

Potential Preventive and Treatment Effects of Arak (*Salvadora Persica*) Against Gentamicin-induced Kidney Disorders in Male Albino Rats

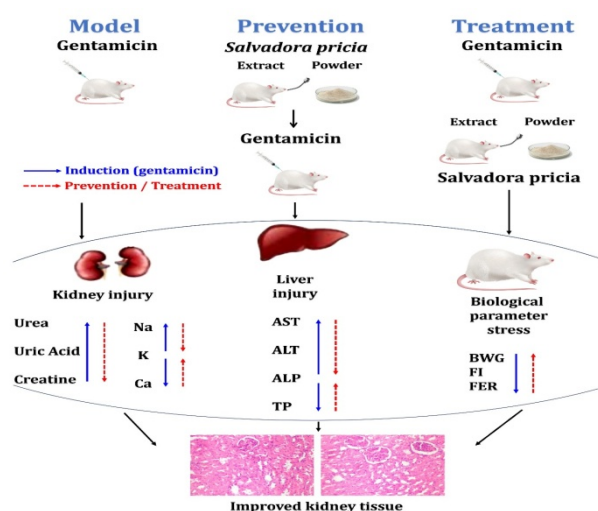
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Abstract With a long history in folk medicine for centuries, arak (*Salvadora persica*) was used in different fields including oral hygiene, food, cosmetics, fuel, and even as a medicine. In an attempt to open new horizons for the use of this plant in medical fields, the current study was conducted with the aim of exploring the potential preventive and treatment effects of *Salvadora persica* on kidney disorders induced by gentamicin in male albino rats. To achieve this purpose, sixty six male albino rats were divided into three main groups. The first group (negative control) was fed basal diet (BD), the second group (treatment group) was injected with gentamicin to cause kidney damage, then it was treated with *Salvadora persica* powder (SPP) or ethanol extract (SPEE), the third group (prevention group) was treated with SPP or SPEE, followed by injection with gentamicin. In addition, the last two groups contained within their subgroups a positive control group that was injected with gentamicin and fed BD. At the end of the experiment, data indicated that gentamicin-treated rats exhibited significantly ($p \leq 0.05$) decreased in biological parameters (BWG, FI and FER) and increase in liver functions (AST, ALT and ALP), kidney functions (urea, uric acid and creatinine), and serum lipid profile (TGs, TC and LDL-C) compared to the normal group. However, intervention with SPP or SPEE (2.5 and 5.0 % g/100g diet) in feeding rats for 26 days led to significantly ($p \leq 0.05$) improvements in all of those parameters by different rates. The rate of improvement was higher in the treatment group than the prevention group. Also, all treatments in which SPP was used recorded greater effectiveness compared to the SPEE. In all treatment, the rate of improvement in both biological and biochemical tested parameters of the nephrotoxic rats were exhibited a dose- dependent manner. These findings provide a basis for the use of SPP or SPEE for the prevention and treatment of nephrotoxicity. Data also supports the benefits of *Salvadora persica* supplementation to diet in alleviating disorders/side effects associated with kidney antibiotics, including gentamicin.



Keywords: Swak, body weight gain, kidney functions, liver functions, serum lipid profile, minerals, urine, histology

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1. Introduction

Kidney is a vital and principal organ which has a wide range of functions, including remove waste products and drugs from the body, balance the body's fluids, release hormones that regulate blood pressure, produce an active form of vitamin D that promotes strong, healthy bones, eliminate toxins, and control the production of red blood cells [1]. It receives blood through the renal artery and passes through a kidney structure called the nephron, where waste and excess water exit the bloodstream. Kidney disease occurs when the nephrons inside the kidneys, which act as blood filters, are damaged. This leads to the buildup of waste and fluids inside the body [2]. Drug overdoses, accidental or from chemical overloads of drugs such as antibiotics or chemotherapy, may also cause the onset of chronic kidney disease (CKD). Overuse of common drugs such as aspirin, ibuprofen, and acetaminophen (paracetamol) can also cause chronic kidney damage [3].

CKD is a very real and growing problem, as indicated by demographic trends. The total number of treated patients has markedly increased during the last three decades all over the world including Egypt [4]. Persistent abnormalities in urine, abnormalities in structure, or reduced excretory renal function suggestive of a loss of functional nephrons are the hallmarks of CKD. Most CKD patients run the risk of developing accelerated cardiovascular disease and passing away. In many parts of the world, the limited availability of renal replacement therapy poses a challenge for individuals who develop end-stage renal disease. Low nephron count at birth, nephron loss with aging, and acute or chronic kidney injuries brought on by toxic exposures or illnesses (such as obesity and type 2 diabetes mellitus) are risk factors for the onset and progression of CKD [5]. Early detection or prevention, treating the underlying cause (if possible) to stop the disease's progression, and paying attention to unresolved secondary processes that contribute to continuous nephron loss are the main goals of CKD patient care. The mainstays of therapy include renin-angiotensin system inhibition, blood pressure regulation, and disease-specific interventions [6,7]. Diagnosis and treatment are necessary for CKD complications that impact cardiovascular health and quality of life, such as anemia, metabolic acidosis, mineral and bone disorders, secondary hyperparathyroidism and Hyperkalemia [6,8,9,10].

Several decades ago, many therapeutic strategies have been proposed to prevent or treat kidney disease and its complications, including the use of plant parts. This therapeutic approach has been used to overcome many of the problems associated with the use of pharmaceuticals (synthetic drugs), which have undesirable side effects, especially with prolonged use, in addition to the high cost that is usually beyond the reach of most low-income people like those who live in primitive and rural areas [11]. Therefore, this therapeutic strategy was used to overcome these mentioned problems, especially after our previous studies demonstrated that plant parts are an important and sustainable resource for many bioactive compounds, which represent an interesting and mostly untapped source for the development of new drugs for kidney disease [12,13,14,15].

Arak or Siwak (*Salvadora persica*) is a small, soft, light-yellow woody tree that branches to form a large leafy bush with a widely spreading crown, flexible branches, and green-yellow flowers, with a life span of 25 years. It grows in dry and desert areas, preferably with black and loamy soils, and can form up to 10% of the local vegetation in some natural habitats. Moreover, it is an evergreen perennial halophyte capable of growing under extreme conditions, from very dry environments to highly saline soils [16,17]. It possesses high potential for economic value as a source of oil and medicinal compounds. *Salvadora persica* has a long history in folk medicine dating back centuries. It has been used as a medicine, food, fuel, cosmetics, and even for dental hygiene. Previous studies on the phytochemistry of its various components have revealed a variety of bioactive compounds including alkaloids, flavonoids, glycosides, sterols, terpenes, and carbohydrates [18,19]. Elements containing sulfur as well as compounds containing sulfur are present. Furthermore, a great deal of research has been done on its biological and industrial applications. Experiments have revealed a wide range of pharmacological activities, such as wound-healing, antidepressant, antitumor, antimicrobial, antioxidant, analgesic, anthelmintic, anti-inflammatory, anti-ulcer, sedative, anticonvulsant, anti-osteoporosis, and hypo-lipidemic properties [20]. Supplementing with *Salvadora persica* in the context of gentamicin-induced nephrotoxicity and hepatotoxicity reduces oxidative stress and stops the development of gentamicin-induced acute renal and liver toxicity [21]. The antioxidant and anti-inflammatory activities of the components of the plant extract, such as flavonoids, alkaloids, glycosides, steroids, carbohydrates, tannins, and saponins, are most likely responsible for these hepatoprotective and nephroprotective qualities [22]. Despite the several studies conducted on this *Salvadora persica* and its relationship with various diseases, information regarding its various effects on kidney disease is still limited. Therefore, the present study aims to investigate the potential preventive and treatment effects of arak (*Salvadora Persica*) on kidney disorders induced by gentamicin in male albino rats.

2. Materials and Methods

2.1. Materials

2.1.1. *Salvadora Persica*

Arak or siwak (*Salvadora persica*) obtained from the Company of Agricultural Seeds, Perfumery and medical Plants (Harraz), Ahmed Maher St., El-Darb El-Ahmar, Cairo, Egypt. The plant part was botanically confirmed by plant taxonomy scientists, Faculty of Agriculture, Menoufia University, Shebin El-Kom, Egypt. The plant part is best kept in a cool, dry, and dark location to reduce oxidation of their contents,

2.1.2. Reagents and Chemicals

Gentamicin was purchased from Sigma Chemical Co., St. Louis, MO, USA. Basal diet constituents (casein, vitamin and minerals mixture etc.) supplied by Morgan Chemical Company, Cairo, Egypt. All other chemicals,

reagents and solvents (Except as otherwise stated) in analytical grade were purchased from El-Ghomhorya Company for Trading Drug, Chemicals and Medical Instruments, Cairo, Egypt.

2.1.3. Kits

Kit's assays for Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), serum urea, serum creatinine, serum uric acid, serum lipids profile (triglycerides, TGs; total cholesterol, TC; high density lipoprotein cholesterol, HDL-c) were purchased from BIODIAGNOSTIC, Dokki, Giza, Egypt.

2.1.4. Machines

UV-visible-light spectrophotometer (UV-160A; Shimadzu Corporation, Kyoto, Japan) was used for all biochemical assays. Atomic absorption spectrophotometer, type Perkin-Elmer, Model 2380, Champaign, IL was used for elements determination.

2.1.5. Animals and Housing

Animals used in this study, adult male albino Sprague-Dawley rats (150±5g per each) were obtained from the Egyptian company for the Production of Serums, Vaccines and Medicines, Helwan city, Cairo, Egypt. Rats were kept in stainless steel cages under typical laboratory conditions (23±2.0 °C temperature, 59±4.5 % relative humidity, and a 12/12 hour light-dark cycle) and kept under normal healthy conditions. All rats were fed on basal diet (BD) for two-week before starting the experiment for acclimatization.

2.1.6. Standard/Basal Diet (BD)

The basic diet prepared according to the following formula as mentioned by Reeves *et al.*, [23] as follow: protein (10%), corn oil (10%), vitamin mixture (1%), mineral mixture (4%), choline chloride (0.2%), methionine (0.3%), cellulose (5%), and the remained is corn starch (69.5%). The used vitamins and minerals mixtures component were formulated according to Reeves *et al.*, [23].

2.2. Methods

2.2.1. Preparation of *Salvadora persica* Powder and Extract

Salvadora persica barks were blended and ground into fine powder using an electric grinder (Moulinex Egypt, Al-Araby Co., Egypt), reduced to powder (20 mesh), mixed to obtain homogeneous samples and kept in dark stoppered glass bottles in a cool and dry location until used. *Salvadora persica* ethanol extract (SPEE) was prepared according to the method of Oludemi *et al.*, [24]. In brief, A 5g of *Salvadora persica* powder were extracted in a Soxhlet apparatus (Soxhelt Semiautomatic apparatus Velp company, Italy) for 4-5 h (approximately 20 min per cycle) using 95% ethanol. The solvent was evaporated under reduced pressure (rotary evaporator Büchi R-210, Switzerland) at 40°C and 50 rpm to obtain the dried solvent extract and kept at 4°C until use. The total yield of SPEE was 6.0% (w/w) in terms of the *Salvadora persica* barks powder.

2.2.2. Induction of Impaired Kidney Rat

Gentamicin (aminoglycoside antibiotics) was injected intraperitoneally for seven days to healthy male albino rats. This procedure was done to induce kidney disorders one of the side effects of gentamicin being nephrotoxicity according to Morales *et al.*, [25]. The completion of the induction process was confirmed by drawing random samples from the treated rats and assessing some vital parameters indicating infection.

2.2.3. Experimental Design

All biological experiments performed a complied with the rulings of the Institute of Laboratory Animal Resources, Commission on life Sciences, [26]. Such as illustrated in Figure 1, after the acclimatization period (14 days), rats (n=66), were randomly assigned to three main groups as follow: **First main group (G1, 6 rats)**: served as normal/negative control (Ve⁻), was fed on the BD for 31 days.

Second main group (30 rats): served as treatment group, was injected with gentamicin in day one to five days and divided into five sub groups (6 rats per each) as follow:

- Group 2 (G2) served as positive control (Ve⁺), was fed on the BD for 26 days.
- Group 3 (G3) was fed on the BD plus 2.5 % *Salvadora persica* powder (SPP) for 26 days.
- Group 4 (G4) was fed on the BD plus 5.0 % SPP for 26 days.
- Group 5 (G5) was fed on the BD plus 2.5 % *Salvadora persica* ethanolic extract (SPEE) for 26 days.
- Group 6 (G6) was fed on the BD plus 5.0 % *Salvadora persica* ethanolic extract (SPEE) for 26 days.

Third main group (30 rats): served as prevention group, divided into five sub groups (6 rats per each) as follow:

- Group 7 (G7) served as positive control (Ve⁺), was fed on the BD for 26 days then injected with gentamicin for 5 consecutive days.
- Group 8 (G8) was fed on the BD plus 2.5 % *Salvadora persica* powder (SPP) for 26 days then injected with gentamicin for 5 consecutive days.
- Group 9 (G9) was fed on the BD plus 5.0 % SPP for 26 days then injected with gentamicin for 5 consecutive days.
- Group 10 (G10) was fed on the BD plus 2.5 % *Salvadora persica* ethanolic extract (SPEE) for 26 days then injected with gentamicin for 5 consecutive days then injected with gentamicin for 5 consecutive days.
- Group 11 (G11) was fed on the BD plus 5.0 % *Salvadora persica* ethanolic extract (SPEE) for 26 days then injected with gentamicin for 5 consecutive days.

At the end of the experiments, 31 days, the rats were slaughtered under diethyl ether anesthesia after 12 hours of fasting. Blood samples were obtained through the abdominal aorta and placed in centrifuge tubes then serum was carefully separated after centrifugation at 3000 rpm for 10 minutes to assess the biochemical parameters such

as described by Schermer, [27]. Specimens of the kidney organ were taken immediately after sacrificing rats and immersed in 10% neutral buffered formalin for the histological examination.

2.2.4. Biological Evaluation

Biological evaluation of the different diets was carried out by determination of body weight gain g (BWG), feed intake (FI) daily, feed efficiency ratio (FER) calculated according to Chapman *et al.*, [28] using the following formulas: $BWG\% = (\text{Final weight} - \text{Initial weight}) / \text{initial weight} * 100$ and $FER = \text{Gain in body weight (g)} / \text{Feed Intake (g)}$.

2.2.5. Biochemical Analysis

Different tested parameters in serum were determination using the specific methods as follow: aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities according to Yound, [29], Tietz, [30], and Yound, [29], respectively. Serum total protein was determined according to Nils, [31]. Sodium (Na) and potassium (K) and calcium (Ca) content in plasma samples were determined by the adaptation the method mentioned by Singh *et al.*, [32]. Albumin was determined by a colorimetric method described by Vanessa *et al.*, [33]. Triglycerides (TGs), Total cholesterol (TC) and HDL-

Cholesterol were determined in serum according to the methods of Fossati and Prenape, [34], Richmod, [35] and Lopes-Virella *et al.*, [36], respectively. Low density lipoprotein cholesterol (LDL-c) was assayed according to the equation of Fniedewald *et al.*, [37] as follow: $LDL-c = TC - (HDL-c + TGs/5)$. VLDL (mg/dl) = Triglycerides/5. Serum urea, creatinine and uric acid were determined according to the method of Faweett and Soctt, [38], Bartles *et al.*, [39] and Barham and Trinder, [40], respectively. Urine creatinine was determined according to Kinetic method of Henery, [41].

2.2.6. Histopathological Examination

Specimens of kiney were taken immediately after sacrificing rats and immersed in 10% neutral buffered formalin. The fixed specimens were then trimmed and dehydrated in ascending grades of alcohol, cleared in xylene, embedded in paraffin, sectioned (4-6 μm thickness), stained with hematoxylin and eosin and examined microscopically [42].

2.2.7. Statistical Analysis

The data were statistically analyzed using a one-way ANOVA and a computerized costat program. The results are displayed as mean $\pm$ SD. Significant differences in treatment at ($P \leq 0.05$) were observed [43].

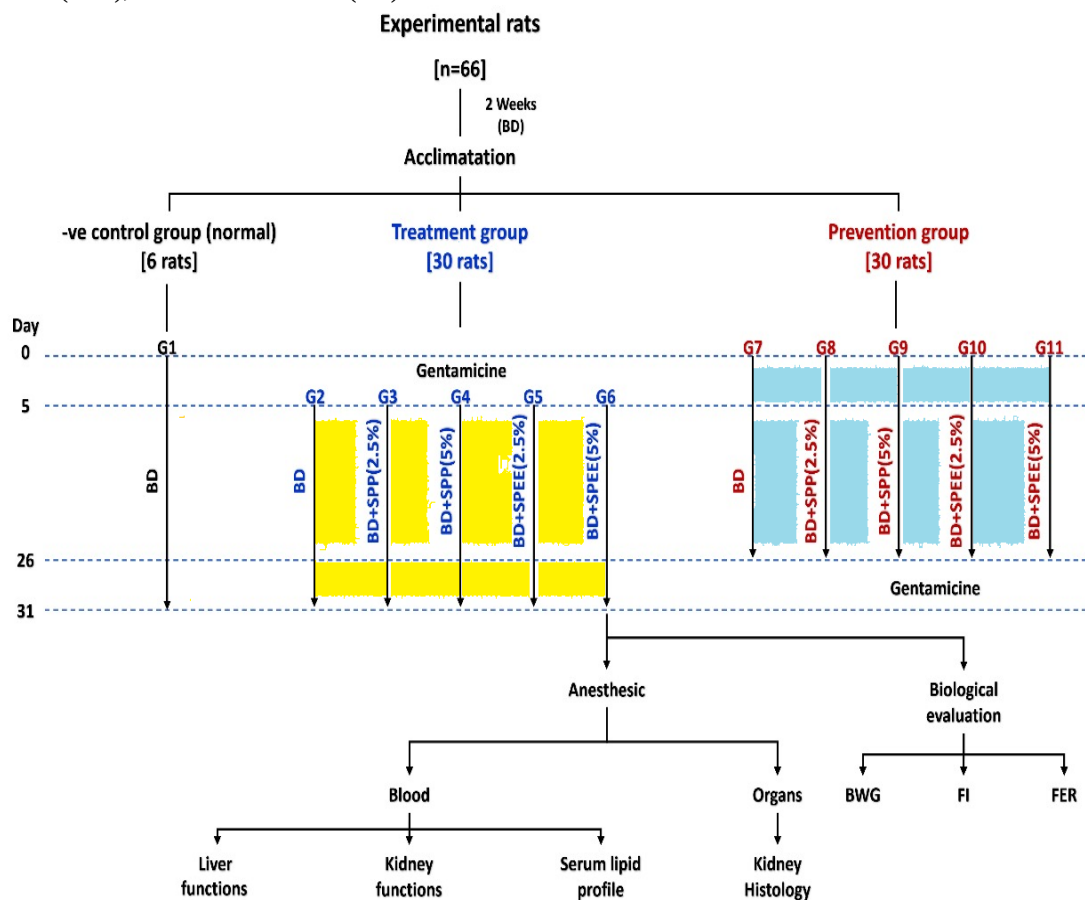


Figure 1. Experimental design of the study

3. Results and Discussion

3.1. Effect of *Salvadora persica* Powder and Its Ethanol Extract on BWG, FI and FER in Rats with Gentamicin-induced Kidney Disorders

Effect of *Salvadora persica* powder and its ethanol extract on BWG, FI and FER in rats with gentamicin-induced kidney disorders was shown in Table 1. Such data indicated that at the end of the experiment (31 days), the gentamicin-treated rats exhibited significantly ($p \leq 0.05$) decreased in BWG, FI and FER by -76.19, -34.64 and -64.29% (for treatment groups) and -80.95, -41.83 and -64.29% (for prevention groups) compared to the normal group, respectively. However, intervention with *Salvadora persica* powder and methanolic extract (2.5 and 5.0 % g/100g diet) in feeding rats for 26 days led to significantly ($p \leq 0.05$) increase on the BWG, FI and FER of the nephrotoxic rats (model control) by different rates. The rate of improvement was higher in the treatment group than the prevention group. Also, all treatments in which *Salvadora persica* powder was used recorded greater effectiveness compared to the extract of the same substance. In all treatment, the rate of increasing in BWG, FI and FER of the nephrotoxic rats were exhibited a dose-dependent manner. Such data are in agreement with several authors who reported that gentamicin induced significantly decreasing in BWG, FI and FER in rats [44]. Also, El-Agoz, and Domma *et al.*, [12,13] reported that CKD reveal significant reduction of the body weight and feed efficiency ratio due to the malnutrition as the result of poor food intake, maldigestion, malabsorption and abnormalities in the metabolism and storage of nutrients. The same direction was reported by El-Agoz, [13] who found that patients with CKD are ill and commonly lose weight. Intervention with SPP or SPEE in the protocol feeding of rats led to an improvement in BWG, FI and FER by different rates. The reason for this can be attributed to the fact that both SPP and SPEE contains many biologically active compounds (polyphenolics, flavonoids, salvadorine, cyanogenic glycosides, lignans, saponins, alkaloids, tannins, linoleic acid, stearic acid, salvadouria, vitamin C, silica, organic sulfur compound and different salts which have a significant and effective effect in this direction [14,18,19,44]. Also, Hooda *et al.*, [45] reported that STZ-diabetic rats reduced body weight which was significantly restored by root hydroalcoholic extract of *Salvadora persica*. In line with this trend, several studies have come to confirm that injected rats by kidney disorders inducers such gentamicin caused decrease in BW, FI and FER which improved by consumption of plant parts contains bioactive compounds such as found in *Salvadora persica* [9,14,15]. The higher effective of *Salvadora persica* powder which was recorded than the extract of its could be attributed to the extract with free of insoluble fibers. Like insoluble fiber can play a key role in controlling weight by making the animal feel full. Also, eating lots of insoluble fiber also helps keep the animal regular and digestive health [46,47].

3.2. Effect of *Salvadora persica* Powder and Its Ethanol Extract on Serum Lipid Profile in Rats with Gentamicin-Induced Kidney Disorders

Effect of *Salvadora persica* powder and its ethanol extract on serum lipid profile in rats with gentamicin-induced kidney disorders was shown in Table 2. Such data indicated that at the end of the experiment (31 days), the gentamicin-treated rats exhibited significantly ($p \leq 0.05$) increased in TGs, TC, LDL-c and VLDL-c by 9.86, 3.56, 45.755 and 9.86% (for treatment groups) and 113.38, 134.24, 552.66 and 113.38% (for prevention groups) compared to the normal group, respectively. The opposite direction was observed for HDL-c which decreased by the ratio of -1.0% (for treatment groups) and -55.0% (for prevention groups) compared to the normal group. However, intervention with *Salvadora persica* powder and methanolic extract (2.5 and 5.0 % g/100g diet) in feeding rats for 26 days led to significantly ($p \leq 0.05$) decrease on the TGs, TC, LDL-c and VLDL-c, and increase in HDL-c of the nephrotoxic rats (model control) by different rates. The rate of improvement was higher in the treatment group than the prevention group. Also, all treatments in which *Salvadora persica* powder was used recorded greater effectiveness compared to the extract of the same substance. In all treatment, the rate of decreasing in TGs, TC, LDL-c and VLDL-c and increasing in HDL-c of the nephrotoxic rats were exhibited a dose-dependent manner. Such data are according with that obtained by Khan *et al.*, [48], who found that *Salvadora persica* at a dose level of 500 mg/kg during 4 weeks treatment reduced serum TC, TGs, LDL-c, VLDL-c while increased serum HDL-c on diabetic rats. They also interpreted such effects by elements associated with sulphonyl urea alkaloids, which have been found in *Salvadora persica* by multiple researchers, exhibit α -glucosidase inhibitory activity as indicated by β -sitosterol, and may be responsible for the extracts hypolipidemic effects. Also, El Rabey *et al.*, [49] found that diet containing 10 g/kg and 20 g/kg of *Salvadora persica* powder reduced serum TC, TGs, LDL-c and VLDL-c and elevated HDL-c on diabetic rats. The mechanism of *Salvadora persica* on lipid profile parameters is increasing the rate of cholesterol degradation, blocking the intestinal absorption of cholesterol, increasing the removal of cholesterol as bile acids or other sterols, interfering with lipoproteins, and lowering LDL cholesterol levels through the use of flavonoids, which significantly raise LDL receptor mRNA levels and increase hepatic uptake and degradation of LDL cholesterol are some of the proposed mechanisms for altering the lipid profile [50]. Furthermore, The different biological effects (hypolipidemic, antioxidant and scavenging activities) of *Salvadora persica* are probably due to the presence of bioactive constituents such organic sulfur compounds, elemental sulfur, flavonoids, salvadorine, cyanogenic glycosides, lignans, saponins, alkaloids, tannins, linoleic acid, stearic acid, salvadouria, vitamin C, silica, and different salts cause decreasing the cholesterol absorption by deactivating the coenzyme-A

(HMG-CoA) reductase hydroxymethylglutaryl [51]. On the other side, McAnlis *et al.*, [52] found that phenolics having a high affinity for protein was bound to albumin and never incorporated into the LDL particle. Also, the possible hypocholesterolemic effects of several dietary components, such as found in *Salvadora persica* including alkaloids, polyphenoles, organic sulfur compounds, flavonoids, salvadorine, lignans, saponins, alkaloids, tannins, salvadorene etc., have attracted much interest [53].

Such compounds exert their beneficial effects on cardiovascular health including improve the serum lipid profile parameters by antioxidant, scavenging and anti-inflammatory activities [54,55,56,57,58,59]. Additionally, the presence of such bioactive compounds in *Salvadora persica* were significantly reduced LDL oxidation *in vitro* from various oxidases including 15-lipoxygenase, copper-ion and linoleic acid hydroperoxide [52,60,61,62,63].

Table 1. Effect of *Salvadora persica* powder and its ethanol extract on BWG, FI and FER in rats with gentamicin-induced kidney disorders

Groups		BWG (g/d/rat)	FI (g/d/rat)	FER
G1: Control (-ve), Normal		2.1±0.04 ^d	15.3±0.06 ^a	0.14±0.008 ^b
Treatment groups	G2: Control (+ve)	0.5±0.08 ^h	10±0.08 ^h	0.05±0.001 ^c
	G3: SPP (2.5%)	2.6±0.06 ^b	12.2±0.09 ^c	0.21±0.007 ^a
	G4: SPP (5.0%)	2.8±0.03 ^a	13.5±0.07 ^b	0.21±0.003 ^a
	G5: SPEE (2.5%)	2.5±0.03 ^c	11.8±0.04 ^{def}	0.22±0.009 ^a
	G6: SPEE (5.0%)	2.6±0.01 ^b	11.9±0.05 ^{de}	0.22±0.001 ^a
Prevention groups	G7: Control (+ve)	0.4±0.04 ⁱ	8.9±0.08 ⁱ	0.05±0.004 ^c
	G8: SPP (2.5%)	1.7±0.02 ^f	11.7±0.04 ^{ef}	0.15±0.003 ^b
	G9: SPP (5.0%)	1.85±0.034 ^e	12.00±0.029 ^d	0.15±0.004 ^b
	G10: SPEE (2.5%)	1.6±0.08 ^g	11.3±0.04 ^g	0.14±0.009 ^b
	G11: SPEE (5.0%)	1.74±0.001 ^f	11.6±0.005 ^f	0.15±0.009 ^b
LSD		0.08	0.18	0.1

Each value represents mean ± SD (n=5). Means under the same column with different prescript letters are significantly different at $p \leq 0.05$. SPP, *Salvadora persica* powder form, SPEE, *Salvadora persica* ethanol extract. BWG, body weight gain, FI, feed intake, FER, feed efficiency ratio.

Table 2. Effect of *Salvadora persica* powder and its ethanol extract on serum lipid profile in rats with gentamicin-induced kidney disorders

Groups		TGs (mg/dl)	TC (mg/dl)	HDL-c (mg/dl)	LDL-c (mg/dl)	VLDL-c (mg/dl)
G1: Control (-ve), Normal		71±0.17 ^j	73±0.88 ^j	40±0.33 ^d	18.8±0.06 ^k	14.2±0.04 ^g
Treatment groups	G2: Control (+ve)	78±0.21 ⁱ	75.6±0.08 ⁱ	39.6±0.09 ^b	27.4±0.01 ⁱ	15.6±0.08 ^b
	G3: SPP (2.5%)	62.3±0.06 ^k	70.3±0.06 ^k	40.1±0.06 ^a	17.7±0.06 ^j	12.5±0.03 ^h
	G4: SPP (5.0%)	112±0.11 ^c	79±0.14 ^g	20±0.39 ⁱ	36.6±0.07 ^g	22.4±0.02 ^{gb}
	G5: SPEE (2.5%)	89.3±0.05 ^h	77±1.11 ^h	28.5±0.06 ^d	30.6±0.03 ^h	17.9±0.05 ^e
	G6: SPEE (5.0%)	78±0.21 ⁱ	75.6±0.08 ⁱ	39.6±0.09 ^b	27.4±0.01 ⁱ	15.6±0.08 ^b
Prevention groups	G7: Control (+ve)	151.5±0.26 ^b	171±0.39 ^a	18±0.36 ⁱ	122.7±0.04 ^a	30.3±0.09 ^a
	G8: SPP (2.5%)	111.3±0.06 ^d	118.5±0.06 ^c	38.2±0.3 ^c	58.5±0.09 ^c	22.3±0.08 ^b
	G9: SPP (5.0%)	105±0.27 ^e	117±0.48 ^d	39.5±0.05 ^b	56.5±0.08 ^d	21.0±0.33 ^c
	G10: SPEE (2.5%)	89±0.33 ^f	87.1±0.02 ^e	19.5±0.08 ^g	49.8±0.06 ^e	17.8±0.37 ^e
	G11: SPEE (5.0%)	96±0.36 ^g	85.6±0.03 ^f	21.5±0.15 ^e	44.9±0.03 ^b	19.2±0.09 ^d
LSD		0.366	0.799	0.414	0.095	0.095

Each value represents mean ± SD (n=5). Means under the same column with different prescript letters are significantly different at $p \leq 0.05$. SPP, *Salvadora persica* powder form, SPEE, *Salvadora persica* ethanol extract. TGs, triglycerides, TC, total cholesterol, HDL-c, high density lipoprotein cholesterol, LDL-c, low density lipoprotein cholesterol, VLDL-c, very low density lipoprotein cholesterol.

3.3. Effect of *Salvadora persica* Powder and Its Ethanol Extract on Liver Functions in Rats with Gentamicin-Induced Kidney Disorders

Effect of *Salvadora persica* powder and its ethanol extract on liver functions (AST, ALT, ALP, and TP) in rats with gentamicin-induced kidney disorders was shown in Table 3. Such data indicated that at the end of the experiment (31 days), the gentamicin-treated rats exhibited significantly ($p \leq 0.05$) increased in AST, ALT and ALP by 139.13, 102.63 and 137.89 % (for treatment groups) and 189.13, 121.05 and 324.24% (for prevention groups) compared to the normal group, respectively. The opposite direction was observed for TP which decreased by the ratio -38.46 % (for treatment groups) and -40.00%

(for prevention groups) compared to the normal group. However, intervention with *Salvadora persica* powder and methanolic extract (2.5 and 5.0 % g/100g diet) in feeding rats for 26 days led to significantly ($p \leq 0.05$) decrease on the AST, ALT and ALP, and increase in TP of the nephrotoxic rats (model control) by different rates. The rate of improvement was higher in the treatment group than the prevention group. Also, all treatments in which *Salvadora persica* powder was used recorded greater effectiveness compared to the extract of the same substance. In all treatment, the rate of decreasing in AST, ALT and ALP and increasing in TP of the nephrotoxic rats were exhibited a dose- dependent manner. Such as reviewed by several authors medications face limitations of gentamicin due to the fact that one of the major its side effects of is creating hepatotoxicity [44]. Increased production of reactive oxygen species (ROS), which can

be seen after the use of gentamicin in cells, is effective in inducing toxic impacts of this drug on the structure and function of tissues [64,65]. For example, free radicals causes lipid peroxidation to all cell organelles membrane-bound fatty acids. Serial enzyme measurements, AST, ALT and ALP are often considered sensitive markers for determining the course of liver damage due to their presence of the cytoplasm facilitates blood flow after liver cell damage [53,66,67]. Data of the present study showed that both *Salvadora persica* powder and methanolic extract significantly ($p \leq 0.05$) reducing AST, ALT and ALP levels which demonstrating that it can prevent live cells damage. This prophylactic/curative effects could be attributed to *Salvadora persica* powder and methanolic extract content of some important nutrients and bioactive constituents such organic sulfur compounds, elemental sulfur, flavonoids, salvadorine, cyanogenic glycosides, lignans, saponins, alkaloids, tannins, linoleic acid, stearic acid, salvadorene, vitamin C, silica, and different salts [18,19,20]. In similar studies, plant parts and their extracts contains such bioactive compounds exhibit protective/treatment activities against liver injury induced by toxic chemicals and gentamicine [53,68,69,70,71]. These findings are consistent with Alam and Galal, [21] who found that hydroalcoholic extract of *Salvadora persica* reduced ALT, ALP and TP in rats which may be due to its antioxidant effect which decrease the hepatic cell damage caused by gentamicin and help in regeneration of the cell membrane. Also, Alaraj *et al.*, [72] found that *Salvadora persica* aqueous extract in the paracetamol reduced AST, ALT and ALP in rats. It may be concluded that *Salvadora persica* powder or extract reduces liver damage caused by gentamicin. This effect may be due to one or more of the following mechanisms: 1) multiple biological effects of *Salvadora persica* have been reported including antioxidant and scavenging activities, [58] 2) *Salvadora persica* extracts contained the highest amount of crude extract, which revealed high concentrations of antioxidant enzymes i.e. peroxidase, catalase, and polyphenoloxidase [73], 3) *Salvadora persica* has anti-inflammatory properties including proinflammatory cytokines, nitric oxide synthases, apoptotic pathways, and oxidative/antioxidative pathways involved in gentamicin-induced hepatotoxicity [57], and 4) ability of *Salvadora persica* extracts to reduce bilirubin levels through the extract of active regulators that increase the activity of enzymes, transporter synthesis, and steps related to bilirubin clearance pathway [69,74,75,76].

3.4. Effect of *Salvadora persica* Powder and Its Ethanol Extract on Kidney Functions in Rats with Gentamicin-Induced Kidney Disorders

Effect of *Salvadora persica* powder and its ethanol extract on serum urea, uric acid and creatinine as well as urine creatinine in rats with gentamicin-induced kidney disorders was shown in Table 4. Such data indicated that at the end of the experiment (31 days), the gentamicin-treated rats exhibited significantly ($p \leq 0.05$) increased in

serum urea, uric acid and creatinine by 96.97, 59.46 and 40% (for treatment groups) and 66.67, 45.95 and 0.00% (for prevention groups) compared to the normal group, respectively. The opposite direction was observed for the urine creatinine which decreased by the ratio -70.00 % (for treatment groups) and -30.00% (for prevention groups) compared to the normal group. However, intervention with *Salvadora persica* powder and methanolic extract (2.5 and 5.0 % g/100g diet) in feeding rats for 26 days led to significantly ($p \leq 0.05$) decrease on the serum urea, uric acid and creatinine of the nephrotoxic rats (model control) by different rates. The rate of improvement was higher in the treatment group than the prevention group. Also, all treatments in which *Salvadora persica* powder was used recorded greater effectiveness compared to the extract of the same substance. In all treatment, the rate of decreasing in serum urea, uric acid and creatinine and increasing in urine creatinine of the nephrotoxic rats were exhibited a dose-dependent manner. Urea is formed in the liver as the end product of protein metabolism. During ingestion, protein is broke down into amino acids. These amino acids are catbolized and free ammonia is formed. The ammonia is combined to form urea [66]. Urea, the major product of protein catabolism and measuring is the most popular laboratory procedure for assessing renal functions [77]. Creatinine is a catabolic product of creatine phosphate, which is used in skeletal muscle concentration. In the skeletal muscle serum creatinine levels are elevated by renal disease and dehydration [66]. Uric acid is a waste product that's created when the body breaks down chemicals called purines in food and drinks. Most uric acid dissolves in the blood, passes through the kidneys and leaves the body in urine [78]. Gentamicin induces nephrotoxicity by inhibiting protein synthesis in renal cells that specifically causes necrosis of cells in the renal proximal tubule, resulting in acute tubular necrosis, followed by acute renal failure [79]. In the current work, the intervention with *Salvadora persica* have been more efficient for reducing serum level of urea, uric acid and creatinine, the biomarkers of kidney functions stress induced by CKD. Also, kidney showed inflammation and necrosis after paracetamol treatment which was significantly reduced in mice pretreated with *Salvadora persica* [72]. A single overdose of paracetamol caused significant elevations of urea, uric acid, and creatinine compared with the control mice group. Pretreatment with *Salvadora persica* significantly prevented paracetamol -induced changes in renal biomarkers. All of such data are in accordance with many authors who reported that many bioactive compounds (dietary fiber, phenolics and flavonoids) such as found in *Salvadora persica* exhibited protective effects against gentamicin-induced nephrotoxicity in rats [12,80]. Also, Bustos *et al.*, [81] reported that flavonoids as protective agents against oxidative stress induced by gentamicin in systemic circulation. Furthermore, several authors investigated that supplementation with fiber increases fecal nitrogen excretion and lowers serum urea nitrogen concentration in chronic renal failure patients consuming a low-protein diet [13,82].

Table 3. Effect of *Salvadora persica* powder and its ethanol extract on liver functions in rats with gentamicin-induced kidney disorders

Groups		ALT (U/l)	AST (U/l)	ALP (U/l)	TP (g/dL)
G1: Control (-ve), Normal		38±0.25 ^k	46±0.27 ^j	66±0.31 ⁱ	6.5±0.04 ^a
Treatment groups	G2: Control (+ve)	77±0.31 ^b	110±0.3 ^b	157±0.14 ^b	4.00±0.14 ^c
	G3: SPP (2.5%)	47±0.24 ⁱ	62.2±0.06 ^s	76.3±0.08 ^s	4.45±0.008 ^{bc}
	G4: SPP (5.0%)	46.6±0.08 ^j	40.5±0.07 ⁱ	62.4±0.02 ^j	6.34±0.001 ^a
	G5: SPEE (2.5%)	69±0.27 ^d	72±0.29 ^f	80±0.35 ^f	4.00±0.18 ^c
	G6: SPEE (5.0%)	48±0.07 ^h	61.1±0.05 ^h	71.7±0.08 ^h	4.6±0.05 ^{bc}
Prevention groups	G7: Control (+ve)	84±0.19 ^a	133±0.17 ^a	280±1.65 ^a	3.9±0.09 ^c
	G8: SPP (2.5%)	52.3±0.08 ^s	95.3±0.03 ^c	85.1±0.02 ^e	4.4±0.04 ^{bc}
	G9: SPP (5.0%)	61.5±0.04 ^e	62.1±0.08 ^s	76.2±0.06 ^s	5.00±0.21 ^b
	G10: SPEE (2.5%)	70±0.11 ^f	84±0.16 ^d	96.2±0.01 ^c	4.00±0.93 ^d
	G11: SPEE (5.0%)	75±0.18 ^c	80±0.13 ^e	89.3±0.03 ^d	4.5±0.03 ^{bc}
LSD		0.45	0.64	0.33	0.50

Each value represents mean ± SD (n=5). Means under the same column with different prescript letters are significantly different at $p \leq 0.05$. SPP, *Salvadora persica* powder form, SPEE, *Salvadora persica* ethanol extract. ALT, alanine amino transferees, AST, aspartate aminotransferase, ALP, alkaline phosphatase, TP, total protein.

Table 4. Effect of *Salvadora persica* powder and its ethanol extract on kidney functions in rats with gentamicin-induced kidney disorders

Groups		Urea in serum (mg/dl)	Uric acid in serum (mg/dl)	Creatinine in serum (mg/dl)	Creatinine in urine (mg/dl)
G1: Control (-ve), Normal		30±0.11 ^g	3.7±0.11 ^d	0.5±0.005 ^{bc}	50±0.25 ^a
Treatment groups	G2: Control (+ve)	59±1.12 ^a	5.9±0.05 ^a	0.7±0.001 ^a	15±0.1 ^k
	G3: SPP (2.5%)	46±0.008 ^d	4.3±0.56 ^c	0.5±0.008 ^{bc}	48±0.03 ^c
	G4: SPP (5.0%)	43±0.2 ^e	3.9±0.25 ^d	0.6±0.003 ^{ab}	49±0.11 ^b
	G5: SPEE (2.5%)	54±0.25 ^f	4.5±0.33 ^{bc}	0.7±0.07 ^a	42±0.88 ^s
	G6: SPEE (5.0%)	58±0.3 ^a	4.2±0.07 ^c	0.6±0.009 ^{ab}	43±0.5 ^f
Prevention groups	G7: Control (+ve)	50±1.39 ^c	5.4±0.07 ^a	0.5±0.15 ^{bc}	35±0.06 ^j
	G8: SPP (2.5%)	45±0.29 ^d	4.6±0.8 ^b	0.5±0.006 ^{bc}	44±0.08 ^e
	G9: SPP (5.0%)	49±0.05 ^c	4.3±0.05 ^c	0.4±0.008 ^c	45±0.9 ^d
	G10: SPEE (2.5%)	49±0.88 ^c	4.9±0.02 ^b	0.4±0.01 ^c	40±0.25 ^h
	G11: SPEE (5.0%)	38±0.09 ^f	4.5±0.03 ^{bc}	0.4±0.12 ^c	36±0.41 ⁱ
LSD		1.053	0.55	0.105	0.602

Each value represents mean ± SD (n=5). Means under the same column with different prescript letters are significantly different at $p \leq 0.05$. SPP, *Salvadora persica* powder form, SPEE, *Salvadora persica* ethanol extract.

3.5. Effect of *Salvadora persica* Powder and Its Ethanol Extract on the Levels of Na, K and Ca in Blood Serum and Urine in Rats with Gentamicin-Induced Kidney Disorders

Effect of *Salvadora persica* powder and its ethanol extract on the levels of Na, K and Ca in blood serum and urine in rats with gentamicin-induced kidney disorders Table 5. Such data indicated that at the end of the experiment (31 days), the gentamicin-treated rats exhibited significantly ($p \leq 0.05$) decreased in Na (95.14%) and increased in K (10.55%) and Ca (12.0%) (for treatment groups) and -93.71, 3.77 and 10.75% (for prevention groups) in serum compared to the normal group, respectively. In urine, the gentamicin-treated rats exhibited significantly ($p \leq 0.05$) decreased in Na (-2.80%) and Ca (83.51%) and increased in K (630%) (for treatment groups) and -3.50, -87.63 and -40.0 % (for prevention groups) in urine compared to the normal group, respectively. However, intervention with *Salvadora persica* powder and methanolic extract (2.5 and 5.0 % g/100g diet) in feeding rats for 26 days led to significantly ($p \leq 0.05$) decrease Na and Ca and increase K in serum, and decrease in Na and K and increase Ca in urine of the

nephrotoxic rats (model control) by different rates. The rate of improvement was higher in the treatment group than the prevention group. Also, almost treatments in which *Salvadora persica* powder was used recorded greater effectiveness compared to the extract of the same substance. In all treatment, the rate of improvement of the nephrotoxic rats were not exhibited a dose- dependent manner. In similar studies, Khatak *et al.*, [83] and Akhtar *et al.*, [84] found that the feeding of *Salvadora persica* diets leads to increase Ca in urine while decrease in serum. The effect was more pronounced as *Salvadora persica* concentration increased. The *Salvadora persica* have natural therapeutic values as diuretic tonic plant. Also, Bokhary *et al.*, [85] reported that the cyclophosphamide+*Salvadora persica* had significant improvements in the renal biochemical parameters (creatinine, urea and calcium) enhanced anti-oxidative and anti-inflammatory effects in rats. In general, calcium is the most abundant mineral found in the body. About 99 percent of the calcium in the body is in bones and teeth. The remaining 1 percent is found in blood and soft tissues. The body uses calcium to form strong bones and teeth, help muscles contract and relax for normal movement, transmit nerve impulses, make blood clot normally, regulate cell secretions, cell division and cell multiplication and assist with enzyme reactions [86]. The kidney plays a key role in this process by the fine

regulation of calcium excretion. More than 95% of filtered calcium is reabsorbed along the renal tubules. In the proximal tubules, 60% of filtered calcium is reabsorbed by passive mechanisms. Parathyroid hormone (PTH) and vitamin D are responsible for maintaining calcium concentrations in the blood within a narrow range of values [87]. Higher serum sodium concentration has been reported to be a risk factor for the development of incident chronic kidney disease (CKD). Increased serum sodium concentration is a risk factor for estimated glomerular filtration rate (eGFR) decline in CKD [88]. Kidney disease can cause too much potassium in the body. They don't remove enough potassium and some medications treated may cause the potassium level to go up. Too much potassium can be dangerous and cause muscle weakness, numbness or tingling, a slow or irregular heartbeat and sudden death due to a stopped heart [89]. For all of the above reasons, minerals measurements, Na, K and Ca are often considered sensitive markers for determining the course of kidney damage. Data of the present study showed that both *Salvadora persica* powder and methanolic extract significantly improved such minerals level which demonstrating that it can prevent kidney cells damage. This prophylactic/curative effects could be attributed to *Salvadora persica* powder and methanolic extract content of some important nutrients and bioactive constituents such organic sulfur compounds, elemental sulfur, flavonoids, salvadorine, cyanogenic glycosides, lignans, saponins, alkaloids, tannins, linoleic acid, stearic acid, salvadouria, vitamin C, silica, and different salts [18,19,20]. In similar studies, plant parts and their extracts contains such bioactive compounds exhibit protective/treatment activities against kidney injury induced by toxic chemicals and gentamicin [70,81,82,83,84,90]. Thus, the improvements in the renal biochemical parameters (Na, K and Ca) induced by *Salvadora persica* inn this study could be attributed to its anti-oxidative and anti-inflammatory effects.

3.6. Effect of *Salvadora persica* Powder and Its Ethanol Extract on Rat Kidney Histological Disorders Induced by Gentamicin

Effect of *Salvadora persica* powder and its ethanol extract on rat kidney histological disorders induced by gentamicin was shown in Figure 2. Microscopically, kidneys sections of rats from group 1 revealed the normal histological structure of renal parenchyma (Photos 1 & 2). In contrariwise, kidneys of rats from group 2 exhibited congestion of intertubular renal blood vessel (Photo3) and vacuolar degeneration of epithelial lining renal tubules (Photos 4 & 5). On the other hand, kidneys of rats from group 3 described slight vacuolar degeneration of epithelial lining some renal tubules (Photos 6 & 7) and congestion of intertubular renal blood vessel (Photo8). Moreover, kidneys of rats from group 4 revealed congestion of intertubular renal blood vessel (Photos 9 & 10) and slight vacuolar degeneration of epithelial lining some renal tubules (Photo11). Meanwhile, some examined sections from group 4 showed slight congestion of intertubular renal blood capillaries (Photos 12 & 13),

whereas other sections described few interstitial inflammatory cells infiltration (Photo14). Otherwise, kidneys of rats from group 6 exhibited no histopathological alterations (Photos 15 & 16). In adverse, kidneys of rats from group 7 revealed vacuolar degeneration of epithelial lining renal tubules, interstitial nephritis (Photo17), proteinaceous cast in the lumen of renal tubules, cystic dilatation of renal tubules (Photo18) and focal necrosis of renal tubules associated with inflammatory cells infiltration (Photo19). Meanwhile, some sections from group 8 exhibited no histopathological changes (Photo20), whereas other sections showed congestion of renal blood vessels (Photo21). Moreover, some examined sections from group 9 manifested no histopathological changes (Photos 22 & 23), whereas other sections showed vacuolar degeneration of epithelial lining renal tubules and focal necrosis of renal tubules associated with inflammatory cells infiltration (Photo24). Likewise, some kidneys of rats from group 10 described no histopathological changes (Photo25), whereas other sections manifested vacuolar degeneration of epithelial lining some renal tubules (Photo26) and interstitial and periglomerular few inflammatory cells infiltration (Photo27). Meanwhile, kidneys of rats from group 11 demonstrated vacuolar degeneration of epithelial lining some renal tubules (Photos 28 & 29) and small focal necrosis of renal tubules (Photo30). Kidneys are particularly susceptible to ROS attacks as they play a vital role in metabolic and filtration processes. Oxidative stress caused by ROS primarily triggers the release of an array of pro-inflammatory cytokines, which in turn leads to nephrotic inflammation and ultimately impairs renal function. Data of the present study indicated that inducing rats with gentamicin led to a statistically significant ($p \leq 0.05$) increase in the mean values of serum urea, uric acid and creatinine compared to those in the negative control group. It is widely recognized that serum urea and creatinine levels serve as biomarkers for assessing glomerular filtration rate, which is used as an indicator in clinical research to evaluate renal function. Our histopathological examination results showed a marked congestion of intertubular renal blood vessel and vacuolar degeneration of epithelial lining renal tubules in the kidney of intoxicated rats with gentamicin. These observations may indicate the presence of nephrotic glomerular dysfunction, leading to increased serum uric acid, creatinine and urea concentrations in rats exposed to gentamicin. Several authors reported that induced rats with different toxic chemicals resulted in renal damage alongside marked DNA fragmentation and alteration in DNA integrity in the kidney [91]. The increase in serum urea concentration may be attributed to excessive degradation of proteins and enzymes caused by reactive oxygen species [92]. Moreover, an elevated serum creatinine level signifies the retention of creatinine in the bloodstream, consequent to the progressive kidney degradation caused by exposure to reactive metabolites of gentamicine, which readily generates free radicals [93,94]. In several studies, plant parts and their extracts contains bioactive compounds such as found in *Salvadora persica* exhibit protective/treatment activities against kidney histological injury induced by toxic chemicals including gentamicin [70,92,93,95].

Table 5. Effect of *Salvadora persica* powder and its ethanol extract on the levels of Na, K and Ca in blood serum and urine in rats with gentamicin-induced kidney disorders

Groups		Serum (mEq/L)			Urine (mEq/L)		
		Na	K	Ca	Na	K	Ca
G1: Control (-ve), Normal		116± 0.29 ^f	7.96± 0.008 ^a	4.0± 0.18 ^h	143± 1.25 ^a	10± 0.08 ^h	97± 1.22 ^a
Treatment groups	G2: Control (+ve)	5.64± 0.007 ^f	8.8± 0.08 ^a	52± 0.05 ⁱ	139± 0.24 ^a	73± 1.11 ^a	16± 0.05 ^j
	G3: SPP (2.5%)	6.34± 0.002 ^{de}	6.83± 0.005 ^c	83± 0.01 ^d	136.5± 0.09 ^c	41± 1.25 ^e	47± 0.25 ^e
	G4: SPP (5.0%)	6.46± 0.009 ^{de}	6.79± 0.003 ^c	95± 0.99 ^c	135.5± 0.05 ^e	51± 0.88 ^d	48.5± 0.05 ⁱ
	G5: SPEE (2.5%)	6.18± 0.003 ^d	4.33± 0.006 ^f	69± 1.04 ^g	135.5± 0.02 ^e	54± 1.05 ^c	35± 0.66 ^g
	G6: SPEE (5.0%)	6.12± 0.007 ^e	4.25± 0.004 ^g	110± 0.88 ^b	135.5± 0.01 ^e	63± 0.09 ^b	72± 1.47 ^c
Prevention groups	G7: Control (+ve)	7.29± 0.494 ^b	8.26± 0.001 ^b	47± 0.04 ^j	138± 0.27 ^b	6± 0.02 ⁱ	12± 0.03 ^k
	G8: SPP (2.5%)	6.84± 0.005 ^c	6.86± 0.004 ^c	75± 0.66 ^f	138± 0.15 ^b	50± 1.36 ^d	42± 0.63 ^f
	G9: SPP (5.0%)	6.53± 0.01 ^d	6.73± 0.001 ^c	78± 0.03 ^e	135.5± 0.01 ^e	34± 0.08 ^f	77± 1.05 ^b
	G10: SPEE (2.5%)	6.35± 0.001 ^{de}	4.7± 0.04 ^d	60± 0.69 ^h	136.5± 0.06 ^c	33± 0.25 ^f	32± 0.08 ^h
	G11: SPEE (5.0%)	6.25± 0.002 ^{de}	4.46± 0.009 ^e	69± 0.06 ^g	136± 0.12 ^d	14± 0.05 ^g	68± 0.49 ^d
LSD		0.27	0.10	1.29	0.27	1.29	1.24

Each value represents mean ± SD (n=5). Means under the same column with different prescript letters are significantly different at $p \leq 0.05$. SPP, *Salvadora persica* powder form, SPEE, *Salvadora persica* ethanol extract.

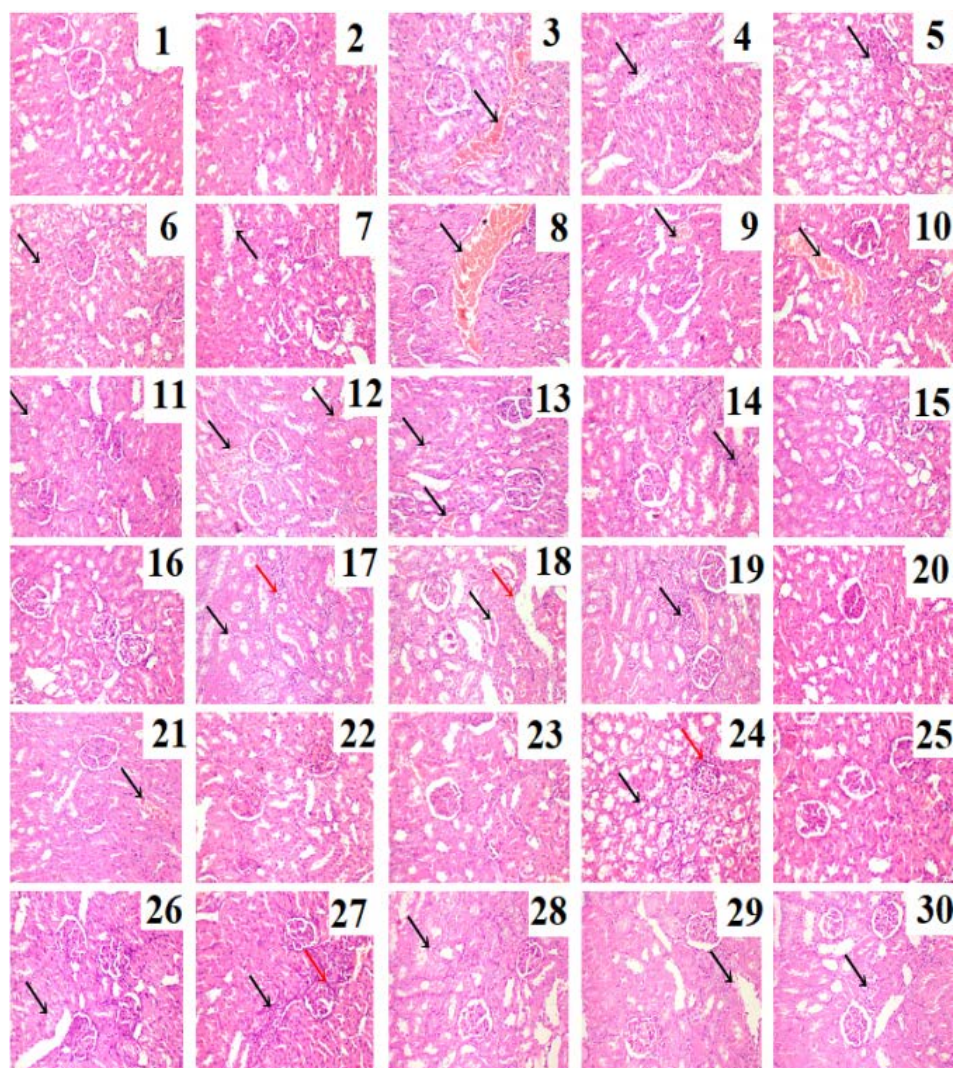
**Figure 2. Effect of *Salvadora persica* powder and its ethanol extract on rat kidney histological disorders induced by gentamicin**

Photo 1. Photomicrograph of kidney of rat from group 1 showing normal histological structure of renal parenchyma, **Photo 2.** Photomicrograph of kidney of rat from group 1 showing normal histological structure of renal parenchyma, **Photo 3.** Photomicrograph of kidney of rat from group 2 showing congestion of intertubular renal blood vessel (arrow), **Photo 4.** Photomicrograph of kidney of rat from group 2 showing vacuolar degeneration of epithelial lining renal tubules (black arrow), **Photo 5.** Photomicrograph of kidney of rat from group 2 showing vacuolar degeneration of epithelial lining renal tubules (black arrow), **Photo 6.** Photomicrograph of kidney of rat from group 3 showing slight vacuolar degeneration of epithelial lining some renal tubules (black arrow), **Photo 7.** Photomicrograph of kidney of rat from group 3 showing vacuolar degeneration of epithelial lining some renal tubules (black arrow), **Photo 8.** Photomicrograph of kidney of rat from group 3 showing congestion of intertubular renal blood vessel (arrow), **Photo 9.** Photomicrograph of kidney of rat from group 4 showing congestion of intertubular renal blood vessel (arrow), **Photo 10.** Photomicrograph of kidney of rat from group 4 showing congestion of intertubular renal blood vessel (arrow), **Photo 11.** Photomicrograph of kidney of rat from group 4 showing slight vacuolar degeneration of epithelial lining some renal tubules (arrow), **Photo 12.** Photomicrograph of kidney of rat from group 5 showing slight congestion of intertubular renal blood capillaries (arrow), **Photo 13.** Photomicrograph of kidney of rat from group 5 showing slight congestion of intertubular renal blood capillaries (arrow), **Photo 14.** Photomicrograph of kidney of rat from group 5 showing few interstitial inflammatory cells infiltration (arrow), **Photo 15.** Photomicrograph of kidney of rat from group 6 showing no histopathological alterations, **Photo 16.** Photomicrograph of kidney of rat from group 6 showing no histopathological alterations, **Photo 17.** Photomicrograph of kidney of rat from group 7 showing vacuolar degeneration of epithelial lining renal tubules (black arrow) and interstitial nephritis (red arrow), **Photo 18.** Photomicrograph of kidney of rat from group 7 showing proteinaceous cast in the lumen of renal tubules (black arrow) and cystic dilatation of renal tubules (red arrow), **Photo 19.** Photomicrograph of kidney of rat from group 7 showing focal necrosis of renal tubules associated with inflammatory cells infiltration (black arrow), **Photo 20.** Photomicrograph of kidney of rat from group 8 showing no histopathological changes, **Photo 21.** Photomicrograph of kidney of rat from group 8 showing congestion of renal blood vessel (black arrow), **Photo 22.** Photomicrograph of kidney of rat from group 9 showing no histopathological changes, **Photo 23.** Photomicrograph of kidney of rat from group 9 showing no histopathological changes, **Photo 24.** Photomicrograph of kidney of rat from group 9 showing vacuolar degeneration of epithelial lining renal tubules (black arrow) and focal necrosis of renal tubules associated with inflammatory cells infiltration (red arrow), **Photo 25.** Photomicrograph of kidney of rat from group 10 showing no histopathological changes, **Photo 26.** Photomicrograph of kidney of rat from group 10 showing vacuolar degeneration of epithelial lining some renal tubules (black arrow), **Photo 27.** Photomicrograph of kidney of rat from

group 10 showing interstitial (black arrow) and periglomerular (red arrow) few inflammatory cells infiltration, **Photo 28.** Photomicrograph of kidney of rat from group 11 showing vacuolar degeneration of epithelial lining some renal tubules (black arrow), **Photo 29.** Photomicrograph of kidney of rat from group 11 showing vacuolar degeneration of epithelial lining some renal tubules (black arrow), and **Photo 30.** Photomicrograph of kidney of rat from group 11 showing small focal necrosis of renal tubules (arrow) (H & E X 400).

4. Conclusion

Arak (*Salvadora persica*) is a small evergreen tree native to the Middle east, Africa and India and Its sticks are traditionally used as a natural toothbrush called swak. With a long history in folk medicine for centuries, it was used in different fields including oral hygiene, food, cosmetics, fuel, and even as a medicine. Our finding indicated that dietary intervention with *Salvadora persica* powder or extract by 2.5 and 5% g/100 diet are able to treat and prevent kidney injuries induced by gentamycin. The manipulation process includes improving the kidney functions, liver functions enzymes activities, serum lipid profile and histological changes thereby adversely affecting the injuries process to the benefit of the biological system. These findings provide a basis for the use of *Salvadora persica* powder or extract for the prevention and treatment of nephrotoxicity. Data also supports the benefits of *Salvadora persica* supplementation to diet in alleviating disorders/side effects associated with kidney antibiotics, including gentamicin.

Ethical Considerations

The ethical issues of this study was reviewed and approved by the Scientific Research Ethics Committee (SREC, Approval #17-SREC-03-2019), Faculty of Home Economics, Menoufia University, Shebin El-Kom, Egypt.

Conflict of Interest

The authors declare that they have no conflict of interest in publishing this paper.

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Authors' Contribution

Yousif Elhassaneen participated in retrieving conceptual information, validating the results, preparing a

draft of the paper, performed a critical revision to structure the content intellectually, and gave approval for the final version to be published. Fatma ElZahraa ElSherif made significant contributions to the concept and design of the work, developing the study protocol and draft paper preparation. Sherif Sabry participated in developing the study protocol and preparing the draft of the paper. Mai Khafagi participated in retrieving conceptual information, validating the biological results, and preparing the draft of the paper. Basma Hashem conducted the experimental procedures and validations, data acquisition, compilation, analysis, and interpretation and also was involved in retrieving conceptual information and draft paper preparation.

Abbreviations

ALT, Alanine aminotransferase, ALP, alkaline phosphatase, AST, aspartate aminotransferase, BWG, body weight gain, FER, feed efficiency ratio, FI, feed intake, HDL-C, high density lipoprotein, SD, standard deviation, SPP, *Salvadora persica* powder form, SPEE, *Salvadora persica* ethanol extract, TC, total cholesterol, TG's, triglycerides.

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