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Protective Effects of Onion Oil and Selenium against Cisplatin-Induced Nephrotoxicity and Oxidative Stress in Rats

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ABSTRACT

Background: Nephrotoxicity is an inherent of certain anticancer drugs. **Aim:** This study aimed to assess the protective effect of onion oil and selenium against cisplatin-induced nephrotoxicity in male rats. **Results**: Cisplatin (5 mg/kg, i.p.) caused significant increases in serum sodium, blood urea nitrogen, serum creatinine, total sodium and potassium excreted in urine, urine volume and lipid peroxides measured as the malondialdehyde content of kidney, with significant decreases in serum total protein, creatinine clearance, reduced glutathione content of kidney and kidney superoxide dismutase activity as compared to the control group. On the other hand, administration of onion oil (100 mg/kg, p.o.) or selenium (1 mg/kg, p.o.) for 14 days with a single cisplatin dose on the 10th day ameliorated the cisplatin-induced nephrotoxicity as indicated by the restoration of kidney function and oxidative stress biomarkers. **Conclusion:** Onion oil and selenium showed protective effects against cisplatin-induced nephrotoxicity.
KEYWORDS: Onion oil; Selenium; Anti-oxidant; Cisplatin; Nephrotoxicity

INTRODUCTION

Cisplatin (cis-diamminedichloroplatinum (II)) is one of the most effective chemotherapeutic agents widely used in the treatment of a variety of malignancies including head, neck, ovarian and testicular cancers.[1] However, the full clinical utility of cisplatin is limited by its nephrotoxicity. [2] Approximately 28% to 36% of patients receiving an initial dose (50–100 mg/m^2) of cisplatin develop acute nephrotoxicity. Vigorous hydration has not been effective in eliminating cisplatin toxicity. Also, the use of diuretics may complicate the electrolyte disturbance induced by cisplatin. Discontinuation of cisplatin remains the only option in cases of progressive nephrotoxicity. [3] In addition to direct tubular toxicity in the form of apoptosis and necrosis,[4] vascular factors,[5] and inflammation[6] that have been implicated in the pathogenesis of cisplatin-mediated nephrotoxicity, several other studies demonstrated that cisplatin induced oxidative stress is involved in the development of renal tubule injury.[7] The involvement of oxidative stress was further supported by the fact that free radical scavengers and antioxidants prevent cisplatin-induced nephrotoxicity.[8] Many antioxidants were investigated for their preventive abilities against cisplatin-induced nephrotoxicity. Some researches advised the use of enriched diets with natural antioxidants like vitamin E, ascorbic acid, and methionine.[9] Other studies reported that the use of sulfhydryl-containing drugs, such as captopril, diethyldithiocarbamate, sodium thiosulfate, N-acetylcysteine, and lipoic acid, could also exert antioxidant activity.[10]

Onions (*Allium cepa* L.) possess strong, characteristic aromas and flavours, which have made them important ingredients of food. Onions and onion flavours (essential oil) are important seasonings widely used in food processing. Several studies had demonstrated that onions possess several biological properties, such as antibacterial,[11] antimutagenic[12] and antioxidant activities[13]. The most important active constituents in onion oil are organosulfur compounds which are reactive, volatile, odour producing and lachrymatory.[14]

Selenium is a trace element that is essential in small amounts. Humans and animals require selenium for the function of a number of selenium-dependent enzymes, also known as selenoproteins. Selenium maximizes the activity of antioxidant selenoenzymes such as selenium-containing glutathione peroxidases (GPx) which

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are antioxidant enzymes that reduce potentially damaging reactive oxygen species (ROS). [15]

Therefore, the aim of this study is to assess the possible protective effects of onion oil and selenium against cisplatin-induced nephrotoxicity in rats.

MATERIAL AND METHODS

Animals

Male adult Sprague-Dawley rats weighing 230-260 g were used in the present study. They were obtained from the breeding colony maintained at the animal house of the National Organization for Drug Control and Research (NODCAR, Cairo, Egypt). Animals were caged in seven groups, given suitable food (Purina chow) and water was allowed *ad libitum*. Animals were subjected to an adaptation period of 2 weeks in the animal house before experiments. The experiments were conducted in accordance with the ethical guidelines for investigations in laboratory animals and were approved by the Ethical Committee of Faculty of Pharmacy, Cairo University, Egypt and comply with the Guide for the Care and Use of Laboratory Animals.[16]

Chemicals

Cisplatin was purchased from EMIC for pharmaceutical industry (Cairo, Egypt) in form of parenteral vial with concentration of 50 mg/ml. Onion oil was obtained from a commercial source (Hashem Brothers Company, Benisuef, Egypt). Selenium was obtained from Sigma Aldrich Co. (USA). 5,5-Dithiobis(2-nitrobenzoic acid), pyrogallol and reduced glutathione (GSH) were purchased from Sigma-Aldrich Co. 2-thiobarbituric acid (TBA), malondialdehyde (MDA) (1,1-3,3-tetraethoxypropane), superoxide dismutase (SOD) and trishydroxylmethylaminomethane were purchased from Fluka (Hannover, Germany). Blood urea nitrogen (BUN), serum sodium, serum potassium and serum total protein kits were all purchased from Spectrum (Obour City - Cairo, Egypt). All other chemicals were of analytical grade or equal quality.

Experimental Design

Forty-two rats were classified into seven groups (six rats each) and subjected to treatment as follows: *Group I*: Received saline and served as normal control, *Group II*: Received 2% Tween 80 (emulsifying agent for onion oil), *Group III*: Received cisplatin in a single dose of 5 mg/kg, i.p.[17] (nephrotoxic group), *Group IV*: Received onion oil in a dose of 100 mg/kg, p.o.[18] for 14 days, *Group V*: Received selenium in a dose of 1 mg/kg, p.o.[19] for 14 days, *Group VI*: Received onion oil in a dose of 100 mg/kg, p.o. for 14 days with a single dose of cisplatin (5 mg/kg, i.p.) on the tenth day, *Group VII*: Received selenium in a dose of 1 mg/kg, p.o. for 14 days with a single dose of cisplatin (5 mg/kg, i.p.) on the tenth day.

Sample Preparation

On the fifth day after cisplatin injection, animals were anaesthetised with light ether and retro-orbital blood using a capillary tube in non-heparinized tubes and serum was separated by centrifugation for 20 min. at 4000 r.p.m. and stored at - 20^{o}C in order to measure serum electrolytes and serum kidney function parameters using colorimetric assay kits according to the manufacturer's protocol. Urine samples were collected by housing the rats individually in metabolic cages with free access to food and water so as to obtain 24-hours urine collections. Urine volume and urine specific gravity were measured then urine samples were stored at - 20^{o}C in order to measure urinary electrolytes by a flame spectrophotometer and further urinary kidney function parameters using a colorimetric assay kit according to the manufacturer's protocol. The animals were euthanized and their kidneys were rapidly isolated for biochemical investigations that includes determination of kidney contents of MDA, GSH and SOD activity.

1.1. Biochemical Analysis

Isolated kidneys were washed in ice-cold saline then used to prepare a 10% (w/v) homogenate in 0.1 M Tris buffer (pH 7.4) with motor- driven teflon glass homogenizer (Glas-Col Co., CA, USA) and divided into three aliquots. The first one was used for determination of malondialdehyde (MDA) according to the method of Buege and Aust [20] as modified by Deniz *et al.*[21] While the second one was deproteinized with ice-cold 5% sulfosalicylic acid then centrifuged at 1000 xg for 15 minutes using high speed brushless centrifuge MPW-350 (MPW Med. Instruments, Poland) and the obtained supernatant was used

for the estimation of glutathione (GSH) according to the method described by Beutler *et al.* [22] The third portion of the homogenate was centrifuged at 10,000 xg for 30 minutes at 4°C using Sigma 3K30 cooling centrifuge (Germany) and the clear supernatant was used for determination of superoxide dismutase (SOD) activity according to the method described by Marklund and Markland.[23]

Statistical Analysis

All values are presented as means ± standard error of the means (SE). Statistical analysis was performed using GraphPad Prism version 5 (GraphPad, San Diego, CA, USA). Comparison between different groups was carried out using one-way analysis of variance (ANOVA), followed by Tukey-Kramer's multiple comparisons test. Difference was considered significant when $P \leq 0.05$.

RESULTS

Table 1 shows that injection of cisplatin (i.p.) in a single dose of 5 mg/kg caused significant increases in serum sodium (69%), serum creatinine (733%), and BUN (920%), and a significant decrease in serum potassium level (37%) as compared to normal control group.

Moreover, cisplatin produced significant increases in total sodium and potassium excreted in urine and urine volume (289%, 222% and 119% respectively) and a significant decrease in urinary creatinine level (41%) in comparison to control group (Table 2). Furthermore, cisplatin produced significant increases in kidney MDA content (118%) and renosomatic index (139%) and significant decreases in the SOD activity (63%), GSH renal content (56%) and creatinine clearance (87%) as compared to normal control group (Table 3 & 4).

In contrast, administration of onion oil (100mg/kg) for 14 days with a single cisplatin dose on the 10th day significantly attenuated the elevated levels of BUN (77%), serum creatinine (76%), total sodium and potassium excreted in urine (57% and 42%, respectively), as well as urine volume (48%) and relative kidney weight (17%) and significantly increased creatinine clearance (375%) as compared to cisplatin group. Furthermore, it decreased kidney MDA content by (32%) and increased SOD activity and GSH renal content (135% and 88%, respectively) in comparison to cisplatin control group (Table 1, 2, 3 & 4).

Similarly, treatment of animals with selenium (1 mg/kg) for 14 days with a single cisplatin dose on the 10th day significantly reduced the elevated levels of BUN (86%), serum creatinine (91%), total sodium and potassium excreted in urine (83% and 86%, respectively), as well as urine volume (78%) and relative kidney weight (18%) and significantly increased serum potassium (100%) and creatinine clearance (316%) (as compared to the cisplatin-treated group). Furthermore, it decreased the MDA renal content by (36%) and increased SOD activity and GSH renal content (174% and 103%, respectively) in comparison to cisplatin group (Table 1, 2, 3 & 4).

DISCUSSION

Cisplatin is a major antineoplastic weapon used for the treatment of solid tumors. Its chief dose-limiting side effect is nephrotoxicity, which requires a reduction of dose or discontinuation of the treatment.[24] Cisplatin is toxic to renal proximal tubules.[25]

The present study was designed to investigate whether onion oil or selenium administration could afford protection against cisplatin-induced nephrotoxicity.

Our results revealed that cisplatin produced significant elevation in serum sodium, total sodium and potassium excreted in urine, serum creatinine, urinary creatinine, BUN, urine volume and relative kidney weight as well as a significant decrease in the serum potassium and creatinine clearance suggesting an acute nephrotoxicity. The electrolyte disturbances may be due to a specific membrane or transport system abnormality.[26] The increase in renosomatic index is suggested to be an indication of kidney damage caused by an increase in the glomerular volume and cellular degenerative changes, including cytoplasmic vacuolization of the proximal tubular cells, and tubular dilation.[27] Cisplatin administration induces damage at the renal tubule and distorts its ability to reabsorb water and cause polyuria, which can also lead to polydipsia.[28] Recent studies reported that cisplatin administration leads to increase urine output.[29] Elevation of

serum and urinary creatinine and BUN levels beside reduction in creatinine clearance indicate glomerular damage as a consequence of reactive oxygen species (ROS). Furthermore, cisplatin caused a significant decline in the activity of the antioxidant enzyme (SOD), significant depletion of GSH, and enhancement of MDA production in the renal tissue. These findings are consistent with those of Ali *et al.* [30], Fouad *et al.*[31] and Yadav *et al.*[32].

It was evidenced that cisplatin nephrotoxicity occurs as a result of oxidative stress and increased generation of superoxide anion, hydrogen peroxide, and hydroxyl radicals due to the increased activity of NADPH oxidase, xanthine oxidase and adenosine deaminase.[33] These free radicals damage the lipid components of the cell membrane via peroxidation and denaturing its proteins, which subsequently lead to enzymatic inactivation.[34] Moreover, cisplatin-induced tubular damage could be explained by the fact that, as fast as cisplatin is in the interior of the cells, the hydrolysis product (chloride atoms replaced by water molecules) reacts with GSH in the cytoplasm and DNA in the nucleus.[35] The produced cisplatin-DNA intrastrand cross-links result in cytotoxicity (apoptosis/ necrosis).[36] The present study demonstrated that pretreatment with onion oil or selenium ameliorated cisplatin-induced alterations in serum potassium, serum and urinary creatinine, creatinine clearance, BUN, total sodium and potassium excreted in urine, urine volume and renosomatic index. In addition, onion oil or selenium significantly mitigated the lipid peroxidation in the rat kidney induced by cisplatin as manifested by the decreased MDA level, accompanied by the increased GSH content and enhanced activity of SOD. These results could be attributed to the potential antioxidant effect of onion oil[37] and selenium[38] and are in agreement with those obtained by Helen *et al.*[18] who demonstrated that onion oil is an effective antioxidant against the oxidative damage caused by nicotine . Moreover, our results are consistent with Flora *et al.*[39] who revealed the protective effect of selenium against cadmium-induced nephrotoxicity and hepatotoxicity.

In conclusion, onion oil or selenium protected the kidney tissue against cisplatin-induced nephrotoxicity in rats but selenium exhibited better renoprotective activity than onion oil. The antioxidant activities might be considered the main factors responsible for such nephroprotective effects as selenium is a well-known antioxidant and onion oil contains two major groups of flavonoids found in onions : anthocyanins (cyanidin and peonidin glycosides)[40] and flavonols (quercetin, isorhamnetin, kaempferol and their glycosides)[41]. The most abundant flavonols in onions are quercetin 4'-O-β-D-glucoside and quercetin 3,4'-O-β-D-diglucoside, which account for more than 85% of the total flavonoid content [11]. Therefore, onion oil or selenium represents a potential candidate to prevent renal injury, which is a major and dose-limiting problem during the cisplatin therapy.

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TABLE 1. Effect of onion oil or selenium on kidney function parameters in serum in cisplatin-treated rats.

Treatment / Parameter	Normal Control (Saline)	Normal Control (Tween 80)	Onion Oil (100mg/kg)	Selenium (1mg/kg)	Cisplatin group (5mg/kg)	Onion Oil (100mg/kg) + Cisplatin (5mg/kg)	Selenium (1mg/kg) + Cisplatin (5mg/kg)
Serum sodium (mmol/L)	**130 ± 3.263**	**97.69 ± 6.239**	**118.2±6.695**	**131.8±6.041**	**220*±14.04**	**218.9*[a]± 8.402**	**205* ±1.132**
Serum potassium (mmol/L)	**9.508±0.338**	**9.128 ± 0.588**	**9.175±0.468**	**10.6±0.771**	**5.993*±0.164**	**6.418*[a]±0.355**	**11.96[b]±1.155**
BUN (mg/dL)	**18.19±1.805**	**9.384 ±0.293**	**12.89±0.524**	**16.57±1.513**	**185.5*±0.037**	**43.02*[ab]±4.269**	**26.76[b]±1.735**
Creatinine (mg/dL)	**0.57 ± 0.061**	**0.738 ± 0.102**	**0.709±0.037**	**0.889±0.027**	**4.747*±0.514**	**1.134[b]± 0.135**	**0.451[b]±0.039**
Total Protein (g/dL)	**4.533±0.147**	**5.684 ± 0.089**	**6.301±0.431**	**7.486*±0.566**	**5.202±0.206**	**5.303 ± 0.021**	**6.737±0.438**

Data are expressed as means ± SEM of six rats per group.
[*] Significantly different from normal control (saline) group at $p < 0.05$.
[a] Significantly different from normal control (Tween 80) at $p < 0.05$.
[b] Significantly different from cisplatin control at $p < 0.05$.

TABLE 2. Effect of onion oil or selenium on kidney function parameters in urine in cisplatin-treated rats.

Treatment / Parameter	Normal Control (Saline)	Normal Control (Tween 80)	Onion Oil (100mg/kg)	Selenium (1mg/kg)	Cisplatin Control (5mg/kg)	Onion Oil (100mg/kg) + Cisplatin (5mg/kg)	Selenium (1mg/kg) + Cisplatin (5mg/kg)
Total sodium excreted (mmol)	**0.655±0.087**	**0.428± 0.018**	**0.517±0.012**	**0.527±0.051**	**2.546*±0.133**	**1.099*^{ab}±0.078**	**0.433^{b}±0.027**
Total potassium excreted (mmol)	**0.435±0.033**	**0.432 ± 0.031**	**0.408 ± 0.010**	**0.429±0.047**	**1.399*±0.05**	**0.819*^{ab}±0.021**	**0.2*^{ab}±0.025**
Creatinine (mg/dl)	**16.7±1.389**	**16.7± 2.944**	**19.52±1.829**	**20.28±1.392**	**9.792*± 1.172**	**17.7^{b} ±1.832**	**16.62^{b}± 0.635**
Urine Volume (ml)	**5.45±0.262**	**4.542±0.164**	**3.85±0.096**	**3.833± 0.558**	**11.920*± 0.8**	**6.167^{b}±0.279**	**2.667*^{ab}± 0.105**
Urine specific gravity (gm/ml)	**1.005±0.004**	**1.019±0.002**	**0.976 ±0.016**	**0.986±0.003**	**1.016±0.005**	**1.015±0.001**	**0.944*^{ab}±0.026**

Data are expressed as means ± SEM of six rats per group.
* Significantly different from normal control (saline) group at $p < 0.05$.
[a] Significantly different from normal control (Tween 80) at $p < 0.05$.
[b] Significantly different from cisplatin control at $p < 0.05$.

TABLE 3. Effect of onion oil or selenium on oxidative stress parameters in kidney homogenate in cisplatin treated rats.

Treatment / Parameter	Normal Control (Saline)	Normal Control (Tween 80)	Onion Oil (100mg/kg)	Selenium (1mg/kg)	Cisplatin Control (5mg/kg)	Onion Oil (100mg/kg) + Cisplatin (5mg/kg)	Selenium (1mg/kg) + Cisplatin (5mg/kg)
MDA (nmol/gm tissue)	**8.598±0.499**	**7.844 ± 0.639**	**9.018±0.842**	**9.903± 0.605**	**18.81*±0.396**	**12.81*^{ab}±0.555**	**11.97*^{ab}±0.621**
SOD (mcg/mg protein)	**68.78±1.021**	**68.62 ± 0.765**	**68.94±0.861**	**70.56±0.722**	**25.29*± 1.755**	**59.410^{b}±1.108**	**69.31^{b}±0.517**
GSH (mg/gm tissue)	**0.22±0.008**	**0.199 ± 0.006**	**0.203±0.006**	**0.208±0.006**	**0.096*± 0.008**	**0.180*^{b} ±0.008**	**0.195^{b}±0.01**

Data are expressed as means ± SEM of six rats per group.
* Significantly different from normal control (saline) group at $p < 0.05$.
[a] Significantly different from normal control (Tween 80) at $p < 0.05$.
[b] Significantly different from cisplatin control at $p < 0.05$.

TABLE 4. Effect onion oil or selenium on creatinine clearance and relative kidney weight in cisplatin-treated rats.

Treatment / Parameter	Normal Control (Saline)	Normal Control (Tween 80)	Onion Oil (100mg/kg)	Selenium (1mg/kg)	Cisplatin Control (5mg/kg)	Onion Oil (100mg/kg) + Cisplatin (5mg/kg)	Selenium (1mg/kg) + Cisplatin (5mg/kg)
Creatinine Clearance (ml/min)	**3.243±0.291**	**2.148*±0.182**	**2.089*±0.323**	**2.023*±0.157**	**0.412*±0.033**	**1.956*[b]±0.212**	**1.714*[b]±0.166**
Relative Kidney Weight (%)	**0.723±0.018**	**0.662±0.03**	**0.738±0.024**	**0.63±0.031**	**1.006*±0.037**	**0.84[b]±0.037**	**0.827[b]±0.026**

Data are expressed as means ± SEM of six rats per group.
[*] Significantly different from normal control (saline) group at $p < 0.05$.
[a] Significantly different from normal control (Tween 80) at $p < 0.05$.
[b] Significantly different from cisplatin control at $p < 0.05$.