Pharmacogn. Res., 2023; 15(3):544-550.
https://www.phcogres.com

Original Article

Evaluation of Protective Effects of Polyphenols of the Marine Brown Alga *Ecklonia cava* against Potassium Bromate Induced Nephrotoxicity in Rats

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ABSTRACT

Background: *Ecklonia cava* is a kelp (brown algae) genus belonging to Lessoniaceae with plenty of Eckol-type phlorotannins. It exhibits antioxidant, anti-inflammatory, and antibacterial activity. **Objectives:** This study investigated *Ecklonia cava* (EC) polyphenols for their protective effects against $KBrO_3$-induced nephrotoxicity in rats. **Materials and Methods:** The polyphenolic fraction was isolated from EC. Group, I was control (untreated), and group II was administered $KBrO_3$ (135 mg/kg b.w) intragastric for four weeks. Group III was administered ECPP (200 mg/kg b.w) concurrently with $KBrO_3$ (135 mg/kg b.w) orally, and Group VI was administered Rutin (100 mg/kg b.w) along with $KBrO_3$ (135 mg/kg b.w) orally. The protective effects of ECPP on $KBrO_3$-induced nephrotoxicity in rats were assessed for the biochemical parameters of serum, various antioxidant enzymes, and histopathological changes in kidneys. **Results:** The level of serum of Blood Urea Nitrogen (BUN), uric acid, and creatinine was suggestively augmented (p<0.001) when treated by $KBrO_3$. The activity of antioxidant enzymes, superoxide dismutase, catalase, glutathione peroxidase, and FRAP (ferric ion reducing antioxidant parameter) were diminished (p<0.001). At the same time, lipid peroxidation and nitric oxide were raised (p<0.001) with $KBrO_3$ treatment in the kidneys. In addition, the protein carbonyl level was amplified (p<0.001) with $KBrO_3$ administration. Histological studies presented renal damage in $KBrO_3$-treated animals where tissue injury was abridged in ECPP pretreatment groups. **Conclusion:** These results suggest that ECPP functions as an antioxidant in vivo by scavenging reactive oxygen species, which helps preclude oxidative renal injury in rats treated with $KBrO_3$.

Keywords: *Ecklonia cava*, Nephroproductive activity, Antioxidant, Polyphenols, Potassium bromate.

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Received: 01-03-2023;
Revised: 25-04-2023;
Accepted: 17-05-2023.

INTRODUCTION

Potassium bromate ($KBrO_3$; CAS No. 7758-01-2) is not a naturally occurring compound but is synthesized by passing bromine vapour through a potassium hydroxide solution when animated.[1] Potassium bromate ($KBrO_3$) has been used extensively for water disinfection, hair-coloring solutions, cosmetics, and food.[2] Toxicological studies have recommended that $KBrO_3$ is: an oxidizing agent; that causes hepatotoxicity,[3] neurotoxicity, and thyroid toxicity;[4] and persuades the development of mesothelioma tumors in experimental animals as well as renal carcinomas in animals and humans.[5] $KBrO_3$ is a stout oxidizing agent employed in flour milling, as an ingredient in fish paste in Japan, in cheese making, in beer malting, and as a constituent of cold hair-wave liquids and an oxidizing compound.[6] Bromate is quickly absorbed from the gastrointestinal tract, at least in part unaffected. The distribution of bromate is throughout the body, and its presence in plasma, urine, and other tissues as bromide.[7] Bromate is abridged to bromide in several body tissues, probably by GSH or other sulfhydryl-containing compounds.[8] Most bromate is evacuated in the urine, either as bromate or bromide, but some may leave the body in the faeces. Bromine has been sensed in the adipose tissue of mice following long-term treatment with bromate.[9] Several studies have scrutinized the mechanisms by which bromate causes renal toxicity. DNA damage and lipid

DOI: 10.5530/pres.15.3.057

peroxidation can happen in the kidney due to exposure to bromate, which causes generative reactive intermediates.[10]

Ecklonia cava, an edible marine brown alga, is used as a food ingredient, animal feed, fertilizer, and raw material to make fucoidan and phlorotannin.[11] EC is also used as a herbal medication in Seanol, a polyphenolic extract, and Ventol, a phlorotannin-rich natural agent with two significant ingredients, phlorotannins and sterols.[12] Polyphenols isolated from *Ecklonia cava* species exhibit antioxidant,[13] anti-inflammatory, antibacterial, anti-diabetic, anticancer, anti-photoaging, anti-HIV, anti-hypertensive, hepatoprotective, and anti-allergic actions.[14] Due to these frequent health benefits, researchers are keen to clarify their pharmacological potential. Sufficient information regarding the pharmacological activities of terrestrial plants is obtainable; however, such information is imperfect for marine species. Ecklonia-derived polyphenols are unlike those found in land-based plants and are perhaps the most effective antioxidants in nature, 10–100 times more potent than other polyphenols.[15] The Oxygen Radical Absorbance Capacity (ORAC) score of such a polyphenol is more than 8300. The water-soluble polyphenols found in land-based plants have a half-life of about 30 min, and their antioxidant powers diminution very quickly.[16] The present study was therefore intended to explore the effect of ECPP on $KBrO_3$-induced nephrotoxicity in Wistar rats by the purpose of biochemical parameters and histological changes.

MATERIALS AND METHODS

Chemicals and Reagents

Trichloroacetic acid (TCA), γ-Glutamyl-p-nitroanilide, reduced Nicotinamide Adenine Dinucleotide Phosphate (NADPH), glycylglycine, Bovine Serum Albumin (BSA), Thiobarbituric Acid (TBA), 1,2-dithio-bis Nitro Benzoic Acid (DTNB), 1-chloro-2,4-Dinitrobenzene (CDNB), Flavine Adenine Dinucleotide (FAD), glucose-6-phosphate, 2,6-dichlorophenolindophenol, and Perchloric Acid (PCA) were procured from Sigma Chemicals Co., St. Louis, USA.

Experimental Animals

Wistar rats weighing between (150-200 gm) were preserved in standard laboratory conditions at room temperature (25±2°C) with 12 hr light/dark cycle. The animals were given pellet chow and water *ad libitum*. The Institutional Animal Ethics Committee (IAEC) permitted the study protocol at Karnataka College of Pharmacy, Bangalore, Karnataka. Studies were accomplished following the CPCSEA guidelines with registration number 1564/PO/Re/S/11/CPCSEA.

Isolation of *Ecklonia cava* Polyphenols

Dried, fine powders of EC were exposed to continuous hot extraction with 70% methanol for 3 hr with reflux at 70-75°C three times uninterruptedly. The extract was concentrated to half its volume and partitioned with n-hexane (×5) to eliminate pigments and lipids. The aqueous fraction contained soluble polyphenols (positive with the Folin–Ciocaulteu's phenol reagent) precipitated with ethylacetate (1:1), concentrated in a rotary evaporator, and lyophilized to obtain buff crystals. The polyphenol fraction was elected ECPP.[17]

Determination of Polyphenolic Concentration

The concentration of polyphenol was evaluated using the Folin–Ciocaulteu's method.[18] A tannic acid standard was utilized to build the calibration curve. The absorbance against a blank was measured at 750 nm.

Induction of Nephrotoxicity

The animals were randomly grouped into four groups: Group I: Normal control (untreated); Group II: $KBrO_3$ (135 mg/kg b.w; oral) for 28 days, Group III: ECPP (200 mg/kg b.w; oral) + $KBrO_3$ (135 mg/kg b.w; oral); and Group IV: Rutin (100 mg/kg b.w; oral)[19] + $KBrO_3$ (135 mg/kg b.w; oral). The treatment groups were treated with ECPP or Rutin concurrently with $KBrO_3$ for 28 successive days.

Analysis of Serum

Analysis of serum for Blood Urea Nitrogen (BUN), uric acid, and creatinine were assessed by using standard AMP diagnostic kits.

Assessment of Antioxidant Profile

The animals were forfeited then the kidneys were isolated and rapidly transferred to ice-cold phosphate-buffered saline (PBS pH-7.4). It was maintained free of blood and other tissue fluids and weighed. Then renal tissue was homogenized in ice-cold Tris HCl buffer of strength 10 Mm of pH-7.4 to a concentration of 10% w/v. The acquired homogenate was centrifuged at 7000 rpm for 25 min under normal conditions. The clear supernatant was composed and employed for enzymatic studies.[20]

Superoxide Dismutase Assay (SOD)

SOD activity of kidney tissues was determined by the method of Kakkar *et al.*[21] The mixture for this method contains 0.1 mL of phenazine methosulphate (186 μmoL), 1.2 mL of sodium pyrophosphate buffer (0.052 mmoL; pH 7.0), and 0.3 mL of supernatant of kidney homogenate. The enzyme reaction was started by adding 0.2 mL of NADH (780 μmol) and stopped after 1 min by adding 1 mL of glacial acetic acid. The amount of chromogen formed was assessed by recording color intensity at 560 nm. Results are articulated in units/mg protein.

Catalase Assay (CAT)

CAT activities were assessed by the Chance and Maehly method[22] with some variations. The reaction solution of CAT activities contained 1.95 mL phosphate buffer (50 MM, pH 7.0), 1.0 mL H_2O_2 (0.17 MM), and 0.05 mL homogenate (10%, w/v)

in a total volume of 3.0 mL was added. The absorbance at 240 nm by using a spectrophotometer was measured. The absorbance change for 0 min and 1 min was recorded. Results are stated in units/min.

Lipid Peroxidation Assay

To 1.0 mL of the sample, 2.0 mL of TCA- TBA-HC1 reagent was added and mixed carefully. The solution was heated for 15 min in a boiling water bath. After cooling, the flocculent precipitate was detached by centrifugation at 1,000 g for 10 min.[23] The absorbance was assessed at 535 nm against a blank that comprised all the reagents except the sample. The results were stated as nmoles of MDA formed/min/mg protein using an extinction coefficient of the chromophore 1.56 x 105 Mem and articulated as nmoles of MDA formed/min/mg protein.

Glutathione Peroxidase Assay

0.2 mL of tris buffer, 0.2 mL of EDTA, 0.1 mL of sodium azide, and 0.5 mL of tissue homogenate were added.[24] This mixture added 0.2 mL of glutathione and 0.1 mL of hydrogen peroxide. The contents were mixed well and incubated at 37°C for 10 min along with a tube containing all the reagents except the sample. After 10 min, the reaction was arrested by adding 0.5 mL of 10% TCA, centrifuged, and the supernatant was evaluated for glutathione by Ellman's method. To 2.0 mL of the supernatant, 3.0 mL of disodium hydrogen phosphate solution and 1.0 mL of DTNB reagent were added. The colors developed were read at 412 nm. Standards in the 200-1000 jag range were taken and treated comparably. The activity was articulated in terms of fig of glutathione consumed/min/mg protein.

Nitric Oxide (NO) Measurement

Kidney NO levels were indirectly assessed by measuring the nitrite levels using a colorimetric method based on the Griess reaction.[25] 100 µL of the analyzed sample was added to 600 µL of the Griess reagent (equal volumes of 2% sulfanilamide in 2.5% phosphoric acid and 0.1% w/v N'1-(1-naphthyl)-N-2-diethyl ethylenediamine in distilled water were mixed just before use), the mixture was assorted, and after 10 min, the absorbance at 540 nm was measured. NO contents were articulated as µM/g tissue protein.

Determination of FRAP Activity

FRAP activity was examined by measuring the total antioxidant potential of kidney homogenate. A working reagent (prepared by mixing 25 mL of acetate buffer, 2.5 mL of 10 mM/L Fe^{3+}-TPTZ in 40 mM of HCl, and 2.5 mL of $FeCl_3$-$6H_2O$) (300 µL) was mixed with 10 µL of the sample (kidney homogenate) and 30 µL of distilled water. In this assay, the electron-donating capability of the antioxidant was measured by the change in absorbance at 593 nm when a blue-colored Fe^{2+}-tripyridyltriazine (Fe^{2+} TPTZ) compound is formed from a colorless oxidized Fe^{3+} form.[26] Calibration curves were created from an aqueous solution of $FeSO_4$ at different concentrations ranging from 10 to 2000 µM/L. The working reagent was prepared by mixing 25 mL of acetate buffer, 2.5 mL of Fe^{3+}-TPTZ (10 mM/L in 40 mM/L of HCl), and 2.5 mL of $FeCl_3$-$6H_2O$ (20 mM/L).

Determination of Total Carbonyl Protein

The protein content of kidney lysate was determined by the Bradford method.[27] In 2 glass tubes, 200 µL of the supernatant kidney was added. To the tubes, 800 µL of 10 mmol/L DNPH in 2.5 mol/L HCl was added, then 100 µL of 20% TCA. The final pellets were liquefied in 500 µL of guanidine hydrochloride 6 mol/L and left for 10 min at 37°C with general vortex mixing. Insoluble materials were detached by additional centrifugation. Protein carbonyl concentration was assessed from the absorbance at 370 nm, applying the molar extinction coefficient of 22.0/mmol/L per cm.

Histopathological Determination

For the microscopic evaluation, tissues were fixed in a fixative (absolute ethanol 60%, formaldehyde 30%, and glacial acetic acid 10%) and embedded in paraffin, sectioned at 4 µm and afterwards stained with hematoxylin/eosin. Sections were considered under a light microscope. Slides of all the treated groups were studied and snapped. A pathologist studied and permitted each section without saying its treatment nature.

Statistical Analysis

The results are articulated as mean±S.E.M from n=6 rats in each group. The significance of difference among the groups was evaluated using a one-way Analysis of Variance (ANOVA) followed by Tukey's test. Values of p<0.001 reflected significance.

RESULTS

Effect of *Ecklonia cava* Polyphenols on Average Body Weight and Relative Weight of Kidney in Rat Figure 1 depicts the protective effects of *Ecklonia cava* polyphenols alongside $KBrO_3$ administered to rats in body weight and relative kidney weight. Administration of $KBrO_3$ to rats pointedly augmented (p<0.001) the relative kidney weight while meaningfully diminished

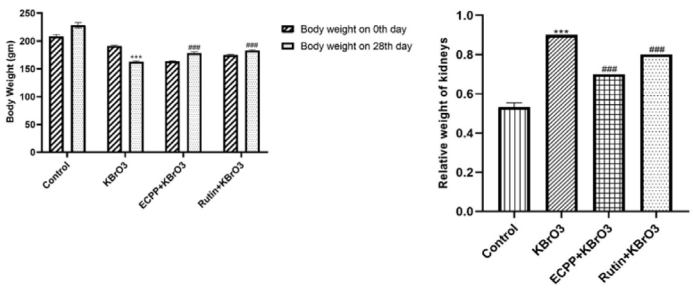

Figure 1: Protective effects of *Ecklonia cava* polyphenols concomitantly with $KBrO_3$ administered to rats in body weight and relative kidney weight

(p<0.001) the body weight of rats as compared to the control group. Administration of ECPP concomitantly with $KBrO_3$ steadily restored (p<0.001) the surge in body weight and relative kidney weight as compared to the $KBrO_3$ group.

Protective effects of *Ecklonia cava* polyphenols concomitantly with $KBrO_3$ administered to rats in body weight and relative kidney weight control group. Serum levels of these parameters were knowingly (p<0.001) improved by administration of ECPP concomitantly with $KBrO_3$ compared to $KBrO_3$-treated rats

Effect of *Ecklonia cava* Polyphenols on Serum Profile

Figure 2 displays the assessment of serum biomarkers i.e., creatinine, BUN, and uric acid, which assess the functional integrity of the kidneys. Administration of $KBrO_3$ significantly (p<0.001) augmented the level of blood urea nitrogen, uric acid, and creatinine while expressively (p<0.001) lessened the total protein, albumin, and globulin as compared to the control group. Serum levels of these parameters were knowingly (p<0.001) improved by administration of ECPP concomitantly with $KBrO_3$ compared to $KBrO_3$-treated rats.

Effect of *Ecklonia cava* Polyphenols on Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase, and Ferric Ion Reducing Antioxidant Parameter (FRAP) Activity

Figure 3 illustrates the effect of *Ecklonia cava* polyphenols alongside $KBrO_3$ in the activities of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and FRAP in kidney homogenates. The enzymatic activities diminished (p<0.001) when compared with the control group, and those activities were upturned ominously (p<0.001) on animals pretreated with ECPP parallel with potassium bromate.

Effect of *Ecklonia cava* Polyphenols on Lipid Peroxidation and Nitric Oxide (NO)

Figure 4 demonstrates the effect of *Ecklonia cava* polyphenols concurrently with $KBrO_3$. Potassium bromate-challenged rats exhibited suggestively (p< 0.001) higher levels of tissue MDA (a lipid peroxidation marker) and NO. Animals treated with *Ecklonia cava* polyphenols alongside $KBrO_3$ showed pointedly (p< 0.001) changed levels of MDA and NO levels compared to the $KBrO_3$ control group.

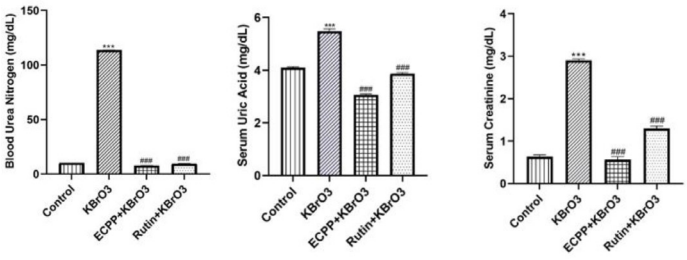

Figure 2: Assessment of serum biomarkers i.e., creatinine, BUN, and uric acid.

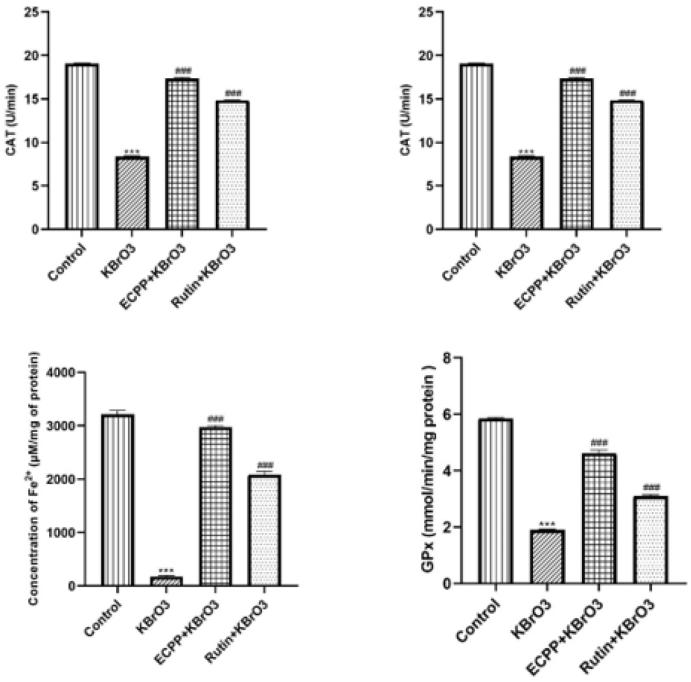

Figure 3: Illustrates the effect of *Ecklonia cava* polyphenols alongside $KBrO_3$ in the activities of antioxidant enzymes.

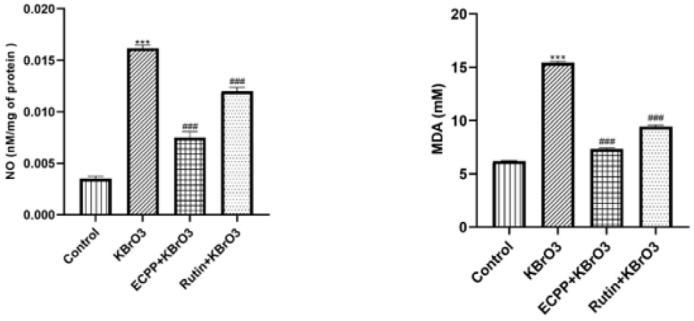

Figure 4: Demonstrates the effect of *Ecklonia cava* polyphenols concurrently with $KBrO_3$ on NO and MDA.

Effect of *Ecklonia cava* Polyphenols on Total Carbonyl Protein

The total carbonyl protein, which is a marker for oxidative stress, was found to be greater (p<0.001) in animals treated with $KBrO_3$ when compared with the control group. The content of carbonyl protein level was abridged (p<0.001) on animals pretreated with ECPP alongside potassium bromate. [Figure 5].

Effect of *Ecklonia cava* Polyphenols on Histological Changes of Kidneys

Histopathological variations of kidneys under the effect of *Ecklonia cava* polyphenols alongside $KBrO_3$ on kidney histopathology. The normal control exposed the normal architecture of the glomerulus containing a tuft of capillaries enclosed by Bowman's capsule (arrow) [Figure 6A].

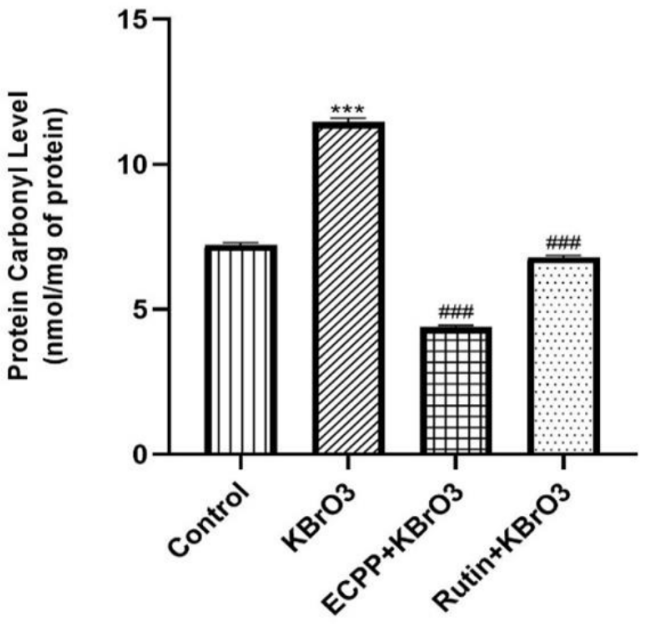

Figure 5: Demonstrates the effect of *Ecklonia cava* polyphenols concurrently with $KBrO_3$ on protein Carbonyl level.

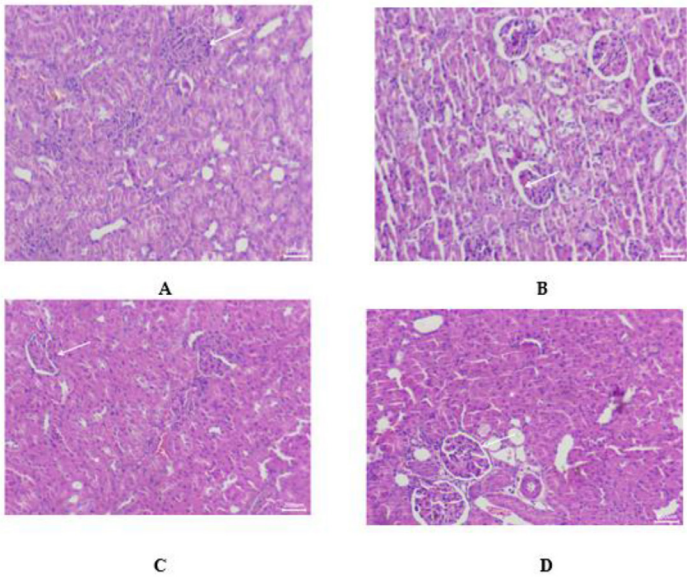

Figure 6: Histopathological variations of kidneys under the effect of *Ecklonia cava* polyphenols alongside $KBrO_3$.

Renal tissue treated with $KBrO_3$ displays the distortion of the normal architecture of the glomerulus encompassing vacuoles and the separation of a tuft of capillaries from Bowman's capsule representing degeneration (arrow). The proximal and distal convoluted tubules exposed desquamation of lining simple cuboidal epithelial cells (asterisk) and necrosis. Dilatation of tubules with apoptotic cells was detected [Figure 6B]. Group treated with ECPP concurrently with $KBrO_3$ shows the normal architecture of the glomerulus comprising a tuft of capillaries surrounded by Bowman's capsule (arrow). The proximal and distal convoluted tubules are lined by simple cuboidal epithelial cells with cytoplasm staining pink in color and distally placed nucleus staining blue color (asterisk). ECPP improved the toxic fluctuations near the control rat [Figure 6C]. Kidney viewing the normal architecture of glomerulus containing a tuft of capillaries surrounded by Bowman's capsule (arrow) when treated with Rutin alongside $KBrO_3$ but dilatation of tubules was detected in a few places [Figure 6D].

DISCUSSION

Acute kidney failure happens when kidneys unexpectedly cannot filter waste products from the blood. When kidneys lose their cleaning ability, dangerous levels of waste may accumulate, and blood's chemical makeup may get out of steadiness. Acute kidney failure, also termed acute renal failure or acute kidney injury, progresses quickly over a few hours or days. Acute kidney failure is most common in people who are already hospitalized, predominantly in critically ill people who necessity intensive care. Between 8-10% of the adult population have some form of kidney injury, and every year millions die prematurely of problems related to kidney failure. Since kidney failures are becoming one of the significant causes of death worldwide, it has become a number one precedence to develop medicines that meritoriously treat renal ailments. Isolated polyphenols from *Ecklonia cava* are one of the most active ingredients with powerful antioxidants.[28] In this study, animals treated with $KBrO_3$ were found to have declined in body weight but amplified in relative kidney weight compared to the control group. Those variations were earlier determined.[29] Animals treated with *Ecklonia cava* polyphenols concurrently with $KBrO_3$ have augmented body weight and reduced relative kidney weight, which proposes that ECPP can relieve $KBrO_3$-induced nephrotoxicity in Wistar rats.

High serum levels of creatinine, BUN, and total protein lead to kidney toxicity. This study exhibited that $KBrO_3$ administration caused an upsurge in the serum level of BUN, uric acid, creatinine, total protein, albumin, and globulin. Those serum parameters can be notified to that of standard control by ECPP administration which was indicated in this study where the administration of Ecklonia cava polyphenols alongside $KBrO_3$ ensued in reduced serum BUN, uric acid, creatinine, total protein, albumin, and globulin. The results recommended that ECPP prevented $KBrO_3$-induced toxicity in the kidney. There is an indication that elaborate oxidative stress and ROS in the mechanism of $KBrO_3$-induced nephrotoxicity in animals.[30] Many studies displayed that different plant extracts can pointedly reprieve the renal damage induced by $KBrO_3$.[31]

The activity of the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, and Ferric Ion Reducing Antioxidant Parameter (FRAP) was found to be knowingly reduced in the $KBrO_3$ treated group compared with that of

the control group. Antioxidant activity with $KBrO_3$ has been considered in in-vivo experimental animals, which exhibited condensed in those parameters.[32] However, the pretreatment of ECPP concurrently with $KBrO_3$ alerted the biochemical variations caused by $KBrO_3$ in rats. ECPP presented a potential protective effect in the activities of antioxidant enzymes in animals treated with ECPP alongside $KBrO_3$. The antioxidant activity was expressively higher in animals treated with ECPP parallel with $KBrO_3$ compared with those of the $KBrO_3$-treated group.

Oxidative stress shows a significant role in $KBrO_3$-persuaded nephrotoxicity in rats and is causing cellular lesions and necrosis of the kidneys.[33] Different studies presented the role of free radicals in lipid peroxidation and that of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and Ferric Ion Reducing Antioxidant parameters (FRAP) in averting their actions.[34] Antioxidant enzymes such as SOD, CAT, and GPx offset free radicals and are measured as the first cellular defence barrier against oxidative stress. The current study displayed that the administration of $KBrO_3$ ominously augmented lipid peroxidation by the production of MDA and NO and caused a reduction in FRAP compared to the normal group. Administration of ECPP alongside $KBrO_3$ suggestively lessened MDA and NO and raised FRAP activity compared to diseased animals. Free radical scavengers are known to prevent renal failure by reducing tubular damage, improving the regenerative response of tubular cells, and preservation of renal blood flow.[35-36] Thus, the antioxidant activity of $KBrO_3$ was established in our studies, and the results propose the implication of this antioxidant property contributing to its nephroprotective activity.[37-40]

Total carbonyl protein is a latent biomarker to regulate the physiological state of the cell, tissue, or organ. Administration of $KBrO_3$ to rats augmented total carbonyl protein compared to the control group. However, the $KBrO_3$-induced change was pointedly lessened by the administration of ECPP concurrently with $KBrO_3$. In the current study, histological examination by H&E staining presented $KBrO_3$ induced the alteration of the typical architecture of glomerulus comprising vacuoles and separation of a tuft of capillaries from Bowman's capsule representing degeneration. The proximal and distal convoluted tubules disclosed desquamation of lining simple cuboidal epithelial cells (asterisk) and necrosis. In addition, dilatation of tubules with apoptotic cells was detected. Evaluation of animals in the ECPP (200 mg/kg) treated group specifies that the isolated polyphenols combat the poisonous effects of $KBrO_3$ and kidney histology exposed near normal histological architecture. Potassium bromate ($KBrO_3$) induced oxidative stress might endorse the formation of various vasoactive mediators that can distress renal function straight by initiating renal vasoconstriction or declining the glomerular capillary ultrafiltration coefficient. This action will diminish the glomerular filtration rate, leading to proteinuria. Administration of ECPP alongside $KBrO_3$ in rats amended the toxicity of $KBrO_3$ in kidneys to reinstate the level of the studied parameters in a concentration-dependent way. These results propose that ECPP can be a nephroprotective agent against $KBrO_3$-induced toxicity.

CONCLUSION

Our results demonstrated that *Ecklonia cava* polyphenols employ their nephroprotective effect against $KBrO_3$-persuaded toxicity in an *in vivo* model. Therefore, we suggest that isolated brown alga *Ecklonia cava* polyphenols can be measured as a safe nephroprotective complement. The protective potential may include scavenging latent and antioxidant ability to enhance the $KBrO_3$-induced toxicity.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ECPP: *Ecklonia cava* polyphenols; **$KBrO_3$:** Potassium bromate; **SOD:** Superoxide dismutase.

SUMMARY

The *Ecklonia cava* polyphenols, concurrently with $KBrO_3$, augmented the activity of antioxidants of SOD, CAT, GPx, and FRAP in kidney-homogenated tissue. By lessening their activity, they also warned about lipid peroxidation, nitric oxide, and total protein carbonyl level. *Ecklonia cava* polyphenols, alongside $KBrO_3$ have preserved the normal value of blood urea nitrogen, uric acid, and creatinine. Tubular dilatation, tubular cell swelling, and glomerular injuries were standardized by EC polyphenols concurrently with $KBrO_3$.

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Cite this article: Redhwan MAM, Samaddar S, Hariprasad MG, Hard SAAA, Deka G, Godfrey A. Evaluation of Protective Effects of Polyphenols of the Marine Brown Alga *Ecklonia cava* against Potassium Bromate Induced Nephrotoxicity in Rats. Pharmacog Res. 2023;15(3):544-50.