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Research Article

Protective Effect of Vitamin E and Quercetin on Colistin Induced Nephrotoxicity in Adult Male Albino Rats

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Abstract

Background: Colistin is one of the few remaining therapeutic options available for the treatment of infections caused by multidrug-resistant gram-negative bacteria. Notwithstanding its efficiency, nephrotoxicity is the major adverse effect that impedes the ability to administer high doses of colistin. Renal toxicity due to colistin was reported to be mainly present as acute tubular necrosis.

Objective: To evaluate that quercetin and vitamin E would show a protective effect against nephrotoxicity induced by colistin due to renoprotective effects.

Patient and Method: Fifty-six adult male albino rats of local strain weighing 150 ± 20g were purchased from the animal house of Assiut university. We measured kidney function tests and determination of oxidative stress biomarkers in renal tissues.

Results: There were significant differences among studied groups regarding creatinine, urinary GGT, BUN and MDA ($p < 0.05$). Also, colistin administration caused an increase in serum creatinine, urinary GGT, MDA, urea, and blood urea nitrogen (BUN) level versus the control group.

Conclusion: Based on reviewed studies, stress oxidative beside activating inflammatory and apoptotic pathways are the main mechanism of colistin nephrotoxicity. Quercetin and vitamin E could attenuate colistin-induced nephrotoxicity by decreasing oxidative stress and inflammation and increasing antioxidants.

Keywords: *Colistin; Nephrotoxicity; Quercetin; Vitamin E*

Introduction

One of the few remaining pharmaceutical choices for treating infections brought on by multidrug-resistant Gram-negative bacteria is colostine [1]. Despite its effectiveness, the main side effect that prevents the administration of high doses of colistin is nephrotoxicity. According to reports, acute tubular necrosis is the primary manifestation of colistin-induced renal damage [2]. The length of time and

dosage of colistin are factors in nephrotoxicity. Colistin-induced renal failure is believed to be brought on by proximal tubule dysfunction. Numerous experimental studies have demonstrated that this development of nephropathy may be caused by oxidative stress and apoptotic activity and that it is reversible [3]. Numerous pharmaceutical treatments, including ascorbic acid, melatonin, and vitamin E, have been shown to improve colistin-induced nephropathy [3].

Fruits and vegetables include the flavonoid quercetin, which has special biological qualities that may enhance cognition and physical performance while lowering the risk of illness [4]. Anti-carcinogenic, anti-inflammatory, antiviral, antioxidant, and psychostimulant activities, as well as the capacity to inhibit lipid peroxidation, platelet aggregation, and capillary permeability, as well as the ability to stimulate mitochondrial biogenesis, are the basis for potential benefits to overall health and disease resistance [5].

Due to its powerful antioxidant activity, quercetin is a bioactive molecule that is frequently employed in traditional Chinese medicine and herbal medicine. Numerous studies on quercetin's antioxidant properties have been conducted in recent years, including topics like how it affects glutathione, enzymatic activity, signaling pathways, and reactive oxygen species (ROS) brought on by environmental and toxicological causes [6].

One of the key bioflavonoids, quercetin is known for its anti-inflammatory, anti-hypertensive, vasodilator, anti-obesity, anti-hypercholesterolemic, and anti-atherosclerotic properties and is found in more than 20 different types of plant material [7].

As a suspected radical scavenger and well-known antioxidant, vitamin E (vit E) is presumably a key inhibitor of membrane lipid peroxidation. It is a lipid-soluble substance that easily crosses cell membranes and has an impact on both membranes and cells [8]. Numerous studies have shown that vitamin E has a positive impact on drug-induced nephrotoxicities, including those caused by gentamicin, vancomycin, and cisplatin [1].

Our theory was that the renoprotective properties of quercetin and vitamin E would demonstrate a protective impact against nephrotoxicity brought on by colistin.

Materials and Methods

Animals under study

At the Assiut University's animal home, 56 adult male albino rats of the local strain, weighing 150.20g, were purchased. The faculty Ethical Committee Guidelines for the Care and Use of Laboratory Animals at our university were strictly followed in all animal procedures. The animals were maintained on a conventional diet of commercial rat food and tap water, and they were housed in adequate cages (20 x 32 x 20 cm for every 3 rats) in the environmentally controlled breeding room (temperature: 22.2°C, humidity: 60.5%, 12h dark/light cycle). Prior to the trial, they were held for two weeks to acclimate to the new surroundings.

Experimental design

In a prior investigation, the administration of Colistin at a dose of 450,000 IU/kg/day caused severe tubular damage. Only a small amount of protection was offered by Vitamin E co-treatment alone [2]. In order to provide complete protection, we looked into the effects of combining two antioxidants, vitamins E and quercetin. Animals were divided into eight groups (n = 7) at random as follows:

- **Group 1:** For one week, a normal control group underwent treatment with normal saline, receiving 1 ml/kg/day of sterile saline orally.
- **Group 2:** Colistin is used to treat kidney damage. Colistin was administered to rats via intramuscular injection twice daily at intervals of 12 hours for a week [9].

- **Group 3:** Standard control vitamin E was administered as part of the treatment for a month as a daily oral gavage (20 mg/kg body weight) [10].
- **Group 4:** A normal control was given quercetin (25 mg/mL solution) at a dosage of 50 mg/kg body weight over the course of a month [11].
- **Group 5 (Vitamin E and quercetin):** Normal controls received daily oral vitamin E (20 mg/kg b.w.) and quercetin (25 mg/mL solution) was also administered orally at a dose of 50 mg/kg body weight via gavage for one month.
- **Group 6 (Vitamin E and colistin):** 450,000 IU/kg/day of colistin were administered intramuscularly twice daily, 12 hours apart, for one week. Additionally, 20 mg/kg b.w. of vitamin E was administered orally for one month.
- **Group 7 (Quercetin and Colistin):** 450,000 IU/kg/day of colistin were administered intramuscularly twice daily (12 hours apart) for one week. Additionally, quercetin (25 mg/mL solution) was also administered orally at a dose of 50 mg/kg body weight via gavage for one month.
- **Group 8(Colistin, vitamin E, and quercetin):** 450,000 IU/kg/day of colistin were administered intramuscularly twice daily, 12 hours apart, for one week. Treatment for nephrotoxicity with colistin by the administration of vitamin E, and quercetin .
- Additionally, 20 mg/kg b.w. of vitamin E was administered orally and gavage administration of quercetin (25 mg/mL solution) for month[12].

Collection of urine samples

Prior to necropsy, overnight urine samples from each animal were collected in individual metabolic cages over ice at the conclusion of the experiment. Urine samples were centrifuged at 1000g for 5 minutes while animals were given free access to water. For analysis, the supernatant was aliquoted into Eppendorf tubes.

Collection of blood samples

Blood samples were taken from the jugular vein of anaesthetized, euthanized animals, and then separated for analysis after being centrifuged for 15 minutes at 5000 rpm.

Preparation of renal tissues samples

The kidneys were then removed, 500 mg were homogenised in 5 ml of lysis buffer, which was made up of 50 mM Tris and 150 mM sodium choloride (NaCl) and was adjusted to pH 7.4 and centrifuged at 8000g for 10 minutes. The supernatant was then collected for biochemical analysis and the measurement of reduced *glutathione (GSH)*, *Malondialdehyde* (MDA), *glutathione Peroxidase (GPX)*, *catalase (CAT)* levels.

Biochemical assays

Determination of NAG and GGT levels

Using a Hitachi 917 and Roche Diagnostics' reagents, the levels of N-acetyl-Dglucosaminidase (NAG), -glutamyl-transferase (GGT), total protein, and creatinine were assessed in urine (Mannheim, Germany).

Kidney function tests

According to the manufacturer's instructions for the colorimetric kit, plasma levels of creatinine, uric acid, and blood urea nitrogen (BUN) were measured (Biodiagnostic Co., Cairo, Egypt). Measurement of plasma Cr level.

Oxidative stress biomarkers in renal tissues

Malondialdehyde (MDA), a lipid peroxidation marker, was measured spectrophotometrically in the renal tissue [13]. The concentrations of various enzymatic antioxidants were measured using colorimetric techniques. According to, the oxidising reaction of nitro blue tetrazolium (NBT) was used to measure supper oxide dismutase activity [14]. H_2O_2 was used to quantify CAT activity, according to simple spectrophotometric assay [15]. GPx activity and reduced Glutathione (GSH) assay with colorimetric method [16].

Statistical analysis

Information is presented as mean SD (standard deviation). One-way analysis of variance (ANOVA) and the Tukey post-hoc test was used to determine the statistical significance of differences between experimental groups. 0.05 was used as the P value for significance.

Results

With reference to creatinine, urinary GGT, BUN, and MDA, a total of fifty-six adult male albino rats revealed that there were significant variations between the study groups ($p < 0.05$). Additionally, compared to the control group, colistin treatment increased the levels of serum creatinine, urinary GGT, MDA, urea, and blood urea nitrogen (BUN) (Table 1).

Variable	Creatinine (Mg/dL)	Urinary GGT (U/ g Cr)	BUN	MDA
Control	0.40 ± 0.04	663 ± 33.5	24.3 ± 4.32	41.3 ± 3.67
Colistin	0.96 ± 0.07	743 ± 36.9	85.7 ± 9.15	75.9 ± 6.94
Colistin and Quercetin	0.5 ± 0.052	677 ± 38.1	43.5 ± 11.0	69.6 ± 5.02
Colistin, quercetin and vit E	0.49 ± 0.05	684 ± 28.9	39.8 ± 6.34	63.8 ± 3.46
Colistin and vit E	0.58 ± 0.06	700 ± 31.7	51 ± 9.59	68.7 ± 4.83
Quercetin	0.39 ± 0.05	662 ± 34.2	24.5 ± 4.50	41.1 ± 5.05
Quercetin + vit E	0.41 ± 0.03	662 ± 39.3	24.1 ± 3.72	40.3 ± 4.36
Vit E	0.39 ± 0.05	660 ± 33.2	24.5 ± 5.06	40.8 ± 2.60
F	142.2	6.8	88.02	113.3
P value	< 0.001*	< 0.001*	< 0.001*	< 0.001*

Table 1: *Kidney functions among the studied groups of rats.*

**Consider a statistically significant. BUN: Blood Urea Nitrogen; MDA: Malondialdehyde; GGT: γ-Glutamyl Transferase.*

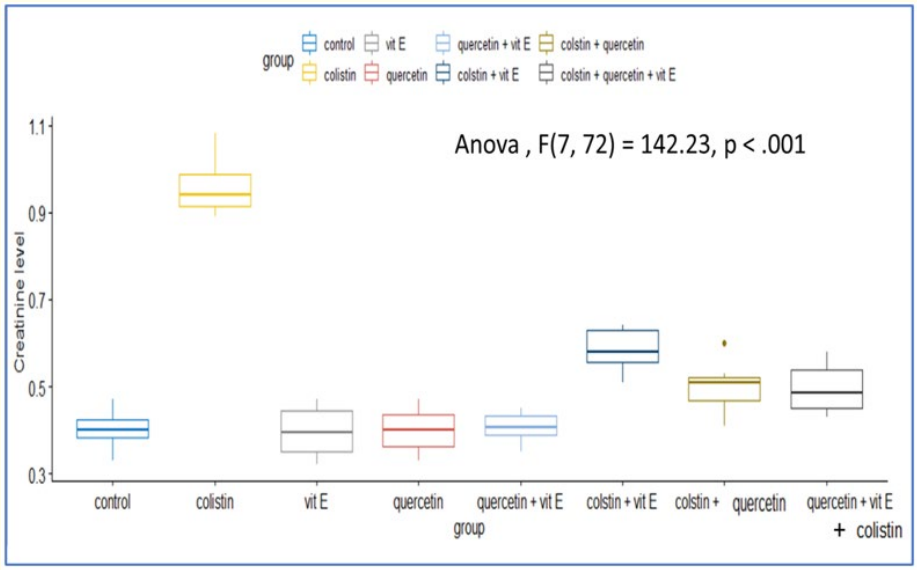

Figure 1: *Shows the ANOVA test for serum creatinine level in mg/dL, which shows a significant difference between the groups.*

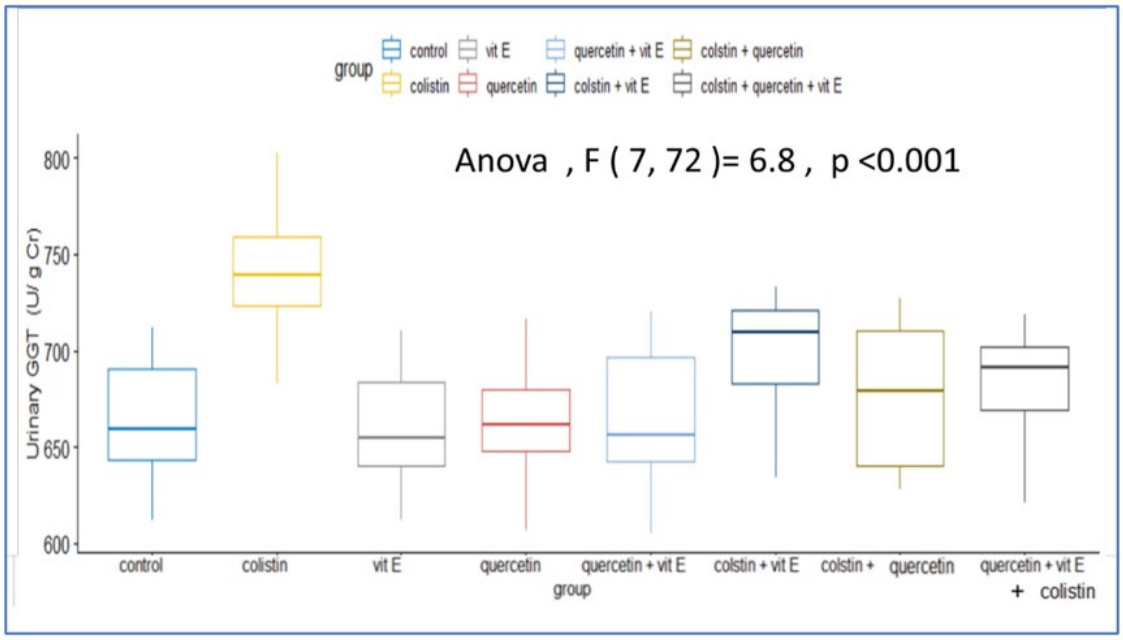

Figure 2: *Shows the ANOVA test for urinary GGT level in 5 U/g Cr which shows a significant difference between the groups.*

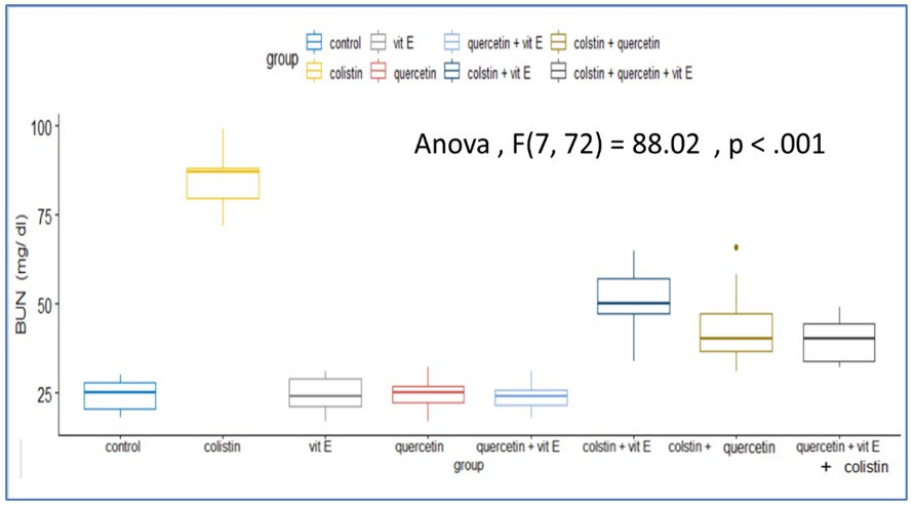

Figure 3: *Shows the ANOVA test for the BUN level in (mg/dL) which shows a significant difference between the groups.*

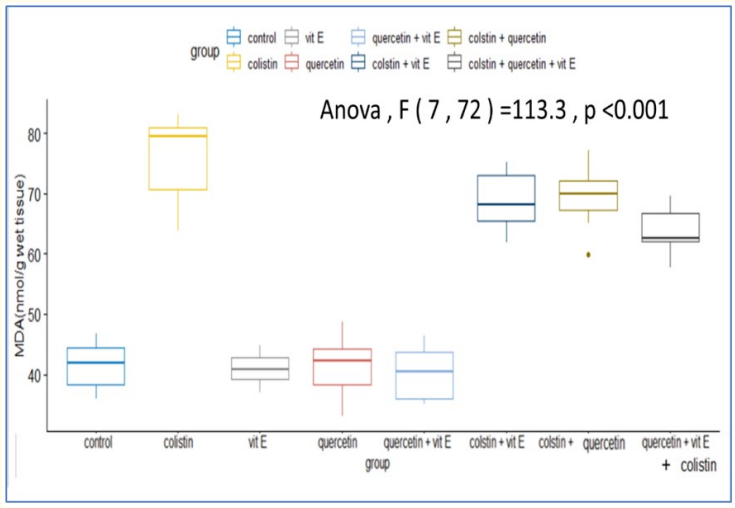

Figure 4: *Shows the ANOVA test for the MDA level in (nmol/g wet tissue) which shows a significant difference between the groups.*

Also, there were significant variations in GSH, GPX, and CAT between the study groups ($p < 0.05$). Additionally, there is a notable decrease in the mean CAT, GSH, and GPX compared to the control group (Table 2).

Variable	GSH (mg/g wet tissue)	GPX	CAT (µmol/mg/protein)
Control	101 ± 3.91	28.5 ± 1.54	582 ± 3.62
Colistin	89.6 ± 1.68	20.4 ± 1.74	569 ± 4.43
Colistin and Quercetin	95.6 ± 5.02	22.7 ± 1.3	573 ± 4.64
Colistin, quercetin and vit E	97.8 ± 4.04	24.9 ± 1.51	577 ± 3.94
Colistin and vit E	95.6 ± 5.57	22.6 ± 2.32	573 ± 5.01
Quercetin	101 ± 3.45	28.8 ± 2.12	582 ± 3.9
Quercetin + vit E	101 ± 4.95	28.5 ± 2.45	582 ± 3.2
Vit E	100 ± 3.73	28.2 ± 2.40	582 ± 4.67
F	9.5	29.06	14.7
P value	<0.001*	<0.001*	<0.001*

Table 2: *Oxidative stress indicators among the studied groups of rats.*

**Consider a statistically significant. GSH: Glutathione; GPX: Glutathione Peroxidase; CAT: Catalase.*

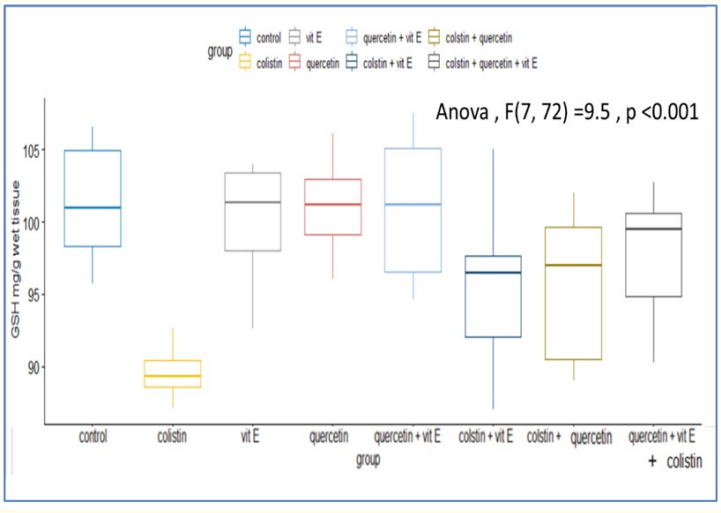

Figure 5: *Shows the ANOVA test for the GSH level in (nmol/g wet tissue) which shows a significant difference between the groups.*

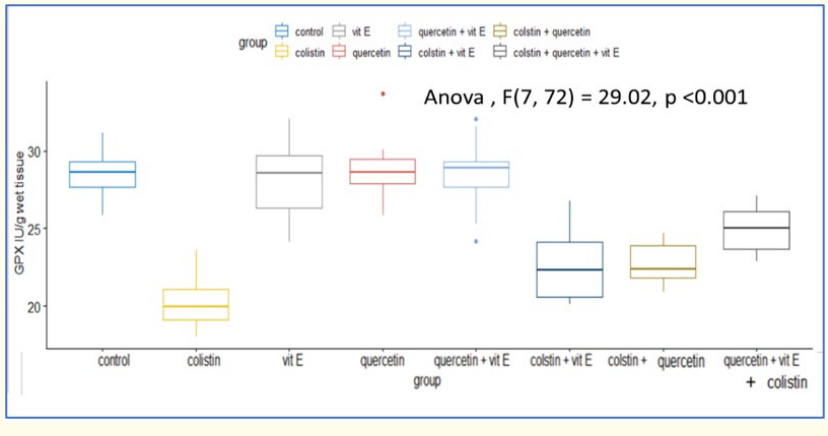

Figure 6: *Shows the ANOVA test for the GPX level in (IU/g wet tissue) which shows a significant difference between the groups.*

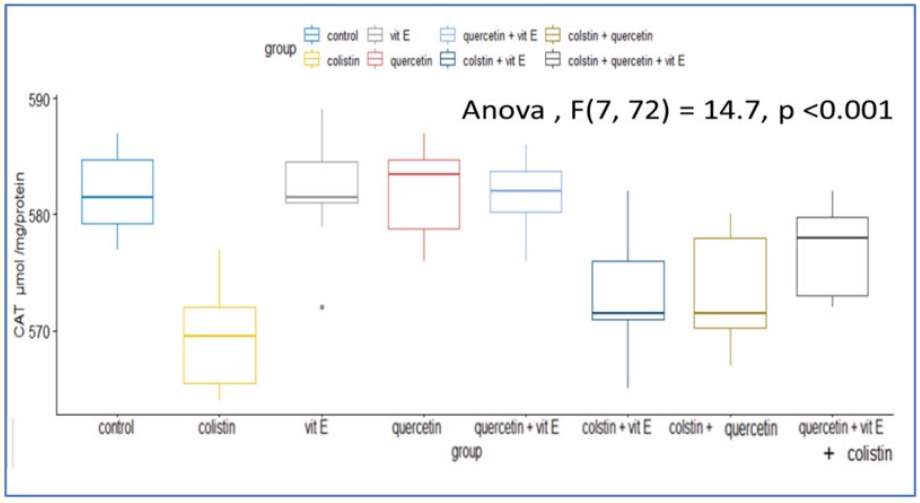

Figure 7: *Shows the ANOVA test for the CAT level in µmol/mg/protein which shows a significant difference between the groups.*

Additionally, potassium levels did not significantly differ between the study groups ($p > 0.05$). While there was a significant difference in sodium levels across the study groups ($p < 0.05$), since the mean sodium has significantly decreased compared to the control group (Table 3).

Variable	Sodium	Potassium (mmol/L)
Control	139 ± 1.60	5.25 ± 0.39
Colistin	137 ± 2.15	4.84 ± 0.29
Colistin and Quercetin	138 ± 1.49	5.05 ± 0.19
Colistin, quercetin and vit E	139 ± 1.10	5.19 ± 0.22
Colistin and vit E	139 ± 1.78	5.06 ± 0.33
Quercetin	140 ± 2.59	5.29 ± 0.46
Quercetin + vit E	139 ± 1.93	5.17 ± 0.34
vit E	140 ± 1.84	5.23 ± 0.48
F	2.5	1.17
P value	0.024*	0.118

Table 3: *Electrolytes among control, colistin, Colistin + quercetin, colistin +quercetin+ vit E, colistin + vit E, quercetin, quercetin + vit E and vit E studied groups.*

**Consider a statistically significant.*

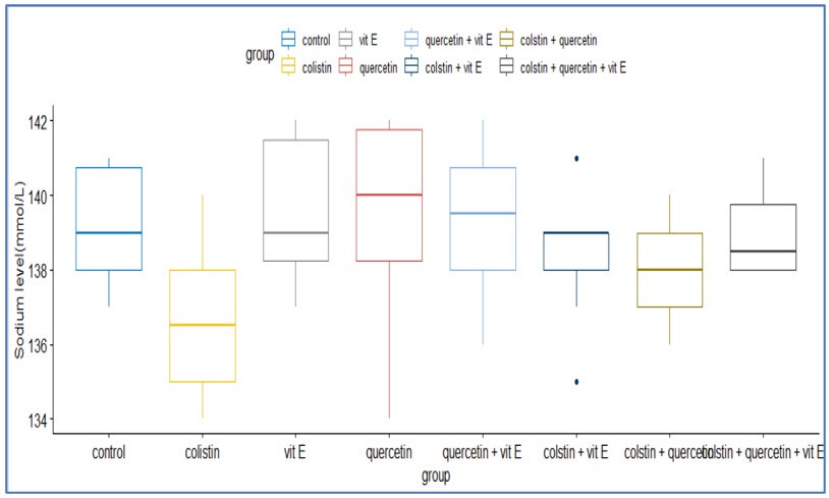

Figure 8: *Shows the ANOVA test for the Sodium level in (mmol/L) which shows a significant difference between the groups.*

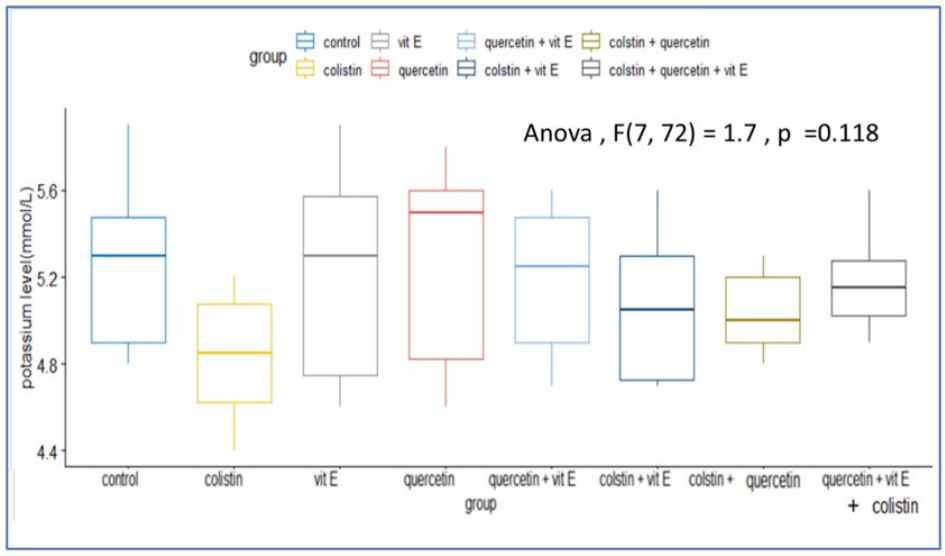

Figure 9: *Shows the ANOVA test for the potassium level in (mg/dL) which shows a Non-significant difference between the groups.*

Discussion

A polypeptide antibiotic called colistin is mostly made up of polymyxins A and B [17]. Due to its significant nephrotoxicity and neurotoxicity, it was taken off the market after being originally made accessible for clinical usage in the 1960s [18]. One of the most prevalent flavonoids in the human diet, quercetin is thought to have a variety of health benefits, including anti-inflammatory and cardiovascular protection [19]. Previously, quercetin significantly reduced the risk of nephrotoxicity by strongly inhibiting oxidative stress

and inflammation [20]. A potent antioxidant and free radical scavenger, vitamin E is a fat-soluble substance. It can be used to effectively prevent kidney damage brought on by oxidative stress and the generation of reactive oxygen species (ROS) [21].

Flavonoids like quercetin and antioxidants like vitamin E work directly to scavenge oxygen radicals. Additionally, flavonoids have the capacity to donate hydrogen atoms to tocopheryl radicals, recycling anti-oxidants like a-tocopherol in the process. This may be the cause of the potentiation of vitamin E's therapeutic effects by quercetin, which lessen renal impairment by reducing BUN, serum creatinine, and renal thiobarbituric acid reactive substances (TBARS) levels [22]. So, the purpose of the study was to determine whether the renoprotective effects of quercetin and vitamin E would provide protection against nephrotoxicity brought on by colistin.

The current study showed that, regarding creatinine, urinary GGT, BUN, MDA , GSH, GPX, and CAT, there were notable changes across the studied groups. Additionally, compared to the control group, colistin treatment increased the levels of serum creatinine, urinary GGT, MDA and blood urea nitrogen (BUN). The mean CAT, GSH, and GPX are significantly lower than in the control group. The current study is close to the study of Ghlissi., et al. [23] who found that, a modest focal tubular dilation was seen after 7 days of colistin treatment in rats given 300,000 IU/kg/day IM, although acute tubular necrosis was more pronounced in the group given 450,000 IU/kg/day of colistin. Additionally, the current study showed that colistin administration led to a considerable rise in plasma levels of Cr, urine GGT, and MDA as well as a decrease in the antioxidant enzymes CAT, GPx, and GSH in the renal tissue. Another study by Ghlissi., et al. [8] noted similarly considerable perturbation of oxidative stress indicators was found in colistin group renal tissue. The MDA enhancement establishes the relevance of lipid peroxidation. Additionally, there has been a considerable drop in CAT, and GPx activity. The findings in current study suggest that the underlying mechanism of colistin-induced nephrotoxicity may involve oxidative stress. Reactive oxygen species (ROS) produced by mitochondria have been shown to start renal cell apoptosis, which ultimately results in renal dysfunction. Oxidative stress has been reported to play a major role in tubular toxicity caused by many drugs, including gentamicin, amikacin, vancomycin, and cisplatin [24].

The combination of quercetin plus colistin administration to rats led to a significant reduction in the elevated levels of BUN, and serum creatinine, according to a study on the protective effect of quercetin against gentamicin-induced nephrotoxicity in rats by Abdel-Raheem., et al. [25]. In current stud, the involvement of reactive oxygen species (ROS) in colistin -induced nephrotoxicity was evaluated by using the antioxidant quercetin and assessing changes in the biochemical indicators of oxidative stress, primarily GSH, GPX and CAT activity. According to reports, quercetin inhibits xanthine oxidase activity while also scavenging free superoxide and hydroxyl radicals to provide its antioxidant properties. According to reports, quercetin inhibits xanthine oxidase activity and lipid peroxidation in addition to scavenging free superoxide and hydroxyl radicals to provide its antioxidant properties [26]. According to these findings, quercetin's powerful anti-oxidant activity is linked to its - OH groups on the side of the phenyl ring [6]. In hippocampal CA1 neurons of gerbils suffering from ischemia injury, pretreatment with quercetin has been found to boost the levels of endogenous antioxidant enzymes, including GSH peroxidase and CAT [27]. Similar to this, a prior study demonstrated that quercetin supplementation at a dose of 40 mg/kg/day for four weeks significantly decreased the kidney damage caused by cadmium (Cd) in rats by increasing the activities of antioxidant enzymes (such as CAT and glutathione peroxidase) and the levels of vitamin C and vitamin E in the kidneys [28].

The use of antioxidants, such as vitamin E or N-acetyl-cysteine, has been demonstrated in numerous studies to be protective in lowering the incidence rate of acute kidney injury (AKI) brought on by colistin [29]. In the current study taking vitamin E before receiving colistin therapy slowed the rise in serum creatinine. But to keep the level of antioxidants high in this study, vitamin E was given with colistin treatment [1]. Ghlissi., *et al*. [8] reported that, Changes in antioxidant parameters and Lipid peroxidation (LPO) indicators might be partially avoided by co-treating with vitamin E at a daily dose of 100 mg/kg/day. These benefits could result from vitamin E's ability to scavenge free radicals and protect cellular membranes from oxidative damage. Additionally, it was discovered that vitamin E administration enhanced tubular regeneration and restored the altered biomarkers in the colistin-treated mice, including elevated MDA levels and decreased GSH activity. Contrarily, discontinuing colistin alone did not result in a significant improvement in renal function.

Another study by Zal., *et al*. [30] Both vitamin E and quercetin improved renal function to some extent, but it was a combination treatment of the two that lowered BUN and serum creatinine levels to those seen in the controls, according to a study of the effects of vitamin E and quercetin in attenuating chronic cyclosporine induced nephrotoxicity in male rats. Hsiu., *et al*. [31] in rats and pigs, it was shown that a combination of 10 mg/kg cyclosporine and 50 mg/kg quercetin each day dramatically reduced cyclosporine bioavailability. Also, Mostafavi- pour., et al. [32] and Satyanarayana., *et al*. [33] reported that Injecting quercetin intraperitoneally in rats can partially repair the morphological alterations to the kidneys caused by colistin. However, Zal., *et al*. [33] found that any of the two antioxidants, when supplied alone, was able to normalise the level of kidney GPx. Neither vitamin E nor quercetin were able to reduce the level of renal MDA to values found in the control groups. When it came to repairing antioxidant enzyme activities, quercetin was more effective on its own than vitamin E. However, combining the two reduced kidney MDA, BUN, and serum creatinine to levels seen in the vehicle control groups while also normalizing the level of all antioxidant enzymes.

Conclusion

According to reviewed studies, the primary mechanism of colistin nephrotoxicity is stress oxidative, which also activates inflammatory and apoptotic pathways. By reducing oxidative stress and inflammation and raising antioxidant levels, quercetin and vitamin E can lessen the nephrotoxicity that colistin causes.

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Conflict of Interest

No conflict of interest

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