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Abstract

Cisplatin is a chemotherapeutic drug used to treat cancer patients. The main secondary effect results from Cisplatin treatment is nephrotoxicity. The objective of this study was to evaluate the possible therapeutic effect of cantaloupe, grape, and pumpkin seeds on Cisplatin induced nephrotoxicity in rats.

Materials and Methods: forty two rats were randomly assigned (7/group). G1, (-ve) control, G2, (+ve) control rats were injected with Cisplatin (6 mg/kg body weight) for one time, G3,4,5,6 rats injected and were received 7.5% of (cantaloupe, grape, and pumpkin seeds) or a mixture of all, respectively. Blood samples were collected, and the renal tissues of the rats were removed. Biological analyses were calculated.

Results: injected Cisplatin in rats increased levels of plasma cholesterol (TC), triglycerides (TG), Very low-density lipoprotein cholesterol (VLDL), (LDL), and decrease high-density lipoprotein (HDL), and caused abnormal renal functions. For the treated groups, body weight gain (BWG), food intake (FI), and feed efficiency ratio (FER) and also histologic changes improved for seeds diets groups. Serum creatinine, urea, uric acid, and nitric oxide concentrations were significantly increased at (P<0.5) in (+ve) group compared to the (-ve) group, while albumin was significantly lower at (P<0.5), in contrast to the treated groups with seeds.

Key Words: fruit seeds, renal dysfunction, lipid profile, body weight gain.
Introduction:

The kidney is a vital organ in the body. The kidneys are located on the right and left sides behind the abdominal cavity in the shape of a bean. The kidneys perform many functions of the body such as excretion, filtration, homeostasis, maintaining electrolyte balance, detoxification, and release of harmful metabolites and drugs. Several clinical conditions lead to kidney damage (World Kidney Day, 2015). The Kidney involves different cell types sifted through into the nephron, which is the basic utilitarian unit of the kidney. Any elevation that results in the loss of these cells can cause kidney damage and lead to renal failure (Barnett & Cummings, 2018). The severe damage to the kidneys subsequently leads to the death of individuals. About 10% of the world’s population is affected by chronic kidney disease (CKD), and millions die each year because they cannot get affordable treatment (World Kidney Day, 2015). Based on the prevalence of kidney disease in Egypt of 366 per million according to El Arbagy et al. (2016) considering that the population of Egypt is 90,000,000. According to Abbas et al. (2020) the prevalence of kidney disease among Egyptians was estimated at 21, 65%.

Xenobiotics, for example, cisplatin, are currently known to exert harmful impacts by means of free radical-mediated mechanisms. Cisplatin is a chemotherapy medication used to treat patients with several cancers such as bladder, ovarian, head, neck, lung, testicular, cervical, and esophageal (Michel and Menze, 2019). The administration of cisplatin is largely controlled in patients with cancer due to its association with various side effects. Acute kidney injury (AKI) is the foremost severe side effect of cisplatin-induced toxicity because high doses of cisplatin are linked to nephrotoxicity (Singh et al., 2018).

In recent years, seeds and nuts have received growing attention due to the high nutraceutical and therapeutic value of their bioactive components (Rezig et al., 2019). The ability of some of these indigenous vegetables and fruits to provide and maintain good health for us at relatively cheaper costs and availability spurs
and generates interest. Medicinal plants have been used as traditional and indigenous drugs for ages (Ratnam et al., 2017). World Health Organization (WHO) has moreover endorsed the beginning of studies to recognize and portray new herbal preparations from locally known plants and the headway of new dynamic therapeutic agents (Yadav et al., 2017). Universally, 80% of the total populace is assessed to only depend on plants and plant products for example cantaloupe, grape, and pumpkin) seeds as sources of medication (Ogbera et al., 2010).

Cantaloupe (Cucumis melo var. cantalupensis) seeds contain various vitamins, minerals, and unsaturated fats. It contains vitamin C, fiber, carbohydrate, potassium, sodium, calcium, phosphorus, iron, niacin, protein, polyunsaturated fat, and absolutely a lot of water. It also has high beta-carotene; it can fight free radicals and completely prevent cancer and tumors. This is recommended mainly in the case of anemia, atherosclerosis, gout, rheumatism, cardiovascular, kidney, and liver diseases (Ivanova, 2012). Therapeutic effects are present in cantaloupe seeds including analgesic, anti-inflammatory, and anti-oxidant effects (Chen et al., 2014).

Grape (Vitis vinifera Linn.) seeds are treated as waste if the extracts are not manufactured and it is determined that nearly 10–12 kg of grape seeds in 100 kg of wet residues (Matthaus, 2008). Grape seed is a complex mixture of polyphenols containing flavonoids, and proanthocyanidins that display multi-organ protection (Turki et al., 2016). Grape seeds are a relatively cheap source of antioxidant compounds; its proportion is 38–52% on a dry matter basis (Cadiz-Gurrea et al., 2017). Procyanidins are the most common flavonoids present in grapes. Grape seed proanthocyanidin extract (GSPE) is rich in polyphenols which play an important role as a metabolic regulator and reactive oxidative species (ROS) scavenger (Gil-Cardoso et al., 2017). GSPE significantly protects against oxidative stress damage more effectively than vitamins C, E, and beta-carotene (Hassan et al, 2013). In recent years, grape seed has become increasingly popular on the market as a nutritional supplement (Yamakoshi et
High dosage was even shown to improve renal injury in rats through its anti-oxidant and anti-inflammatory properties (Bao et al., 2015).

Pumpkin (Cucurbita maxima) seeds are largely considered agro-industrial waste (Amin et al., 2019), they serve as energy sources for nutrients with interesting nutritional properties (Abou-Zeid et al., 2018). The seeds are green consumable seeds that are rich in nutty flavor. Pumpkin seeds are a nutritional treasure as they are a robust source of good quality fat, carbohydrates, minerals, protein, fibers, various antioxidants, and other phytochemical compounds (Yu et al., 2021). Past investigations revealed that the seed has been used in customary medicine for the treatment of infections, including, diabetes, hypertension, kidney, and urinary issue (Ratnam et al., 2017; Yadav et al., 2017).

Therefore, the present study aimed to evaluate the possible therapeutic effects of cantaloupe, grape, and pumpkin seeds on Cisplatin-induced nephrotoxicity in adult male rats.

Materials and Methods
Materials
Chemicals:
Cis–diammine dichloride platinum and kits for biochemical analysis were purchased from Sigma- Aldrich Chemical Company, Cairo Governorate, Egypt.

Samples of seeds:
Cantaloupe, grape, and pumpkin seeds were purchased from the Agriculture Research Centre, Cairo, Egypt.

Methods
Preparation of cantaloupe, grape, and pumpkin seeds powder:
Cantaloupe, grape, and pumpkin seeds were cleaned to remove all impurities, washed, and dried in a drying oven at temperature 50°C for 3 days. The seeds were milled into a fine powder using a laboratory mill (LM 120 Perten Instruments, USA) (Nahed et al.,
The ground powder sieves on a 355 mesh sieve. The powder was packed in polyethylene bags and stored at ambient temperature until use (Anju et al., 2018).

**Experimental diet**

The basal diet was purchased from Al-Gomhorya Company (Cairo, Egypt). It consists of casein 14%, corn seed oil 10%, salt mixture 3.5%, vitamin mixture 1%, corn starch 56.7%, sucrose 10%, fiber 5%, and choline chloride 0.25% according to Reeves et al., (1993)

**Experimental animals**

Forty-two adult male Sprague- Dawley albino rats weighing (190±10)g were obtained from National Research Center in Giza-Cairo. The rats were acclimated for a week prior to enrollment in the study. They were placed in a controlled room at 23 ± 2°C, with a humidity of 60±5%, and a 12-hour light-dark cycle without any stressful stimuli. All rats were housed individually in metallic cages under healthy environmental conditions and had free access to water and a standard diet. The experimental protocols were approved by the Animal-Humane ethics committee of the National Institute of Nutrition in Cairo.

**Chemical analysis**

Proximate analysis was carried out to assess moisture, protein, fat, ash, and fiber content of cantaloupe, grape, and pumpkin seeds were performed using the standard methods of the Association of Official Analytical Chemists (AOAC, 2005). The proximate analysis was performed in triplicate to obtain a mean value of all nutrients.

Carbohydrate content was calculated by the by difference:

\[
\text{Carbohydrate content (\%)} = 100 - (\text{Moisture\%} + \text{Fat\%} + \text{Protein\%} + \text{Ash\%} + \text{Fiber \%})
\]
Phytochemicals analysis

- **Determination of total phenolic content**
  The total phenolic content (TPC) of cantaloupe, grape, and pumpkin seeds was determined using the Folin-Ciocalteu’s method in Bhalodia et al., (2011). The unknown sample concentration was determined in terms of mg GAE/g.

- **Determination of DPPH activity**
  The antioxidant activity of extracts was calculated in terms of DPPH (2,2-diphenyl-1-picryl-hydrazin-hydrate) activity using the method of Saavedra et al., (2015).

**Induction of renal dysfunction:**

Cis-Diammine Dichloride Platinum (CDDP) has been used to induce renal dysfunction. Thirty-five rats were injected intraperitoneally with a single dose of Cis-Diammine Dichloride Platinum (6 mg/kg body weight for one time) was dissolved in physiological saline solution (1mg/ml) within 1 hour before injection according to Iseri et al., 2007 and Liu et al., 2017.

**Experimental protocol**

The rats were assigned randomly into 6 equal groups (7 rats per group). **Group 1**, untreated rats (the negative control group) rats were fed on a basal diet for 6 weeks, **Group 2**, (the positive control group) rats were injected with Cis-Diammine Dichloride Platinum (6 mg/kg body weight) for one time according to Liu et al., 2017, and were fed on a basal diet for 6 weeks, **Group 3**, Rats were injected with Cisplatine (6 mg/kg body weight) and received 7.5% cantaloupe seeds (Mohammed et al., 2015) for 6 weeks, **Group 4**, Rats were injected with Cisplatine (6 mg/kg body weight) and received 7.5% grape seeds for 6 weeks, **Group 5**, Rats were injected with Cisplatine (6 mg/kg body weight) and received pumpkin seeds for 6 weeks, **Group 6** Rats were injected with Cisplatine (6 mg/kg body weight) and received 7.5% a
mixed dose of cantaloupe, grape, and pumpkin seeds for 6 weeks. 7.5% of cantaloupe, grape, and pumpkin seeds were added instead of corn starch. The rats were weighed on the first day of the experiment and at the end of the experiment. They were housed individually in cylindrical wire cages.

**Body weight gain (B.W.G %)**

The body weight of each rat was measured by a weighing scale of electronic digital balance with an accuracy of 0.1 gram (Pushton, Henan, China), and recorded at the beginning, twice weekly in the first four weeks, and then once weekly in the following two weeks. The total diet consumed per group during the period of the experiment was calculated by subtracting the diet remaining for each at the end of the interval of weighing from that allocated to the rats at the start of the interval of all groups feed wastage was subtracted from that allocated to the rats.

**Organs weight**

The organs (liver–kidney) were excised, rinsed in chilled saline solution, then blotted on filter paper, and weighed separately to calculate the absolute and relative organs weight (Li et al., 2021).

**Collection of blood samples:**

At the end of the treatment period of 6 weeks, animals were fasted for 12-16 hours and were sacrificed under light diethyl ether anesthesia. Blood samples were collected in heparinized tubes from the hepatic portal vein by cardiac puncture. Blood was centrifuged at 3500 r.p.m. for 15 min. (was used for serum preparation and the prepared serum was stored at -20°C) for various biochemical analyses (Moke et al., 2015).
Biological studies:

Food intake, body weight gain% (BWG %), feed efficiency ratio (FER) according to Chapman et al. (1959) Using the following equation.

\[ \text{Final weight} - \text{Initial weight} \]
\[ \text{BWG} \% = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \]

\[ \text{The gain in body weight (g/day)} \]
\[ \text{FER} = \frac{\text{Food Intake (g/day)}}{\text{Organ weight}} \times 100 \]

\[ \text{The relative weight of organs as a} \% = \frac{\text{Organ weight}}{\text{Animal body weight}} \times 100 \]

Biochemical analysis:

Serum was used to estimate total cholesterol (TC) and high-density lipoprotein (HDL) were determined according to the colorimetric method described by MacLachlan et al., (2000). Total lipid was evaluated by method Knight et al., (1972). Determination of triglycerides (TG) in serum was done by using a Cayman colorimetric assay kit (Cole et al., 1997). Serum low-density lipoprotein (LDL) was calculated from the values of (TC), HDL, and triglycerides using Friedewald equation: \[ \text{LDL (mg/dl)} = \text{TC} - (\text{HDL-c} + \text{TG}/5) \] (Ahmadi et al., 2008). Very low-density lipoprotein cholesterol (VLDL) was determined by method Friedewald et al., (1972). Serum nitric oxide (NO) was evaluated by nitrite reeducates method using Total Nitric Oxide Kit (Beyotime, Haimen, China, S0023) (Cortas and Wakid, 1990). Uric acid was determined by method Fossati et al., (1980). Serum urea was measured according to the modified Berthelot - Searcy method Henry, (1991). Serum creatinine activity was determined
using the application of the Jafe reaction (Wilson and Walker, 2000). Albumin was evaluated by method Doumas et al., (1971).

**Histological analysis:**
After taking the blood samples, an abdominal incision was made and the kidneys were separated from the adipose tissue surrounding them. The kidney specimens were immersed rapidly in neutral buffered formalin for 36 hours. The fixed specimens were trimmed and dehydrated in ascending grades of ethyl alcohol, cleared in xylene, finally embedded in paraffin wax. Sections were cut using a microtome (4-6) microns (um) thickness and stained with Hematoxylin and Eosin (H&E) for examining microscopically (Akomolafe et al., 2020). The following scoring system was used for the histopathological assessment of tissues under light microscopy: 0 = normal kidney, 1 = minor injury (0–5%), 2 = moderate injury (5–25%), 3 = moderate injury (25–75%), and 4 = severe injury (75–100%) (Colbay et al., 2010).

**Statistical analysis**
The obtained data of biological evaluations were statistically analyzed and were expressed as mean ± standard deviation, and comparison was done using one-way analysis of variance and Duncan's multiple range tests. Significant differences between different groups were accepted at p ≤ .05 (Snedecor and Cochran, 1967).
Results and Discussion

Table (1): Gross chemical composition of cantaloupe, grape, and pumpkin seeds (% on DWT)^a

<table>
<thead>
<tr>
<th>Types of Seeds</th>
<th>Moisture %</th>
<th>Protein %</th>
<th>Fat %</th>
<th>Ash %</th>
<th>Fiber %</th>
<th>Carbohydrate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantaloupe seeds</td>
<td>5.95&lt;sup&gt;b&lt;/sup&gt;± 0.27</td>
<td>20.31&lt;sup&gt;a&lt;/sup&gt;± 1.36</td>
<td>29.21</td>
<td>3.14&lt;sup&gt;a&lt;/sup&gt;± 1.47</td>
<td>28.10&lt;sup&gt;a&lt;/sup&gt;± 0.17</td>
<td>13.29&lt;sup&gt;b&lt;/sup&gt;±0.77</td>
</tr>
<tr>
<td>Grapes seeds</td>
<td>9.91&lt;sup&gt;b&lt;/sup&gt;± 0.29</td>
<td>11.41&lt;sup&gt;b&lt;/sup&gt;± 1.37</td>
<td>16.71&lt;sup&gt;b&lt;/sup&gt;± 1.49</td>
<td>2.93&lt;sup&gt;b&lt;/sup&gt;± 0.19</td>
<td>33.38&lt;sup&gt;a&lt;/sup&gt;± 0.50</td>
<td>25.66&lt;sup&gt;a&lt;/sup&gt;±0.89</td>
</tr>
<tr>
<td>Pumpkin seeds</td>
<td>6.97&lt;sup&gt;b&lt;/sup&gt;± 0.28</td>
<td>28.40&lt;sup&gt;a&lt;/sup&gt;± 1.38</td>
<td>29.33</td>
<td>4.40&lt;sup&gt;b&lt;/sup&gt;± 1.48</td>
<td>18.26&lt;sup&gt;a&lt;/sup&gt;± 0.18</td>
<td>13.36&lt;sup&gt;b&lt;/sup&gt;±0.79</td>
</tr>
</tbody>
</table>

* dwt basis= dry weight basis
Each value is expressed as the mean± SD (n=3)
Means in the same column with different letters are significantly different at P≤ 0.05

The mean values for the chemical composition of cantaloupe, grape, and pumpkin seeds are tabulated in Table (1). Moisture content was found in the range of 5.95-9.91% for seeds. Hence the low moisture content of seeds indicates their stability against microbial attack and potential longer shelf life (Nishant and Neeraj, 2018). The protein content was low in grape seeds, followed by, cantaloupe and pumpkin seeds. The fat content in seeds ranged from 16.71 to 35.33%. The high-fat content of seeds makes them valuable for their use as a vibrant commercial source of edible oil (Arunima and Vivek, 2021). Ash content of a food product is an index to the nutritive value (mineral content, safety, and quality) (Agoreyo et al., 2011). The ash content of seeds varied from 2.93–4.40. Dietary fiber plays several roles including increasing the shelf life of food products (Kurek and Wyrwisz, 2015). According to (Schneeman, 2002) crude fiber contributes to a healthy digestive and metabolic system in human. Carbohydrate values were 13.29, 22.66, and 22.54 in cantaloupe, grape, and pumpkin seeds respectively. The high carbohydrate content that the samples indicate is a good source of energy for the body.
Hence, nutritionists can recommend the application of dried foods into energy foods (Sultana et al., 2015). The results in the present study are consistent with the previous observations of (Ren et al., 2013) for cantaloupe seeds, Hanaa et al., (2015) for grape seeds, and Arunima and Vivek (2021) and Krimer, (2020) for pumpkin seeds.

Table (2): Total phenolic compounds and antioxidant activity of cantaloupe, grape, and pumpkin seeds (% on DWT)*

<table>
<thead>
<tr>
<th>Types of Seeds</th>
<th>Total phenolic (mg GAE/g)</th>
<th>Antioxidant activity (DPPH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantaloupe seeds</td>
<td>51&lt;sup&gt;a&lt;/sup&gt;± 0.67</td>
<td>14&lt;sup&gt;a&lt;/sup&gt;± 0.47</td>
</tr>
<tr>
<td>Grapes seeds</td>
<td>59&lt;sup&gt;a&lt;/sup&gt;± 0.34</td>
<td>21&lt;sup&gt;a&lt;/sup&gt;± 0.44</td>
</tr>
<tr>
<td>Pumpkin seeds</td>
<td>50&lt;sup&gt;a&lt;/sup&gt;± 0.39</td>
<td>13&lt;sup&gt;a&lt;/sup&gt;± 0.41</td>
</tr>
</tbody>
</table>

* dwt basis= dry weight basis
Each value is expressed as the mean± SD (n=3)
Means in the same column with different letters are significantly different at P≤ 0.05

In the present study, the total phenolic and antioxidant activity of cantaloupe, grape, and pumpkin seeds were shown in Table (2). This study has demonstrated that the total phenolic compounds in seeds ranged from 50-95 (mg GAE/g). The value of total phenolic compounds is closed to those reported by Rababah et al., (2008) who found that the total phenols of different grape seed cultivars extract ranged from 4.66 to 5.12g/100g. Grape seeds are richer in phenols than skins or pulp (Canals et al., 2008). It was well known that phenolic acids act as antioxidants not only because they are able to donate hydrogen or electrons but also, stable radical intermediates, which prevent oxidation of various food components, especially fatty acids and oils (Hanaa et al., 2015). Seeds showed a slight difference in antioxidant activity with the maximum value for the grape seeds (21) and the minimum value for the pumpkin seeds (13). Antioxidants and total phenolic compounds act as non-enzymatic antioxidants that essentially help in eradicating. Reactive oxygen species (ROS) benefit plants as well as human health (Kiani et al., 2021). These
results are in agreement with the results of Akomolafe et al. (2020) who reported TPC 32.90 mg GAE/g in the pumpkin seeds.

Table (3): Effect of feeding cantaloupe, grape, and pumpkin seeds on body weight gain (B.W.G%), feed intake (FI), and feed efficiency ratio (FER) of Cisplatin injected rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial body weight (g)</th>
<th>Final body weight (g)</th>
<th>Body weight gain (g)</th>
<th>B.W.G %</th>
<th>Feed intake (g) (FI)</th>
<th>Feed efficiency ratio (FER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>194 ±1.32</td>
<td>262 ±2.71</td>
<td>68 ±11.13</td>
<td>35.05 ±0.18</td>
<td>714 ±31.84</td>
<td>0.095 ±0.002</td>
</tr>
<tr>
<td>Control (-ve)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>193 ±1.75</td>
<td>237 ±2.04</td>
<td>44 ±4.45</td>
<td>22.79 ±0.838</td>
<td>588 ±55.82</td>
<td>0.075 ±0.001</td>
</tr>
<tr>
<td>Control (+ve)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>191 ±3.82</td>
<td>241 ±1.05</td>
<td>50 ±6.09</td>
<td>26.18 ±1.019</td>
<td>627 ±21.78</td>
<td>0.079 ±0.001</td>
</tr>
<tr>
<td>Group 4</td>
<td>191 ±4.03</td>
<td>244 ±7.24</td>
<td>53 ±3.52</td>
<td>27.75 ±0.793</td>
<td>630 ±61.36</td>
<td>0.084 ±0.001</td>
</tr>
<tr>
<td>Group 5</td>
<td>192 ±3.9</td>
<td>250 ±7.18</td>
<td>58 ±4.51</td>
<td>30.21 ±0.862</td>
<td>672 ±42.45</td>
<td>0.086 ±0.002</td>
</tr>
<tr>
<td>Group 6</td>
<td>193 ±6.62</td>
<td>252 ±5.96</td>
<td>59 ±1.34</td>
<td>30.57 ±1.039</td>
<td>673 ±43.75</td>
<td>0.088 ±0.003</td>
</tr>
</tbody>
</table>

Means in the same column with different letters are significantly different at P ≤ 0.05.

Data presented in Table 3 showed that there was a significant (p ≤ .05) reduction in the B.W.G of cisplatin-induced nephrotoxic untreated group (+ve) when compared with normal control (-ve) or treated groups with different seeds (3, 4, 5, and 6). It could be noticed that there is no significant difference between the values of B.W.G on groups 3, 4. Also, there is no significant difference between groups 5 and 6. Group 6 recorded the best result of all treatments as compared to the (+ve) group. This is in simultaneousness by Nematbakhsh et al., (2013) who found that Cisplatin-incited nephrotoxic untreated rodents exhibited
tremendous decreases in body weight and augmentations in kidney/body weight proportion when appeared differently in relation to the control group. The decrease in body weight observed in cisplatin-induced nephrotoxic untreated rats may be due to a decrease in urine concentrating ability secondary to a decrease in the papillary hypertonicity as reported by some researchers. Grape, cantaloupe, pumpkin seeds, and a mixture of all seeds administration had apparent therapeutic effects on body weight and kidney/body weight proportion in comparison with cisplatin-induced nephrotoxic untreated rats. Data presented in the same Table 3 illustrate that control (+ve) had FI (588 ±55.82g). There was a difference significantly (P<0.05) between control (+ve) and normal rats control (-ve). Also, the mean values of groups 3, 4, 5, and 6 were significantly higher than control (+ve) which were 627±21.78, 630±61.36, 672 ±42.45, and 673±43.75 respectively. There is no significant difference between the 3, 4, 5, and 6 groups in FI. It is clear from Table 3 that group 6 had a significantly higher mean value ±SD of FER than control (+ve) and all treatment groups (3, 4, 5, and 6). The obtained results are in the same trend as Bakr, (2009), Shehata, (2012), Riad, (2014), and Elbanna, (2014) for hepatic rats. Also, Abd El-Meged and Al-Shehri (2020), and Mohammed et al., (2015) found in hepatic rats a gradual increase in relative BWG, FI, and FER when feeding on cantaloupe, and pumpkin seeds.
### Table (4): Effect of feeding cantaloupe, grape, and pumpkin seeds on liver and kidney weight of rats

<table>
<thead>
<tr>
<th>Groups</th>
<th>Liver weight (g)</th>
<th>Kidney weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 Control (-ve)</td>
<td>3.26 ±0.47</td>
<td>0.98 ±0.07</td>
</tr>
<tr>
<td>Group 2 Control (+ve)</td>
<td>4.04 ±0.06</td>
<td>1.57 ±0.21</td>
</tr>
<tr>
<td>Group 3</td>
<td>3.87 ±0.66</td>
<td>1.31 ±0.25</td>
</tr>
<tr>
<td>Group 4</td>
<td>3.98 ±0.37</td>
<td>1.17 ±0.25</td>
</tr>
<tr>
<td>Group 5</td>
<td>3.77 ±0.22</td>
<td>1.1 ±0.05</td>
</tr>
<tr>
<td>Group 6</td>
<td>3.56 ±0.48</td>
<td>0.99 ±0.33</td>
</tr>
</tbody>
</table>

Means in the same column with different letters are significantly different at P≤ 0.05.

It could be noticed in Table (4) that, in the cisplatin-induced nephrotoxic untreated group, there was a significant (P≤.05) increase in the liver and kidney weight in comparison with the control (-ve) group. However, the feeding on cantaloupe, grape, and pumpkin seeds inclusive diet prevented this effect of cisplatin by significantly (P≤.05) decreased kidney weights in comparison with the cisplatin-induced nephrotoxic untreated group, though the decrease was not up to the control level. Nevertheless, there was no statistical difference between the rats in groups (+ve, 3, 4, 5). Also, there was no statistical difference between the rats in group 6 compared to the control (-ve) group. The rise in kidney weight proportion showed that the kidneys of cisplatin-induced nephrotoxic untreated rats were harmed (Lin et al., 2018). It has been reported that toxic kidneys gain weight as the damage increases (Haghigi et al., 2012). These results are in agreement with those reported by Riad (2014), and Elbanna (2014) who found in hepatic rats that an increase in all organs weight
increased, while treatment with tested plants reversed such a change.

Date presented in Table (5) showed that injection of Cisplatin led to a significant (P<0.05) increase in (TC), (VLDL), (LDL), (TG), and (TL) and a significant (P<0.05) decrease in (HDL) in rats. Feeding by cantaloupe, grape, pumpkin seeds and a mixture of all seeds significantly decreased the (TC), (VLDL), (LDL), (TG), and (TL) but significantly increased (HDL) when compared to (+ve) control rats. These results are in agreement with those reported by Zamani et al., (2007) who found in hyperlipidemic New Zealand rabbits that the pulp and the seeds of Citrullus colocynthis were assessed for their effects on the lipid profile. In the treated groups (3, 4, 5, 6), lipid profiles were significantly decreased when compared to the control group (P<0.05). These results are in agreement with those reported by Talabani and Tofiq (2012), who found a significant drop in serum total cholesterol and triglyceride observed at 120 h after the first administration of colocynth seeds oil. The present results are also in agreement with Nicolle et al., (2003) concluded that pumpkin seeds consumption modifies cholesterol absorption and these effects could be interesting for cardiovascular protection. Also, he showed that feeding the pumpkin seeds diet resulted in a decrease of cholesterol and triglycerides in plasma in animals fed on cholesterol-supplemented diets.
Data were presented in **Table 6** showed that intraperitoneal administration of cisplatin prompted renal harm in the untreated group as appeared by significant (P<0.05) ascent in serum creatinine, urea, uric acid, and nitric oxide levels just as significant (P<0.05) decline in serum albumin levels in contrast with the control (+ve) group. Feeding by cantaloupe, grape, pumpkin seeds, and a mixture of all seeds significantly reduced these concentrations in (3, 4, 5, 6) groups compared with the control (+ve) nephrotoxic group. Creatinine, synthesized in the liver, passes into the circulation where it is taken up almost entirely by the skeletal muscles. Its retention in the blood is evidence of kidney impairment. Therefore, the reduced levels of creatinine in serum may imply that the seed mixture had interfered
with creatinine metabolism and its eventual excretion from the
blood. Urea is the main product of protein catabolism. The
increase in serum urea level in the cisplatin group indicates
impairment in the normal kidney function of the animal, as the
mechanism of removing it from the blood might have been
affected. It may also be an indication of dysfunction at the
glomerular and tubular levels of the kidney (Barakat, 2011).

Table (6): Effect of feeding cantaloupe, grape, and pumpkin seeds on
renal function tests in serum

<table>
<thead>
<tr>
<th>Groups</th>
<th>Albumin (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>Urea (mg/dl)</th>
<th>Uric acid (mg/dl)</th>
<th>Nitric oxide (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (-ve)</td>
<td>3.12 ±0.98</td>
<td>0.52 ±0.88</td>
<td>18.99 ±1.94</td>
<td>1.55 ±0.18</td>
<td>11.97 ±0.89</td>
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<tr>
<td>Group 2</td>
<td></td>
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<tr>
<td>Control (+ve)</td>
<td>2.38 ±0.41</td>
<td>1.95 ±0.27</td>
<td>29.17 ±1.16</td>
<td>2.93 ±0.18</td>
<td>27.50 ±1.84</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
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<tr>
<td></td>
<td>3.06 ±0.58</td>
<td>0.73 ±0.22</td>
<td>21.07 ±0.51</td>
<td>1.62 ±0.41</td>
<td>13.26 ±1.00</td>
</tr>
<tr>
<td>Group 4</td>
<td></td>
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<tr>
<td></td>
<td>3.09 ±0.32</td>
<td>0.69 ±0.09</td>
<td>20.36 ±0.42</td>
<td>1.61 ±0.33</td>
<td>13.10 ±0.84</td>
</tr>
<tr>
<td>Group 5</td>
<td></td>
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<tr>
<td></td>
<td>3.05 ±0.27</td>
<td>0.74 ±0.09</td>
<td>21.21 ±0.30</td>
<td>1.63 ±0.16</td>
<td>13.81 ±1.43</td>
</tr>
<tr>
<td>Group 6</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>3.10 ±0.46</td>
<td>0.68 ±0.91</td>
<td>19.19 ±0.33</td>
<td>1.58 ±0.14</td>
<td>13.04 ±3.32</td>
</tr>
</tbody>
</table>

Means in the same column with different letters are significantly different at P ≤ 0.05

These results in Table 6 agree with that reported by Abd
Elwahab, (2021) who reported that there was a trend in lower
levels of rising in serum creatinine and urea after treatment with
grape, guava seeds extract, and a mixture of both. Increased levels
of serum urea, creatinine which usually occurs in certain forms of
infection and in chemical toxicity sufficient result in the
glomerular filtration are significantly indicated by compromising
renal function (Yadav et al., 2016). The increase in the level of
urea and creatinine in serum as observed in cisplatin-induced
untreated rats in this study suggests compromised functional integrity of the kidney. Hypoalbuminemia is a strong predictor of death in patients with renal failure as it is the most abundant protein in renal urine. Patients with lower serum albumin levels have consistently higher morbidity rates (Viswanathan et al., 2004). The significant decrease in serum albumin in untreated rats induced by cisplatin also indicated renal impairment. However, pretreatment with the dietary inclusion of pumpkin seeds inhibits the nephrotoxic effect of cisplatin. This was demonstrated by a significant decrease in urea and creatinine levels in the dietary pumpkin seeds intake groups compared to the untreated group with cisplatin-induced nephrotoxicity. It also increased low albumin levels indicating the seeds’ protective ability against kidney damage as shown in a report by Lin et al. (2018), and Yadav and Upasani, (2018). On the contrary, these results disagree with that reported by Al-Ghaithi et al., (2004) who found that Citrullus colocynthis (Handal) plant extract did not have any effect on blood urea. The obtained results in Table 6 showed a significant (P<0.05) decrease in Albumin level in the control (+ve) group compared to the control (-ve) and treated groups. Meanwhile, the groups treated with cantaloupe, grape, pumpkin seeds, and a mixture of all seeds exhibited no significant difference in albumin, creatinine, urea, uric acid, and nitric oxide as compared with the control (-ve) group.

Histological examination of kidney sections stained with H&E from the normal control (-ve) rats (Group 1) revealed a normal appearance of glomeruli and proximal and renal tubules. Previous studies confirmed that cisplatin may cause glomerular wounds, tubular necrosis, and damage (Khan, Khan, & Sahreen, 2012). This is in line with the outcomes of the current study which indicated various histological alterations including congestion of inter-tubular blood capillaries and renal blood vessels (Figure 1b) with perivascular cellular infiltrations in the renal cortex with vacuolar degeneration in the wall of renal blood vessels (Figure 1b).
Tubular damage was estimated as moderate to severe based on the Klausner classification (black arrow). Our findings were in line with Prerna et al., (2021), and Al-Rashidy et al., (2018) who showed that using cisplatin causes the architectural loss of renal tubules with peritubular dilatation along with severe vascular congestion. Cisplatin-induced renal nephrotoxicity occurs due to either cisplatin being poorly soluble at acidic pH so it precipitates in renal tubules and induces tubular injury or its metabolites or
due to its inhibitory effect on dihydrofolate reductase enzyme (Rizk et al, 2018).
Also, histological examination of the kidney tissues obtained from the treated groups with cantaloupe, grape, and pumpkin seeds and a mixture of all seeds, revealed that no histopathological changes in dilatation/atrophy were seen in the proximal and distal tubules as illustrated in Fig. 1. Similar findings were reported previously by Barakat et al. (2020). Tubular epithelium appeared normal, Figure 1(c, d, e, f). Similar data were recorded by Yun et al., (2020) and Gulsum et al., (2012) in grape seeds who recorded that administration of grape seed decreased the cisplatin-induced nephrotoxicity by increasing antioxidant enzymes in rats. The powerful antioxidant activity of grape seed extract could protect the kidney against induced nephropathy (Ozkan et al., 2012).
Also, these results agree with Amin et al., (2014) for pumpkin seeds who demonstrated that pumpkin seeds have significantly announced improvement of renal structures with as well as attenuated histopathological alterations in cisplatin-injected rats. Due to decrease to decreased renal acidity. So, renal histological changes improved.

Conclusion
In conclusion, Cisplatin consumption causes severe histopathological changes in kidney tissues in rats. Feeding the cantaloupe, grape, and pumpkin seeds have a therapeutic effect on renal damage induced by chronic Cisplatin administration. Future studies may be suggested to evaluate the effectiveness and advantages of using other seeds that have a therapeutic effect on injected Cisplatin rats.

References

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induced nephrotoxicity in adult male albino rats. J. Nephropharmacol. 7(2), 156-163.


تقييم التأثير العلاجي لبذور الشمام والعنب والقزح على السمية الكلوية التي يسببها السيسبلاتين في الفئران

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المستخلص:

السيسبلاتين هو دواء علاجي كيميائي يستخدم لعلاج مرضى السرطانات. التأثير الثاني الرئيسي الناتج عن علاج السيسبلاتين هو السمية الكلوية. الهدف من هذه الدراسة هو تقييم التأثير العلاجي المحتمل لبذور الشمام والعنب والقزح على السمية الكلوية لدى الفئران المحقونة بالسيسبلاتين. المواد والطرق: تم اختيار 42 من الفئران بشكل عشوائي (7 لكل مجموعة)، مجموعة (1): فئران (المجموعة الضابطة السالبة) جرذان تم تغذيتها على الوجبة الأساسية، مجموعة (2): (المجموعة الضابطة الموجبة) جرذان تم حقنها بالسيسبلاتين (6 مجم/كم من وزن الجسم) مرة واحدة فقط، المجموعات (3، 4، 5، 6) جرذان تم حقنها وكذلك تغذت على 7.5% من بذور كل من (بذور الشمام والعنب والقزح) على أو خليط منهم على التوالي، تم إجراء التحليل الكيميائي والمواد الكيميائية النباتية لبذور الشمام والعنب والقزح. وكذلك تم أخذ عينات الدم، وراثة الأنسجة الكلوية من الفئران. تم حساب التحليلات البيولوجية، النتائج: أظهرت النتائج أن حقن السيسبلاتين أدى إلى ارتفاع مستويات الكوليسترول الكلى، والجليسيدرات الثلاثية، والبروتين منخفض الكثافة، والبروتين عالي الكثافة وكذلك تسبب في خلل في وظائف الكلي، بالنسبة للمجموعات المعالجة التي تغذت على البدار عند وزن الجسم ووزن الكلى والكبد والكولسترول الشام، ونسبة كفاءة التغذية، وكذلك التغيرات النسيجية. أيضاً زاد تركز الكرياتينين والبوتريدين وحمض البوليك وأكسيد النتريك زيادة معنوية عند قيمة أقل من 5 في الفئران التي تم حقنها بالسيسبلاتين (المجموعة الموجبة) مقارنة بالمجموعة السالبة الضابطة، بينما تركز الكرياتينين سجل انخفاضاً معنويًا عند قيمة أقل من 5 ، على عكس المجموعات المعالجة بالبذور.

الكلمات المفتاحية: بذور الفاكهة، الفشل الكلوي ، مستوي الدهون، وزن الجسم.