

# Effect of Green Coffee on Cisplatin Induced Renal Apoptosis in Adult Male Albino Rats

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## Abstract

**Background:** Green coffee as a functional food has an antioxidant effect, which can reduce the cancer incidence, promote weight-loss and improve glucose and lipid metabolism, as well as anti-oxidant and anti-inflammatory activity. **Objective:** Assessing the effect of green coffee administration on experimental cisplatin induced renal apoptosis in adult male albino rats of local strain. **Design:** Randomized Block Design was used. **Materials and Methods:** Forty adult male albino rats of local strain were randomly divided into four groups of 10 animals each. G1: control negative group was received isotonic saline (0.5 ml, i.p.) for 30 consecutive days, G2: sham operated group mice were received green coffee extract in water (40 mg/kg/day) for 30 consecutive days, animals of G3 and G4 were administered cisplatin (8 mg/kg/day, i.p.) at 10th day, which is well known to produce significant nephrotoxicity in rats. Animals in G3 were received green coffee extract in water (40 mg/kg/day) and G4 was received isotonic normal saline (0.5 ml, i.p.) for 30 consecutive days. All rats were sacrificed after 30 days and blood was withdrawn for biochemical examinations of kidney function tests (blood urea nitrogen, creatinine and uric acid). Kidneys were removed for determination of renal oxidative stress markers (H<sub>2</sub>O<sub>2</sub>) biochemically and caspase-3 by Immunohistochemical examination. **Results:** Cisplatin administration was associated with significant higher levels of BUN, creatinine, uric acid and H<sub>2</sub>O<sub>2</sub> as compared with normal control group. Green coffee administration in cisplatin-induced renal apoptosis groups produced significant lower levels of BUN, creatinine, uric acid and H<sub>2</sub>O<sub>2</sub> (24.4 ± 4.14, 1.730 ± 0.2830, 5.50 ± 0.850 and 0.51 ± 0.12 respectively) as compared with cisplatin-induced renal apoptosis group not administrated green coffee (27.4 ± 6, 2.04 ± .31, 7.00 ± 1.25 and 1.1 ± 0.16 respectively). Cisplatin administration increased expression of the apoptotic protein caspase-3. In contrast, treatment with green coffee extract attenuated

apoptosis. **Conclusion:** green coffee reduced cisplatin-induced renal apoptosis. Green coffee improved the general condition of cisplatin-induced renal apoptosis rats due to its antioxidant and anti-apoptotic effects.

## Keywords

Green Coffee, Cisplatin and Apoptosis

## 1. Introduction

Green coffee beans have gained popularity as one of the most common drinks all over the world. It contains more than 700 compounds which are responsible for its aromatic and unique flavor. Genus *Coffea arabica* L. and *Coffea canephora* pierre ex. account 60% - 40% of world production. Arabica usually grows in South America and mountain areas of East Africa while Robusta in Vietnam and lowland of Central and West Africa [1].

Chlorogenic acids (CGAs) are cinnamic acid derivatives that have been reported to health benefits such as antibacterial, antiinflammatory activities, diabetes type 2, antioxidant and also have been shown to have a chemo preventive effect [2]. Green coffee is the major source of CGAs in nature (5 - 12 g/100 g) [3]. However, 30% - 50% of CGAs decompose during roasting [4].

Cisplatin (cis-diamminedichloroplatinum (II), CDDP) is widely used as a chemotherapeutic drug used in the treatment of numerous human cancers, including bladder, head and neck, ovarian and testicular cancers, lung, and breast. It is also effective against various types of cancers. However, its resistance and numerous side effects include ototoxicity, gastrotoxicity, and myelosuppression, the main dose-limiting side effect of cisplatin is nephrotoxicity [5] [6]. The kidney is responsible for the excretion of cisplatin and it is the primary site of its accumulation [7]. Multiple mechanisms contribute to renal toxicity following exposure to cisplatin. These include free radical production, loss of antioxidant defense mechanisms and acute renal tubular necrosis which can lead to reduction of glomerular filtration rate (GFR) and renal dysfunction. Beside, the pathological effects involve rise of upregulation of transforming growth factor- $\beta$ , endothelin-1, augmentation of oxidative stress, necrosis, and apoptosis and increase the macrophage/monocyte infiltration to the renal cortex and medulla [8]. The primary causes of cisplatin-induced renal tubular injury are the generation of reactive oxygen species (ROS) and ischemia in the renal microvasculature. Moreover, the straight segment of the proximal tubule in the outer medulla is predominantly damaged by cisplatin which is manifested by apoptosis and necrosis. Cisplatin increases the production of nitric oxide and peroxynitrite in renal tissues. Peroxynitrite stimulates changes in the function and structure of lipid peroxidation, chemical cleavage of deoxyribonucleic acid (DNA), proteins and reduction in cellular defenses by oxidation of thiol pools [9].

Cisplatin-induced renal proximal convoluted tubules' death was originally thought to be the result of oncosis, a type of cell death that is adenosine triphosphate (ATP)-independent and characterized by cell and organelle swelling and lysis [10]. However, histological examination of cisplatin treated kidney tissue demonstrated pathology characteristic of both apoptosis and oncosis [11]. Apoptosis is an active type of cell death that is energy-dependent and characterized by distinct morphological characteristics and activation of a family of cysteine proteases called caspases [12]. Caspase 3 and Caspase 7 belong to the caspase family of proteases that play key roles in the apoptotic process. These enzymes are known as the executioner caspases, and are essentially the effectors or proteins of the cellular apoptotic process [13]. Activation of Caspase-3 has been identified as a key step in Dox mediated apoptosis in non-tumor cells. Both the intrinsic and extrinsic pathways of apoptosis converge at the point of Caspase 3 activation and Doxorubicin (Dox) is known to activate both these pathways [14].

Green coffee as a functional food has antioxidant effects that can reduce the cancer incidence, promote weight-loss and improved glucose and lipid metabolism, as well as anti-oxidant and anti-inflammatory activity [15].

In light of the foregoing data, this study evaluates the protective effects of green coffee in cisplatin-treated rats by measuring renal function, formation of reactive oxygen species, and the presence in situ of caspase-3 as a marker of apoptosis.

## 2. Materials and Methods

### 2.1. Animal Model

All procedures were conducted at Al-Azhar University Assuit, Egypt. Nine weeks old forty male albino rats of local strain (weighing 200 - 250 g) were obtained from Animal House belongs to Nile Pharmaceutical Company, Cairo, Egypt. The animals were housed under controlled conditions with 12 h light/dark cycle, allowed free access to standard food prepared from commercial rat food formula (El-Nasr-Pharmaceutical Co. Egypt) and distilled water. Animals were left one week for acclimatization on laboratory conditions prior to the onset of the experiment. Nephrotoxicity was induced in mice by intraperitoneally (i.p) administered 8 mg/kg of cisplatin which dissolved in normal saline (0.9% NaCl w/w) at final concentration 0.5 mg/ml [16].

### 2.2. Experimental Protocol

#### Animal Grouping

Animals were randomly divided into four groups of 10 animals each (Table 1).

Gr1 and Gr4 were received isotonic saline (0.5 ml, i.p.) for 30 consecutive days, Gr2 and Gr3 were received green coffee extract in water (40 mg/kg/day) [17] for 30 consecutive days, on the 10th day, animals of Gr3 and Gr4 (received single intraperitoneal injection of cisplatin (8 mg/kg). This dose (8 mg/kg) of cisplatin was selected on the basis of its efficacy in causing nephrotoxicity in rats

**Table 1.** Groups classification according to medication received.

Group	Medication	Green coffee	Cisplatin
Gr1 (control negative group)		No	No
Gr2 (sham operated group)		Yes	No
Gr3 (green coffee and cisplatin group)		Yes	Yes
Gr4 (cisplatin group)		No	Yes

Where is Gr1 = group 1, Gr2 = Group 2, Gr3 = Group 3, Gr4 = Group 4.

[18]. Green coffee bean extract was obtained from Puritan's Pride healthy co., ltd, Egypt and cisplatin was obtained from EIMC United Pharmaceuticals, Egypt.

### 2.3. Renal Function Tests

Blood samples were collected under gentle diethyl-ether anesthesia for further biochemical examinations. Creatinine, uric acid and blood urea nitrogen (BUN) levels were evaluated according to manufacturer's instruction of the colorimetric kit (Biodiagnostic Co., Cairo, Egypt).

### 2.4. Reactive Oxygen Species Assays

Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) elimination was measured in the kidney tissue as an indicator of oxidative stress using colorimetric kits (Bio-diagnostic Co., Cairo, Egypt). The transmittance was measured at 510 nm by a UVD-2950 spectrophotometer.

### 2.5. Caspase-3 Detection

Immunohistochemical studies were done for detection of Caspase-3 on paraffin sections of kidney using avidin-biotin peroxidase (DAB, Sigma Chemical Co.) according to the method described by Hsu *et al.*, [19]. Tissue sections were incubated with a monoclonal antibody for caspase-3 (Dako Corp, Carpinteria, CA) and reagents required for the avidin-biotin peroxidase (Vectastain ABC peroxidase kit, Vector Laboratories) method for the detection of the antigen-antibody complex. Each marker expression was localized by the chromagen 3, 3 diaminobenzidine tetra hydrochloride (DAB, Sigma Chemical Co.).

**Caspase activity assay:** Caspase-3 and 9 activities were detected using a colorimetric assay kits from (Abcam, Cambridge, MA, USA). The cells were collected and resuspended in lysis buffer containing 50 mmol/L HEPES, pH 7.4, 0.1% CHAPS, 1 mmol/L DTT, 0.1 mmol/L EDTA and 0.1% Triton X-100. Following incubation for 30 min on ice, lysated cells were centrifuged at 11 000 g for 10 min at 4°C, and the protein concentration in the supernatants was measured using the Bradford dye method. The supernatants were incubated with reaction buffer containing 2 mmol/L Ac-DEVD-AFC for caspase-3 and LEHD-AFC for caspase-9 (Abcam) in a caspase assay buffer at 37°C with 10 mmol/L DTT for 30

min. Caspase activity was determined by measuring the absorbance at 405 nm.

## 2.6. Statistical Analysis

The obtained data were subjected to analysis of variance according to the procedures outlined by Snedecor and Cochran. The mean values were compared according to Duncan's multiple range test (DMRT). The data were analyzed using Co Stat software for windows (version 6.3), (Co Hort Software, Monterey, Calif).

## 3. Results

**Effect of cisplatin injection with and without green coffee extract administration on renal function tests (Table 2):** There was a statistical significant increase in serum creatinine level in both groups III and IV when compared with their corresponding levels in both groups I and II ( $p < 0.05$ ) also it was significantly increased in group IV when compared with its level in group III ( $p < 0.05$ ) (Table 2). The value of serum uric acid was significantly increased in group IV when compared with its level in the three groups (I, II and III) ( $p < 0.05$ ). At the other hand, no statistical significant difference between serum uric acid values in groups I, II and III (Table 2). As regards BUN, there was a statistical significant increase in BUN level in both groups III and IV when compared with their corresponding levels in both groups I and II ( $p < 0.05$ ) while there was no statistical significant difference in its level between groups III and IV ( $p > 0.05$ ) (Table 2).

**Effect of cisplatin injection with and without green coffee extract administration on ROS and Caspase 3 formation (Table 3):** The value of  $H_2O_2$  was significantly increased in group IV when compared with their levels in the three groups (I, II and III) ( $p < 0.05$ ), also the value of  $H_2O_2$  was significantly higher in group III than in group I ( $p < 0.05$ ) (Table 3).

Concerning caspase-3, its mean value in both groups III and IV was significantly increased when compared with their corresponding value in both groups I and II ( $p < 0.05$ ) also caspase-3 value was significantly increased in group IV when compared with its corresponding value in group III ( $p < 0.05$ ) (Table 3).

**Effect of green coffee on Apoptotic Marker (Figure 1):** The apoptotic process was evaluated by detecting the expression of caspase-3 in renal tissue of all groups. Cisplatin administration increased expression of the apoptotic protein caspase-3. In contrast, treatment with GCE attenuated apoptosis. GCE (40 mg/kg) treatment decreased the expression of caspase-3 in the renal tubules (Figure 1).

## 4. Discussion

The aim of the present study was to show the effect of green coffee on cisplatin induced renal apoptosis in adult male albino rats. Previous studies have reported that cisplatin (CI) is an inorganic platinum compound characterized by a

**Table 2.** Comparison between values of renal functions tests in different studied groups.

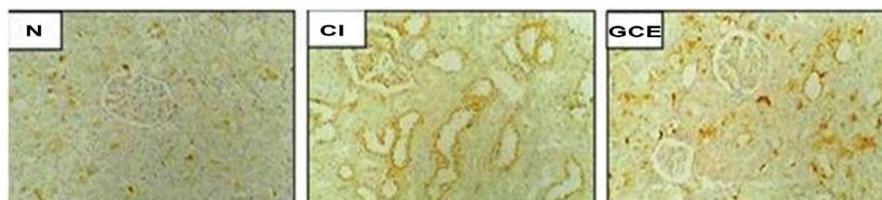
	Gr. I (n = 10)	Gr. II (n = 10)	Gr. III (n = 10)	Gr. IV (n = 10)	F & P value
<b>S. creatinine</b> (mg/dl) <sup>#</sup>	1.44 ± 0.42	1.37 ± 0.21	1.73 ± 0.28 <sup>a,b</sup>	2.04 ± 0.32 <sup>a,b,c</sup>	$\chi^2 = 17.858$ ; p = 0.001*
<b>Uric acid</b> (mg/dl) <sup>#</sup>	5.10 ± 0.74	4.80 ± 0.79	5.50 ± 0.85	7.00 ± 1.25 <sup>a,b,c</sup>	$\chi^2 = 18.206$ ; p = 0.001*
<b>BUN</b> (mg/dl)	16.40 ± 6.20	15.00 ± 4.50	24.40 ± 4.14 <sup>a,b</sup>	27.40 ± 6.00 <sup>a,b</sup>	$F_{(3,36)} = 13.048$ ; p = 0.001*

Data are expressed as mean ± SD. <sup>#</sup> = non parametric statistics;  $\chi^2$  = Chi square of Kruskal Wallis ANOVA test; <sup>a</sup>p < 0.05 relative to group I; <sup>b</sup>p < 0.05 relative to group II; <sup>c</sup>p < 0.05 relative to group III; \*p < 0.05 = significant.

**Table 3.** Comparison between mean values of hydrogen peroxide and caspase-3 in different studied groups.

	Gr. I (n = 10)	Gr. II (n = 10)	Gr. III (n = 10)	Gr. IV (n = 10)	F & P value
<b>H<sub>2</sub>O<sub>2</sub></b>	0.34 ± 0.05	0.39 ± 0.05	0.51 ± 0.12 <sup>a</sup>	1.10 ± 0.16 <sup>a,b,c</sup>	$F_{(3,36)} = 103.366$ ; p = 0.001*
<b>Caspase-3</b>	0.51 ± 0.03	0.51 ± 0.04	0.68 ± 0.1 <sup>a,b</sup>	2.04 ± 0.07 <sup>a,b,c</sup>	$F_{(3,36)} = 1128.674$ ; p = 0.001*

Data are expressed as mean ± SD. <sup>#</sup> = non parametric statistics;  $\chi^2$  = Chi square of Kruskal Wallis ANOVA test; <sup>a</sup>p < 0.05 relative to group I; <sup>b</sup>p < 0.05 relative to group II; <sup>c</sup>p < 0.05 relative to group III; \*p < 0.05 = significant.



**Figure 1.** Effect of green coffee extract on immunohistochemistry (×20; scale bar, 100 μm). Immunohistochemistry for caspase-3 showing positive expression among the renal tubular epithelium in cisplatin administrated groups. Very mild to negative expression of caspase-3 among the tubular epithelial linings in kidneys of green coffee administrated group; N = normal, CI = cisplatin and GCE = green coffee extract (40 mg/kg/day).

broad-spectrum anti-neoplastic effect against a wide variety of tumors [20]. The mechanisms of cisplatin-induced nephrotoxicity are complex and involve numerous cellular processes including oxidative stress, apoptosis, and inflammation [21]. In our study, all groups injected by cisplatin showed significant higher levels in the blood creatinine, blood urea nitrogen and uric acid, and increased expression of the apoptotic protein caspase-3 in comparison to normal control group. Fatima *et al.*, [22] reported that intraperitoneal injection of Cisplatin can increase the serum creatinine and BUN amounts. This in accordance with a study that proven that Cisplatin causes nephrotoxicity and increases parameters of renal function in normal rats [23] by inflammatory processes [24]. In our study, the serum levels of creatinine, BUN, uric acid and ROS in-group administered green coffee extract with Cisplatin injection showed significant reduction compared to the Cisplatin administered group only by showing a better renal

function. This in accordance with a study that proven that rats received oral GCE for 7 days with induction of acute renal failure showed a significant improvement in kidney functions tests (decrease in serum urea, serum creatinine, and blood urea nitrogen) when compared to the ARF model group [18]. This also in agreement with the studies that proven that caffeine in coffee reduce oxidative stress and protect antioxidant system: in hypoxia-induced pulmonary epithelial cells; it is an inhibitor of hydrogen peroxide-induced lipid peroxidation products in human skin fibroblasts, and it reduces tissue lipid peroxidation and ROS production [25] [26]. Since oxidative stress have been carried out as a leading cause in a wide range of chronic diseases, it is important to understand the effect of antioxidants in different physiological and pathological conditions. There is an evidence that GCE has antioxidants effect that may be protective against oxidation reactions by up-regulating in the antioxidant enzymes expression and decreasing cell apoptosis. In our study, treatment with GCE attenuated apoptosis and decreased the expression of caspase-3 in the renal tubules. This in accordance with a study that proven that, Dox treatment of J774.1 macrophages at 1 and 3  $\mu\text{M}$  activated Caspase 3 by 1.7 and 9.6 fold respectively, within 6 h. Pretreatment with GCE for 1 h attenuated Caspase 3 activation in a dose dependent manner. This demonstrates that GCE protects J774.1 macrophages from Dox induced apoptosis robustly and dose-dependently [27]. This results match with the study that says there is extensive evidence that suggests that suppression of activation of Caspase 3 rescues cells from Dox-induced apoptosis in a variety of cell types [28]. Possible explanations for our results are as follows. First, the coffee components may be protective for the glomerular endothelium against the oxidative stress. Chlorogenic acid, Caffeic acid and hydroxyhydroquinone are antioxidants present in green coffee [29]. Antioxidant capacity of green coffee depends on high antioxidant properties of phenolic compounds as chlorogenic acids [30]. These phenolics are highly effective in vitro [31]. Second, the anti-diabetic effect of green coffee will decrease diabetic nephropathy development. Since phenol chlorogenic acid and its degradation products inhibit glucose absorption and hepatic glucose output, it is conceivable that higher coffee intake may be related to a decreased risk of diabetes [32]. The prevalence of renal function impairment also decreased gradually with the increasing frequency of coffee consumption [33]. Our findings are in agreement with those declared by Bioud *et al.* [34] that mentioned the caffeic acid phenethyl ester as a potent reducer of oxidative stress in rat tubular damage induced with Cisplatin and confers good renoprotection. Unfortunately, many pathways contribute to the cisplatin-induced cytotoxic actions on tumor cells [35]. However, our work may seem to be one of the best ways to protect renal tissue from cisplatin-induced injuries without the reduction of tumoricidal activity of the drug but it may have synergistic effect as evidenced by study of Cao, *et al.* [36].

## 5. Conclusion

Green coffee extracts have beneficial effects on controlling cisplatin induced

renal apoptosis by correction of renal function and decreasing cisplatin nephro-toxicity without the reduction of tumoricidal activity of the drug.

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### Author's Contributions

Nour El-Deen A. and Mansour A. involved in the study concept, design and recruitment of animal, induction renal toxicity and follow up, and contributed to data acquisition; Taha A. and Ehab M. Fahmy performed the biochemical tests and Immunohistochemical studies; Nour El-Deen A. and Taha A. performed statistical analysis and designed the figures; Nour El-Deen A. and Mansour A. performed data interpretation; Ehab M. Fahmy, Nour El-Deen A. and Taha A. wrote the manuscript; all the authors reviewed the manuscript and finally approved it for submission.

### Conflicts of Interest

The authors declare that they have no competing interest.

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