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BIOCHEMICAL AND CELLULAR CORRELATES OF ESSENTIAL OIL OF *PISTACIA INTEGERRIMA* J.L. STEWART EX BRANDIS GALLS AGAINST CISPLATIN-INDUCED NEPHROTOXICITY IN MICE

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ABSTRACT

Ethnopharmacological relevance: *Pistacia integerrima* J.L. Stewart ex Brandis (Family Anacardiaceae) galls are used in Indian ethnomedicine for their antiasthmatic, antioxidant anti-inflammatory, sedative, and spasmolytic properties. However, no scientific studies demonstrate its nephroprotective potential against Cisplatin-induced nephrotoxicity. Materials and Methods: The effect of the essential oil of *Pistacia integerrima* (7.5, 15 and 30 mg/kg/day) and standard drug Vitamin E (250 mg/kg/day) on the kidney was examined 5 days after treatment with Cisplatin (12 mg/kg body weight, i.p.) induced oxidative renal damage in mice. Renal injury was assessed by assessment of serum creatinine and blood urea nitrogen. Renal oxidative stress was estimated by renal malondialdehyde levels, reduced glutathione levels and enzymatic activities of superoxide dismutase and catalase. Results: Essential oil of *Pistacia integerrima* (7.5, 15 and 30 mg/kg/day) significantly ($p < 0.001$) protected the nephrotoxicity induced by Cisplatin. The Cisplatin-induced increase in serum urea and creatinine concentrations was reduced in the essential oil of *Pistacia integerrima* treated groups. Essential oil of *Pistacia integerrima* treatment also increased the Cisplatin-induced decline of renal antioxidant enzymes such as superoxide dismutase, catalase, and Glutathione activities. Essential oil of *Pistacia integerrima* increased the concentration of reduced glutathione and protected the increase of Cisplatin-induced lipid peroxidation. Histopathological investigations of the kidney showed a protective effect of the essential oil of *Pistacia integerrima* in mice. The essential oil of *Pistacia integerrima* was found to be effective in protecting against oxidative renal damage. The protection is mediated by preventing the decline of renal antioxidant status. Conclusion: The present investigation demonstrates that the essential oil of *Pistacia integerrima* Stewart ex Brandis has a protective effect on cisplatin-induced experimental nephrotoxicity, and this effect is attributed to its direct anti-inflammatory and strong antioxidant profile. Hence, the essential oil of *Pistacia integerrima* Stewart ex Brandis has a solid potential to be used as a therapeutic adjuvant in cisplatin nephrotoxicity.

Keywords: *Pistacia integerrima,* essential oil, Cisplatin, Nephrotoxicity

INTRODUCTION

Cisplatin (*cis*-diamminedichloroplatinum II) is a simple antitumor agent, widely used in chemotherapy of several types of cancer such as head and neck, testicular, ovarian, bladder and small cell lung cancers[1,2]. Despite its beneficial antitumor action, Cisplatin is associated with dose-related nephrotoxicity[3], gastrointestinal dysfunction, auditory toxicity, and peripheral nerve toxicity[4], hepatotoxicity and spermiotoxicity[5] limit its application in clinical oncology. Nephrotoxicity is a major complication and a dose-limiting factor for cisplatin therapy[6]. Oxidative injury has been implicated in the pathophysiology of Cisplatin-induced nephrotoxicity. Administration of Cisplatin is frequently associated with renal insufficiency and tubular dysfunction. The possible involvement of peroxidative damage caused by reactive oxygen species (ROS) has been suggested in the pathogenesis of cisplatin-induced renal failure[7]. In particular, the hydroxyl radical is highly reactive among oxygen radicals. Once excessive hydroxyl radicals are released, lipid peroxidation, which causes changes in the fluidity and permeability of membranes, is induced[8].

Traditional and alternative medicine systems have employed medicinal plants to remedy various illnesses. Nevertheless, Many ethnopharmacological applications have not yet been proven to be safe and appropriate based on scientific investigations. Several antioxidants and oxygen radical scavengers have been reported to be effective in protection against these injuries[3,9-12]. *Pistacia integerrima* J.L. Stewart ex Brandis (Family- Anacardiaceae) is a moderate-deciduous tree widely distributed in the sub-alpine regions of Himalaya ranging from Indus to Kumaun and is also cultivated in plains[13]. The extracts from galls of *Pistacia integerrima* J.L. Stewart ex Brandis are known to have antioxidant[14], anti-asthmatic[15], antirheumatic effects[16], xanthine oxidase inhibitor and lowering serum uric acid[17]. Polyphenolic substances such as rutin, quercetin-3-*O*-β-D-glucopyranoside, kaempferol-3-*O*-β-D-glucopyranoside, quercetin-3-*O*-(6"-*O*-syringyl)-β-D-glucopyranoside and kaempferol-3-*O*-(4"-*O*-galloyl)-α-L-arabinopyranoside have been found in leaves[17] (Ahmad *et al*., 2008). The biological effects of essential oil extracted from *Pistacia integerrima* Stewart ex Brandis galls cultivated in India have not yet been investigated in relation to potential medical applications for renal diseases. Therefore, in the present study, the nephroprotective potential of essential oil from galls has been evaluated.

MATERIALS AND METHODS

Plant Material

Pistacia integerrima J.L. Stew. Ex Brandis galls were purchased from a local distributor in Mumbai and were authenticated by Dr. Ganesh Iyer. A voucher specimen (no. 007) was deposited in the Herbarium Ramnarain Ruia College, Matunga, Mumbai, of the Bombay University, India.

Extraction of essential oil of *Pistacia integerrima* J.L. Stew. Ex Brandis (EOPI)

Essential oil of *Pistacia integerrima* J.L. Stew. Ex Brandis (EOPI) was obtained by hydro-distillation as described earlier using Clevenger's apparatus[18]. Briefly, fresh air-dried galls of *Pistacia integerrima* J.L. Stew. Ex Brandis (200 g) was crushed and transferred to a round bottom flask containing 200 mL of distilled water. It was then connected to Clevenger's assembly, and distillation was carried out to obtain oil for 4 hours. The procedure was repeated several times to collect enough oil. The oil was dehydrated with sodium carbonate and preserved in an airtight glass container at 4°C until use.

Characterisation of EOPI

The specific gravity of EOPI was measured using a pycnometer. The refractive index of 10 µg/mL EOPI solution in methanol was measured using a refractometer. The composition of the EOPI was analysed by Hewlett-Packard 5970A mass selective detector, directly coupled to an HP 5790A gas chromatograph. A mass spectral survey was performed using the Mass Spectral Library.

Drugs

Vitamin E (> 98% pure), 5,5 dithio-dinitrobisbenzoic acid, and thio-barbituric acid were purchased from Sigma Aldrich (USA). Serum Creatinine and Urea nitrogen estimation kits were purchased from Erba Diagnostic, Mannheim GmbH. Cisplatin was purchased from Fresenius Kabi Oncology Ltd. (Solan, H.P. India). Hydrogen peroxide (H_2O_2), ethylene diamine tetra acetic acid (EDTA), formalin and all other reagents used were of analytical grade purchased form was purchased from Sd fine-Chem Limited, India.

Animals

Swiss albino mice (18-20 g) used in the study were housed under a controlled environment (24 ± 2^0C) and humidity 50 ± 10 %. A 12:12 h light-dark cycle was followed. Animals had free access to water and a standard pelleted laboratory animal diet. For all animal experimentation protocols (Protocol No. 23 & 24/2009), prior approvals were obtained from 'Institutional Animal Ethics Committee', of Bombay College of Pharmacy, Mumbai (registration number CPCSEA-BCP/2010/21) and all studies were performed in accordance with 'Committee for the Purpose of Control and Supervision on Experiments on Animals' (CPCSEA) guideline, Government of India on animal experimentation.

Cisplatin-induced nephrotoxicity in mice

Thirty-six female mice were divided into six groups, each having six animals. Group I was saline control, Group II Cisplatin control, Group III to V were treated with EOPI 7.5, 15 and 30 mg/kg/day, respectively, and group VI received vitamin E (250 mg/kg/day). Each group received a single injection of Cisplatin (12 mg/kg body weight, i.p.) except the saline control group. Essential oil of *Pistacia integerrima* J.L. Stew Ex Brandis (EOPI) was dissolved in 0.02 % v/v solution of Tween 80 in Tyrode solution, sonicated prior to use. The test drug and vitamin E were administrated intraperitoneally 1 h before, 24 h and 48 h after cisplatin injection. Seventy-two hours after cisplatin injection, blood was collected from each mouse under light ether anaesthesia and sacrificed. Kidneys were quickly removed and washed with ice-cold normal saline. Serum samples and kidneys were stored at -20 °C till biochemical and enzymatic estimation.
Biochemical analysis

Serum Creatinine and Urea nitrogen

Serum creatinine and urea nitrogen were estimated by alkaline picric acid method and diacetylmonoxime (DAM) reagent (modified Berthelot method), respectively, using commercially available diagnostic kits (Erba Diagnostic, Mannheim GmbH).

Determination of antioxidant status in the Kidney

Kidney homogenate preparation

Kidneys were quickly removed after sacrificing the animals and washed with ice-cold saline (0.9 % w/v), and 10 % w/v homogenate was prepared in phosphate buffer (0.05 M, pH 7) using Remi tissue homogeniser (RQ-127A) at 4 ^{0}C. The homogenate thus obtained was used for lipid peroxidation, reduced glutathione, superoxide dismutase, and catalase activity.

Estimation of lipid peroxidation

The malondialdehyde content, a measure of lipid peroxidation, is a significant indicator of oxidative stress, which was estimated to be in the form of thiobarbituric acid-reactive substances[19]. Briefly, 0.1 mL of kidney homogenate and 2.5 mL of 0.7 % w/v thiobarbituric acid (TBA) solution in glacial acetic acid 30 % v/v and kept in a boiling water bath for 1 h. The absorbance was recorded at 532 nm using a spectrophotometer (Jasco, V-530, Japan).

Estimation of reduced glutathione

Reduced glutathione, a major low molecular weight scavenger of free radicals in the cytoplasm and an important free radical-mediated lipid peroxidation inhibitor, was assayed[20]. Briefly, the reaction mixture contained 0.2 mL of tissue supernatant / GSH standard, 0.6 mL of 0.2 mol/L Tris–EDTA, 50 µL of 0.01mol/L 5,5dithiobsis (2- nitro benzoic acid) and 2.5 mL methanol. The mixture was incubated at 37 ^{0}C for 30 min with occasional shaking. The mixture was then centrifuged at 4000 rpm for 15 min. The supernatant was separated. The intensity of colour developed was determined at 412 nm using a spectrophotometer (Jasco, V-530, Japan). GSH values were obtained by calibration curve of concentration standard GSH (20 to 200 µg/mL) and absorbance.

Estimation of superoxide dismutase

Superoxide dismutase activity was assayed in terms of its ability to inhibit the radical-mediated chain-propagating autoxidation of epinephrine[21]. The assay system consisted of 0.5 mL kidney homogenate supernatant, 0.5 mL of 0.1 mM EDTA, and 2 mL 0.5% w/v sodium carbonate (pH 10.2). The reaction was started by adding 0.5 mL of 20 mM epinephrine. The change in absorbance was recorded at 480 nm for 3 min using a spectrophotometer (Jasco, V-530, Japan). The result was expressed in units/mg protein.

Tissue catalase (CAT) activity

The catalase test detects the presence of catalase enzymes by decomposing hydrogen peroxide to release oxygen and water catalase[22] (CAT). Briefly, 0.1 mL tissue homogenate was added to 2.9 mL H_2O_2 (30 mM). The change in absorbance was recorded at 240 nm for 3 min using a spectrophotometer (Jasco, V-530, Japan). The Tissue catalase was expressed as units/mg protein.

Histopathology

Kidneys were dissected and fixed in 10 % v/v buffered formalin. The specimens were subjected to sectioning, staining, mounting

and observation. Briefly, after a week, tissues were washed thoroughly in repeated changes of 70 % alcohol and then dehydrated in ascending grades of alcohol (70 to 100 % v/v). After dehydration, the tissues were cleaned in xylene and embedded in paraffin wax. Processed tissues were sectioned (5 µm), taken on clean glass slides and stained by hematoxylin and eosin dyes. Stained slides were examined under an Olympus BX10 optical microscope with an Olympus DP12 camera (Olympus, Japan)[23].

STATISTICAL ANALYSIS

All data were represented as mean ± SEM. Data were statistically analysed using a one-way analysis of variance (using Graph Pad Prism 5). The significant differences between the saline control, cisplatin control, and drug-treated groups were analysed using one ANOVA followed by Dunnett's test.

RESULTS

Characterisation of EOPI

The essential oil was found to be a colourless liquid with a terebinthine odour and a strongly astringent taste. GCMS chromatograph of essential oil of *Pistacia integerrima* (EOPI) revealed Borneol (8.90 %), Cymene (11.54 %), Tetrahydrocarvone (10.27 %), 4-Carvomenthenol (17.06 %), L-terpinen-4-ol (11.93 %), Borneol (8.90 %), α-Terpinene (2.75 %), Levo-bornyl acetate (13.99 %), β-caryophyllene (9.21%) and (-)-Spathulenol (6.35 %). The density and refractive index of EOPI were found to be 0.889 g/mL and 1.215, respectively. The yield of extraction of essential oil from *Pistacia integerrima* J.L. Stew. Ex Brandis galls were found to be 1.73 %. pH of 1 mg/mL EOPI was found to be in the range of 6.5 to 6.8.

Effect on Cisplatin-induced changes in Serum urea and Creatinine

Serum urea and creatinine concentrations significantly increased in the Cisplatin-treated group of animals compared to the saline control group, indicating the induction of severe nephrotoxicity (Figures 1 and 2). Treatment with EOPI (7.5, 15 and 30 mg/kg, i.p.) and vitamin E (250 mg/kg, i.p.) showed a marked decrease in serum urea and creatinine concentrations compared to the Cisplatin control group. The higher dose of the EOPI (30 mg/kg, i.p.) reduced the serum urea and creatinine in the Cisplatin-challenged animals by 53.00 % and 52.44 %, respectively. Similarly, the concentration of urea and creatinine in the Vitamin E (250 mg/kg, i.p.) treated group reduced to 47.51 % and 51.08 %, respectively.

Effect on antioxidant profile in the kidney homogenate

Effect on Cisplatin-induced changes in lipid peroxidation.

Malonaldehyde (MDA) levels were increased significantly in the kidney of Cisplatin-treated mice ($p < 0.05$) as compared to control (Figure 3). Chronic treatment with Vitamin E (200 mg/kg) and EOPI (7.5, 15 and 30 mg/kg, i.p.) produced a significant ($p < 0.05$) and dose-dependent reduction in MDA levels in the kidney of Cisplatin-treated mice with a more potent reduction in EOPI treated mice as compared to Vitamin E group.

Estimation of reduced glutathione

The reduced glutathione levels were significantly ($p < 0.05$) decreased in the kidney of Cisplatin-treated mice as compared to control (Figure 4). This reduction was significant and dose-dependently reversed by the treatment with Vitamin E (200 mg/kg) and EOPI (7.5, 15 and 30 mg/kg, i.p.) in kidneys of Cisplatin-treated mice with more potent effects with EOPI treatment.

Effect on Cisplatin-induced superoxide dismutase.

The activities of renal SOD in the Cisplatin and the extract-treated groups of animals are presented in (Figure 5). Renal SOD activity was decreased significantly in the Cisplatin-treated group of animals compared to saline control group ($p < 0.05$). Treatment with the EOPI dose-dependently (7.5, 15 and 30 mg/kg, i.p.) prevented the Cisplatin-induced decline of catalase activity significantly ($p < 0.05$). Treatment with the extract (30 mg/kg, i.p.) significantly elevated the SOD levels in Cisplatin (89.86%) treated animals compared to saline-treated animals.

Tissue catalase (CAT) activity

The activity of CAT in the Cisplatin-treated group was found to be decreased drastically compared to saline control animals (Figure 6). Treatment with the EOPI (7.5, 15 and 30 mg/kg, i.p.) prevented the Cisplatin-induced decline of catalase activity. The extract restored catalase activity by 67.66 %, 82.32 % and 88.23 % at 5, 15 and 30 mg/kg doses, respectively, in the animals with Cisplatin-induced renal damage.

Effect on Cisplatin-induced Histopathological changes

Histological examination of the saline control group showed no abnormality in the kidneys. In the Cisplatin control group, tubular necrosis, haemorrhages in glomeruli, and pyknotic nuclei indicate renal toxicity. Pretreatment with EOPI (7.5 mg/kg, i.p.) showed mild haemorrhages. EOPI showed regenerative changes at 15 and 30 mg/kg, i.p. No abnormality was detected in the Vitamin E and EOPI-treated group (Figure 7).

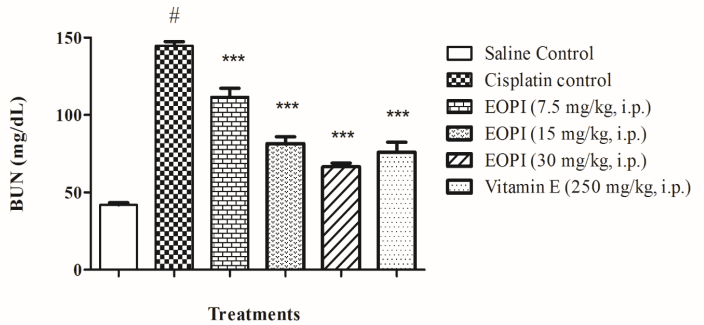

Figure 1: Effect of EOPI on Blood Urea Nitrogen in Cisplatin-induced nephrotoxicity in mice.
Each value represents the mean ± SEM of six mice. Statistical comparison was performed by one-way ANOVA followed by Dunnett's test, # $p < 0.01$ different from the saline control group; *** $p < 0.001$ different from the Cisplatin control group.

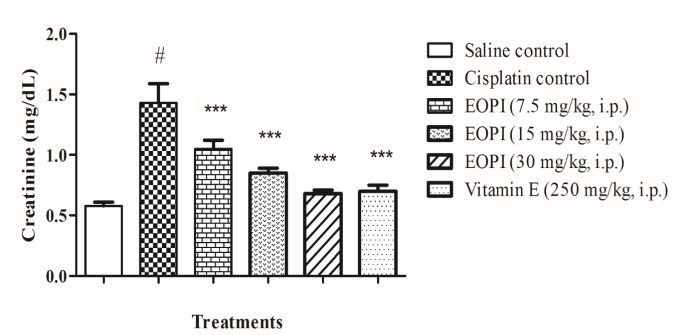

Figure 2: Effect of EOPI on Blood Urea Nitrogen in Cisplatin-induced nephrotoxicity in mice. Each value represents the mean ± SEM of six mice. Statistical comparison was performed by one-way ANOVA followed by Dunnett's test, # p < 0.01 different from the saline control group; *** p < 0.001 different from the Cisplatin control group.

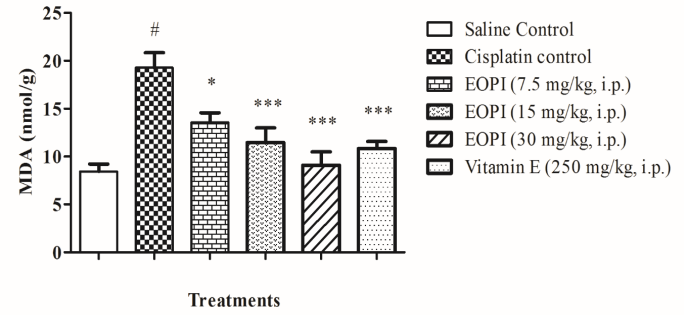

Figure 3: Effect of EOPI on MDA in Cisplatin-induced nephrotoxicity in mice.
Each value represents the mean ± SEM of six mice. Statistical comparison was performed by one-way ANOVA followed by Dunnett's test, # p < 0.01 different from the saline control group; *** p < 0.001 different from the Cisplatin control group.

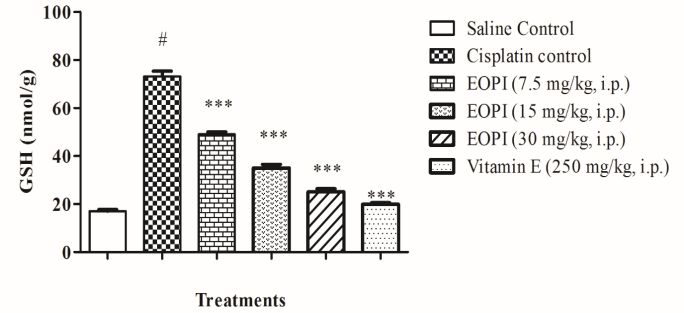

Figure 4: Effect of EOPI on reduced glutathione in Cisplatin-induced nephrotoxicity in mice.
Each value represents the mean ± SEM of six mice. Statistical comparison was performed by one-way ANOVA followed by Dunnett's test, # p < 0.01 different from the saline control group; *** p < 0.001 different from the Cisplatin control group.

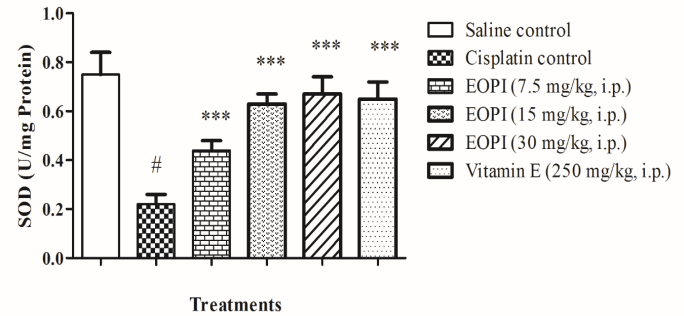

Figure 5: Effect of EOPI on SOD in Cisplatin-induced nephrotoxicity in mice.
Each value represents the mean ± SEM of six mice. Statistical comparison was performed by one-way ANOVA followed by Dunnett's test, # p < 0.01 different from the saline control group; *** p < 0.001 different from the Cisplatin control group.

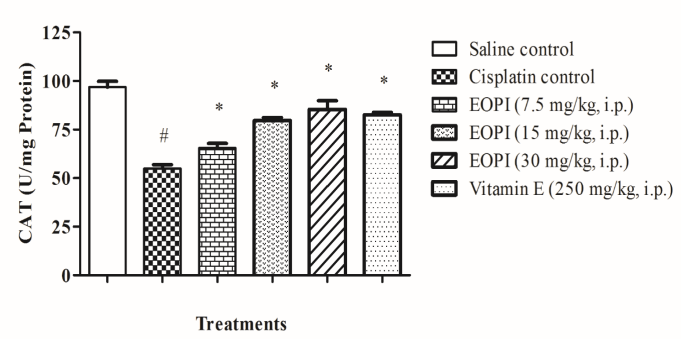

Figure 6: Effect of EOPI on Catalase in Cisplatin-induced nephrotoxicity in mice.
Each value represents the mean ± SEM of six mice. Statistical comparison was performed by one-way ANOVA followed by Dunnett's test, # p < 0.01 different from the saline control group; *** p < 0.001 different from the Cisplatin control group.

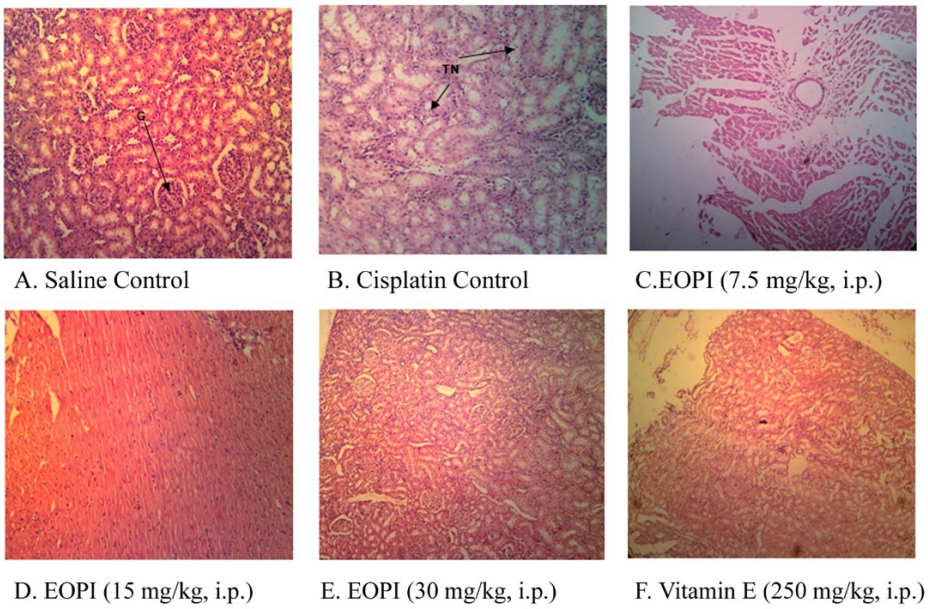

Figure 7: Effect of EOPI on Histopathological alterations in Cisplatin-induced nephrotoxicity in mice.

DISCUSSION

Several strategies have been used to protect cells against cisplatin-induced toxicity, including therapies to prevent the generation of free radicals. It inhibits the development of oxidative damage induced by Cisplatin. For this purpose, most natural antioxidants may be used. In the present investigation, we investigated the effects of essential oil of *Pistacia integerrima* galls on cisplatin-induced nephrotoxicity in mice. An increased serum urea and creatinine levels in renal dysfunction due to a decreased clearance rate compared to the rate of production[24]. Intraperitoneal administration of Cisplatin alone increases serum urea and creatinine, indicating kidney dysfunction, which agrees with previous studies[25,12].

In the present investigation, MDA levels in the kidney homogenate were significantly higher in the cisplatin-treated group than in the control group. Accumulation of Cisplatin in renal mitochondrial induces ROS production and hydroxyl radicals and stimulates renal lipid peroxidation[2,26] damaging cell components (e.g. proteins, lipids and nucleic acids)[27]. The balance usually presents in cells between radical formations, and the antioxidant system protects them against oxidative stress[28]. A significant increase in MDA levels, a marked decrease in the activity of superoxide dismutase and a decline of reduced glutathione were observed in the kidney of Cisplatin- treated mice. The present investigation reveals a significant reduction in malondialdehyde (MDA) production by pretreatment with EOPI *in vivo*.

Cisplatin activates apoptotic pathways for its antitumor action, which is responsible for renal apoptosis below the threshold for necrosis, leading to nephrotoxicity[29]. Nephrotoxicity occurs within one-hour post cisplatin administration. This necessitates the administration of a protective agent before renal damage occurs[30]. The role of oxidant stress in the tissue and lipid peroxides has been investigated in various studies[3,9-12]. On the contrary, an inadequacy in enzymatic and non-enzymatic antioxidant systems caused by Cisplatin has also been reported[5]. Cisplatin induces nephrotoxicity due to the depletion of GSH with enzymatic cleavage with gamma-glutamyl transferase (GGT)[31]. GSH has an important role in maintaining cell integrity as a result of its reduced properties and participation in cell metabolism[28] (Conklin, 2000). The Thiol portion of GSH is very reactive with several chemical compounds like Cisplatin, which may modulate metal reduction[26] (Halliwell, 2001). GSH and catalase are essential, as they catalyse hydrogen peroxide and hydroperoxides. Toxic lipid peroxides combine with two glutathione molecules under the control of glutathione peroxidase to form an inert lipid hydroxyl group, glutathione disulfide (GSSG), and water. After participation in redox reactions, GSH is regenerated from GSSG by the enzyme GSSG reductase using reduced Nicotinamide

Adenine Dinucleotide Phosphate (NADPH) as a cofactor. Like GSH reductase, the aldose reductase depends upon NADPH as a cofactor. Therefore, excessive polyol pathway activation depletes cystolic NADPH and subsequently depletes GSH, leaving the cell vulnerable to free radicals[20].

GSH, Catalase and Superoxide dismutase protect cells against ROS. In the present investigation, decreased activities of these key antioxidants were found in the kidneys of mice treated with Cisplatin. Treatment with EOPI increased the levels of GSH, CAT and SOD in kidney homogenate. These findings conform with the findings of other investigators studying antioxidants in relation to risk factors in diabetic patients and animals treated with cisplatin[26,3,32].

The pharmacological investigation of *Pistacia integerrima* J.L. Stewart ex Brandis has been reported for its antioxidant activity[14]. The antioxidant potential could be attributed to its high polyphenolic contents. The regeneration of damaged tissue may mediate the nephroprotective action of EOPI. The present investigation proved that EOPI administration prevents the nephrotoxic effect of Cisplatin. To minimise the chemotherapy-induced side effects, various agents have been screened. Flavonoids have been reported to show many functions, such as phenolic antioxidants, scavengers of free radicals, chelating agents, and modifiers of various enzymatic and biological reactions[33].

CONCLUSION

The present investigation demonstrated that cisplatin administration increased lipid peroxidation in mice. *Pistacia integerrima* J.L. Stewart ex Brandis galls protect against cisplatin-induced toxicity by inhibition of the inactivation of glutathione and antioxidant system by Cisplatin, up-regulation of superoxide dismutase and catalase levels in the kidney. Thus, moderate EOPI supplementation may protect against cisplatin-induced oxidative stress.

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