AMELIORATION OF CISPLATIN AND GENTAMICIN-INDUCED NEPHROTOXICITY BY SEEDS OF *CUCUMIS SATIVUS*

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ABSTRACT

The aim of the present study was to evaluate the protective effect of hydroalcoholic extract of seeds of *Cucumis sativus* against cisplatin and gentamicin-induced nephrotoxicity in male Albino Wistar rats. 60% hydroalcoholic extract was prepared by hot extraction method. In both cisplatin and gentamicin models, activity of hydroalcoholic extract of *Cucumis sativus* was evaluated in curative and prophylactic regimens at two dose levels i.e., 200 and 400 mg/kg, b.w. In Cisplatin model nephrotoxicity was induced by cisplatin (i.p., 5 mg/kg, b.w.) whereas in Gentamicin experimental model induction of nephrotoxicity was done by gentamicin (s.c, 80 mg/kg, b.w.). Nephrotoxicity was assessed by determining serum markers level, urinary functional parameters. In kidney homogenate renal oxidative stress markers such as Superoxide dismutase (SOD), Catalase (CAT), Lipid peroxidation (LPO) and Glutathione reduced (GSH) were measured. Further histopathological studies were carried out. Treatment with hydroalcoholic extract in cisplatin and gentamicin-induced models in curative and prophylactic regimens significantly attenuated the elevated levels SC, BUN, STP, UTP and LPO In addition, hydroalcoholic extract increased creatinine clearance, SOD, CAT and GSH levels in experimental rats. Histopathological studies also substantiated the results obtained. The findings of the present study provide corroborative scientific evidence for the ethnopharmacological use of seeds of *Cucumis sativus* for urinary ailments.

KEY WORDS: *Cucumis sativus*, Nephrotoxicity, Cisplatin, Gentamicin

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INTRODUCTION

Nephrotoxicity is one of the most common kidney problems and occurs when body is exposed to a drug or toxin. A number of potent therapeutic drugs like aminoglycoside antibiotics, chemotherapeutic agents like cisplatin can adversely affect the kidney resulting in acute renal failure.\textsuperscript{1,2} Cisplatin (cis-diammine dichloro platinum (II), CDDP) is a highly effective chemotherapeutic drug used for the treatment of various types of cancers such as ovarian, bladder, testicular, head and neck, and uterine cervix carcinomas. Therapeutic effects of cisplatin are associated with severe reversible and irreversible side effects including nephrotoxicity, neurotoxicity, bone marrow toxicity, gastrointestinal toxicity and ototoxicity.\textsuperscript{3-4} The highest concentration of cisplatin is found in S3 segment of the proximal tubule followed by the distal collecting tubule and the S1 segment of the proximal convoluted tubule. Gentamicin is a typical aminoglycoside antibiotic widely used in clinical practice for the treatment of infections by Gram-negative microorganisms. Nephrotoxicity is the main limitation to its therapeutic efficacy, which occurs in 10–20% of therapeutic regimes. Gentamicin accumulates in the renal proximal tubular cells through the megalin/cubilin complex receptor, which is responsible for transportation of gentamicin inside the cell. Gentamicin-induced nephrotoxicity is mainly characterized by tubular cell apoptosis and/or necrosis, predominantly in the proximal tubules. Oxidative stress also plays an important role in the nephrotoxicity of gentamicin.\textsuperscript{5} Earlier studies have revealed that nephrotoxicity induced by nephrotoxic drugs can be prevented by some known antioxidants like DL-lipoic acid, Probufocul, Superoxide dismutase (SOD) and alpha tocopherol.\textsuperscript{6} Herbs are generally considered safe and proved to be effective against various human ailments and their use in therapeutics has been gradually increasing. In ancient medicine various herbs were prescribed to treat renal disorders. \textit{Cucumis sativus} is one such plant, the seeds of which were used by folklore of Rayalaseema for treating renal ailments due to its cooling and diuretic properties.\textsuperscript{7-9} But till date there were no reports on systematic evaluation of the nephroprotective effect of seeds of \textit{Cucumis sativus}. Hence, the present study was designed to investigate the nephroprotective effect of hydroalcoholic extract of \textit{Cucumis sativus} (HAECS) on gentamicin and cisplatin-induced nephrotoxicity in male Albino Wistar rats.

MATERIALS AND METHODS

\textbf{Collection of Plant material}

Seeds of \textit{Cucumis sativus} were purchased from Srisu Agrichem Private Ltd., Kalyanpuri, Uppal and authenticated by Botanist Dr. Madhava Chetty, Herbarium keeper, Department of Botany, Sri Venkateswara University, Tirupati and a specimen (Specimen Number:512) was deposited in Department of Botany, Sri Venkateswara University, Tirupati, India.

\textbf{Preparation of hydroalcoholic extract}

Seeds were shade dried and powdered in Wiley mill. 200gm of seed powder was macerated with ethanol and water in the ratio of 60:40 for 24h and refluxed for 3h, then filtered. The filtrate was subjected to distillation under reduced pressure and the procedure was repeated for three times. Thus obtained extract was air dried and allowed to concentrate under reduced pressure to get the semi-solid residue.\textsuperscript{10}

\textbf{Preliminary phytochemical studies}

Preliminary phytochemical studies were carried out for HAECS as per standard procedures for the presence of various phyto constituents like alkaloids, flavonoids, saponins, tannins, terpenoids, steroids, carbohydrates, fats and oils, etc.\textsuperscript{11}

\textbf{Experimental animals}

Healthy Wistar male albino rats between 2-3 months of age and weighing about 150-200g were used in the present study. Animals were maintained in polypropylene cages and had free access to standard food and water \textit{ad libitum}. The experimental protocol was approved by Institutional Animal Ethical Committee (IAEC) and carried out according to the guidelines of Committee for the purpose of Control and Supervision of Experiments on animals (CPCSEA). Registration number and date of registration was 1677/PO/a12/IAEC-Feb-14/08. Acute toxicity studies: Acute toxicity studies for HAECS were carried out according to the 423 guidelines of Organization for Economic Co-operation and Development (OECD).\textsuperscript{12} Assessment of nephroprotective activity: The present animal study experiment was conducted in two experimental models of drug-induced nephrotoxicity. In each model rats were systematically randomized into eight groups of six each. In Cisplatin treatment schedule, only higher dose of the extract was administered to Group-IX animals to observe the effect of plant extract on kidneys. In this model, nephrotoxicity was induced by single intra-peritoneal administration of cisplatin at a dose of 5mg/kg, b.w.

\textbf{Treatment schedule for Cisplatin-induced nephrotoxicity}

\textbf{Group-I} : Vehicle from day 1 to day 5

\textbf{Group-II} : Curative control-Cisplatin (5 mg/kg, \textit{i.p.}) on day 1 + vehicle from day 5 to day 9

\textbf{Group-III} : Curative effect-Cisplatin (5 mg/kg, \textit{i.p.}) on day 1 + hydroalcoholic extract (200mg/kg, b.w.) from day 5 to day 9

\textbf{Group-IV} : Curative effect-Cisplatin (5 mg/kg, \textit{i.p.}) on day 1+ hydroalcoholic extract (400mg/kg, b.w.) from day 5 to day 9

\textbf{Group-V} : Prophylactic control - vehicle from day 1 to day 5 + cisplatin (5mg/kg, \textit{i.p.}) on day 5

\textbf{Group-VI} : Prophylactic effect-Hydroalcoholic extract (200mg/kg, b.w.) from day 1 to day 5 + cisplatin (5mg/kg) on day 5.

\textbf{Group-VII} : Prophylactic effect- Hydroalcoholic extract (400mg/kg, b.w.) from day 1 to day 5 + cisplatin (5mg/kg) on day 5.

\textbf{Group-VIII} : Standard: Cisplatin (5 mg/kg, \textit{i.p.}) on day 1+ Cystone (5ml/kg, b. w.) from day 5 to day 9.

\textbf{Group-IX} : Only higher dose of the extract (400mg/kg, b.w.) for five days. On day 5, time gap of minimum one hour was maintained between the administration of extract and Cisplatin in prophylactic regimen. In
gentamicin experimental model, Gentamicin was administered subcutaneously at a dose of 80mg/kg, b.w. daily for 9 days.

**Treatment schedule for Gentamicin-induced nephrotoxicity**

- **Group-I** - Animals were administered with vehicle for ten days. (Normal control group)
- **Group-II** - Animals received 80mg/kg/day s.c. of gentamicin for 9 days and vehicle from day 10 to day 19. (Curative control Group)
- **Group-III** - Animals received higher dose (400 mg/kg, b.w.) of hydro alcoholic extract (p.o.) from day 11 to day 19. (Prophylactic higher dose group)
- **Group-IV** - Animals received 80mg/kg/day s.c. of gentamicin for 9 days and higher dose (400 mg/kg, b.w.) of hydro alcoholic extract (p.o.) was given from day 10 to day 19. (Curative higher dose group)
- **Group-V** - Animals received vehicle for 10 to day 19 and 80mg/kg/day s.c. of gentamicin from day 11 to day 19. (Prophylactic lower dose group)
- **Group-VI** - Animals received lower dose (200 mg/kg, b.w.) of hydro alcoholic extract from day 10 to 19 and standard Cystone from day 11 to day 19. (Prophylactic lower dose group)
- **Group-VII** - Animals received higher dose (400 mg/kg, b.w.) of hydro alcoholic extract from day 10 to day 19 and standard Cystone from day 10 to day 19. (Standard group)
- **Group-VIII** - Animals received 80mg/kg/day s.c. of gentamicin for 9 days and Standard Cystone from day 10 to day 19. (Standard group)

**Biochemical Studies**

On day 5 and 9 in cisplatin model and on day 9 and 19 in gentamicin model, urine was collected by keeping rats individually in metabolic cages; on following day animals were sacrificed by cervical decapitation. Blood samples were collected by cardiac puncture and were used for estimation of serum markers. Kidneys were isolated and urine was collected by keeping rats in ice cold 0.05 M phosphate buffer pK 7.8 to obtain a 20% (w/v) homogenate. The homogenates were centrifuged at 10,000 rpm for 15 min and the clear supernatant obtained was used for the analysis of antioxidant enzymes. Antioxidant studies were carried out by the estimation of levels of Catalase, Superoxide dismutase, reduced Glutathione and Lipid peroxidation.

**Histopathological studies**

Kidneys of two animals from each group were used for histological studies. The isolated kidneys were fixed in 10% buffered formalin and processed to paraffin wax. Sections were stained with haematoxylin and eosin and were examined under light microscope.

**Statistical analysis**

The statistical data was expressed as mean ± SEM. Parametric data which include all the biochemical parameters were analysed using one way Analysis of variance (ANOVA) and compared using Tukey-Kramer multiple comparison tests. A probability value of p<0.05 was considered as significant.

**RESULTS**

**Preliminary phytochemical studies**

Preliminary phytochemical studies revealed the presence of phytoconstituents like flavonoids, triterpenoids, glycosides, saponins, carbohydrates, fats and oils.

**Acute toxicity studies**

HAECs was found to be safe up to 2000mg/kg, b.w. No signs of toxicity were observed. Based on these studies, 200 and 400 mg/kg, b.w. were selected as lower and higher doses.

**Pharmacological studies of HAECs against cisplatin-induced nephrotoxicity**

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>BUN (mg/dl)</th>
<th>SC (mg/dl)</th>
<th>STrP (g/dl)</th>
<th>UTrP (mg/24hrs)</th>
<th>CiCr (ml/hr/100gbd.wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>15.63±0.4</td>
<td>0.75±0.02</td>
<td>6.37±0.17</td>
<td>8.35±0.12</td>
<td>16.18±0.26</td>
</tr>
<tr>
<td>Curative control</td>
<td>30.7±25.5</td>
<td>1.69±0.02</td>
<td>8.73±0.11</td>
<td>22.2±0.30</td>
<td>6.63±0.18</td>
</tr>
<tr>
<td>Curative lower dose</td>
<td>24.83±0.40</td>
<td>1.24±0.03</td>
<td>7.67±0.10</td>
<td>17.2±0.26</td>
<td>9.75±0.25</td>
</tr>
<tr>
<td>Curative higher dose</td>
<td>17.77±0.30</td>
<td>0.92±0.02</td>
<td>7.08±0.08</td>
<td>11.4±0.21</td>
<td>13.07±0.21</td>
</tr>
<tr>
<td>Prophylactic control</td>
<td>35.18±0.38</td>
<td>1.89±0.03</td>
<td>10.17±0.16</td>
<td>27.5±0.20</td>
<td>4.93±0.14</td>
</tr>
<tr>
<td>Prophylactic lower dose</td>
<td>27.05±0.49</td>
<td>1.35±0.05</td>
<td>9.17±0.08</td>
<td>19.4±0.23</td>
<td>8.28±0.16</td>
</tr>
<tr>
<td>Prophylactic Higher dose</td>
<td>23.1±0.25</td>
<td>1.0±0.03</td>
<td>7.9±0.07</td>
<td>15.2±0.16</td>
<td>11.42±0.29</td>
</tr>
<tr>
<td>Standard</td>
<td>16.35±0.69</td>
<td>0.92±0.02</td>
<td>6.76±0.20</td>
<td>10.2±0.30</td>
<td>14.32±0.32</td>
</tr>
<tr>
<td>Only higher dose</td>
<td>15.08±0.23</td>
<td>0.76±0.03</td>
<td>6.62±0.09</td>
<td>9.02±0.11</td>
<td>16.62±0.23</td>
</tr>
</tbody>
</table>

Each value represents the Mean ± S.E.M from 6 animals in each group. a: p<0.01 when compared with normal group. b:p<0.01 when compared with curative control c: p<0.01 when compared with prophylactic control.
In Group IX animals which were treated only with higher dose of the extract, there is no significant difference in the levels of Serum markers, Urinary markers and renal stress markers relative to normal animals. The levels of SC, BUN, $S_T$, and $U_T$ were increased and $Cl_Cr$ decreased markedly in cisplatin control animals when compared with normal animals. Administration of HAECS in curative and prophylactic regimen ameliorated the effects induced by cisplatin.

**Table 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>LPO (nm/100mg of tissue)</th>
<th>SOD (units/mg of tissue)</th>
<th>CAT (units/mg of tissue)</th>
<th>GSH (nm/100mg of tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.80±0.04</td>
<td>26.42±0.47</td>
<td>45.98±0.58</td>
<td>21.13±0.30</td>
</tr>
<tr>
<td>Curative control</td>
<td>6.10±0.20*</td>
<td>14.81±0.39*</td>
<td>14.03±0.43*</td>
<td>5.63±0.14*</td>
</tr>
<tr>
<td>Curative lower dose</td>
<td>3.93±0.28*</td>
<td>18.97±0.31*</td>
<td>26.33±0.39*</td>
<td>11.92±0.50*</td>
</tr>
<tr>
<td>Curative higher dose</td>
<td>1.46±0.13*</td>
<td>23.63±0.77*</td>
<td>38.18±0.75*</td>
<td>19.18±0.34*</td>
</tr>
<tr>
<td>Prophylactic control</td>
<td>7.87±0.16*</td>
<td>12.88±0.31*</td>
<td>12.64±0.31*</td>
<td>5.47±0.36*</td>
</tr>
<tr>
<td>Prophylactic lower dose</td>
<td>5.73±0.16*</td>
<td>17.03±0.18*</td>
<td>21.73±0.46*</td>
<td>10.15±0.33*</td>
</tr>
<tr>
<td>Prophylactic higher dose</td>
<td>2.51±0.16*</td>
<td>22.28±0.31*</td>
<td>30.47±0.50*</td>
<td>16.07±0.27*</td>
</tr>
<tr>
<td>Standard</td>
<td>1.36±0.04</td>
<td>24.05±0.62</td>
<td>38.18±0.75</td>
<td>19.86±0.37</td>
</tr>
<tr>
<td>Only higher dose of the extract</td>
<td>0.84±0.02</td>
<td>26.33±0.20</td>
<td>45.78±0.32</td>
<td>20.98±0.35</td>
</tr>
</tbody>
</table>

Each value represents the Mean ± S.E.M from 6 animals in each group. a: p<0.01 when compared with normal group. b: p<0.01 when compared with curative control. c: p<0.01 when compared with prophylactic control.

Lipid peroxidation was significantly increased in cisplatin control groups compared with normal and HAECS treated animals. Renal SOD, CAT and GSH levels were significantly decreased in cisplatin alone treated group due to oxidative stress. HAECS treatment had increased the levels of antioxidant enzymes decreased by cisplatin.

**Pharmacological studies of HAECS against Gentamicin-induced nephrotoxicity**

**Table 3**

<table>
<thead>
<tr>
<th>Group</th>
<th>BUN (mg/dl)</th>
<th>SC (mg/dl)</th>
<th>$S_T$ (g/dl)</th>
<th>$U_T$ (mg/24hrs)</th>
<th>$Cl_Cr$ (ml/hr/100gbd.wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>17.67±0.49</td>
<td>0.72±0.05</td>
<td>6.2±0.17</td>
<td>6.67±0.33</td>
<td>18.17±0.48</td>
</tr>
<tr>
<td>Curative control</td>
<td>31.33±0.56</td>
<td>1.48±0.08*</td>
<td>8.02±0.07</td>
<td>19.5±0.72</td>
<td>7.5±0.43*</td>
</tr>
<tr>
<td>Curative lower dose</td>
<td>28.83±0.70</td>
<td>1.01±0.09</td>
<td>7.02±0.06</td>
<td>13.17±0.31*</td>
<td>10.83±0.31*</td>
</tr>
<tr>
<td>Curative higher dose</td>
<td>19.33±0.42</td>
<td>0.85±0.07</td>
<td>6.53±0.05</td>
<td>7.5±0.8</td>
<td>13.67±0.33*</td>
</tr>
<tr>
<td>Prophylactic control</td>
<td>37.83±0.65</td>
<td>1.65±0.08*</td>
<td>9.87±0.09*</td>
<td>24.67±0.62*</td>
<td>5.83±0.40*</td>
</tr>
<tr>
<td>Prophylactic lower dose</td>
<td>29.67±0.67</td>
<td>1.32±0.05</td>
<td>9.15±0.06*</td>
<td>17.33±0.42*</td>
<td>8.3±0.42*</td>
</tr>
<tr>
<td>Prophylactic higher dose</td>
<td>22.17±0.54</td>
<td>0.97±0.08</td>
<td>8.38±0.05*</td>
<td>10.67±0.42*</td>
<td>9.83±0.31*</td>
</tr>
<tr>
<td>Standard</td>
<td>17.5±0.43</td>
<td>0.78±0.05</td>
<td>6±0.09</td>
<td>6.67±0.49</td>
<td>15.67±0.49</td>
</tr>
</tbody>
</table>

Each value represents the Mean ± S.E.M from 6 animals in each group. a: p<0.01 when compared with normal group. b: p<0.01 when compared with curative control. c: p<0.01 when compared with prophylactic control.

In Gentamicin control groups, SC, BUN, $S_T$, $U_T$ had increased and $Cl_Cr$ had decreased significantly as compared to normal animals. In both curative and prophylactic regimens, treatment of HAECS reversed the effects induced by Gentamicin in dose dependent manner.

**Table 4**

<table>
<thead>
<tr>
<th>Group</th>
<th>LPO (nm/100mg of tissue)</th>
<th>SOD (units/mg of tissue)</th>
<th>CAT (units/mg of tissue)</th>
<th>GSH (nm/100mg of tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.85±0.13</td>
<td>28.17±0.75</td>
<td>44.88±0.99</td>
<td>20.17±0.60</td>
</tr>
<tr>
<td>Curative control</td>
<td>5.03±0.35</td>
<td>14.83±0.11*</td>
<td>15.33±0.59</td>
<td>5.62±0.15*</td>
</tr>
<tr>
<td>Curative lower dose</td>
<td>2.48±0.18</td>
<td>19.02±0.52</td>
<td>24.07±0.83</td>
<td>9.35±0.2</td>
</tr>
<tr>
<td>Curative higher dose</td>
<td>1.35±0.14</td>
<td>22.17±0.76*</td>
<td>42.77±0.59</td>
<td>17.35±0.55</td>
</tr>
<tr>
<td>Prophylactic control</td>
<td>6.45±0.37</td>
<td>10.67±0.76*</td>
<td>13.48±0.73</td>
<td>4.37±1.1</td>
</tr>
<tr>
<td>Prophylactic lower dose</td>
<td>2.61±0.17</td>
<td>14.83±0.31*</td>
<td>21.02±0.58</td>
<td>6.38±0.42</td>
</tr>
<tr>
<td>Prophylactic higher dose</td>
<td>2.03±0.13</td>
<td>19.83±0.95</td>
<td>32.53±0.50</td>
<td>11.8±0.46</td>
</tr>
<tr>
<td>Standard</td>
<td>1.03±0.01</td>
<td>26.33±0.88</td>
<td>44.20±0.72</td>
<td>19.4±0.49</td>
</tr>
</tbody>
</table>

Each value represents the Mean ± S.E.M from 6 animals in each group. a: p<0.01 when compared with normal group. b: p<0.01 when compared with curative control. c: p<0.01 when compared with prophylactic control.
In animals administered with Gentamicin alone, LPO was increased and SOD, CAT and GSH were decreased significantly compared to normal animals. Treatment with HAECS had decreased LPO and increased SOD, CAT and GSH dose dependently in bothcurative and prophylactic regimens.

**DISCUSSION**

In the present study, seeds of *Cucumis sativus* were evaluated for nephroprotective action against cisplatin and gentamicin-induced nephrotoxicity. Cisplatin is a widely used potent anti-neoplastic agent. Higher doses of cisplatin are generally contraindicated due to many adverse effects including nephrotoxicity. Previous studies have demonstrated that several mechanisms are responsible for cisplatin-induced nephrotoxicity including oxidative stress, inflammation, fibrogenesis and apoptosis. Similarly the use of gentamicin, an aminoglycoside antibiotic with a wide spectrum of activities against Gram-positive and Gram-negative bacterial infections but with high preference for the latter, is equally associated with nephrotoxicity as its side-effect.

Gentamicin nephrotoxicity is characterized by the desquamation of proximal tubules, tubular fibrosis, tubular necrosis and epithelial edema of the proximal tubules. Thus, Cisplatin and Gentamicin-induced nephrotoxicities are well established experimental models of drug-induced nephrotoxicity.

Cisplatin at a dose of 5 mg/kg, b.w. induced nephrotoxicity in rats. Gentamicin at a dose of 80 mg/kg, b.w. subcutaneously, for nine days in rats is known to cause significant nephrotoxicity. In experimental animals, administration of HAECS at a dose of 400 mg/kg, b.w. had not shown any abnormalities on kidney revealing that the extract is safe. Induction of cisplatin and gentamicin encountered acute kidney dysfunction as evidenced by significant elevation of serum creatinine, BUN, serum total protein, urinary total protein and decreased creatinine clearance. Treatment with the HAECS at the dose level of 200 mg/kg, b.w. and 400 mg/kg, b.w. had significantly lowered the levels of SC, BUN, S\textsubscript{TP}, U\textsubscript{TP} and increased the Cl\textsubscript{O}. Present study also demonstrated that animals which received cisplatin and gentamicin alone reduced renal SOD, CAT and GSH levels compared to the normal animals. HAECS significantly mitigated the lipid peroxidation in the rat kidney in dose dependent manner. Further HAECS increased the renal SOD, CAT and GSH levels in both cisplatin and gentamicin models. The results of the present study demonstrate that the HAECS significantly enhanced antioxidant defence against gentamicin induced oxidative damage in renal tissues. Histopathological views of renal sections in cisplatin and gentamicin alone treated group showed the degeneration and necrosis in tubules and swelling in glomerulus, as compared to normal group. The regenerative changes in renal tissue had been observed in HAECS treated animals confirming its nephroprotective activity. Recently, there has been renewed interest in medicinal plants that have been found to have certain preventive measures in the treatment of diseases. Previously many medicinal plants like *Pedalium murex*, *Lepidium sativum*, *Pongamia pinnata*, *Aerva lanata*, *Crataeva nurvala*, *Dichrostachys cinerea* were reported to possess nephroprotective action against drug-induced nephrotoxicity.

Present study supports the earlier results elevation of serum markers levels and decreased creatinine clearance due to cisplatin and gentamicin. HAECS ameliorated these elevated levels which may be due to prevention of tubular necrosis and glomeruli damage. Earlier experimental findings suggested that the free radicals and ROS are involved in cisplatin and gentamicin-induced renal damage due to the depletion of GSH concentration and antioxidant enzyme activities in the kidneys. These observations support the mechanism of nephrotoxicity induced by cisplatin and gentamicin in animals which is partially related to the depletion of renal antioxidant system. The animals which received either Cisplatin or Gentamicin alone exhibited depletion in antioxidant levels and elevated LPO levels. Rats which received HAECS reversed all the effects. This may be attributed to free radical scavenging property of extract as well as direct antioxidant action. Histopathological studies demonstrated structural changes in renal tissue by induction of cisplatin and Gentamicin which has been supported by many researchers. Further preliminary phytochemical screening revealed the presence of phytoconstituents like flavonoids and triterpenoids which were reported to possess anti-oxidant properties. Hence present study revealed that these phytoconstituents may partially be responsible for anti-oxidant property of the extract. Thus the biochemical parameters, antioxidant studies and histopathological studies proved the nephroprotective activity of hydroalcoholic extract of seeds of *Cucumis sativus*.

**Figure 1**

**HISTOPATHOLOGY SLIDES FOR CISPLATIN-INDUCED MODEL**

This article can be downloaded from www.ijpbs.net
Group-I: Photomicrograph of histological section of rat kidney showing the normal architecture of glomeruli (normal group) with lower magnification (10X).

Group-II: Photomicrograph of histological section of kidney treated with Cisplatin only (Curative control) showing congestion in glomeruli with haemorrhage.

Group-III: Photomicrograph of histological section of kidney treated with 200mg/kg, b.w. of the extract showing mild regeneration of the kidney tissue with lower magnification (Curative lower dose).

Group-IV: Photomicrograph of histological section of kidney treated with 400mg/kg, b.w. of the extract showing significant regenerative changes with almost normal cyto-architecture (Curative higher dose).

Group-V: Photomicrograph of histological section of kidney treated with Cisplatin only (prophylactic control) showing the degenerative changes in kidney with cytoplasmic vacuolization and degenerative Bowman's capsule.

Group-VI: Mild regenerative changes in kidney tissue of the rat treated with 200mg/kg, b.w. (Prophylactic lower dose).

Group-VII: Kidney tissue showing regenerative changes in tubules and glomeruli treated with 400mg/kg, b.w. (Prophylactic higher dose).

Group-VIII: Regeneration of kidney tissue similar to normal cyto-architecture (standard).

Group-IX: Photomicrograph of histological section of kidney tissue showing normal organization of glomeruli, Bowman's capsule treated only with higher dose of the extract.

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Group-I: Photomicrograph of histological section of kidney (normal group) showing normal organization of tubular epithelial cells and glomeruli. Group-II: Photomicrograph of histological section of rat kidney treated with Gentamicin alone (curative control) showing cytoplasmic vacuolations and karyolysis. Group-III: Photomicrograph of histological section of rat kidney treated with lower dose of the extract (200 mg/kg, b.w.) showing mild regenerative changes but still congestion in glomeruli, glomerular atrophy were seen (Curative lower dose). Group-IV: Photomicrograph of histological section of rat kidney treated with higher dose of the extract (400 mg/kg, b.w.) showing regenerative changes in tubules and glomeruli (Curative higher dose). Group-V: Photomicrograph of histological section of kidney showing congestion in glomeruli, glomerular atrophy and disappearance of nuclei in tubular cells. (Prophylactic control) Group-VI: Photomicrograph of histological section of rat kidney showing presence of cast cells and intertubular haemorrhage at 200mg/kg, b.w. (Prophylactic lower dose) Group-VII: Photomicrograph of histological section of rat kidney showing regenerative changes at 400mg/kg, b.w. (Prophylactic higher dose). Group-VIII: Photomicrograph of histological section of rat kidney showing normal cyto-architecture. (Standard).
CONCLUSION

The findings of the present study reveal the nephroprotective activity of seeds of *Cucumis sativus* in Cisplatin and Gentamicin-induced models. Thus it provides a corroborative scientific evidence for the ethnomedicinal use of seeds of *Cucumis sativus* for urinary troubles.

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