefore, the existing inquiry was aimed at assessing the alleviation or protective effects of vitamin E and immulant on linezolid-induced renal injury in rats.

MATERIALS AND METHODS

Chemicals:

Linezolid: LZD® (Global Napi, Egypt) was attained from Sigma-Aldrich Chemical Pvt Limited, India, available as tablets (600 mg/tablet). Tween 80 and Vitamin E were attained from Al-Gomhoria Co. Ltd., Egypt. Vitamin E was prepared immediately before use by dissolving it in Tween 80. *E. purpurea* extract in the form of immulant tablets (175 mg/tablet) was acquired from Arab Company for Pharmaceuticals and Medicinal Plants (Cairo, Egypt). The immulant was prepared immediately before use by dissolving it in distilled water.

Animals and Experimental Design:

In this inquiry, 35 mature male Sprague Dawley rats of 150–200 g body weight were employed. The Animal House at the Fac. of Vet. Med., University of Zagazig in Egypt, is where the rats were acquired. Water and food were given "*ad libitum*." The following room conditions were present in the stainless-steel cages where the animals were kept: $21 \pm 5^\circ\text{C}$, $50 \pm 10\%$ relative air humidity, 12 hours of light, and 12 hours of darkness. Before the trial, the animals were given a week to get used to the lab environment. Every technique complied with the university's experimental animal care policies, which were authorized by the ZU-IACUC Committee of Zagazig

University, Faculty of Veterinary Medicine in Egypt.

Thirty-five animals were disaggregated randomly into seven equal groups. The 1st group (G1) was kept as a control, which took distilled water (0.5 ml/200 g/day), which was used as a solvent for LNZ and immulant. The 2nd group (G2) received Tween 80 (0.5 ml/200 g/day), which was used as a solvent for Vit E. The 3rd group (G3) received LNZ (54 mg/kg b.wt). The 4th group (G4) received Vit E (90 mg/kg b.wt). The 5th group (G5) received immulant (15.75 mg/kg b.wt). The 6th (G6) and 7th (G7) groups received Vit E plus LNZ and immulant plus LNZ, respectively, at the same doses.

All treatments were prepared freshly before use and given by oral gavage daily for 14 days for all groups. In accordance with Paget and Barnes (1964), the dosages of LNZ, vitamin E, and immulant were determined.

Blood sampling:

Rats were sacrificed after 24 h following the latest dose under light ether anesthesia for sampling. Blood was drawn right away and separated into two portions, one of which was placed in a tube containing EDTA anticoagulant for hematological examination. To separate the serum, the remaining portion was transferred into a different plain tube devoid of anticoagulant, allowed to coagulate at room temperature, and then centrifuged for 20 minutes at 5000 rpm (Hashem *et al.*, 2022). Sera were kept at -20°C for biochemical inquiry.

Hematobiochemical analysis:

The total and differential leukocyte counts were determined using a hematological autoanalyzer (Automated Hematology Analyzer Edan H30).

Serum urea, creatinine, inorganic phosphorus (Ph), and calcium (Ca) were determined using the SPINREACT kit (SPINREACT, Ctra. Santa Coloma, SPAIN). A biodiagnostic kits CONTRACT (Bio-diagnostic. Com., 29 Tahreer St., Dokki, Giza, Egypt) was used to measure the amounts of malondialdehyde (MDA) and other antioxidant indices in the serum, such as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD).

Histopathological and immunohistochemical studies:

The kidney was promptly removed after sacrifice and preserved in 10% neutral-buffered formalin. An automated tissue processor was used to process the formalin-preserved kidney tissue. Melted paraffin wax was then used to saturate the samples, which were subsequently blocked out and embedded. Hematoxylin and eosin were used to stain paraffin slices of 4–5 μm thickness (Suvarna *et al.*, 2013).

For immunohistochemical analysis, 5 μm -thick paraffin slices were mounted on positively charged glass slides (Biogenex, Fremont, CA, USA). After an overnight soak in xylene, paraffin sections were run through 100, 95, 75, and 50% ethanol. The sections were coated with a single drop of the supersensitive primary monoclonal antibody (Caspase 3). The slides were washed in PBS for 5 minutes following a 60-minute incubation period with secondary antibody. A biotin-streptavidin (BSA) system was used to observe the response after the primary antibody had initially attached to the relevant antigen (Hsu *et al.*, 1981). Diaminobenzidine (DAB) was utilized for the permanent visualization of the antigen-antibody reaction, and hematoxylin was employed for counterstaining. Following 20 minutes of application of two drops of DAKO EnVision, PBS was used for rinsing. The slides were washed in buffer to remove the

diaminobenzidine (DAB) chromogen after it had been applied for 10 to 20 minutes, or until the appropriate brown color was reached. Mayer's hematoxylin (Hx) was used as a counterstain for the slices' nuclei. Depending on the degree of nuclear staining, sections were immersed in Hx solution for three to five minutes, then washed with tap water, subjected to an acid-alcohol differentiation, and then washed again with tap water. Canada balsam was used to mount air-dried slides.

For myeloperoxidase immunohistochemistry, slides were heated in a pressure cooker. Use 0.075% Tween 20 in Tris-buffered saline for ten minutes to extract the antigen (Carson, 1997). To suppress endogenous peroxidase activity, the samples were then treated in 0.3% v/v H_2O_2 in methanol for 20 minutes at room temperature (Harlow and Lane, 1988). After 30 minutes of room temperature incubation with a 1:1500 diluted polyclonal rabbit anti-human myeloperoxidase antibody, the sections were stained. Utilizing the avidin-biotin-horseradish peroxidase technique, immunostaining was performed with DAB as the chromogen.

Statistical analysis:

The mean $\pm$ standard error of the mean was used to express the data. SPSS software version 20 was used to evaluate the hemato-biochemical data and the data from the image analyzer. The analysis of variance (ANOVA) test was used for statistical analysis. Differences were considered significant at $P \leq 0.05$ and non-significant at $P \geq 0.05$.

RESULTS

Leukocyte indices:

As shown in Table (1), LNZ (54 mg/kg⁻¹ per day) administration induced a reduction of WBC, lymphocyte, neutrophil, and monocyte numbers in rat blood when paralleled to control. This suppression of LNZ was partially improved by vitamin E (G6) or

immulant (G7) treatment, as there are significant increases in the total and differential leukocyte count when matched with the LNZ group. This picture was returned to the control values. The eosinophil and basophil counts showed non-significant changes in all treated groups. Administration of vitamin E and an immulant alone demonstrated non-statistical dissimilarities in the leukocyte parameters in contrast to control groups (G1 & G2). Renal functional markers and antioxidants: At 14 days post-treatment, the serum urea, creatinine, and pH levels revealed a significant ($P \leq 0.001$) rise in LNZ-intoxicated rats in association with the control groups, while the serum Ca level declined significantly (Table 2). The combination of LNZ with vitamin E or an immulant resulted in indistinguishable renal biomarker values from those of the controls.

These results indicated complete improvement and relieving effects of vitamin E or the immulant in the treated groups that were exposed to LNZ. Compared to control groups, serum activity of antioxidants (SOD, CAT, and GPx) was diminished significantly in LNZ-treated rats. However, serum MDA was noticeably augmented in LNZ-treated rats, as epitomized by a significant rise in MDA level compared to control rats. Rats treated with Vit E (G6) or immulant (G7) expressed a significant decrease in MDA level with significantly elevated serum antioxidant activities; compared to the LNZ group, these were returned nearly close to values of controls. In the vitamin E or immulant-treated groups (G4&5), antioxidant and MDA evaluations did not significantly change compared to the control groups (Fig. 1 A-D).

Table 1: Effect of Vit E and Immulant on leukogram in rats treated with DW (G1), Tween 80 (G2), LNZ (G3), Vit E (G4), Immulant (G5), Vit E+LNZ (G6) and Immulant + LNZ (G7) orally for 14 days.

Item	G1	G2	G3	G4	G5	G6	G7
WBCs ($\times 10^3/\mu\text{L}$)	17.83 ^a ± 0.78	17.70 ^a ± 1.74	11.51 ^c ± 0.94	17.00 ^a ± 1.10	16.70 ^a ± 3.90	13.90 ^{ab} ± 2.11	13.10 ^b ± 2.69
Neutrophils ($\times 10^3/\mu\text{L}$)	1.86 ^a ± 0.33	1.99 ^a ± 0.60	1.00 ^c ± 0.17	1.98 ^a ± 0.28	1.68 ^a ± 1.37	1.58 ^b ± 0.41	1.61 ^{ab} ± 0.17
Lymphocytes ($\times 10^3/\mu\text{L}$)	14.22 ^a ± 0.54	14.00 ^a ± 1.98	9.40 ^c ± 0.92	13.90 ^a ± 1.06	13.00 ^a ± 1.98	11.00 ^b ± 2.19	10.10 ^b ± 2.39
Monocytes ($\times 10^3/\mu\text{L}$)	1.36 ^a ± 0.07	1.31 ^a ± 0.10	0.80 ^b ± 0.12	1.24 ^a ± 0.04	1.24 ^a ± 0.50	0.98 ^{ab} ± 0.18	1.02 ^{ab} ± 0.14
Eosinophils ($\times 10^3/\mu\text{L}$)	0.34 ^a ± 0.04	0.36 ^a ± 0.01	0.32 ^a ± 0.01	0.34 ^a ± 0.01	0.34 ^a ± 0.07	0.35 ^a ± 0.04	0.32 ^a ± 0.04
Basophils ($\times 10^3/\mu\text{L}$)	0.06 ^a ± 0.02	0.05 ^a ± 0.03	0.05 ^a ± 0.01	0.06 ^a ± 0.02	0.05 ^a ± 0.01	0.05 ^a ± 0.01	0.06 ^a ± 0.03

Values are expressed as mean $\pm$ SE. The different superscripts (a-c) for the same parameter are significantly different at $P \leq 0.05$. DW: Distilled water; LNZ: Linezolid; Vit E: Vitamin E; WBCs: White blood cells. (n=5).

Table 2: Effect of Vit E and immulant on renal function markers in rats treated with DW (G1), Tween 80 (G2), LNZ (G3), Vit E (G4), Immulant (G5), Vit E+LNZ (G6) and Immulant + LNZ (G7) orally for 14 days.

Item	G1	G2	G3	G4	G5	G6	G7
Urea (mg/dl)	29.33 ^c ± 4.06	29.00 ^c ± 1.53	71.00 ^a ± 1.15	28.67 ^c ± 1.20	29.00 ^c ± 0.58	60.33 ^b ± 0.88	54.67 ^b ± 2.85
Creatinine (mg/dl)	1.10 ^{cd} ± 0.06	0.95 ^{cd} ± 0.04	2.23 ^a ± 0.24	1.02 ^{cd} ± 0.04	0.86 ^d ± 0.08	1.73 ^b ± 0.15	1.42 ^{bc} ± 0.01
Ph (mg/dl)	2.93 ^b ± 0.09	2.97 ^b ± 0.12	3.30 ^a ± 0.06	2.80 ^b ± 0.06	2.87 ^b ± 0.03	2.42 ^c ± 0.06	2.40 ^c ± 0.04
Ca (mg/dl)	9.47 ^a ± 0.19	9.23 ^a ± 0.20	6.50 ^c ± 0.12	9.50 ^a ± 0.17	9.37 ^a ± 0.09	8.80 ^{ab} ± 0.06	8.60 ^{ab} ± 0.06

Values are expressed as mean $\pm$ SE. The different superscripts (a-d) for the same parameter are significantly different at $P \leq 0.05$. DW: Distilled water; LNZ: Linezolid; Vit E: Vitamin E; Ph: Phosphorus, Ca: Calcium. (n=5).

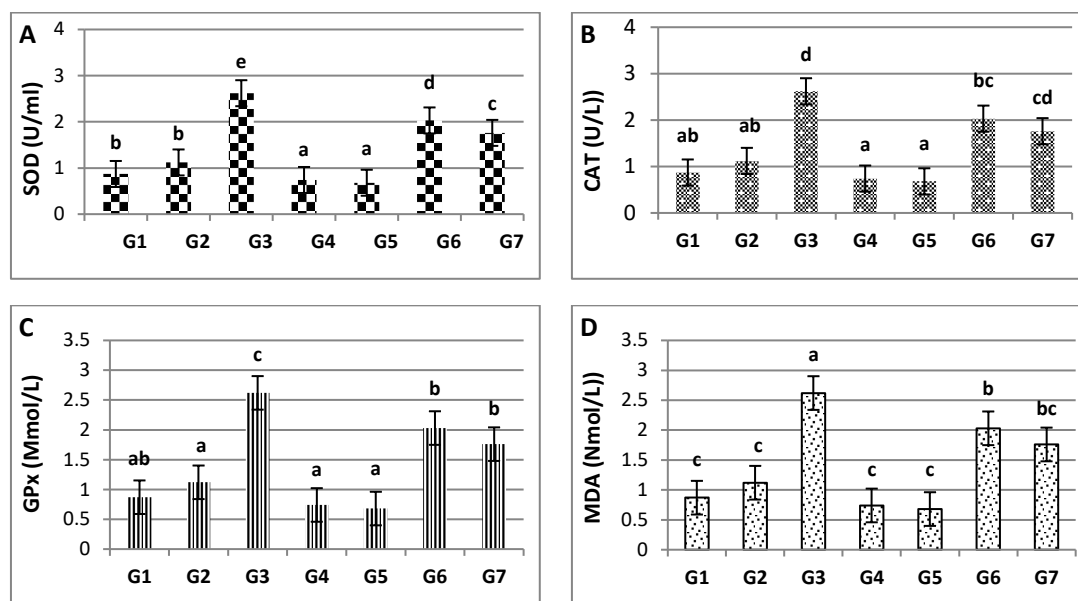


Fig. 1 A-D: Effect of Vit E or immulant on serum SOD, CAT, and GPx activities and MDA level in male rats treated with distilled water (G1); Tween 80 (G2); LNZ (G3), Vit E (G4), Immulant (G5), Vit E+LNZ (G6) and Immulant+LNZ (G7) orally for 14 days. Values are expressed as mean $\pm$ SE. Different letters above the bar's indicant a significant difference at $P \leq 0.05$. (n=5).

Histopathological findings

Sections from the kidneys of treated rats with DW (G1, control), Tween 80 (G2), Vit. E (G4), immulant (G5), Vit. E + LNZ (G6), and immulant + LNZ (G7), almost all of them showed closely related mild changes represented by renal tubular epithelial cloudy swelling, dilated collecting tubules, and some lobulated glomeruli, in addition to mildly dilated renal blood vessels (**Fig. 2 A-N**). However, the lesions in LNZ-treated rats (G3) were more severe, characterized by the presence of a large number of shrunken, lobulated glomeruli; tubular epithelial cloudy swelling and hydropic degeneration; dilated collecting tubules and ducts; and intra-tubular hyaline and cellular casts. Moreover, dilated renal blood vessels could also be encountered (**Fig. 2 E&F**).

Immunohistochemical findings

The renal tissues demonstrated negative expression of caspase 3 in control groups (G1 and G2) (**Fig. 3 A&B**). Mild expression of the used marker was recorded

in groups 4, 5, 6, and 7 as 3.99%, 7.20%, 7.64%, and 8.50%, respectively (**Fig. 3 D-G**); meanwhile, LNZ-intoxicated rats (G3) showed a slightly higher expression of caspase 3 (11.24%) as compared with other positive groups (**Fig. 3 C**).

DISCUSSION

The oxazolidinone antibiotic linezolid (LNZ) is commonly used as a treatment decision for judgmentally sick patients in the intensive care unit (Liu *et al.*, 2023) and is an actual therapy opportunity for severe infections caused by drug-resistant gram-positive bacteria (Chien *et al.*, 2000). Despite indications of higher exposure and myelosuppression in renal impairment, LNZ is given to all patients at a set dosage (Crass *et al.*, 2019). Patients with normal renal function have kidneys that eliminate around 30% of LNZ (Slatter *et al.*, 2001; Bai *et al.*, 2022). Additionally, linezolid and blood urea nitrogen or creatinine clearance were found to be correlated by Cattaneo *et al.* (2016).

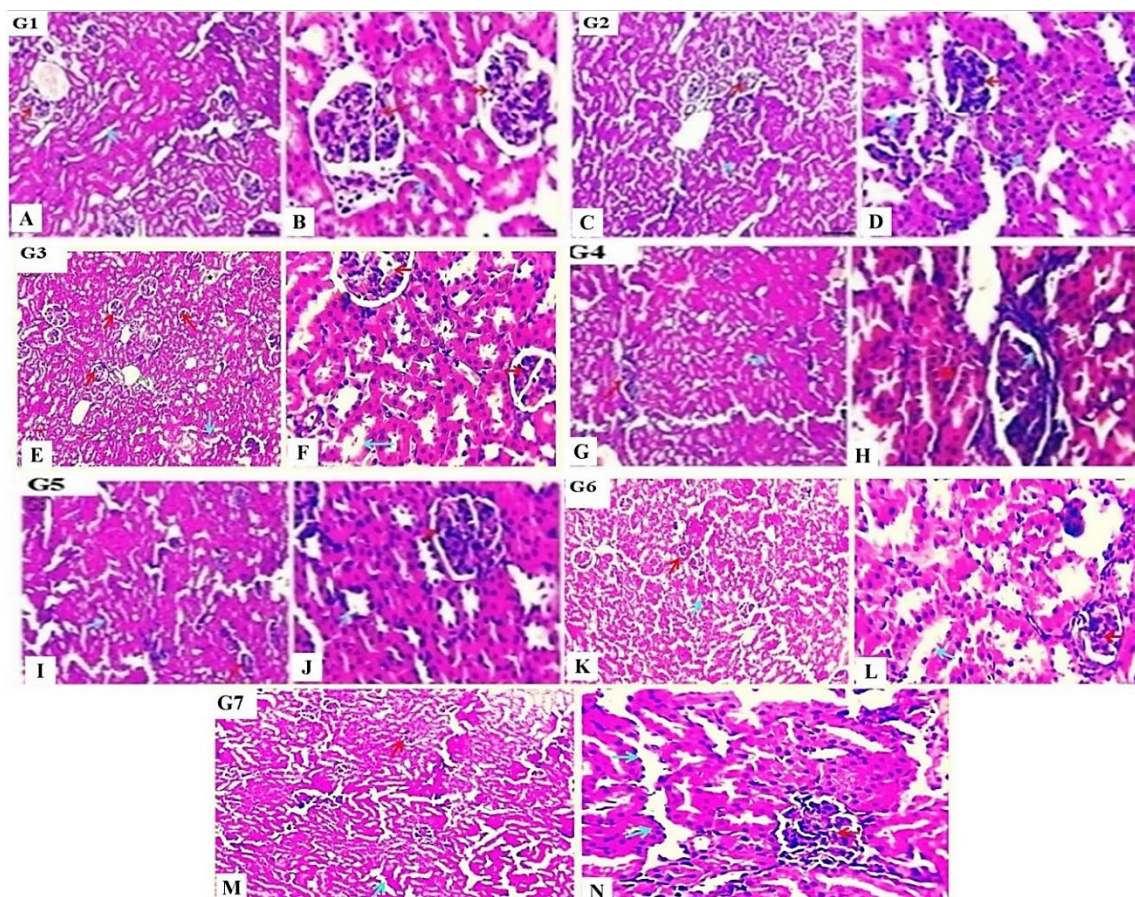


Fig. 2 (G1-7): Photomicrographs from kidneys of control (G1 A&B), tween treated (G2 C&D), Vit E treated (G4 G&H), immulant treated (G5 I&J) beside those of Vit E-linezolid (G6 K&L) and immulant-Linezolid treated rats (G7 M&N) showing mild changes represented by renal tubular epithelial cloudy swelling (light blue arrows), dilated collecting tubules (green asterisks) and some lobulated glomeruli (red arrows), in addition to mildly dilated renal blood vessels (black asterisks). Linezolid-treated rats (G3 E&F) showing a large number of shrunken, lobulated glomeruli (red arrows), tubular epithelial cloudy swelling and hydropic degeneration (light blue arrows), dilated collecting tubules and ducts (green asterisks), and intra-tubular hyaline and cellular casts (red asterisk). Mildly dilated renal blood vessels can also be observed (black asterisk). H&E X 100, 400.

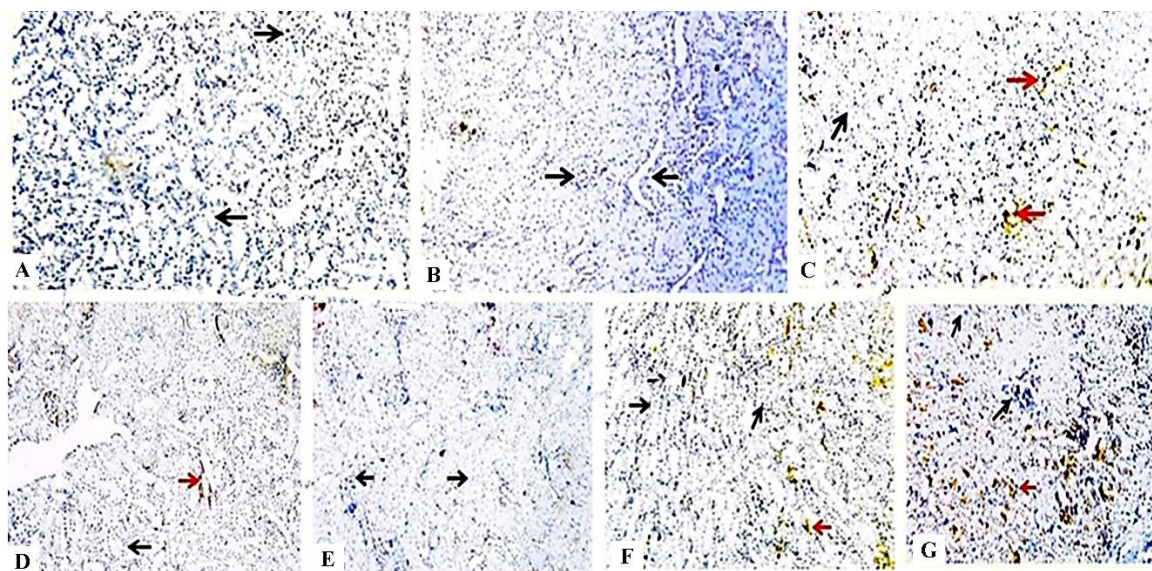


Fig. 3 (G1-7): Photomicrographs from kidney tissues of the different experimental groups immune-stained by caspase 3 showing mild expression of the used marker in groups 4 (D), 5 (E), 6 (F) and 7 (G), meanwhile LNZ exposed group (G3 C) showed a slightly higher expression of the caspase 3 as compared with the other groups. Black arrows point to negative cells and red arrows to the positive ones. X 400.

The extant inquiry was established to evaluate the potential incomes of Vit E or *E. purpurea* against linezolid-induced harmful effects in male rats.

Both creatinine and urea are metabolic waste products that are freely filtered by the glomeruli of the kidneys (Johnson and John, 2011). Furthermore, it has been demonstrated that plasma urea increases in situations of decreased effective circulating blood volume and renal perfusion, as well as in acute and chronic renal disease (Stevens *et al.*, 2006).

In the present experiments, rises in serum levels of creatinine, urea, and phosphorus, with hypocalcemia by LNZ, are an indication of abnormal renal function or renal impairment. The drug's interaction with the cell membrane may have caused the changes in kidney function biomarkers in LNZ-treated rats. This might have resulted in altered cell membrane permeability and loss of functional integrity, as well as concurrent histology abnormalities in kidney tissues that show renal failure (Wu *et al.*, 2006; Hindawy and Hendawy, 2019). This observation runs in line with recent studies by Natsumoto *et al.* (2014), Vivekanandan *et al.* (2018), and Abd El Fadil *et al.* (2019). Furthermore, Abdo Said *et al.* (2019) reported that LZD increased urea and creatinine serum levels in male albino rats that received LZD for 14 successive days, and this subsidizes the idea that LZD can cause renal inflammation (Nayak *et al.*, 2012).

However, treatment with vitamin E or an immunulant for 14 days resulted in complete improvement in the kidney biomarker values compared with the LNZ-intoxicated group. Our findings were in synchronization with Abdalla *et al.* (2016) and Hashem *et al.* (2020). Similarly, renal biomarker levels were decreased in rats given both vitamin E and cadmium (Karabulut-Bulan *et al.*, 2008) or in rats exposed to diethylnitrosamine-induced hepatic and renal damage and treated with *E. purpurea* (Rezaie *et al.*, 2013). Furthermore, Abdel-Wahhab *et al.* (2024) reported that animals treated with *E. purpurea* (EP) before bifenthrin intoxication had serum creatinine and urea levels that were

nearly identical to those of the normal control; this outcome illustrates how EP's anti-inflammatory and anti-apoptotic properties work in inebriated rats.

Antioxidant enzymes are important for maintaining homeostasis in proper cell function and are also employed as indicators of oxidative stress (Gutteridge, 1995). Oxidative stress was generated by LNZ and confirmed by high levels of lipid peroxidation markers and low GSH, CAT, and GPx activities (Halliwell and Gutteridge 2007; Lv *et al.* 2019).

The antioxidant indicators (SOD, CAT, and GPx) significantly dropped in the current study, and the amount of oxidative products (MDA) in the serum of the LNZ-intoxicated group noticeably increased as well. These results suggest that LNZ exposure induces oxidative stress, as reported by Wang *et al.* (2014), who stated that LNZ may have a tonic effect, mostly via reducing antioxidative activity by increasing the quantity of free radicals. Previous studies have shown that antioxidant enzyme activities generally decrease after oxidative damage (Stockham and Scott, 2002). The death of renal cells that produce or inhibit these enzymes by ROS may be the cause of the decrease of antioxidant enzyme activity in rats given LZN. The initial line of defense against oxygen poisoning is thought to be the enzymes CAT and SOD (Tan *et al.*, 2018). The SOD enzyme spurs the conversion of superoxide anion into H_2O_2 , which is then reduced by the CAT enzyme into H_2O , and a decrease in their activities could result in vast radical production (Choudhuri *et al.*, 2020).

Besides, GPx converts peroxide to a harmless molecule to conserve the cellular membrane (Wang *et al.*, 2019). Our results were parallel to other reports (Wang *et al.*, 2016; Vivekanandan *et al.*, 2018). Also, Abd El Fadil *et al.* (2019) showed a rise in MDA level and a reduction in CAT and SOD activities during LNZ administration (100 mg/kg) for 14 consecutive days. Lipid peroxidation causes oxidative deterioration of polyunsaturated fatty acids with an increase in free radical concentration, which causes

cellular infiltration and renal damage. This was confirmed by histopathological and immunohistochemical results in the renal tissue.

Antioxidants were augmented; meanwhile, MDA levels dwindled when vitamin E or an immulant was administered with LNZ in comparison to the LNZ group. Such results are consistent with preceding studies on vitamin E (Alasmari *et al.*, 2018; Ibrahim *et al.*, 2019; Vivekanandan *et al.*, 2022) or *E. purpurea* (Ezz, 2011; Mao *et al.*, 2021; Abdel-Wahhab *et al.*, 2024). It is commonly recognized that vitamin E is the cornerstone of an efficient antioxidant treatment because it stops free radicals from spreading throughout tissues and reacts with them to generate a tocopheryl radical, which scavenges peroxy radicals (Traber and Stevens, 2011; Wang *et al.*, 2014). The primary derivatives of *E. purpurea* (immulant) with strong antioxidant activity are caffeic and cichoric acids (Hashem *et al.*, 2018; Koriem, 2020). Furthermore, Tsai *et al.* (2012) suggested that the phenolic content and cichoric acid of *E. purpurea* may be responsible for the plant's antioxidant action. While alkamides have not demonstrated any antioxidant action, they can regenerate cichoric acid by adding hydrogen to the oxidized cichoric acid, enhancing its activity. Cichoric acid, like flavonoids, exhibits an efficient capacity to scavenge radicals (Thygesen *et al.*, 2007). The antioxidants were improved significantly in rats pretreated with *E. purpurea* and then intoxicated with hexavalent chromium (El-Demerdash *et al.*, 2024). Additionally, when CCL4 generated oxidative stress, *E. purpurea* triggered the activity of the antioxidant system (CAT and glutathione transferase) (Matsiopa *et al.*, 2012). Moreover, Joung and Son (2024) inspected the effect of *E. purpurea* on patients with kidney injury and found an improvement in BUN, serum creatinine, and estimated glomerular filtration rate values.

The histopathological and immunohistochemical results confirmed the reported biochemical data; the kidney tissues had significant histological alterations as a

result of LNZ exposure. Similar histological changes in the kidney have been documented previously (Nayak *et al.*, 2012; Abdel Aziz *et al.*, 2017). According to the histology results of the kidneys of rats given LNZ, the oxidative damage caused by LNZ may be the cause of notable changes to the kidney's architecture. Similarly, LNZ-treated rat kidneys showed cloudy swelling of tubular epithelium with mild interstitial nephritis (Hindaw and Hendawy, 2019).

However, Vit E or immulant plus LNZ-treated animals resulted in an improvement in renal tissues as compared with the LNZ-intoxicated group, as Vit E and *E. purpurea* demonstrated improvement in the pathological changes and caspase expressions as a tool of immunohistochemical examinations. Analogous fallouts were obtained by Badr *et al.* (2022) and Abdel-Wahhab *et al.* (2024). Since vitamin E is a cell membrane hydrophobic compound, it is one of the main endogenous antioxidants that reduces lipid peroxidation and targets free radicals, thus protecting mitochondrial membranes from damage by ROS (Ghliissi *et al.*, 2018; Eid *et al.*, 2020). Scavenging oxygen radicals and preventing lipid peroxidation with vitamin E help to maintain renal glomerular structure and function (Badr *et al.*, 2022). The morphological structure of the kidney cortex was improved (restored) when *E. purpurea* was administered to rats whose kidneys had been damaged by CCL4; the cytoplasm became clear, the nuclei took on distinct shapes, the tubule lumens widened, and the volume of the blood vessels increased (Matsiopa *et al.*, 2012). Moreover, histopathological examinations at both kidney and liver exhibited limited improvement in the damage seen in ischemia-reperfusion injury after *Echinacea* administration (Bayramoglu *et al.*, 2011).

CONCLUSION

Finally, LNZ inebriation caused alterations in the antioxidant defense and biochemical markers, in addition to histological and immunohistochemical changes in the kidneys. Furthermore, supplementing LNZ-

treated rats with Vit E or *E. purpurea* reduced oxidative damage and recovered the majority of the assessed parameters. As a result, vitamin E and *E. purpurea* had a significant radical scavenging ability by strengthening the antioxidant defense system and reducing free radical formation. Furthermore, our findings support vitamin E and *E. purpurea*'s application as a renoprotective supplement. Vit E or *E. purpurea* supplementation decreased oxidative damage and restored most of the evaluated parameters in LNZ-treated rats.

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التأثيرات الوقائية لنبات إشنسا بوربوريا وفيتامين هـ ضد تلف الكلى الناجم عن اللينزوليد في الجرذان

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يعمل المضاد الحيوي لاينزوليد (Linezolid, LNZ) بشكل جيد ضد المكورات المعوية المقاومة للفانكوميسين والبكتيريا إيجابية الجرام. على الرغم من أن قلة الصفائح هي التأثير الدموي الضار الأكثر شيوعاً الناجم عن لاينزوليد، فإن قلة الكريات الشاملة هي مضاعفة غير شائعة يمكن أن يكون لها عواقب وخيمة على الكلى. تم تصميم الدراسة الحالية للتحقيق في التأثير الوقائي المحتمل لـ *Echinacea purpurea* (immulant) وفيتامين E ضد بعض الآثار السلبية للينزوليد في ذكور الجرذان. تم إجراء هذا البحث على خمسة وثلاثين جرذاً ذكراً، يبلغ عمرهم شهرين ويتمتعون بصحة جيدة ويزنون ١٥٠-٢٠٠ جرام، مقسمين عشوائياً إلى ٧ مجموعات متساوية. تلقت جرذان المجموعة الأولى ٠,٥ مل / ٢٠٠ جرام / يوم من الماء المقطر (المجموعة الضابطة)، تلقت المجموعة الثانية توين ٨٠ (٠,٥ مل / ٢٠٠ جرام / يوم)، المجموعة الثالثة أعطت LNZ (٥٤ مجم / كجم من وزن الجسم)، المجموعة الرابعة تلقت فيتامين هـ (٩٠ مجم / كجم من وزن الجسم)، المجموعة الخامسة تلقت إيميولاند (١٥,٧٥ مجم / كجم من وزن الجسم)، المجموعة السادسة والسابعة تلقت فيتامين هـ + LNZ، وإيميولاند + LNZ على التوالي بنفس الجرعات السابقة. كانت العلاجات عن طريق الفم لمدة ١٤ يوماً متتالياً لجميع المجموعات. أدى التعرض لـ LNZ نقصاً كبيراً في الكريات الدم البيضاء وقلة الخلايا اللمفاوية وقلة الخلايا متعادلة الصبغات وقلة الخلايا الوحيدة في دم الجرذان عند مقارنتها بالضوابط. زاد بشكل ملحوظ من تركيزات الكرياتينين واليوريا والفسفور وMDA في مصل الدم، بينما انخفضت مستويات الكالسيوم وSOD, CAT and GPx في مصل الدم بشكل ملحوظ مقارنة بمجموعة التحكم. لقد أدى العلاج بـ فيتامين هـ أو العلاج بإيميولاند مع LNZ إلى تحسن واضح. من الناحية المرضية، أظهرت الجرذان المعالجة بـ LNZ تورماً غائماً في الظهارة الأنبوبية للكلى وتنكساً مائياً، وأنابيب وقنوات تجميع متوسعة، إلى جانب وجود طبقة زجاجية وخلوية داخل الأنبوب. بالإضافة إلى ارتفاع التعبير عن بروتين الموت الذاتي الكاسباس ٣ في أنسجة الكلى لدى الجرذان المعالجة بـ LNZ مقارنة بالمجموعات المعالجة الأخرى. أدى الإعطاء المشترك لفيتامين هـ أو إيميولاند مع LNZ إلى تخفيف جميع الآثار الجانبية الضارة تقريباً الناجمة عن التعرض لـ LNZ مقارنة بالجرذان المعالجة بـ LNZ. علاوة على ذلك، فقد عززوا بشكل كبير البنية النسيجية للكلى والمناعة الكيميائية لتعبير الكاسباس ٣ في أنسجة الكلى. وفي الختام، يظهر فيتامين E أو إيميولاند تأثيرات مشجعة في حماية الكلى ومضادات الالتهابات ومضادات الأكسدة وتحسين الضرر الكلوي الناجم عن لينزوليد.