Original Article

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Coenzyme Q_{10} and resveratrol protect against paclitaxel-induced nephrotoxicity in rats

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Abstract

Renal dysfunction caused by anticancer drugs may involve oxidants production. Antioxidants have shown potential therapeutic effects on some disease conditions. This study examined the protective abilities of coenzyme Q_{10} (CoQ_{10}) and resveratrol (RSV) against paclitaxel (PCL)-induced renal dysfunction in rats. Adult male albino rats (n=45) (210-230 g) were divided into 9 groups of n=5. Groups C-E orally received CoQ_{10} (20 mg/kg), RSV (20 mg/kg) and CoQ_{10}+ RSV daily for 5 days, respectively. Group F received PCL (20 mg/kg) intraperitoneally ($_{ip}$) on day 5. Groups G-I were orally supplemented with CoQ_{10}, RSV and CoQ_{10}+ RSV daily for 5 days before a dose of PCL (20 mg/kg) on day 5. Group A (Placebo control) and Group B (Solvent control) received normal saline (0.2 mL) and corn oil (0.2 mL) daily for 5 days, respectively. The rats were anesthetized; blood samples were collected and assessed for serum biochemical markers. Kidneys were assessed for melondialdehyde, antioxidants (superoxide dismutase, glutathione, glutathione peroxidase and catalase) and histology. Body and kidney weights were normal ($p>0.05$) in PCL administered rats when compared to placebo control. Serum electrolytes, total protein, albumin and kidney antioxidant levels were significantly ($p<0.001$) decreased whereas, serum creatinine, urea, uric acid and kidney malondialdehyde levels were significantly ($p<0.001$) increased in PCL administered rats when compared to control. Hypercellular glomerulus and tubular necrosis were observed in the kidneys of PCL administered rats. PCL-induced renal dysfunction was significantly reversed by CoQ_{10} ($p<0.05$), RSV ($p<0.01$) and CoQ_{10}+RSV ($p<0.001$) supplementations when compared to PCL. CoQ_{10} and RSV may clinically protect against PCL associated renal dysfunction

Keywords: Antioxidants, Taxel, Kidney, Toxicity, Protection, Rat

1. Introduction

Oxidative stress is a consequence of increased production and accumulation of oxygen reactive species (ROS) in cells, which surpasses the functional abilities of cellular antioxidants (1). At high concentration, ROS causes damage to biomolecules consequently disrupting their structures and functional capacities (2) Oxidative stress has been implicated in a number of disease conditions and in the pathophysiology of kidney diseases (3). The kidneys are susceptible to oxidative stress -induced dysfunction due to their high reliance on mitochondria and adenosine triphosphate (ATP) to facilitate the function of the nephron (4). Oxidative stress -induced kidney dysfunction has been characterised by lipid peroxidation (LPO) and the incapacitation of antioxidant activity (4). LPO produces secondary products, which can stimulate cascades of toxic reactions in the kidney (5).

Paclitaxel (PCL), an anticancer drug prevents cell division by enhancing the assembly of abnormal and stable microtubules especially from

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β-tubulin heterodimers and inhibits their depolymerisation (6). It is widely used for the treatment of a variety of cancers such as ovarian, breast cancers, and Kaposi's sarcoma (7). It is used as monotherapy or in combination with other anti-cancer drugs (8). The use of PCL may be safe, but the possible occurrence of nephrotoxicity has been documented, which may undermine its application. Nephrotoxicity of grade III or IV may occur with the use of PCL (9). Additive renal damage has occurred in combination with some anti-cancer medications (10). Alterations in kidney morphology in the form of necrotic and apoptotic changes in tubules and focal atrophy of glomerular tufts have been experimentally associated with PCL (11).

Co-enzyme Q_{10} (CoQ_{10}), a lipid-soluble benzoquinone is present in most human tissues and is essential for life and health of every living cell (12). It acts as a principal player in the electron transport chain of mitochondria responsible for the synthesis of adenosine triphosphate, which is essential for aerobic respiration (13). CoQ_{10} is an antioxidant that scavenges and neutralizes ROS, thereby curtailing oxidative stress (12). As an anti-inflammatory agent, it inhibits proinflammatory mediators' production by modulating nuclear factor kappa B (NF-kB) pathways (14). CoQ_{10} has promising therapeutic activities in diseases such as cardiovascular diseases, cancer, neurodegenerative disorders and diabetes (15). It has also shown promising renal protective activities in chromate-induced kidney dysfunction (16), diabetic nephropathy (17) and in doxorubicin-induced renal oxidative stress (18).

Resveratrol (RSV) is a stilbenoid type of natural phenol and a phytoalexin produced by several plants (19). It is an antioxidant that scavenges free radicals and secondary radicals formed as a result of biomolecular interaction with free radicals (20). It can increase the expression of some enzymes, which maintain oxidation-reduction balance in cells (21). Besides its antioxidant effect, RSV has shown anti-inflammatory effect by curtailing the activities of proinflammation mediators (22). RSV attracts increasing attention due to its wide range of biological activities on different diseases such as cancers, neurodegenerative, and cardiovascular diseases (23). It has shown potential renal protective activity through restored kidney morphology and reduced LPO in rat exposure to cadmium (24). It has inhibited oxidative stress in 5-fuorouracil-induced renal dysfunction (25) and renal inflammation in cadmium exposed rats (26). RSV has improved renal function in diabetic rats (27). Due to a paucity of scientific literature, this study evaluated the protective activities of Co 10 and RSV against-PCL-induced nephrotoxicity in rats.

2. Material & methods

2.1. Animals and drugs

Adult male rats of albino strain (210-230 g) were purchased from the animal breeding unit of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, Niger Delta University, Bayelsa State, Nigeria. The rats were kept in polypropylene cages and maintained at 25±2 °C and 12 h light/dark cycle and allowed to acclimatize for two weeks. The rats had access to standard rat diet and water *ad libitum*. PCL injection used was manufactured by Getwell Pharmaceuticals Gurgaon, Haryana, India. RSV was manufactured by Swanson Health Products, Fargo, USA whereas COQ_{10} was manufactured by Bactolac Pharmaceuticals Inc 7 Oser Avenue, Hauppauge, NY 11788, USA.

2.2. Treatment and animal sacrifice

Forty-five adult male albino rats randomly grouped (A-I) were used. Group A (Placebo control) and Group B (Solvent control) received normal saline (0.2 mL) and corn oil (0.2 mL) intraperitoneally (ip) daily for 5 days, respectively. Groups C-E (n=5 /group) orally received CoQ_{10} (20 mg/kg) (28), RSV (20 mg/kg) (29) and CoQ_{10}+ RSV in corn oil daily for 5 days, respectively. Group F (n=5) received PCL (20 mg/kg) in normal saline once on day 5. Groups G-I (n=5 /group) were supplemented orally with CoQ_{10} (20 mg/kg), RSV (20 mg/kg) and CoQ_{10}+ RSV daily for 5 days before receiving a dose of PCL (20 mg/kg) on day 5. On day 6, the rats were sacrificed using diethyl ether anaesthesia. Blood samples were collected from the heart, centrifuged (1500 g, for 20 min) and sera were collected and evaluated for biochemical parameters. Kidney samples were excised, rinsed in cold saline and homogenized in 0.1 M Tris-HCl

solution buffered (pH 7.4). The homogenates were centrifuged (2000g for 20 min) and the supernatants were collected and evaluated for melondialdehye (MDA), superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPx) and catalase (CAT) concentrations.

2.3. Biochemical evaluations

Freshly separated sera were estimated for creatinine, urea, uric acid, total protein, albumin, sodium, potassium, chloride and bicarbonate using an author analyzer. Kidney GSH was determined by the method described by Sedlak and Lindsay (1968) (29). GPx was measured as described by Rotruck et al. (1973) (30). CAT was assayed as described by Aebi, (1984) (31). SOD was measured as reported by Sun and Zigman (1978) (32). MDA was measured as reported by Buege and Aust (1978) (33).

2.4. Histological examination of the kidney

The kidneys were fixed in 10% buffered formalin for 24 hr. Kidneys were processed for paraffin wax embedding. Three micro meter sections were cut using a microtome and stained with hematoxylin and eosin and assessed for histological changes using a light microscope

2.5. Statistical analysis

Data was presented as mean ± standard error of mean (SEM) of five rats per group. Data was analyzed using One-way Analysis of Variance (ANOVA) followed by Tukey's *post hoc test* using Graph Pad Prism (Version 5.0, Graph Pad Software Inc., La Jolla, California, U.S.A.). Significance was considered at $p<0.05$ $p<0.01$ and $p<0.001$

3. Results

3.1 Effects of coenzyme Q 10 and resveratrol on body weight, kidney weight and serum biochemical parameters of paclitaxel-treated rats

Body and kidney weights were normal ($p>0.05$) in rats that received individual doses of CoQ_{10}, RSV and PCL when compared to placebo control (Table 1). Serum creatinine, urea, uric acid, total protein and albumin levels were normal in rats that received CoQ_{10} and RSV when compared to control. In contrast, significant ($p<0.001$) increases in serum urea, creatinine and uric acid levels with significant ($p<0.001$) decreases in total protein and albumin levels occurred in rats that received PCL when compared to control (Figures 1-5). However, serum urea, creatinine, and uric acid levels were significantly decreased whereas serum total protein and albumin levels were significantly increased in rats supplemented with CoQ_{10} ($p<0.05$), RSV ($p<0.01$) and CoQ_{10}+RSV when compared to PCL (Figures 1-5).

3.2 Effects of coenzyme Q 10 and resveratrol on serum electrolytes of paclitaxel-treated rats

Normal ($p>0.05$) serum electrolytes (potassium, chloride, sodium and bicarbonate levels) were observed in rats that received CoQ_{10} and RSV when compared to placebo control. On the

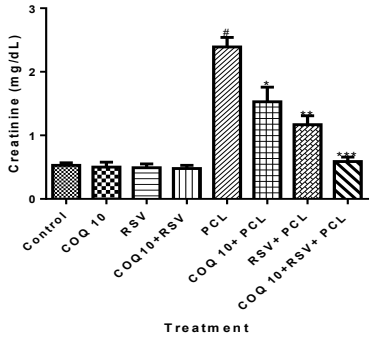

Figure 1. Effects of coenzyme Q_{10} and resveratrol on serum creatinine of paclitaxel –treated albino rats
CoQ_{10}: Coenzyme Q_{10}, RSV: Resveratrol, Data as mean±SEM, n=5, #p<0.001 Significant difference when compared to control, *p<0.05, **p<0.01, *** p<0.001 Significant difference when compared to PCL, SEM: Standard error of mean.

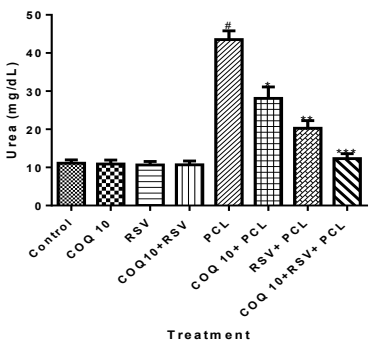

Figure 2. Effects of coenzyme Q_{10} and resveratrol on serum urea of paclitaxel –treated albino rats
CoQ_{10}: Coenzyme Q 10, RSV: Resveratrol, Data as mean±SEM, n=5, #p<0.001 Significant difference when compared to control, *p<0.05, **p<0.01, *** p <0.001 Significant difference when compared to PCL, SEM: Standard error of mean.

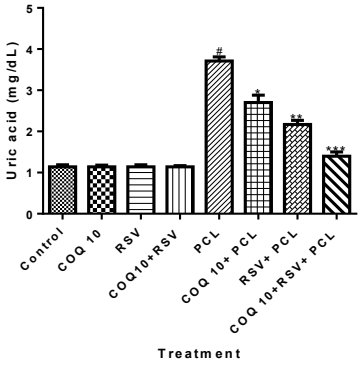

Figure 3. Effects of coenzyme Q_{10} and resveratrol on serum uric acid of paclitaxel –treated albino rats.
CoQ_{10}: Coenzyme Q_{10}, RSV: Resveratrol, Data as mean±SEM, n=5, #p<0.001 Significant difference when compared to control, *p<0.05, **p<0.01, *** p<0.001 Significant difference when compared to PCL, SEM: Standard error of mean.

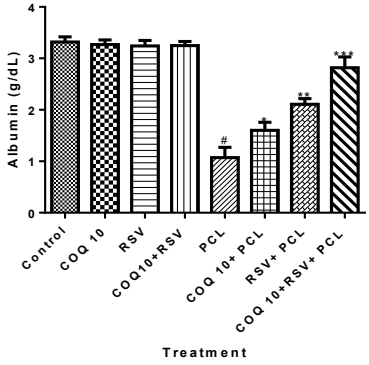

Figure 4. Effects of coenzyme Q_{10} and resveratrol on serum albumin of paclitaxel –treated albino rats.
CoQ_{10}: Coenzyme Q_{10}, RSV: Resveratrol, Data as mean±SEM, n=5, #p<0.001 Significant difference when compared to control, *p<0.05, **p<0.01, *** p<0.001 Significant difference when compared to PCL, SEM: Standard error of mean.

other hand, serum electrolytes were significantly (p<0.001) decreased in rats that received PCL when compared to control (Table 2). However, serum electrolytes were significantly increased in rats supplemented with CoQ_{10} (p<0.05), RSV (p<0.01) and CoQ_{10}+ RSV (p<0.001) when compared to PCL (Table 2).

3.3 Effects of coenzyme Q 10 and resveratrol on kidney oxidative stress indices of paclitaxel-treated rats

Kidney antioxidants (GSH, SOD, GPx, CAT) and MDA levels were normal (p>0.05) in rats that received CoQ_{10} and RSV when compared to placebo control. On the other hand, antioxidants were significantly (p<0.001) decreased whereas

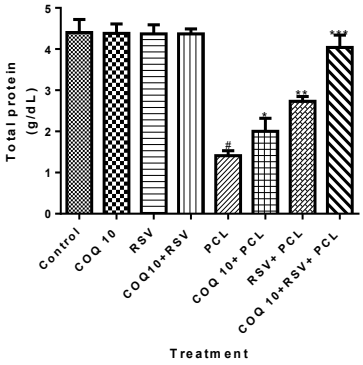

Figure 5. Effects of coenzyme Q_{10} and resveratrol on serum total protein of paclitaxel –treated albino rats.
CoQ_{10}: Coenzyme Q_{10}, RSV: Resveratrol, Data as mean±SEM, n=5, #p<0.001 Significant difference when compared to control, *p<0.05, **p<0.01, *** p<0.001 Significant difference when compared to PCL, SEM: Standard error of mean.

MDA levels were significantly (p<0.001) elevated in rats that received PCL when compared to control (Table 3). However, kidney antioxidants were significantly elevated whereas MDA levels were significantly decreased in rats supplemented with CoQ_{10} (p<0.05), RSV (p<0.01), and CoQ_{10}+RSV (p<0.001) when compared to PCL (Table 3).

3.4 Effects of coenzyme Q 10 and resveratrol on kidney histology of paclitaxel-treated rats

Normal kidney histology was observed in control rat (Fig 6 A), but hypercellular glomerulus and tubular necrosis were observed in rat that received PCL (Fig 6 B). The kidney of CoQ_{10} supplemented rat showed hypercellular glomerulus and normal renal tubule (Fig 6 C), Also, the kidney of RSV supplemented rat showed hypercellular glomerulus and normal renal tubule (Fig 7 D). However, the kidney of CoQ_{10} + RSV supplemented rat showed normal glomerulus and renal tubule (Fig 6 E).

4. Discussion

Renal dysfunction is a primary adverse effect of some anticancer drugs and may lead to a variety of functional consequences which include glomerular or tubular dysfunction, hypertension and impairment in renal endocrine function. The potential of some anticancer drugs to cause renal dysfunction may increase in the presence of existing borderline or overt pre-existing chronic kidney disease (34). Renal dysfunction caused by

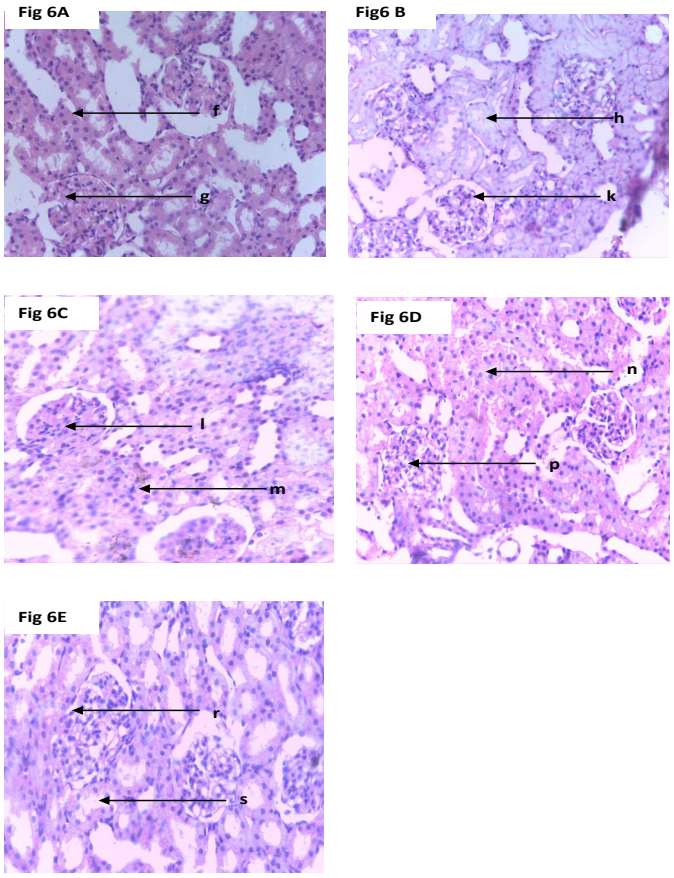

Figure 6. Normal kidney glomerulus (f) and renal tubule (g) were observed in the control rat (Fig 6 A). Hypercellular glomeruli (h) and mild tubular necrosis (k) were observed in PCL-treated rat (Fig 6 B). Hypercellular glomerulus (l) and normal renal tubule (m) were observed in CoQ_{10} (20 mg/kg) supplemented rats (Fig 6 C). Hypercellular glomerulus (n) and normal renal tubule (p) were observed in RSV (20 mg/kg) supplemented rats (Fig 6 D). Normal glomerulus (r) and renal tubules (s) were observed in CoQ_{10}+RSV supplemented rats (Fig 6E).

anticancer drugs may involve the production of oxidants (3). Experimental studies have reported promising protective activities of antioxidants on renal dysfunction caused by chemical assaults (24). This study assessed whether CoQ_{10} and RSV supplementations can surmount PCL-induced renal dysfunction in rats. The current study observed normal body and kidney weights in PCL-administered rats. The assessment of serum urea and creatinine remain a widely used metric to assess

Table 1. Effects of coenzyme Q_{10} and resveratrol on body and kidney weights of paclitaxel-treated rats.

Treatments	Final body weight (g)	Absolute kidney weight (g)	Relative kidney weight (%)
Control	220.8±12.0	0.69±0.01	0.31±0.05
CoQ_{10}	221.7±17.5	0.64±0.06	0.29±0.05
RSV	226.3±13.6	0.68±0.05	0.30±0.02
CoQ_{10}+RSV	221.1±14.4	0.65±0.09	0.29±0.03
PCL	215.3±17.2	0.67±0.01	0.31±0.07
CoQ10 + PCL	220.4±15.1	0.66±0.07	0.30±0.09
RSV + PCL	222.7±15.2	0.64±0.06	0.28±0.03
CoQ_{10}+RSV + PCL	225.5±13.0	0.68±0.08	0.30±0.05

COQ_{10}: Coenzyme Q_{10}, RSV: Resveratrol, Data as mean±SEM, n=5, SEM: Standard error of mean.

Table 2. Effects of coenzyme Q_{10} and resveratrol on serum electrolytes of paclitaxel-treated rats.

Treatment	Potassium (mmol/L)	Chloride (mmol/L)	Sodium (mmol/L)	Bicarbonate (mmol/L)
Control	2.81±0.03	149.55±5.84	148.67±3.30	14.46±0.91
CoQ_{10}	2.83±0.05	146.73±3.00	145.17±2.47	14.28±0.75
RSV	2.84±0.03	148.53±4.37	144.91±4.84	14.64±0.81
CoQ_{10}+RSV	2.26±0.08	153.67±8.23	143.16±4.27	14.19±0.92
PCL	1.04±0.02#	147.12±2.94#	62.07±1.27#	7.68±0.35#
CoQ_{10}+ PCL	1.90±0.05 π	70.56±2.52 π	96.46±0.99 π	10.79±0.52 π
RSV+ PCL	1.92±0.08*	98.55±1.29*	121.15±2.80*	13.94±0.66*
CoQ_{10}+RSV+ PCL	2.45±0.02**	144.37±2.30**	166.64±5.60**	14.11±0.78*

Coenzyme Q_{10}, RSV: Resveratrol, n=5, Data as mean±SEM, #p<0.001 difference when compared to placebo control, π p<0.05,*p<0.01, **p<0.001 Significant difference when compared to PCL, SEM: Standard error of mean.

kidney function. The estimation of uric acid, total protein and albumin may predict the progression of renal disease (24). Serum electrolytes, regulated by the kidney play important roles in metabolic pathways, enzyme activation, acid-base balance, and muscular-function (35). The estimation of serum electrolytes can predict renal status (36). In this study, compromised renal status was conspicuous in PCL-treated rats. This was confirmed by elevated serum creatinine, urea, and uric acid levels with decreased serum total protein, albumin and electrolytes. This observation supports earlier findings (9, 10). Endogenous antioxidants form defence shield that neutralize excess ROS. Excess cellular ROS concentration can undermine antioxidant function causing oxidative stress leading to structural and functional damage to biomolecules (lipids, proteins, and DNA) (37, 38). The present study observed depleted kidney antioxidants in PCL-treated rats. The observed decrease in kidney antioxidants can increase the vulnerability of the kidney to more ROS attack. LPO is a ROS-induced phenomenon. It is a consequence of the oxidation of polyunsaturated fatty acid, which produces a number of by-products including malondialdehyde (MDA). LPO by-products can react with and incapacitate kidney phospholipids, proteins, amino groups and nucleic acids, thus causing renal dysfuntion (39). Over the years, MDA has been used to validate the occurrence of LPO (40). In this study, PCL increased kidney MDA concentration, which is a sign of LPO. Furthermore, PCL

Table 3. Effects of coenzyme Q_{10} and resveratrol on kidney oxidative stress indices of paclitaxel-treated rats.

Treatment	MDA nmole/mgprotein	GSH µmole/mgprotein	CAT U/mgprotein	GPx U/mgprotein	SOD U/mgprotein
Control	0.34±0.02	7.84±0.25	22.22±2.56	19.07±1.07	24.54±2.35
CoQ_{10}	0.35±0.02	7.86±0.20	22.64±2.23	19.41±1.00	25.28±2.98
RSV	0.33±0.01	7.89±0.34	23.15±2.12	19.63±1.00	25.72±2.90
CoQ_{10}+RSV	0.31±0.01	7.90±0.33	23.92±2.19	19.94±1.99	26.45±2.10
PCL	1.86±0.09#	1.83±0.09#	8.24±0.54#	5.635±0.18#	7.00±0.15#
CoQ_{10}+ PCL	1.39±0.07π	3.46±0.11 π	11.33±0.81 π	8.082±0.23 π	11.23±0.30 π
RSV+ PCL	0.84±0.04*	4.57±0.17*	15.64±0.99*	11.56±0.60*	15.64±1.70*
CoQ_{10}+RSV+ PCL	0.38±0.02**	7.61±0.39**	20.17±1.33**	18.10±1.09**	22.85±2.20**

MDA: Malondialdehyde GSH: Glutathione, CAT: Catalase, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, COQ 10: COQ_{10}, RSV: Resveratrol, n=5, Data as mean±SEM, #p<0.001 Significant difference when compared to placebo control, π p<0.05,*p<0.01, ** p<0.001 Significant difference when compared to PCL.

impacted detrimentally on the kidney morphology by causing hypercellular glomerulus and tubular necrosis, which correlates with alterations in biochemical indices. Experimentally, Rabah reported similar kidney morphological changes caused by PCL (11). The mechanisms of the induction of renal dysfunction by PCL are not well established. However, in the current study, PCL might have caused renal damage through generated ROS leading to kidney oxidative stress. Oxidative stress can damage kidney biomolecules such as DNA, lipids and proteins consequently altering kidney morphology. Under stress full conditions, or chemical assaults, renal tubular cells generate excess ROS, which can incapacitate cellular functions and cause cell death (3, 4). In the present study, PCL –induced renal dysfunction was ameliorated by CoQ_{10} and RSV supplementations. This was characterised by restored functional status of serum biochemical markers and increased kidney antioxidant capacity. It was also marked by decreased MDA activity and restored kidney morphology. This observation correlates with the protective impact of CoQ_{10} against chromate-induced renal dysfunction in rats (41). It also correlates with the protective activity of RSV on gentamicin-induced renal damage in rats (42). CoQ_{10} and RSV might have offered protection by curtailing the impact of oxidative stress on the kidney by inhibiting ROS generated by PCL. RSV is an antioxidant that has unusual strong ability to scavenge and neutralise free radicals. It can inhibit LPO primarily by removing lipid peroxides produced in membranes (43). It has been associated with the activation of enzymes that remove free radicals (44) and can protect biomolecules including DNA, proteins and lipids from oxidative stress-induced damage (45). CoQ_{10} is a lipid soluble antioxidant that scavenges free radicals, inhibits oxidative stress and protects proteins, lipids and DNA (46). It can stabilize plasma membrane and other intracellular membranes thereby protecting membrane phospholipids from peroxidation (47). CoQ_{10} can enhance antioxidant gene expression and the syntheses of endogenous antioxidants (48). In this study, the protection against PCL-induced renal damage was best when CoQ_{10} and RSV were co-administered. This observation may be due to their complementary effects. Conclusion: CoQ_{10} and RSV may be clinically used for PCL associated nephrotoxicity.

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None declared.

Conflict of Interest

None declared.

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