Abstract—The aim of the present study was to investigate the protective role of Epigallocatechin Gallate (EGCG) and coenzyme Q10 (CoQ10) on cisplatin (CP)-induced nephrotoxicity in male wister rats. The nephroprotective effect of CoQ10 was investigated in rats with acute renal injury induced by a single i.p. injection of cisplatin (7 mg/kg body wt). EGCG (50 mg/kg body wt, i.p.) and CoQ10 treatment (10 mg/kg body wt, i.p.) was administered for 6 consecutive days, starting from 2 day before cisplatin administration. EGCG and CoQ10 significantly reduced blood urea nitrogen and serum creatinine levels which were increased by cisplatin. In addition, CP induced alterations in the activities of superoxide dismutase and catalase, malondialdehyde (MDA) and reduced glutathione (GSH) levels were significantly attenuated by both EGCG and CoQ10 in the cortical and medullary homogenates of the kidney. In conclusion, both EGCG and CoQ10 can act as protector and equally effective agents against CP-induced alterations in antioxidant parameters of the rat kidney.

Keywords—Cisplatin, Coenzyme Q10, EGCG, nephrotoxicity, oxidative damage.

I. INTRODUCTION

Cancer is the leading cause of death in developed countries and the second leading cause of death in developing countries [1]. Cisplatin (CP) is a commonly used chemotherapeutic agent against solid tumors [2]. Unfortunately, its clinical use is limited by severe side effects in normal tissues. Nephrotoxicity is a frequent adverse effect with about 25–35% patients displaying decline of renal function after a single dose of cisplatin [3]. Studies have shown that the CP-induced injury and necrosis in the rat kidney are predominantly localized in S3 subsegments of proximal tubular epithelial cells where it is preferentially accumulated [4]. Cisplatin chemotherapy induces a reduction in the antioxidant status, leading to a failure of the antioxidant defense against free-radical damage generated by antitumor drugs. Several investigators have hypothesized the oxidative stress mechanism of cisplatin-induced nephrotoxicity that is related to depletion of the antioxidant defense system [5], [6] and inhibitory effect of cisplatin on antioxidant enzymes activities [7], [8]. Cisplatin-induced oxidative stress in the kidney was partially prevented by antioxidant treatments. A diet rich in natural antioxidants in combination with anticancer therapy is found to be effective in reducing morbidity and mortality in addition to diminishing toxicity and side effects of chemotherapeutic agents [9]-[11]. Despite intensive investigation, the mechanisms underlying cisplatin-induced nephrotoxicity are not fully understood. Epigallocatechin Gallate (EGCG) is a polyphenol flavonoid isolated from green tea. EGCG has anti-oxidant, anti-inflammatory, and anti-tumorigenic properties [12]. Researchers at the University of Kansas have found new evidence confirming that a compound in a green tea supplement, EGCG provides stronger damage protection of cells and their genetic material (DNA) than the well-known antioxidants vitamins E and C and the antioxidant compound in red wine. Coenzyme Q10 (CoQ10) is another known powerful antioxidant which scavenges free radicals, prevents the initiation and propagation of lipid peroxidation in cellular biomembranes, and helps regeneration of α-tocopherol [13], [14]. CoQ10 is an endogenous lipid-soluble benzo-quinone compound that functions as a diffusible electron carrier in the mitochondrial respiratory chain [15]. Taking into consideration the potential clinical use of CP and the numerous health benefits of EGCG and CoQ10, the present work was undertaken to study the CP-induced nephropathy and its protection by EGCG and CoQ10.

II. MATERIAL AND METHOD

A. Chemicals And Drugs

Cisplatin powder was obtained from Sigma Chemical Company, USA. Cisplatin was dissolved in normal saline, while EGCG purchased from Zhejiang Yixin pharmaceutical company China (99% minimum purity by HPLC) and was dissolved in normal saline. CoQ10 was obtained from Herb store USA and was prepared in 1% aqueous solution of Tween 80.
**B. Experimental Design**

Male wister rats, weighing 180-220g were used in the experiment. The animals were kept at standard housing facilities (24±1 °C, 45±5% humidity and 12 h light/dark cycle). They were supplied with standard laboratory chow and water, and left to acclimatize for 1 week before the experiments. The mice were randomly divided into six groups (n=8, each). **First Group** - received a single i.p. injection of normal saline (vehicle of cisplatin) and served as control. **Second Group** - Nephrotoxicity was induced by a single i.p. injection of cisplatin at a dose of 7mg/kg body wt. **Third group** - received EGCG (50 mg/kg body wt) for 6 consecutive days starting 2 day before cisplatin administration. **Fourth Group** - received Coenzyme Q10 (10 mg/kg body wt) for 6 consecutive days starting 2 day before cisplatin administration. **Fifth Group** - received a daily i.p. injection of the vehicle of EGCG for 6 consecutive days. **Sixth Group** - received a daily i.p. injection of the vehicle of CoQ10 for 6 consecutive days. The body weight of each animal was recorded after completion of drug administration.

**C. Sample Preparation And Biochemical Studies**

The animals were sacrificed 6 days (4 days after the cisplatin treatment). Blood samples were collected and centrifuged for 10 min at 5000 rpm to obtain serum which were stored at −20 °C for subsequent measurement of blood urea nitrogen (BUN) and serum creatinine levels using colorimetric assay kits from Biodiagnostic, Egypt. The kidneys were isolated decapsulated and their fresh weight was recorded. The cortex was carefully separated from medulla. 10% (w/v) homogenate was prepared in cold potassium phosphate buffer (0.05M, pH 7.4). The homogenates were centrifuged at 5000 rpm for 10 min at 4 °C. The resulting supernatant was used for determination of malondialdehyde (MDA) and reduced glutathione (GSH) levels, and catalase and superoxide dismutase (SOD) activities using colorimetric assay kits from Biodiagnostic, Egypt.

**D. Statistical Analysis**

All data are expressed as mean±SEM for at least 4–5 different preparations. Statistical evaluation was conducted by one-way ANOVA and by unpaired Student’s t-test using SPSS 7.5 software.

A probability level of p < 0.05 was selected as indicating statistical significance. The changes between various groups were compared with control values for better understanding and clarity.

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**TABLE I**

<table>
<thead>
<tr>
<th>Group</th>
<th>BUN (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>Kidney/body-weight ratio (×1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>24±3.6</td>
<td>0.9±0.03</td>
<td>60±4.5</td>
</tr>
<tr>
<td>CP</td>
<td>106±20.2</td>
<td>2.3±0.3*</td>
<td>131±9.5</td>
</tr>
<tr>
<td>CP+EGCG</td>
<td>77.2±15.5</td>
<td>1.62±0.4*</td>
<td>95.0±8.4</td>
</tr>
<tr>
<td>CP+CoQ10</td>
<td>91.6±13.1</td>
<td>1.57±0.3*</td>
<td>90.6±8.3</td>
</tr>
<tr>
<td>ECCG</td>
<td>18.4±1.2</td>
<td>0.72±0.1</td>
<td>70.0±5.0</td>
</tr>
<tr>
<td>CoQ10</td>
<td>22.8±3.9</td>
<td>0.9±0.1</td>
<td>71.8±6.3</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SEM.

* Significantly different at p < 0.05 from control by one-way ANOVA.

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**III. RESULT**

**A. Effects Of CoQ10 On BUN, Serum Creatinine And Kidney/Body-Weight Ratio**

Animals received a single dose of cisplatin (7mg/kg body wt, i.p.) showed significant increases in BUN and serum creatinine levels, and kidney/body- weight ratio as compared to the control group. CoQ10 and EGCG treatment resulted in a significant reduction in BUN, serum creatinine level and kidney/body-weight ratio (Table I).

**B. Effect Of EGCG And CoQ10 On CP-Induced Alterations In Antioxidant Defense Parameters In Rat Renal Tissues.**

The effect of CP, CP+EGCG, CP+CoQ10, ECCG and CoQ10 was determined on the parameters of antioxidant defense system such as lipid peroxidation (LPO), GSH, SOD, and catalase (Table II). CP administration to the rats resulted in a profound increase in the production of malondialdehyde (MDA), an end-product of lipid peroxidation in the renal cortex and medulla. However, the increase in LPO was much more pronounced in the renal medulla than cortex. GSH was found to be significantly decreased in renal tissues but the effect is more profound in medulla. These changes in LPO and total GSH were associated with marked decrease in the activity of both SOD and catalase. The slightly more in medulla than cortex EGCG and CoQ10 treatment significantly increased the activity of SOD, catalase and GSH level with marked decrease of LPO in renal cortex and medulla.

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**IV. DISCUSSION**

Antioxidant status is potential biomarker to determine the physiological state of a cell, tissue, or organ. It has been reported that some toxicants including certain drugs [16], [11] and heavy metals including CP [17], [18] exert their toxic effects by inducing the generation of reactive oxygen species (ROS). Increased Production of ROS has been suggested to induced nephrotoxicity and tissue injury which is mediated in
part by disturbance in the balance of antioxidant defense system [19]. These antioxidant enzymes protect the cell against cytotoxic ROS. CP has been shown to generate ROS and to inhibit antioxidant enzymes in renal tissues. CP results in increased NO production in the renal tissue, excess NO depletes intracellular GSH increasing the susceptibility to oxidative stress [19] which is involved in the pathogenesis of cisplatin nephrotoxicity. Also, CP treatment enhance lipid peroxidation (LPO), different studies have shown that cytotoxicity of CP is probably due to combination of insults including peroxidation of cell membrane, mitochondrial dysfunction, inhibition of protein synthesis and DNA damage in the kidney [8], [21], [22]. It has been suggested that CP induces renal damage by free radical generation, such as hydroxyl radical and superoxide anion, by altering arginine metabolism, by increasing activity of calcium independent nitric oxide synthase and more recently by apoptosis [23].

In agreement with previous studies, the present findings supports that oxidative stress, increased lipid peroxidation, depletion of antioxidant defense mediators are implicated in the pathogenesis of cisplatin-induced acute renal injury. Also the present comparative study demonstrates that EGCG and CoQ10 which are powerful antioxidants significantly enhanced antioxidant defense mechanism. This can be supported by a marked increase in SOD and catalase activities and GSH level associated with lowering of LPO in the cortex and medulla. EGCG and CoQ10 induced reductions in serum creatinine and BUN levels along with weight loss can be considered as healthy indicators.

Our results indicates that Both EGCG and CoQ10 are equally effective in protecting CP induced alterations in oxidative stress parameters.

### TABLE II

**Effects of Coenzyme Q10 (CoQ10) treatment treatment on renal malondialdehyde (MDA), reduced glutathione (GSH) and catalase and superoxide dismutase (SOD) activities in rats exposed to acute cisplatin (CP) nephrotoxicity**

<table>
<thead>
<tr>
<th>Group</th>
<th>SOD</th>
<th>Medulla</th>
<th>Cortex</th>
<th>medulla</th>
<th>cortex</th>
<th>Medulla</th>
<th>GSH</th>
<th>Cortex</th>
<th>Medulla</th>
<th>MDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>62±3.2</td>
<td>73.2±2.2</td>
<td>88.0±4.8</td>
<td>71±6.2</td>
<td>2.22±0.1</td>
<td>2.2±0.1</td>
<td>45.4±2.4</td>
<td>36.5±2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP</td>
<td>40.2±3.6*</td>
<td>43.3±3.4*</td>
<td>32.2±1.0</td>
<td>29.9±3.6</td>
<td>1.5±0.0*</td>
<td>1.1±0.2*</td>
<td>86.0±3.3*</td>
<td>60.0±4.5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP+EGCG</td>
<td>50.6±2.8**†</td>
<td>72.5±3.5†</td>
<td>48.5±4**</td>
<td>43.8±1.8**</td>
<td>3.0±1.2**</td>
<td>2.4±0.2**†</td>
<td>48.3±5.3†</td>
<td>43.0±3.5†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CP+CoQ10</td>
<td>62.7±4.4†</td>
<td>70.6±4.0†</td>
<td>49.4±2.5†</td>
<td>45.8±6.4**</td>
<td>2.8±0.2**</td>
<td>2.9±3.3†</td>
<td>52.7±9.5†</td>
<td>44.2±4.0**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECGG</td>
<td>67.3±2.7</td>
<td>65.8±2.8</td>
<td>87.9±5.6</td>
<td>77.7±1.5</td>
<td>2.8±0.3†</td>
<td>2.3±0.0</td>
<td>54.2±2.4†</td>
<td>40.2±2.3†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CoQ10</td>
<td>68±3.2</td>
<td>71.1±2.4</td>
<td>84.2±5.0</td>
<td>81.9±2.4</td>
<td>2.5±0.3*</td>
<td>2.1±0.1</td>
<td>48.8±3.1</td>
<td>31.3±2.5*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are mean±SEM of 3–4 different preparations. Values in parentheses represent percent change from control.

NS: Not Significant.

* Significantly different from control.
† Significantly different at p < 0.05 from CP by one-way ANOVA

### REFERENCES


