Inhibitory Effects of Grape Seeds Powder, Extract and Oil on Gentamicin Induced Nephrotoxicity in Rats

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Abstract

This study was designed to determine the inhibitory effect of grape seeds powder, extract and oil on gentamicin-induced nephrotoxicity in rats. The study was carried out on 30 adult albino male rats Sprague-Dawley strain were classified into two groups: The first group (n= 6) left as normal control group(-ve), fed on basal diet, the second group(n= 24) injected with gentamicin (100 mg/kg/day for 7 days i.p). These animals were divided into 4 groups 6 rats each of these, control (+ve) group and 3 groups were treated with grape seeds powder (10 % of diet ), grape seeds extract (300mg/kg b.w. orally by stomach tube) and grape seeds oil (4 ml/kg b.w. orally by stomach tube) respectively.

The treatment period was designed for eight weeks. The results revealed that, Gentamicin injection induced marked nephrotoxicity as evidenced by significant elevation in serum levels of creatinine, urea, uric acid, A/G ratio, MDA, renin hormone, phosphorus and potassium, with significant reduction in serum levels of total protein, albumin, globulin, (SOD), (GPX), (GST), catalase antioxidant enzymes, erythropoietin hormone (EPO), vitamin D and Ca. While the rat groups treated with grape seeds powder, extract and oil showed significant improvement of the levels of serum total protein, albumin, globulin, kidney tissue superoxide dismutase (SOD), glutathione peroxidase (GPX), glutathione transferase (GST), catalase antioxidant enzymes, erythropoietin hormone (EPO) and vitamin D, and significant decrease in serum creatinine, urea, uric acid, albumin/globulin ratio, kidney tissue malondialdehyde (MDA), renin hormone, phosphorus and potassium compared with control(+ve) group. In conclusion, feeding rats with grape seeds powder, extract and oil may significantly reduce nephrotoxicity, So this study recommend the use of grape seeds especially grape seeds oil or grape seeds extract for humans suffering nephrotoxicity, could be of value.

Key words : Grape seeds, Grape seeds extract, Oil, Nephrotoxicity, kidney damage, Gentamicin, Rats.

Introduction

Antibiotics are the most widely used drugs. These drugs can prevent many problems caused by infections. However, antibiotics can have side effects and damage various body organs, including the liver, kidney, brain, blood, skin, eyes, mouth and others (Ayatollahi, 2005).

Gentamicin (GM) is an aminoglycoside antibiotic, used to treat many types of bacterial infections, particularly those caused by gram-negative bacteria (Nykjaer et al., 2009). It is highly effective against gram negative bacilli with a concentration dependent antibacterial action and post-antibiotic effect (ability to suppress bacterial growth for a period of time after the drug level has fallen below the minimal inhibitory concentration (MIC) of the bacteria) (Wiesenfeld and
Aminoglycosides, like GM have been widely used in clinical situations because of its efficacy and low cost. However, aminoglycosides present a serious drug induced nephrotoxicity which is linked to their accumulation in renal cortex and their capacity to bind the phospholipids and to induce intracellular lesions. Evidence suggests that aminoglycoside induced nephrotoxicity occurs after few days of therapy (Sweileh, 2009).

Nephrotoxicity is a major complication characterized by functional alterations including inhibition of protein synthesis, reduced glutathione depletion, lipid peroxidation and mitochondrial damage. Oxidative damage is thought to be one of the main mechanisms involved in nearly all chronic renal pathologies. Administration of gentamicin to rats induced a marked renal failure, characterized with a significant increase in plasma creatinine and urea concentrations. A significant increase in kidney MDA and a decrease in GSH concentrations were observed in gentamicin-treated rats (Fauconneau et al., 1995).

Grape seed extract has long been recognized to possess many properties, including antioxidant, anti-inflammatory, anticarcinogenic, platelet aggregation inhibiting, and metal chelating properties (Bagchi et al., 1998).

Grape seeds which are produced of grape fruit industries contain polyphenol members of the family of proanthocyanidins. Structurally, the proanthocyanidins are a group of complex compounds made up of oligomers and polymers of polyhydroxyflavan-3-ol monomer units (Rice-Evans et al., 1996). Grape seeds also contain lipids, protein, carbohydrates, besides 5% to 8% polyphenols, mainly flavonoids including gallic acid, the monomeric flavan-3-ols catechin, epicatechin, gallocatechin, epigallocatechin, and epicatechin 3-O-gallate, and procyanidin , dimers, trimers and more highly polymerized procyandin (Shi et al., 2003).

Grape seeds powder is an effective anti-aging drug in preventing the oxidative stress associated loss of membrane surface charge, which thereby maintains the erythrocyte membrane integrity and functions in elderly (Purushotham et al., 2005).

Grape seeds extracts contain exceptionally high amounts of total polyphenols (10.3-11.1% on a dry weight basis), and indicate that wine industry by-products, including grape seeds but also red grape pomace and stems, are very rich sources of antioxidant polyphenols compared with other agri-food solid wastes, and therefore their exploitation as a source of added-value products may be more cost-effective and merits a profounder investigation (Dimitris et al., 2007).

Grape seed oil has a very high level of antioxidant vitamin E (60-120 mg/100g), which makes the oil very stable. The antioxidant property is claimed to be the mechanism of hepatoprotective activity. The grape seed oil exhibits a variety of interesting properties such as reducing platelet aggregation, prevents hypertension caused by sodium excess, and normalizes lesions occurring from obesity and diabetes (Bagchi et al., 2002). Grape seed oil contains tannins at levels higher than other seed oils 0.8–1.5% unsaponifiable lipids, mainly esters as β-sitosterol, campesterol and stigmasterol (Rao, 1994).

The objective of this study was to investigate the inhibitory effect of grape seeds consumption either as powder, extract or oil against gentamicin induced nephrotoxicity in rats.
Materials and Methods

Materials:

Grape seeds (*Vitis vinifera*): Grape samples were obtained from local market in Mansoura city, Egypt. The grape were taken and washed with tap water, then particles of skins and pulp adhering to the seeds were removed by hand, and the seeds were washed with tap water, dried in air then grinded into fine powders and saved in polyethylene bag and stored under freezing.

Gentamicin: Gentamicin (Garamycin® injection), an amino glycoside antibiotic, was obtained from Memphis Company for Pharmaceutical and Chemical Industries, Cairo, Egypt. It is dispensed in the form of ampoules, each containing 40 mg/mL of gentamicin sulphate. Gentamicin is given to rats in dose a 100 mg/kg/day for 7 days intraperitoneally for inducing renal damage according to previous studies as reported by (Farombi and Ekor 2006).

Experimental Animals: Thirty male albino rats of Sprague Dawley strain were purchased from Laboratory Animal Colonies, Pharmacology Departement Faculty of Medicine, Mansoura University. The average weight was 140 ± 10g.

Standard Diet: Standard diet was prepared according to (NRC, 1995).

Kits: were obtained from Biodiagnostic Co. Egypt.

Chemicals: were purchased from EI-Gomhorya Company, El-Mansoura city, Egypt.

Methods:

Extraction of the hydro-alcoholic extracts:
The extraction procedure for the hydro-alcoholic extract was carried out according to Charles et al.(1993), 250 g of sample under investigation were macerated in one liter of ethanol overnight at room temperature, then filtered and the crude extract was collected. Another portion of 1000ml of ethanol were added to each residue of samples and boiled for 2 h under refluxing in a water bath and then filtered. The filtrate was collected to the previous crude extract. In the same manner 1000 ml portion of distilled water were added to each residue of samples and left at room temperature overnight, then filtered. The filtrate was added to the previous crude extract. Another volume of distilled water was added to the residue, boiled for 2 h under reflux condenser, and filtered. The hot water filtrate was added to the previous crude extract to form the hydro-alcoholic crude extract. Each of hydro-alcoholic extracts was evaporated to dry under reduced pressure at 60oC, and then the dried hydro-alcoholic extracts were individually kept in dark bottles and stored in a deep freezer until usage.

Oil extraction: Grape seeds powder was de-oiled with hexane (one part powder to 10 parts hexane, w/v). The mixture was shaken for 10 minutes at room temperature and left at room temperature over night; the extract was separated from the solid by Buckner apparatus. The residue was re-extracted with the same solvent four times, and then the solvent removed under reduced pressure by using a rotary evaporator.
Chemical Study: Moisture, protein, fat and ash of grape seeds were determined according to the methods of the (AOAC 2000), while total carbohydrates were calculated by difference as following: Carbohydrates % = 100 - (moisture % + protein % + fat % + ash %).

Experimental Rats Design: Rats were kept under observation for seven days for adaptation and fed on standard diet. Then 6 rats kept as normal control group and 24 rats were injected with gentamicin in dose a 100 mg/kg/day for 7 days intraperitoneal to induce renal damage and classified into control positive group and 3 treated rat groups. One group was treated with grape seeds powder (10 % of diet). The second group was treated with grape seeds extract (300mg/kg b.w. orally by stomach tube) and the third group was treated with grape seeds oil (4 ml/kg b.w. orally by stomach tube) according to Maheswari and Rao (2005). Food and water was provided ad-libtum. Food intake was recorded daily and body weight of rats was measured once weekly. At the end of the experimental period (eight weeks), the rats were anaesthetized by diethyl ether and sacrificed. Blood samples were collected from jugular vein and centrifuged at 3000rpm for 15 min to obtain serum. Animals were quickly dissected and the kidney samples were immediately removed, washed, minced and homogenized in ice-cold sodium, potassium phosphate buffer (0.01 M, pH 7.4) containing 1.15% KCl in homogenizer. The homogenates were centrifuged at 3000rpm for 15 min for further biochemical analysis.

Laboratory Analysis: Serum creatinine, urea and uric acid were estimated according to Bonsens and Taussky (1984), Patton and Crouch, (1977) and Fossati et al. (1980), respectively. Serum total protein, albumin and globulin were determined as described by the method of Weichselbaum (1946), Bartholomev and Delany (1966), and Coles (1974), respectively. Kidney superoxide dismutase (SOD), glutathione peroxidase (GPX), glutathione transferase (GST), malondialdehyde (MDA) and catalase were determined according to Beuchamp and Fridovich (1971), Tapple (1978), Moran et al. (1979), Uchiyama and Mihara (1978) and Cohen et al. (1970), respectively. Renin and erythropoietin (EPO) renal hormone and vitamin D were estimated according to Van-Kats et al. (2001), Valerie et al. (2006) and Wilkie et al. (1958) respectively. Estimation of some serum mineral (Ca, P and K) samples according to Pupsa et al. (1994).

Calculation of Some Parameters: Food efficiency ratio was determined according to the method of Chapman et al (1950), while albumin/globulin (A/G) ratio was calculated using albumin and globulin values for each individual sample.

Statistical Analysis: The obtained data were statistically analyzed using computerized SPSS (Statistic Program Sigmastat, Statistical Soft-Ware, SAS Institute, Cary, NC). Effects of different treatments were analyzed by one way ANOVA (Analysis of variance) test using Duncan’s multiple range test and p<0.05 was used to indicate significance between different groups (Snedecor and Cochran, 1967).

Results and Discussion

The chemical composition of grape seeds was illustrated in Table 1. The main constituents of grape seeds were moisture which was (5.98 g/100g) and ash was (2.62 g/100g). The value of protein (7.51 g/100g) but the value of fat was (18.23 g/100g) while the value of carbohydrate (65.66g/100g). The results of elementary chemical composition of grape seeds agreed with those reported by Kamel et al., (1985) revealed that grape seeds, comprise 20 to 26% of the pomace, have a high protein content. They also have 10 to 20% oil, with high vitamin E content, which has very
important effects on human health. Grape seed oil mainly consists of triglycerides (TG), which are rich in unsaturated fatty acids, such as oleic and linoleic acids, compared to other oil-rich seeds. The poly-unsaturated fatty acids such as linoleic and linolenic acids are essential for the human metabolism because of the lack of enzymes responsible for synthesis of these fatty acids. For this reason, they could be used as foods, and so its oil (Barron et al., 1988; Schuster, 1992 and Ohnishi et al., 1990).

The statistical data in Table 2 showed that, Gentamicin induced nephrotoxicity rat group (control +ve) showed a significant decrease in final body weight, body weight gain and food efficiency ratio compared with normal control (-ve) group. The rat groups treated with grape seeds powder, extract and oil showed a non significant difference in weight gain, food intake and FER compared with normal group but showed a significant increase in final body weight, body weight gain and food efficiency ratio compared with control (+ve) group. The results are in agreement with Maldonadu et al., (2003) who revealed that the significant and progressive weight loss in gentamicin treated rats may possibly be due to the injury of renal tubules and the subsequent loss of the tubular cells to reabsorb water, leading to dehydration and loss of body weight. Polyphenols present in grape seed might have reduced food intake and prevented weight gain. In vitro experiments showed that polyphenols stimulated lipolysis, which is hypothesized to be particularly effective in overweight subjects who might show a reduced lipolysis (Tebib et al., 1996; Ardevol et al., 2000 and Fisher et al., 2002). The efficacy of grape-seed extract may be effective in reducing energy intake, while satiety is sustained. The mechanism of grape seed in the short term could be due to delayed absorption of the diet, which might support sustained satiety while subjects ingest less food (Langhans and Scharrer, 1987; McCarty and Scharrer, 1994 and Kamphuis et al., 2003). Grape seed oil is an important source for the production of conjugated linoleic acid (CLA), which has demonstrated to reduce body fat in several animal models, independent of the type or quantity of dietary fat consumed (Luque-Rodriguez et al., 2005).

The results in Table 3 indicated that control (+ve) rat group showed a significant increase in levels of creatinine, urea, uric acid and albumin/globulin ratio but showed a significant decrease in total protein, albumin and globulin compared with normal control (-ve) group. The rat groups treated with grape seeds powder and extract showed a significant increase in creatinine, While The rat groups treated with grape seeds oil showed non significant difference in creatinine compared with normal group. The rat groups treated with grape seeds powder showed a significant increase in urea, While the rat groups treated with grape seeds extract and oil showed non significant difference in urea compared with normal control (-ve) group. The rat groups treated with grape seeds powder and extract showed a significant increase in uric acid and showed a significant decrease in total protein compared with normal control (-ve) group. The rat group treated with grape seeds oil showed significant decrease in uric acid and showed a significant increase in total protein compared with normal control (-ve) group. On the other hand there was a significant decrease in levels of creatinine, urea, uric acid and albumin/globulin ratio but showed a significant increase in total protein, albumin and globulin in rat groups treated with grape seeds powder, extract and oil compared with control (+ve) group. This explanation is in line with the study by Hala (2012) who revealed that administration of gentamicin induced a marked renal failure, characterized with reduced glomerular function, while is reflected by marked significant increase in the serum levels of creatinine, urea and uric acid concomitant with significant decrease in serum levels of total protein. Catechin analogues such as (-) -epicatechin 3-o-gallate (ECG) and EGCG found in grape seed extract are known to have many physiological
effects, such as to exert suppressive effects on renal failure (Nakagawa et al., 2004; Yamabe et al., 2006). The free radical scavenging ability of proanthocyanidins and flavonoids present in grape seed extract (Sato et al., 2005) may account for the nephroprotective action of grape seed extract against gentamicin induced nephrotoxicity. Similar results were reported in a study by Yousef et al., (2009) in which renal toxicity was caused by cisplatin and grape seed extract was used for protection. Thus, grape seed extract indirectly corrects body homeostasis through its improvement of kidney function. In addition to those studies they studied the nephrotoxicity of grape seed extract and reported that grape seed extract has no nephrotoxicity (Abd El-wahab et al., 2008). The current study proved that grape seeds extract and oil have nephroprotective effect too, where; grape seeds extract and oil could return back the creatinine and urea levels to normal and significantly reduced the elevation in uric acid level.

The results in Table 4 indicated that control (+ve) rat group showed significant decrease in kidney SOD, GPX, GST and catalase but showed a significant increase in kidney MDA compared with normal control (-ve) group. The rat groups treated with grape seeds powder and extract showed a significant decrease in kidney SOD and GPX, While The rat group treated with grape seeds oil showed significant increase in kidney SOD and GPX compared with normal control (-ve) group. The rat groups treated with grape seeds powder, extract and oil showed significant decrease in kidney GST and catalase, while it showed a significant increase in kidney MDA compared with normal control (-ve) group. On the other hand the rat groups treated with grape seeds powder, extract and oil showed significant increase in kidney SOD, GPX, GST and catalase while it showed a significant decrease in kidney MDA compared with control (+ve) rat group. The results are in agreement with Yang et al., (1995) who reported that Gentamicin increased superoxide anion production, hydrogen peroxide and hydroxyl radicals by kidney mitochondria. Free radicals cause peroxidation of membrane phospholipids, protein denaturation and DNA chain break. Most significant biological damage by reactive oxygen metabolites are reaction with unsaturated lipid peroxidation and thus their peroxidation. This effect caused changes in membrane fluidity and finally membrane molecules are permeable to even as large as enzymes (Inoue and Kawanishi., 1995). A significant increase in kidney MDA and a decrease in glutathione concentrations were observed in gentamicin treated rats and severe proximal renal tubular necrosis followed by renal failure (Fauconneau et al., 1995). Antioxidants are compounds that act as inhibitors of the oxidation process and are found to inhibit oxidant chain reaction at small concentration and thereby eliminate the threat of pathological processes. Phenolic compounds present in medicinal plants have been reported to possess powerful antioxidants activity (Maldonadu et al., 2003). Grape seeds are rich sources of monomeric phenolic compounds such as catechin, epicatechin and dimeric, trimeric and tetrameric proanthocyanidins (Shin et al., 2010). These molecules possess a structure that confers on them an antioxidant property, which has been demonstrated to exert a novel spectrum of biological, pharmacological, therapeutic, and chemoprotective effects against oxygen free radicals and oxidative stress, which can be used as herbal remedies especially for controlling oxidative damages (El-Ashmawy et al., 2007and Dulundu et al., 2007). Several studies have indicated that extracts obtained from grape seed inhibit enzyme systems that are responsible for the production of free radicals, and that they are antimutagenic and anticarcinogenic (Pinheiro et al., 2010). For this reason, grape seed extract is widely consumed as a dietary supplement in addition to the chemotherapeutic agents in cancer treatment (Çetin et al., 2008).

Grape seed extracts have been reported to possess a broad spectrum of pharmacological, and therapeutic effects including anti-inflammatory activity and reduced apoptotic cell death (Ashtiyani et al., 2013). Grape seed extracts are known to have high antioxidant activity and contain numerous polyphenols. The polyphenols have been shown to
have positive effects on vascular injury, it is also known to have free radicals scavenging and antimutagenic activity (Çetin et al., 2008). Grape seeds oil is an extract by-product obtained from the grape seed and it contains a variety of biologically active species used for protection against oxidative stress induced by free radicals and ROS (Baiges et al., 2010 and Ashtiyani et al., 2013). In relation to their polyphenol compounds, GSO contains mainly flavonoids, all involved in ameliorating the oxidative stress in vitro and in vivo through their ability to balance the oxidant-antioxidant status (Sehirli et al., 2008). Procyanidolic oligomers (leucocyanidines, LCs) extracted from grape seeds are known to have antioxidant and antimutagenic activities, and a protective effect against cardiovascular disease. Administration of LCs markedly decreased the activities of NADPH-cytochrome P450 reductase, P4501A1, P4501A2, and P4503A4, but significantly increased the activities of glutathione S-transferase and phenolsulfotransferase in rat liver. However, the activities of antioxidant enzymes were not affected by LC administration. The inhibition of P450s and increases in phase II enzyme activities indicate a role for LCs as a chemopreventive agent against toxic or carcinogenic metabolites of P450 isozymes (Seo-Kyung et al., 2001).

The statistical data in Table 5 presented that, control (+ve) rat group showed significant increase in renin hormone but showed a significant decrease in erythropoietin (EPO) renal hormone and vitamin D compared with normal control (-ve) group. The group treated with grape seeds powder showed a significant increase in renin hormone. While the groups treated with grape seeds extract and oil showed significant decrease in renin hormone compared with normal control (-ve) group. The groups treated with grape seeds powder, extract and oil showed significant decrease in erythropoietin (EPO) renal hormone and vitamin D compared with normal control (-ve) group. On the other hand, the groups treated with grape seeds powder, extract and oil showed significant decrease in renin hormone but showed a significant increase in erythropoietin (EPO) renal hormone and vitamin D compared with the control (+ve) rat group. The results are in agreement with Li et al. (2002) and Yuan et al. (2007) who revealed that renin angiotensin system (RAS) in the kidney is a mandatory mediator of renal injury. Vitamin D hormone has a negative regulatory effect on renin angiotensin system by suppressing renin expression. It is shown that vitamin D receptor-absent mutant mice develop more severe renal damage (e.g., interstitial fibrosis, increased albuminuria, and glomerulosclerosis) than wild-type counterparts in diabetic state Zhang et al., (2008) or under postrenal acute kidney injury, because of enhanced activation of the RAS in the kidney (Zhang et al., 2010). Gentamicin induced kidney damage is linked with lipid peroxidation, and protein oxidation in the renal cortex with reducing activity of renal antioxidant enzymes (Stojiljkovic et al., 2008 and Lopez-Novoa et al., 2011). Grape seed extract (GSE) contains several active components including flavonoids, polyphenols, anthocyanins, proanthocyanidins and procyanidines. It contains 70-95% standardized proanthocyanidins (Ferreira and Li, 2000).

These flavonoids have demonstrated a marked spectrum of biological, pharmacological, therapeutic, and chemoprotective properties against oxygen free radicals and oxidative stress. Grape seed proanthocyanidin extract (GSPE) has more powerful antioxidative activity than other well-known antioxidants, including vitamin C, vitamin E, and gallic acid (Ariga, 2004). GSPE has various biological functions including anti-aging, potent phytochemical antioxidants, antibacterial, antiviral, antiinflammatory, anti-allergic, and vasodilatory actions. Various reports have shown that long term dietary supplementation of polyphenols improved the cognitive performance in aged rats (Alia et al., 2003; Balu et al., 2006; Abdelgawad et al., 2012).
The statistical data in Table 6 presented that the control (+ve) rat group showed significant decrease in serum Ca while showed significant increase in serum P and K values compared with normal control (-ve) group. The groups treated with grape seeds powder, extract and oil showed non-significant changes in serum Ca while showed significant decrease in P and K values compared with the (+ve) control group. The results are in agreement with Finn(1977) and Laurent et al., (1988) who revealed that kidneys are responsible for the elimination of metabolic waste and the control of the amount and composition of the body fluids. Nephrotoxicity can result in systemic toxicity causing: decreased ability to excrete body wastes, inability to maintain body fluid and electrolyte balance and decreased synthesis of essential hormones. Gentamicin increases generation of reactive oxygen species (ROS) such as superoxide anions, hydroxyl radicals, hydrogen peroxide, and reactive nitrogen species in the kidney (Balakumar et al., 2008).

Kidneys play a central role in the regulation the balance of body salt and water, hence disordered regulation of renal functions is responsible for the altered balance of salt and water. The increase of Potassium appeared to be due to reduced excretion of K aggravated by leakage of intracellular potassium into blood stream as a result of gentamicin induced lesions in renal tubular epithelium (Heibashy & Abdel Moneim, 1999). Serum phosphorus was significantly increased, conversely, serum calcium was significantly decreased in gentamicin injected rats. Similar results were obtained by Hruska et al., (1975) and Burnier et al., (1996).

In conclusion, gentamicin induced nephrotoxicity in rats and the consumption of grape seeds especially oil and extract can improve efficiency of kidney function and the healthy status because of their antioxidant effect.
Table (1):
Elementary chemical composition of grape seeds sample (g/100g).

<table>
<thead>
<tr>
<th>Chem. Comp.</th>
<th>Moisture</th>
<th>Ash</th>
<th>Protein</th>
<th>Fat</th>
<th>Carbohydrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grape Seeds</td>
<td>5.98±0.14</td>
<td>2.62±0.17</td>
<td>7.51±0.52</td>
<td>18.23±0.47</td>
<td>65.66±0.22</td>
</tr>
</tbody>
</table>

Each value is the mean of three replicates ± SD.

Table (2):
Nutritional indicators of normal control and renal damage rat groups treated with grape seeds powder, extract and oil.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Groups</th>
<th>Initial weight (g)</th>
<th>Final weight (g)</th>
<th>Weight gain (g)</th>
<th>Food intake(g)</th>
<th>FER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal control (-ve)</td>
<td>141.67±1.52 a</td>
<td>191.33±4.16 bc</td>
<td>51.00±2.64 a</td>
<td>16.84±0.23 ab</td>
<td>0.049±0.002 ab</td>
</tr>
<tr>
<td></td>
<td>Positive control (+ve)</td>
<td>144.00±2.64 a</td>
<td>163.00±5.56 d</td>
<td>22.67±4.50 b</td>
<td>15.33±0.32 b</td>
<td>0.025±0.004 c</td>
</tr>
<tr>
<td></td>
<td>grape seeds powder</td>
<td>143.67±4.04 a</td>
<td>184.00±2.64 c</td>
<td>50.00±6.08 a</td>
<td>16.70±0.32 b</td>
<td>0.049±0.005 ab</td>
</tr>
<tr>
<td></td>
<td>grape seeds extract</td>
<td>147.33±3.78 a</td>
<td>200.00±5.29 abc</td>
<td>45.67±2.08 a</td>
<td>16.72±0.04 b</td>
<td>0.044±0.001 b</td>
</tr>
<tr>
<td></td>
<td>grape seeds oil</td>
<td>145.00±2.00 a</td>
<td>200.67±5.68 a</td>
<td>51.67±1.52 a</td>
<td>17.32±0.38 a</td>
<td>0.053±0.003 a</td>
</tr>
</tbody>
</table>

Mean values in each column having different superscript (a, b, c, d) are significant.
Means with the same letter are insignificantly different.
### Table (3):

Effect of grape seeds powder, extract and oil on some renal functions parameters of the experimental rat groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Creatinine (mg/dl)</th>
<th>Urea (mg/dl)</th>
<th>Uric acid (mg/dl)</th>
<th>Total protein (g/dl)</th>
<th>Albumin (g/dl)</th>
<th>Globulin (g/dl)</th>
<th>A/G ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control (-ve)</td>
<td>0.68±0.01</td>
<td>27.65±1.32</td>
<td>2.78±0.06</td>
<td>8.05±0.051</td>
<td>4.52±0.12</td>
<td>3.53±0.07</td>
<td>1.28±0.06</td>
</tr>
<tr>
<td>Positive control (+ve)</td>
<td>2.07±0.02</td>
<td>72.12±1.95</td>
<td>5.87±0.05</td>
<td>5.11±0.078</td>
<td>3.19±0.02</td>
<td>1.86±0.06</td>
<td>1.64±0.07</td>
</tr>
<tr>
<td>Grape seeds powder</td>
<td>0.79±0.02</td>
<td>40.52±0.78</td>
<td>3.62±0.04</td>
<td>7.60±0.042</td>
<td>3.73±0.11</td>
<td>3.90±0.09</td>
<td>0.95±0.04</td>
</tr>
<tr>
<td>Grape seeds extract</td>
<td>0.74±0.02</td>
<td>29.18±1.13</td>
<td>3.06±0.05</td>
<td>7.90±0.020</td>
<td>3.95±0.04</td>
<td>3.87±0.03</td>
<td>1.03±0.01</td>
</tr>
<tr>
<td>Grape seeds oil</td>
<td>0.71±0.01</td>
<td>26.23±0.67</td>
<td>2.33±0.03</td>
<td>8.17±0.070</td>
<td>4.07±0.04</td>
<td>4.11±0.03</td>
<td>0.98±0.00</td>
</tr>
</tbody>
</table>

Mean values in each column having different superscript (a, b, c, d) are significant. Means with the same letter are insignificantly different.
Table (4):
Effect of grape seeds powder, extract and oil on SOD, GPX, GST, CAT and MDA in kidney tissue of the experimental rat groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>SOD (μg/mg)</th>
<th>GPX (μg/mg)</th>
<th>GST (μg/mg)</th>
<th>CAT (μg/mg)</th>
<th>MDA (mmol/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control (-ve)</td>
<td>82.40±0.48  b</td>
<td>70.43±0.41  b</td>
<td>3.81±0.05  a</td>
<td>3.91±0.07  a</td>
<td>10.12±0.70 e</td>
</tr>
<tr>
<td>Positive control (+ve)</td>
<td>38.82±0.19  e</td>
<td>29.49±0.34  e</td>
<td>1.86±0.06  c</td>
<td>1.64±0.03  e</td>
<td>17.80±0.08  a</td>
</tr>
<tr>
<td>grape seeds powder</td>
<td>72.05±0.08  d</td>
<td>66.21±0.11  d</td>
<td>2.94±0.03  d</td>
<td>2.65±0.05  d</td>
<td>12.27±0.05  b</td>
</tr>
<tr>
<td>grape seeds extract</td>
<td>79.34±0.24  c</td>
<td>69.59±0.37  c</td>
<td>3.14±0.02  c</td>
<td>3.09±0.04  c</td>
<td>11.32±0.27  c</td>
</tr>
<tr>
<td>grape seeds oil</td>
<td>89.78±0.16  a</td>
<td>73.15±0.06  a</td>
<td>3.61±0.09  b</td>
<td>3.53±0.08  b</td>
<td>10.77±0.15  d</td>
</tr>
</tbody>
</table>

Mean values in each column having different superscript (a, b, c, d) are significant. Means with the same letter are insignificantly different.
### Table 5:

Effect of grape seeds powder, extract and oil on serum renin, erythropoietin (EPO) renal hormone and vitamin D of the experimental rat groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Renin (ng/ml/h)</th>
<th>EPO (ng/ml/h)</th>
<th>vitamin D (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control (-ve)</td>
<td>2.34±0.07 ( ^c )</td>
<td>4.39±0.02 ( ^a )</td>
<td>48.65±0.13 ( ^a )</td>
</tr>
<tr>
<td>Positive control (+ve)</td>
<td>4.68±0.03 ( ^a )</td>
<td>1.22±0.03 ( ^e )</td>
<td>19.63±0.16 ( ^e )</td>
</tr>
<tr>
<td>Grape seeds powder</td>
<td>2.75±0.08 ( ^b )</td>
<td>2.98±0.03 ( ^d )</td>
<td>36.65±0.15 ( ^d )</td>
</tr>
<tr>
<td>Grape seeds extract</td>
<td>2.11±0.03 ( ^d )</td>
<td>3.33±0.10 ( ^c )</td>
<td>42.07±0.06 ( ^c )</td>
</tr>
<tr>
<td>Grape seeds oil</td>
<td>1.93±0.03 ( ^e )</td>
<td>3.57±0.06 ( ^b )</td>
<td>44.07±0.35 ( ^b )</td>
</tr>
</tbody>
</table>

Mean values in each column having different superscript (a, b, c, d) are significant. Means with the same letter are insignificantly different.
Table (6): Effect of grape seeds powder, extract and oil on serum Ca, P and K of the experimental rat groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Ca (mg/dl)</th>
<th>P (mg/dl)</th>
<th>K (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control (-ve)</td>
<td>12.34±0.80</td>
<td>4.15±0.33</td>
<td>40.65±0.53</td>
</tr>
<tr>
<td>Positive control (+ve)</td>
<td>8.48±0.60</td>
<td>8.60±0.40</td>
<td>65.84±0.55</td>
</tr>
<tr>
<td>grape seeds powder</td>
<td>9.67±0.68</td>
<td>6.23±0.69</td>
<td>44.97±0.42</td>
</tr>
<tr>
<td>grape seeds extract</td>
<td>9.30±0.62</td>
<td>5.47±0.49</td>
<td>44.48±0.43</td>
</tr>
<tr>
<td>grape seeds oil</td>
<td>10.45±0.52</td>
<td>4.84±0.45</td>
<td>40.51±0.61</td>
</tr>
</tbody>
</table>

Mean values in each column having different superscript (a, b, c, d) are significant. Means with the same letter are insignificantly different.
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التأثير المثبط لمسحوق مستخلص وزيت بذور العنب على السمية الكلوية في الفنر

نتيجة الحقن بالجانتسين

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الملخص العربي

أجريت الدراسة الحالية لتقدير الدور المثبط لمسحوق مستخلص وزيت بذور العنب على السمية الكلوية الناتجة عن الحقن بالجانتسين. وقد أجرى البحث على 20 من فرنان التجارب قسمت هذه الفنر إلى مجموعتين أساسيتين: تركتا الأولى فنران طبيعية وهي المجموعة الضابطة الأساسية والتي نتجت على الغذاء الأساسي والمجموعة الثانية (24 فرن) تم حققيهم بالجانتسين (200 ملجم/ كجم/ اليوم لمدة سبع أيام داخل الغشاء البر ileti) ثم قسمت الفنر إلى أربعة مجموعات وهي مجموعة ضابطة موجبة تغذى على الغذاء الأساسي وثلاث مجموعات معالجة بكل من (مسحوق بذور العنب 10% من الوزن) واستخدام مستخلص بذور العنب 200 ملجم/ كجم من وزن الجسم عن طريق الأوروب المعد (و/و زيت بذور العنب) لكل كجم من وزن الجسم عن طريق الأوروب المعد (و/و زيت بذور العنب) وقد كانت هذه التجربة 8 أسابيع.

ولقد أوضحت النتائج المطلوبة عليها أن الحقن بمادة الجانتسين قد أحدث سمية كلورية درجة عالية. كما يتضح ذلك من خلال درجات أرتفاع ذو دلالة إحصائية في متوسط احتمال الدم من الكرياتينين والبروتيون، وحضيض البروتين والملونات، وهرمون الستيرويد وأيأي الوارد والبوتاسيوم مع حدوث انخفاض ذو دلالة إحصائية في متوسط احتمال الدم من البروتين الكلي والأليافين والجلوتانين والانزيمات الضابطة للكبد. استخدمت جينات الأيض، والجلوتانين بروكسيدين والأليافين تراسفيراز والكلفاز وكما، وتم استخدام إنزيمات اتاحة متوسط احتمال الدم من البروتين الكلي والأليافين، والجلوتانين وذلك بزيادة معنوية. أيضاً أظهرت ارتفاع معنوي في كل من الارتجامات الضابطة للكبد بزيادة معنوية في مستويات سوبر أوميد، والجلوتانين بروكسيدين والأليافين تراسفيراز والكلفاز. الكفاءة أظهرت زيادة معنوية في هرمون الأزينبروتيون، والكلفاز. بينما تم قليل من الأكياس بذور العنب ومستخلص بذور العنب في متوسط الذرة بالكبير في خلال واسعة النطاق يشير إلى تحسين وظائف الكلي لدى حيوانات التجربة.

من خلال النتائج المطلوبة عليها في هذه البحث توصى الدراسة بدعم الوجبات الخاصة بمراض الكلي بذور العنب خاصة زيت بذور العنب ومستخلص بذور العنب لما له من تأثير في تحسين وظائف الكلي لدى حيوانات التجربة.