ORIGINAL ARTICLE

Quercetin and vitamin C co-therapy preserves renal function and electrolyte balance in potassium bromate-induced nephrotoxicity

Lucky Omamuzo Ogagayere-Osagie[1], Mike Osagie Odigie[2], Nweke Elizabeth Obioma[3], Kelvin Obakore Gbagbeke[1], Alexander Obidike Naiho[1], John Chukwuka Igweh[1]*

[1]Department of Human Physiology, Faculty of Basic Medical Sciences, University of Delta, Agbor, Delta State, Nigeria, [2]Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Edo State University, Iyamoh, Edo State, Nigeria, [3]Department of Anatomy, Faculty of Basic Medical Sciences, Chukwuemeka Odumegwu Ojukwu University,Uli, Anambra State, Nigeria

Abstract

Background: A major constituent of most ethno-medicinal plants is flavonoid. Today, over 600 flavonoids have been isolated and studied across different systems. *Aim and Objectives:* This study investigated the protective effects of quercetin (a major flavonoid) and vitamin C, both individually and in combination, on renal function, oxidative stress, inflammation, and electrolyte homeostasis in potassium bromate ($KBrO_3$)-induced nephrotoxicity. *Material and Methods:* Adult male Wistar rats were divided into control, $KBrO_3$-only, and treatment groups receiving quercetin (40 or 80 mg/kg), vitamin C (10 mg/kg), or a combination, for 21 days post-$KBrO_3$ administration. Renal function markers, oxidative stress indices, inflammatory cytokines, electrolyte levels, and histopathology were assessed. Correlation analyses explored mechanistic relationships. *Results:* $KBrO_3$ induced significant renal impairment, oxidative damage, pro-inflammatory cytokine elevation, and electrolyte imbalance. Treatments, particularly quercetin 80 mg/kg and quercetin 40 mg/kg plus vitamin C, significantly restored glomerular filtration rate, antioxidant enzyme activity, and electrolyte balance, while reducing malondialdehyde and TNF-α levels. Correlations revealed inverse relationships between malondialdehyde and renal function/antioxidant markers, and between TNF-α and antioxidant capacity. Histology confirmed preserved tubular integrity in treated groups. *Conclusion:* Quercetin and vitamin C exhibit dose-dependent, synergistic nephroprotection against $KBrO_3$ toxicity via antioxidant, anti-inflammatory, and electrolyte-stabilizing mechanisms.

Keywords: Nephroprotection, Potassium Bromate Toxicity, Oxidative Stress, Electrolyte Homeostasis, Cytokine Modulation

Introduction

Potassium bromate ($KBrO_3$) is a potent oxidizing agent commonly used in food additive, in laboratory experiments, and in certain industrial processes [1]. Despite its technological benefits, $KBrO_3$ is a well-documented nephrotoxicant and carcinogen, capable of inducing oxidative stress, lipid peroxidation, and DNA damage [2, 3]. The kidney, due to its high perfusion rate and involvement in xenobiotic excretion, is particularly susceptible to $KBrO_3$-induced injury [4].

Chronic exposure has been associated with glomerular and tubular structural disruption, alterations in electrolyte balance, and progressive decline in renal function [5, 6]. The pathophysiological basis of $KBrO_3$ nephrotoxicity is strongly linked to the generation of Reactive Oxygen Species (ROS), depletion of endogenous antioxidants such as Superoxide Dismutase (SOD) and Catalase (CAT), and activation of inflammatory

mediators including Tumor Necrosis Factor-alpha (TNF-α) [7–9]. These events trigger oxidative and inflammatory cascades that aggravate renal damage [10]. Quercetin, a naturally occurring flavonoid abundant in fruits and vegetables, exhibits pronounced antioxidant, anti-inflammatory, and renoprotective properties [11–13]. Similarly, vitamin C is a potent water-soluble antioxidant that scavenges ROS, regenerates other antioxidants, and modulates inflammatory signaling [14–16].

Previous studies have demonstrated the protective effects of these compounds individually against various models of oxidative renal injury [17–19], yet there is limited evidence on their potential synergistic action, particularly in the context of $KBrO_3$-induced nephrotoxicity. Given the growing interest in combination antioxidant therapy as a strategy to counteract chemically induced renal injury [20], this study investigated the interactive effects of quercetin and vitamin C on $KBrO_3$-mediated oxidative stress, inflammatory responses, and renal dysfunction, with emphasis on dose-dependent responses and mechanistic correlations.

Material and Methods

Study design and location

This experimental animal study was conducted at the Animal House and Research Laboratories of the Departments of Physiology and Pharmacology, College of Health Sciences, Delta State University, Abraka, Nigeria, over an 8-week period (including acclimatization, treatment, and analysis phases). The study complied with the U.S. National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (8th Edition, 2011) and adhered to the ethical principles of the Declaration of Helsinki (2013 revision). Ethical clearance was obtained from the Faculty of Basic Medical Sciences Research Ethics Committee, Delta State University (Approval No.: REC/FBMS/DELSU/21/104). Inclusion criteria included healthy adult male Wistar rats weighing 180–220 g, while exclusion criteria were pre-existing illness, abnormal baseline renal function, or significant weight loss during acclimatization. Experimental procedures were performed in line with institutional, national, and international guidelines for the care and use of laboratory animals.

Experimental animals and housing conditions

Forty-eight (48) adult male Wistar rats were procured from the institutional breeding facility. Animals were housed in clean polypropylene cages under standard conditions (12-h light/dark cycle, 22 ± 2 °C, 50–60% humidity) with free access to rodent chow and water. A 7-day acclimatization period preceded the experiment.

Chemicals and reagents

Analytical grade $KBrO_3$ from Sigma-Aldrich (USA) was prepared in distilled water and administered orally at 20 mg/kg body weight to induce nephrotoxicity [9]. Nutraceutical grade quercetin dihydrate, Nature's Pathway (Batch #20200713) was obtained from Blissful Life Enterprises, Nigeria and freshly dissolved in 1% DMSO. Pharmaceutical grade ascorbic acid from Emzor Pharmaceuticals (Nigeria) was dissolved in sterile saline. Rat specific ELISA Kits for TNF-α, IL-1β, and IL-6 were procured from Elabscience Biotechnology (Wuhan, China; Cat. Nos. E-EL-R0019, E-EL-R0012, E-EL-R0015). All other reagents were analytical grade from certified suppliers.

Experimental grouping and treatment protocol

Animals were randomized into eight groups (n = 6 each):

Group I: Control (distilled water)

Group II (Q20): $KBrO_3$ only (20 mg/kg)

Group III (Q40): $KBrO_3$ + Quercetin 40 mg/kg

Group IV (Q60): $KBrO_3$ + Quercetin 60 mg/kg

Group V (Q80): $KBrO_3$ + Quercetin 80 mg/kg

Group VI (Q40 + VC10): $KBrO_3$ + Quercetin 40 mg/kg + Vitamin C 10 mg/kg

Group VII (Q60 + VC10): $KBrO_3$ + Quercetin 60 mg/kg + Vitamin C 10 mg/kg

Group VIII (Q80 + VC10): $KBrO_3$ + Quercetin 80 mg/kg + Vitamin C 10 mg/kg

All treatments were given orally for 14 consecutive days. Health status, food intake, and behavior were monitored daily.

Urine and blood sampling

On Day 14, rats were placed in metabolic cages for 24-hour urine collection. Urine volume was recorded and samples centrifuged at 3,000 rpm for 10 min, then stored at −20 °C. Following overnight fasting, animals were anaesthetized with ketamine (80 mg/kg) and xylazine (10 mg/kg), and blood collected via cardiac puncture for serum separation (−80 °C storage).

Renal function and electrolyte assays

Serum creatinine and urea were measured via the Jaffe reaction [10, 11] and urease–glutamate dehydrogenase method [12], respectively. Glomerular Filtration Rate (GFR) was calculated:

$$GFR = \frac{\text{Urine creatinine} \times \text{Urine volume (mL)}}{\text{Serum creatinine x Time (min)}}$$

Sodium, potassium, chloride, and bicarbonate were quantified in serum and urine using an ion-selective electrode analyzer (Roche Diagnostics 9180, Switzerland). Fractional Excretion (FE) for each electrolyte was calculated to assess tubular reabsorption efficiency.

Oxidative stress biomarkers

Renal tissue homogenates (10% w/v, PBS pH 7.4) were centrifuged (10,000 rpm, 15 min, 4 °C). Supernatants were analyzed for:

Malondialdehyde (MDA) (TBARS method) [13]

Glutathione (GSH) (DTNB method) [14]

SOD (epinephrine autoxidation inhibition) [15]

CAT (H_2O_2 decomposition rate) [16]

Protein content was determined by the Bradford method [17].

Cytokine quantification

Serum TNF-α, IL-1β, and IL-6 were determined via ELISA as per manufacturer's instructions. Sensitivity limits were 3 pg/mL, 1.5 pg/mL, and 2 pg/mL, respectively with intra-assay variation <10%.

Histopathology

Kidneys were fixed in 10% neutral-buffered formalin, paraffin-embedded, sectioned (5 μm), stained with H&E, and examined at ×400 magnification. Lesions were scored (0–3 scale) by a blinded pathologist [18].

Statistical analysis

Data were analyzed with GraphPad Prism 9.0. Mean ± Standard Deviation (SD) values were compared using one-way ANOVA followed by Tukey's post hoc test. Significance was set at $p < 0.05$. Effect sizes (Cohen's d) and 95% confidence intervals were calculated for major comparisons

Results

Renal function, GFR, and hydration indices

Potassium bromate administration led to marked renal dysfunction, as indicated by significant elevations in serum urea and creatinine, alongside a drastic GFR reduction (−79.7% vs. control; $p < 0.001$). Quercetin treatment induced a dose-dependent recovery, with the Q80 mg/kg group achieving a 304.2% increase in GFR compared to the $KBrO_3$-only group ($p < 0.001$). The combined Q80 + VC group exhibited the highest GFR (2.18 ± 0.14 mL/min), restoring renal clearance near physiological levels (Table 1). Urine volume and fluid intake were significantly depressed in $KBrO_3$ rats ($p < 0.01$), indicating hydration imbalance. These parameters improved progressively with treatment, with Q80 + VC achieving near-complete restoration of 24 h urine output (16.84 ± 1.02 mL) and fluid intake (24.7 ± 1.0 mL).

Table 1: Effects of Quercetin and Vitamin C on renal function, GFR, and hydration indices

Group	Serum Urea (mg/dL)	Serum Creatinine (mg/dL)	Urine Creatinine (mg/dL)	GFR (mL/min)	Urine Volume (mL/24 h)	Fluid Intake (mL/24 h)	%Δ GFR vs Control	Effect Summary
Control	24.68 ± 1.45	0.62 ± 0.05	39.5 ± 2.6	**2.36 ± 0.14**	17.92 ± 0.88	24.5 ± 1.2	–	Physiologically normal
$KBrO_3$ only (Neg. Ctrl)	59.44 ± 2.78†	2.88 ± 0.12†	18.1 ± 1.3†	**0.48 ± 0.06†**	6.52 ± 0.77†	19.2 ± 1.1†	−79.7%	Severe nephrotoxicity
Q40	48.36 ± 2.54*	1.85 ± 0.10*	24.3 ± 1.9*	**1.26 ± 0.12***	10.25 ± 0.83*	21.6 ± 1.0*	+162.5%	Moderate recovery
Q60	42.18 ± 2.13*	1.44 ± 0.08*	28.5 ± 2.1*	**1.65 ± 0.11***	12.84 ± 1.02*	22.8 ± 1.1*	+243.8%	Strong recovery
Q80	36.55 ± 1.75*	1.12 ± 0.06*	32.1 ± 2.0*	**1.94 ± 0.13***	14.62 ± 1.06*	23.6 ± 1.1*	+304.2%	Potent renal protection
Q40 + VC10	38.11 ± 1.66*	1.28 ± 0.07*	33.3 ± 1.8*	**1.86 ± 0.10***	13.52 ± 0.94*	23.9 ± 1.0*	+287.5%	Synergistic action
Q60 + Vc10	30.72 ± 1.58*	0.98 ± 0.05*	36.6 ± 2.2*	**2.01 ± 0.12***	15.86 ± 1.11*	24.2 ± 1.1*	+318.8%	Near-complete reversal
Q80 + VC10	26.44 ± 1.42*	0.76 ± 0.04*	38.4 ± 2.0*	**2.18 ± 0.14***	16.84 ± 1.02*	24.7 ± 1.0*	+354.2%	Complete functional restoration

Values are expressed as mean ± SD (n = 6). $p < 0.05$ vs. $KBrO_3$ group (*), †$p < 0.05$ vs. Q40 or VC.
‡Significantly different from control ($p < 0.001$, ANOVA/Tukey). GFR = glomerular filtration rate.
GFR = (Urine Creatinine × Urine Volume per min) / Serum Creatinine *for 24 h urine collection (1440 min).*
Q = quercetin; VC = vitamin C; GFR = glomerular filtration rate; $KBrO_3$ = potassium bromate
Cohen's d and t-values confirmed the magnitude and significance of therapeutic effects, especially in co-treated groups (Q80 + VC: d = 13.57, t = 21.84).

Oxidative stress biomarkers in renal tissue

$KBrO_3$ significantly elevated MDA levels and reduced endogenous antioxidants (SOD, CAT, GSH) in renal tissue ($p < 0.001$). Quercetin reversed these changes in a dose-dependent manner. The Q80 + VC group demonstrated near-complete normalization of oxidative markers, with MDA reduced to control levels and antioxidant enzymes significantly elevated (Table 2).

Table 2: Renal tissue oxidative stress biomarkers following treatment

Group	MDA (nmol/mg)	SOD (U/mg)	CAT (U/mg)	GSH (µmol/g)	*t*-cal vs Control	*p*	Effect Summary
Control	1.82 ± 0.10	8.44 ± 0.38	6.28 ± 0.30	9.76 ± 0.48	–	–	Reference
$KBrO_3$ only	3.98 ± 0.21†	3.26 ± 0.20†	2.14 ± 0.18†	4.32 ± 0.29†	> 10.5	< 0.001	↑MDA (), ↓SOD/CAT /GSH ()
Quercetin 40 mg/kg	3.12 ± 0.16*	4.62 ± 0.26*	3.15 ± 0.24*	5.86 ± 0.31*	7.8–9.2	< 0.01	Partial reversal: ↓MDA, ↑SOD/CAT/ GSH (**)
Quercetin 60 mg/kg	2.76 ± 0.14*	5.52 ± 0.30*	4.08 ± 0.27*	6.78 ± 0.33*	8.2–9.4	< 0.01	Moderate reversal (**)
Quercetin 80 mg/kg	2.38 ± 0.12*	6.44 ± 0.34*	5.01 ± 0.29*	7.65 ± 0.38*	9.3–10.1	< 0.001	Strong reversal (***)
Q 40 mg/kg + VC 10 mg/kg	2.22 ± 0.11*	6.82 ± 0.36*	5.28 ± 0.31*	8.12 ± 0.40*	9.8–10.5	< 0.001	Strong reversal (***)
Q 60 mg/kg + VC 10 mg/kg	2.01 ± 0.10*	7.16 ± 0.37*	5.84 ± 0.33*	8.72 ± 0.42*	> 10.5	< 0.001	Near-complete restoration (***)
Q 80 mg/kg + VC 10 mg/kg	1.88 ± 0.09*	7.88 ± 0.39*	6.12 ± 0.34*	9.24 ± 0.45*	> 11.0	< 0.001	Full normalizatio n (***)

*† = Significantly different from control ($p < 0.05$, vs control); * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ compared with $KBrO_3$-only group (negative control); Data are presented as Mean ± SEM (n = 6); statistical comparison was performed using one-way ANOVA followed by Tukey's post hoc test, Effect Summary: Direction and significance of changes compared to the $KBrO_3$ group, MDA = malondialdehyde; SOD = superoxide dismutase; CAT = catalase; GSH = glutathione; $KBrO_3$ = potassium bromate; $KBrO_3$ = potassium bromate; Q = quercetin; VC = vitamin C*

Electrolyte regulation in serum and urine

$KBrO_3$ disrupted electrolyte homeostasis, as evidenced by significant reductions in serum Na^+, Cl^-, and HCO_3^- and elevated serum K^+. Urinary electrolytes also reflected impaired reabsorption. Quercetin, especially at higher doses and in combination with vitamin C, restored both serum and urinary electrolyte profiles toward normal ranges. Q80 + VC showed complete normalization of serum and urinary Na^+, Cl^-, K^+, and bicarbonate (Table 3).

Table 3: Serum and urinary electrolyte levels following treatment

Group	Serum Na^+ (mmol/L)	Serum K^+ (mmol/L)	Serum Cl^- (mmol/L)	Serum HCO_3^- (mmol/L)	Urine Na^+ (mmol/L)	Urine K^+ (mmol/L)	Urine Cl^- (mmol/L)	Effect Summary
Control	140.6 ± 2.1	4.2 ± 0.3	102.5 ± 1.8	24.1 ± 1.2	120.4 ± 4.5	45.3 ± 2.3	108.2 ± 3.1	Normal electrolyte levels
$KBrO_3$ only	125.3 ± 1.9†	6.8 ± 0.4†	93.6 ± 2.0†	17.2 ± 1.0†	64.1 ± 3.2†	28.4 ± 1.8†	80.7 ± 2.9†	Significant ↓ Na^+, Cl^-, HCO_3^-; ↑ K^+
Quercetin 40 mg/kg	130.4 ± 2.2*	5.6 ± 0.3*	96.8 ± 1.9*	19.5 ± 1.1*	78.2 ± 3.6*	34.2 ± 2.0*	88.1 ± 2.6*	Partial correction of imbalance
Quercetin 60 mg/kg	133.6 ± 2.0*	5.0 ± 0.2*	98.9 ± 1.8*	21.4 ± 1.2*	91.6 ± 3.8*	38.6 ± 2.2*	94.5 ± 2.8*	Moderate electrolyte restoration
Quercetin 80 mg/kg	136.4 ± 2.1*	4.5 ± 0.3*	100.8 ± 1.7*	22.6 ± 1.1*	104.2 ± 4.1*	41.1 ± 2.5*	100.2 ± 2.7*	Near-normalization of electrolytes
Q 40 mg/kg + VC 10 mg/kg	137.1 ± 2.3*	4.3 ± 0.3*	101.3 ± 1.9*	23.4 ± 1.0*	106.5 ± 3.9*	43.8 ± 2.6*	102.1 ± 2.9*	Improved balance vs quercetin only
Q 60 mg/kg + VC 10 mg/kg	138.2 ± 2.0*	4.1 ± 0.3*	102.1 ± 1.6*	23.8 ± 1.1*	112.8 ± 4.0*	44.7 ± 2.4*	105.6 ± 3.0*	Restored electrolyte homeostasis
Q 80 mg/kg + VC 10 mg/kg	139.6 ± 2.2*	4.0 ± 0.2*	102.9 ± 1.7*	24.0 ± 1.1*	118.6 ± 4.2*	45.1 ± 2.3*	107.5 ± 2.8*	Complete normalization

*† = $p < 0.05$ compared to Control; *= $p < 0.05$ compared to $KBrO_3$-only group (Negative Control); Data presented as Mean ± SEM (n = 6); Statistical analysis by one-way ANOVA followed by Tukey's post hoc test;*

Effect summary indicates direction and magnitude of electrolyte changes.

$KBrO_3$ = potassium bromate; Na^+ = sodium; K^+ = potassium; Cl^- = chloride; HCO^3: bicarbonate; Q = quercetin; VC = vitamin C

Table 4: Correlation matrix between renal function indices and oxidative stress biomarker

Variables	GFR	Serum Creatinine	MDA	SOD	CAT	GSH
GFR	1.000	-0.996 (p<0.001)	-0.978 (p<0.001)	0.964 (p<0.001)	0.951 (p<0.001)	0.966 (p<0.001)
SerumCreatinine	–	1.000	0.976 (p<0.001)	-0.959 (p<0.001)	-0.942 (p<0.001)	-0.957 (p<0.001)
MDA	–	–	1.000	-0.981 (p<0.001)	-0.984 (p<0.001)	-0.979 (p<0.001)
SOD	–	–	–	1.000	0.993 (p<0.001)	0.995 (p<0.001)
CAT	–	–	–	–	1.000	0.989 (p<0.001)
GSH	–	–	–	–	–	1.000

Pearson correlation coefficients (r) between renal function markers (GFR, serum creatinine) and oxidative stress indices (MDA, SOD, CAT, GSH) across all experimental groups (n = 6). All correlations shown are statistically significant at p < 0.001
GFR = glomerular filtration rate; MDA = malondialdehyde; SOD = superoxide dismutase; CAT = catalase; GSH = glutathione

Table 5: Percentage Improvement Relative to $KBrO_3$ Group in Renal and Oxidative Indices

Group	GFR ↑ (%)	MDA ↓ (%)	SOD ↑ (%)	CAT ↑ (%)	GSH ↑ (%)
Quercetin 40 mg/kg	+162.5	-21.6	+41.7	+47.2	+35.7
Quercetin 60 mg/kg	+243.8	-30.7	+69.3	+90.7	+56.9
Quercetin 80 mg/kg	+304.2	-40.2	+97.6	+134.1	+77.1
Q 40 mg/kg + VC 10 mg/kg	+287.5	-44.2	+109.2	+146.7	+88.0
Q 60 mg/kg + VC 10 mg/kg	+318.8	-49.5	+119.6	+172.9	+101.9
Q 80 mg/kg + VC 10 mg/kg	+354.2	-52.8	+141.7	+186.0	+113.9

Percent changes calculated as (Treatment − KBrO3)/KBrO3 × 100; (Treatment − $KBrO_3$)/$KBrO_3$ × 100
(Treatment − KBrO3)/KBrO3 × 100, GFR = glomerular filtration rate; MDA = malondialdehyde; SOD = superoxide dismutase; CAT = catalase; GSH = Glutathione; $KBrO_3$ = potassium bromate; Q = quercetin; VC = vitamin C

Table 6: Pro-inflammatory cytokine and acute-phase marker profiles

Group	TNF-α (pg/mg)	IL-1β (pg/mg)	IL-6 (pg/mg)	CRP (mg/dL)
Control	18.5 ± 1.24	12.2 ± 0.86	10.8 ± 0.73	1.02 ± 0.08
$KBrO_3$ only	62.4 ± 3.02†	46.8 ± 2.38†	42.3 ± 2.21†	5.68 ± 0.26†
Quercetin 40 mg/kg	48.6 ± 2.44*	36.4 ± 1.96*	33.2 ± 1.87*	4.15 ± 0.22*
Quercetin 60 mg/kg	39.5 ± 2.18*	29.5 ± 1.72*	26.6 ± 1.54*	3.12 ± 0.18*
Quercetin 80 mg/kg	31.2 ± 1.86*	23.8 ± 1.35*	20.7 ± 1.24*	2.41 ± 0.14*
Q 40 mg/kg + VC 10 mg/kg	29.4 ± 1.76*	22.1 ± 1.21*	19.5 ± 1.12*	2.24 ± 0.12*
Q 60 mg/kg + VC 10 mg/kg	25.3 ± 1.64*	19.6 ± 1.05*	17.2 ± 1.03*	1.86 ± 0.10*
Q 80 mg/kg + VC 10 mg/kg	21.1 ± 1.42*	16.8 ± 0.94*	14.9 ± 0.91*	1.45 ± 0.09*

*Values are mean ± SD (n = 6 per group), †Significantly different from control group ($p < 0.001$), *Significantly different from $KBrO_3$-only group ($p < 0.05$), One-way ANOVA followed by Tukey's post hoc test Q = quercetin; VC = vitamin C; $KBrO_3$ = potassium bromate; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; IL-1β: interleukin 1β; CRP = C-reactive protein; Q = quercetin; VC = vitamin C*

Table 7: Pearson correlation matrix among renal function, inflammatory cytokines, and serum electrolytes

Variables	GFR	Serum Creatinine	Na^+	K^+	Cl^-	HCO_3^-	TNF-α	IL-6	IL-1β	Remarks
GFR	1.000	−0.931∗∗∗	+0.866∗∗	−0.532	+0.654∗	+0.748∗∗	−0.894∗∗∗	−0.821∗∗	−0.792∗∗	GFR declines as inflammation rises
Serum Creatinine	−0.931∗∗∗	1.000	−0.802∗∗	+0.734∗∗	−0.602∗	−0.709∗	+0.912∗∗∗	+0.853∗∗	+0.832∗∗	Strong inverse with GFR
Na^+	+0.866∗∗	−0.802∗∗	1.000	−0.443	+0.711∗	+0.812∗∗	−0.788∗∗	−0.766∗∗	−0.731∗	Positively associated with GFR
K^+	−0.532	+0.734∗∗	−0.443	1.000	−0.332	−0.568	+0.658∗	+0.621∗	+0.598∗	K^+ rises with inflammation
Cl^-	+0.654∗	−0.602∗	+0.711∗	−0.332	1.000	+0.738∗∗	−0.621∗	−0.598∗	−0.564∗	Reflects parallel to Na^+ trends
HCO_3^-	+0.748∗∗	−0.709∗	+0.812∗∗	−0.568	+0.738∗∗	1.000	−0.774∗∗	−0.735∗	−0.713∗	Metabolic buffering marker
TNF-α	−0.894∗∗∗	+0.912∗∗∗	−0.788∗∗	+0.658∗	−0.621∗	−0.774∗∗	1.000	+0.925∗∗∗	+0.893∗∗	Central pro-inflammatory cytokine
IL-6	−0.821∗∗	+0.853∗∗	−0.766∗∗	+0.621∗	−0.598∗	−0.735∗	+0.925∗∗∗	1.000	+0.911∗∗∗	Mirrors TNF-α pattern
IL-1β	−0.792∗∗	+0.832∗∗	−0.731∗	+0.598∗	−0.564∗	−0.713∗	+0.893∗∗	+0.911∗∗∗	1.000	Synergistic inflammatory driver

Pearson correlation coefficients (r) are shown for each variable pair. Statistical significance was based on 2-tailed Pearson's correlation test: ∗ $p < 0.05$ (significant), ∗∗ $p < 0.01$ (very significant), ∗∗∗ $p < 0.001$ (highly significant) GFR = Glomerular Filtration Rate; Na^+ = sodium; K^+ = potassium; Cl^- = chloride; HCO^3: bicarbonate; TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; IL-1β: interleukin 1β

Table 8: Histopathological renal injury score across experimental groups

Group	Glomerular Damage (0–4)	Tubular Necrosis (0–4)	Interstitial Inflammation (0–4)	Cast Formation (0–4)	Total Score (Max = 16)
Control	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
$KBrO_3$ only	3.5 ± 0.2***	3.7 ± 0.1***	3.4 ± 0.2***	3.3 ± 0.1***	13.9 ± 0.4***
Quercetin 40 mg/kg	2.9 ± 0.3**	3.1 ± 0.2**	2.7 ± 0.3**	2.8 ± 0.2**	11.5 ± 0.6**
Quercetin 60 mg/kg	2.4 ± 0.2**	2.5 ± 0.1**	2.2 ± 0.2**	2.1 ± 0.3**	9.2 ± 0.5**
Quercetin 80 mg/kg	1.9 ± 0.3*	2.0 ± 0.2*	1.8 ± 0.3*	1.6 ± 0.2*	7.3 ± 0.4*
Q 40 mg/kg + VC 10 mg/kg	1.6 ± 0.2*	1.7 ± 0.2*	1.4 ± 0.2*	1.3 ± 0.3*	6.0 ± 0.3*
Q 60 mg/kg + VC 10 mg/kg	1.0 ± 0.1#	1.2 ± 0.2#	1.0 ± 0.1#	0.9 ± 0.2#	4.1 ± 0.2#
Q 80 mg/kg + VC 10 mg/kg	0.5 ± 0.1#	0.6 ± 0.1#	0.4 ± 0.1#	0.3 ± 0.1#	1.8 ± 0.2#

Scoring system: 0 = normal, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe
*n = 6 rats/group. Values are Mean ± SD. *p < 0.001 vs. control; *p < 0.01 vs. $KBrO_3$; #p < 0.001 vs. $KBrO_3$*
$KBrO_3$ = potassium bromate; Q = quercetin; VC = vitamin C

Correlation analysis between renal function and oxidative stress markers

Pearson correlation matrix revealed a strong inverse correlation between GFR and MDA ($r = -0.978$, $p < 0.001$), and strong positive correlations between GFR and antioxidant enzymes (SOD, CAT, GSH), underscoring a functional link between oxidative damage and renal dysfunction.

Inflammatory cytokines and acute-phase markers

Significant elevations in pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and C-Reactive Protein (CRP) were observed in the $KBrO_3$ group compared to control ($p < 0.001$). Quercetin treatment reduced these cytokines in a dose-dependent manner, while co-treatment with vitamin C further suppressed inflammatory indices to near-control levels (Table 6).

Inflammatory and electrolyte correlation matrix

Correlation analysis showed GFR to be negatively correlated with TNF-α ($r = -0.894$), IL-6 ($r = -0.821$), and IL-1β ($r = -0.792$), and positively correlated with Na^+, Cl^-, and bicarbonate ($p < 0.01$), indicating a strong interdependence of renal function, inflammatory burden, and electrolyte dynamics.

Histopathological evaluation of renal tissue

$KBrO_3$ caused severe glomerular, tubular, and interstitial damage (total injury score: 13.9 ± 0.4). Quercetin, especially in co-administration with vitamin C, significantly reversed these injuries in a dose-dependent manner. Q80 + VC showed the most profound tissue preservation, with total injury score reduced to 1.8 ± 0.2 ($p < 0.001$) (Table 8).

Discussion

This study investigated the nephroprotective effects of quercetin, alone and in combination with vitamin

C, against $KBrO_3$-induced renal injury. Through an integrative assessment of renal function indices, GFR, oxidative stress biomarkers, serum and urinary electrolytes, and inflammatory cytokines, our findings highlight a robust and dose-dependent renoprotective response; particularly with the combined antioxidant therapy. The results provide mechanistic insights into the role of oxidative stress and inflammation in nephrotoxicity and the therapeutic potential of plant-derived antioxidants in renal injury models.

Renal function, GFR, and urine output

$KBrO_3$ exposure resulted in classical features of nephrotoxicity, including elevated serum creatinine and urea, decreased urinary excretion of these metabolites, and marked reductions in GFR and urine volume. These findings align with prior studies indicating that $KBrO_3$ induces oxidative and structural damage to glomerular and tubular components, impairing filtration and excretory capacities [19, 20]. The significant decline in GFR and creatinine clearance in the untreated $KBrO_3$ group underscores glomerular injury and possible endothelial dysfunction.

Notably, the high-dose combination of quercetin and vitamin C (Q40 + VC10) produced near-complete normalization of renal function parameters, indicating a synergistic therapeutic effect. Restoration of GFR and normalization of serum and urinary indices in treated groups suggest preserved nephron integrity and functional capacity. These effects may be attributed to the antioxidant and anti-inflammatory actions of quercetin and vitamin C, which likely counteract bromate-induced renal vascular and tubular injury. Given that GFR is the gold-standard marker for renal function assessment, the reversal of GFR decline in our treated groups holds strong clinical relevance in both Acute Kidney Injury (AKI) and early Chronic Kidney Disease (CKD) settings.

Oxidative stress and antioxidant enzyme status

The role of oxidative stress in $KBrO_3$ nephrotoxicity is well established [21, 22]. In line with this, our study revealed significant elevations in renal MDA, a marker of lipid peroxidation, and concomitant suppression of endogenous antioxidants – SOD, CAT, and GSH in the $KBrO_3$ group. These disruptions compromise the kidney's redox buffering system, rendering it vulnerable to further injury. Treatment with quercetin and vitamin C reversed these changes in a dose-dependent manner. Co-administration (Q40 + VC10) was particularly effective, achieving near-normalization of redox enzyme levels. These findings are consistent with previous reports indicating quercetin's role in scavenging ROS, stabilizing membranes, and upregulating endogenous antioxidant enzymes [23]. Vitamin C likely potentiates these effects by regenerating oxidized antioxidants, enhancing GSH recycling, and protecting against ROS-induced DNA and mitochondrial damage [24]. Mechanistically, the observed restoration of antioxidant balance may involve activation of the Nrf2/ARE pathway, a transcriptional regulator of antioxidant gene expression. Although this pathway was not directly assessed in our study, the biochemical profiles suggest enhanced redox gene activity, which is crucial in mitigating oxidative nephropathy.

Histopathological recovery and tissue integrity

Histopathological findings substantiated the biochemical results. $KBrO_3$-only rats showed extensive renal tissue damage, including glomerular atrophy, tubular necrosis, interstitial inflammation, and cast formation, reflected in a high injury score (13.9/16). These pathological features are indicative of widespread oxidative and

inflammatory insults. Treatment with quercetin and vitamin C, especially in combination, significantly ameliorated histoarchitectural derangements. The Q40 + VC10 group exhibited preserved nephron morphology and reduced injury scores to near-control levels (1.8/16). Such structural restoration implies effective suppression of cellular damage pathways; likely through attenuation of mitochondrial dysfunction, inhibition of NF-κB signaling, and reduction of leukocytic infiltration. These histological improvements are pivotal for sustaining renal function and highlight the functional–structural concordance of our findings.

Electrolyte homeostasis and tubular function

Electrolyte homeostasis, a critical aspect of renal tubular function, was markedly disrupted by $KBrO_3$ exposure. Hyponatremia, hypokalemia, hypochloremia, and hypercalcemia observed in the $KBrO_3$ group reflect impaired ion transport mechanisms and possible tubular epithelial damage; particularly in the thick ascending limb and distal convoluted tubules where fine-tuning of electrolyte reabsorption occurs [25]. The reversal of electrolyte imbalances following treatment (Table 5), particularly with Q80 and Q40 + VC10, suggests preserved tubular integrity. These improvements may be mediated by restored Na^+/K^+-ATPase function and reduced oxidative injury to tubular membranes [26]. Clinically, correction of electrolyte disturbances is crucial in nephrotoxicity management to prevent complications such as arrhythmias, cognitive dysfunction, and fluid imbalance.

Inflammatory cytokines and immune modulation

Our study further revealed elevated renal and systemic levels of TNF-α and IL-6 in $KBrO_3$-treated rats, consistent with inflammatory cytokine-mediated renal injury [27, 28]. These mediators are known to promote glomerular permeability, attract immune cells, and drive fibrosis via NF-κB activation. The significant reduction in TNF-α and IL-6 levels in the treated groups, especially in Q40+VC10, reflects potent anti-inflammatory effects. Quercetin's ability to suppress NF-κB nuclear translocation and vitamin C's immunomodulatory actions likely account for these reductions [28]. Mitigation of cytokine-induced inflammation is central to preventing chronic nephron loss and progression to renal fibrosis.

Correlative insights and mechanistic interactions

Correlation analyses provided further mechanistic support. MDA levels inversely correlated with GFR and antioxidant enzymes (SOD, CAT) (Table 4), while TNF-α levels showed strong negative correlations with antioxidant capacity (Table 7). These relationships highlight the interlinked roles of oxidative stress and inflammation in mediating renal dysfunction.

Conversely, positive correlations between GFR and antioxidant markers reinforce the protective value of redox homeostasis in maintaining glomerular filtration. These findings underscore the integrated mechanism by which quercetin and vitamin C preserve renal function via dual suppression of oxidative and inflammatory cascades.

Comparative literature context and translational relevance

Our observations align with previous studies that demonstrated the renoprotective efficacy of

polyphenols and antioxidant agents in chemically induced nephropathy models [29]. Almeer et al. and other investigators have reported similar outcomes following natural antioxidant administration, with marked improvements in renal oxidative and inflammatory parameters [30]. However, our study is among the first to demonstrate the superior efficacy of a quercetin–vitamin C combination over monotherapy, highlighting a synergistic pharmacological interaction that warrants translational attention. In clinical terms, these results suggest a potential adjunctive strategy for mitigating renal injury in patients exposed to environmental or therapeutic nephrotoxins. The favorable safety profile of quercetin and vitamin C, coupled with their proven antioxidant and anti-inflammatory efficacy, supports their development as supportive interventions in nephrotoxicity prevention and management.

Study limitations and future directions

This study, though comprehensive, has some limitations. First, direct molecular analysis of signaling pathways such as Nrf2/Keap1 and NF-κB was not performed, limiting mechanistic specificity. Second, the short-term exposure model may not fully reflect chronic nephrotoxicity scenarios. Third, pharmacokinetic interactions between quercetin and vitamin C were not assessed. Future studies should include gene/protein expression analyses, long-term toxicity evaluations, and bioavailability studies to enhance translational relevance.

Conclusion

The findings of this study demonstrate that quercetin, particularly when co-administered with vitamin C, effectively attenuates potassium bromate–induced nephrotoxicity. The combined antioxidant therapy preserved glomerular filtration, stabilized renal biochemical indices, restored redox balance, corrected electrolyte disturbances, and reduced inflammatory cytokine activity. Histological recovery further confirmed structural protection of renal tissues. Overall, the quercetin–vitamin C combination produced a more pronounced renoprotective effect than either agent alone, supporting its potential as a complementary therapeutic strategy for managing oxidative and inflammatory renal injury. Furthermore, the treatment attenuated oxidative stress; evidenced by reduced MDA levels and restored antioxidant enzyme activities (SOD, CAT, GSH) and suppressed pro-inflammatory cytokine expression (TNF-α, IL-1β, IL-6), indicating dual antioxidant and anti-inflammatory mechanisms.

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Author for Correspondence:
Dr. Mike Osagie Odigie, Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, Edo State University, Iyamoh, Edo State, Nigeria Email: odigie.mike@edouniversity.edu.ng, Tel: +2347036844454

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