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# Biochemical and Nutraceutical Effect of Ashwagandha (*Withania Somnifera*) Roots on Kidney Functions and Immunomodulatory Activity Disorders in Rats

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**ABSTRACT:**

Numerous plants and their extracts have been shown to significantly affect inflammation and fibrosis and improve renal dysfunction through antioxidant action. This work examined the effect of ashwagandha (*Withania somnifera*) roots powder (ARP), aqueous (ARAEx), and ethanolic extract (AREEx) on nephrotoxic rats. Two main groups of forty adult male albino rats were created. Group 1 control (-) (n=5) and was fed the basal diet (B.D.). The second main group, (n=35), was split into seven groups with five rats each after receiving gentamicin injection to cause nephrotoxicity; group (2): As control (+) fed on B.D., groups (3 and 4): Fed on B.D. Containing (2 and 4 %) of ARP; groups (5 and 6): Fed on B.D. and orally administered with (200 and 400 mg/kg/B.W.) of ARAEx and groups (7 and 8): Fed on B.D. and orally administered with (200 and 400 mg/kg/B.W.) of AREEx, respectively. At the end of the experiment, serum was analyzed for kidney functions, liver functions, lipids profile (sodium, potassium), (HB, WBCs, RBCs, and PLT), glucose, immunoglobulin (IgG, IgA, and IgM), and urine was collected for 24 hours to determine (sodium, potassium, Total protein, and creatinine). According to the results, rats' kidney, liver, immunoglobulin, and lipid profiles were all enhanced better with oral AREEx (400 mg/kg/B.W.). In conclusion, rats handled with AREEx (400 mg/kg/B.W.) showed improved kidney functions, immunomodulatory activity, and histological structure of kidneys through their antioxidant and radical scavenging activities.

***Keywords***: *Nephrotoxicity, Immunity, Ashwaganda roots, Gentamicin, Withanolids and Withaferin-A*

## INTRODUCTION

Debilitating, chronic kidney disease (CKD) is becoming more common globally and placing a financial and social strain on health systems. If kidney replacement therapy is not used to treat kidney failure, the last stage of chronic kidney disease (CKD), it can be fatal [1]. Kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m2 that

lasts for three months or more is characterized as chronic kidney disease (CKD) [2]. It is a condition in which kidney function gradually declines and renal replacement therapy (dialysis or transplantation) becomes necessary. Pathologic abnormalities indicated by imaging investigations or renal biopsies, anomalies in urine sediment, or elevated urinary albumin excretion rates are all considered forms of kidney injury [3]. Cardiovascular risk reduction (e.g., statins and blood pressure control), albuminuria treatment (e.g., angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), avoidance of potential nephrotoxins (e.g., no steroidal anti-inflammatory drugs), and drug dosage adjustments (e.g., many antibiotics and oral hypoglycemic agents) are all part of optimal management of chronic kidney disease (CKD). Additionally, patients need to be monitored for CKD consequences include anemia, hypophosphatemia, vitamin D deficiency, metabolic acidosis, hyperkalemia, and secondary hyperparathyroidism [4]. The immune system exists to protect the host from noxious environmental agent's especially pathogenic organisms, which may be in the form of bacteria, viruses, fungi or parasites. To deal with such an array of threats, the human immune system has evolved to include a myriad of cell types, communicating molecules and functional responses. The immune system is always active, carrying out surveillance, but its activity is enhanced if an individual becomes infected. This heightened activity is accompanied by an increased rate of metabolism, requiring energy sources, substrates for biosynthesis and regulatory molecules. These energy sources, substrates and regulatory molecules are ultimately derived from the diet. Hence an adequate supply of a wide range of nutrients is essential to support the immune system to function optimally [5, 6]. A little woody shrub, Withania somnifera (L.) Dunal (Ws), is a member of the Solanaceae family (Solanaceae Juss.). It is sometimes referred to as "poison gooseberry," "Indian winter cherry," or "ashwagandha," and is typically found in the drier parts of western India. In India's traditional medical system, Ayurveda, the plant is regarded as one of the most significant plants [7]. Numerous pharmacological activities, including anti-inflammatory, anti-diabetic, anti-cancer, anti-microbial, anti-arthritic, anti-stress/adaptogenic, neuro-protective, cardio-protective, hepato-protective, and immunomodulatory qualities, have been demonstrated by W. somnifera. Moreover, it has been demonstrated that W. somnifera can reduce inflammation and reactive oxygen species, modify mitochondrial activity, control apoptosis, and enhance endothelial function. W. somnifera has an essential phytoconstituent called withaferin-A, which is a member of the withanolides class and is used in traditional medicine to treat a variety of ailments [8].W. somnifera may has nephroprotective properties

because of its innate antioxidant and free-radical-scavenging properties. Withanolides, one of W. somnifera's biologically active chemicals, may one day prove to be a potential therapeutic molecule for renal diseases [9]. Phytochemicals such daucosterol, withasomniferol-A, withaferin-A, 2, 3-dihydrowithaferin-A-3-β-O-sulfate, and β-sitosterol, which regulated numerous immune pathways via bioactive-targets and protein-protein interactions, were engaged in the immunomodulation process [10]. The objective of this investigation was to ascertain the effects of varying dosages of ashwaganda roots, aqueous and ethanolic extract (200 and 400 mg/kg of B.W) on various biological and biochemical complication in nephrotoxicity rats.

## 2. Materials and methods

### 2.1 Materials:

#### 2.1.1. The herbal used:

The ashwaganda roots were bought from an herbalist in Cairo City, Cairo Governorate, Egypt.

#### 2.1.2. Gentamycin:

Gentamicin is an antibiotic made of aminoglycosides that Memphis Co. purchased from Pharm. Chem. Ind. in Cairo, A.R.E

### 2.2. Methods:

#### 2.2.1. The plant used:

According to [11], all dry components were ground into a fine powder using an electric grinder and stored in dark, cork-sealed glass bottles in a cool, dry place until used.

#### 2.2.2. The induction of experimental nephrotoxicity:

By injecting gentamycin intraperitoneally at a rate of 100 mg/kg/day for seven consecutive days, normal, healthy male albino rats were made to induce nephrotoxicity in accordance with [12] method.

#### 2.2.3. Extraction of alcoholic ashwaganda roots:

Cold percolation was used to extract powdered ashwagandha roots using 70% ethanol at room temperature. A rotary evaporator operating at 45 °C was used to filter and concentrate the extracted material. Herbal concentrate was lyophilized to produce an ethanolic extract of the plant according to [13].

#### 2.2.4. Preparation of ashwagandha aqueous extract

In a round-bottom flask, 5 g of powdered plant material and 50 ml of distilled water were combined, and the mixture was refluxed for roughly 5 hours at 100 C. Following vacuum filtration to separate the liquid extracts from the solid residue, a rotary evaporator was used to concentrate the mixture. Rats were administered the dosage (200 and 400 mg/kg of B.W) according to [14].

#### 2.2.5. Experimental and animal models design:

In this investigation, forty male albino rats weighing 150±10 g were utilized. The animals were acquired from the Ministry of Health's Vaccine and Immunity

Organization at Helwan University in Egypt. The experiment was conducted at Menoufia University in Shebin El-Kom, Egypt, at the Faculty of Home Economics (MUFHE/S/NFS/19/23). Rats were maintained under standard, hygienic conditions in wire cages at 25 degrees Celsius. Two major groups were created out of all the rats.

One used as Group 1 (-) that was healthy control group fed only the basal diet. The second, which was administered with gentamicin for nephrotoxicity as previously mentioned, was split into the following seven groups:

Group 2 (+): Nephrotoxic rats fed on basal diet and used as positive control group.

Group 3: Nephrotoxic rats fed on basal diet and treated with 2% of ARP.

Group 4: Nephrotoxic rats fed on basal diet and treated with 4% of ARP.

Group 5: Nephrotoxic group fed on basal diet and treated with 200mg\kg of B.W orally of ARAEx.

Group 6: Nephrotoxic rats fed on basal diet and treated with 400mg\kg of B.W orally of ARAEx.

Group 7: Nephrotoxic rats fed on basal diet and treated with 200mg\kg of B.W orally of AREEx.

Group 8: Nephrotoxic rats fed on basal diet and treated with 400mg\kg of B.W orally of AREEx.

Rats' body weight and feed intake were estimated every week during the experiment, and the feed efficiency ratio was computed.

### 2.2.6. Urine and blood sampling collections:

At the conclusion of experiment, a 24-hour urine sample was taken from each rat, and it was tested to determine the following parameters: creatinine, sodium, potassium, and total protein. Additionally, blood serum samples were collected and stored for biochemical analyses.

### 2.2.7. Biochemical of urine and blood analysis:

Using the abdominal aorta, blood samples were taken after the conclusion of the 12-hour fast and scarification of the rats under ether anesthesia. Following the receipt of blood samples in clean, dry centrifuge tubes, the blood was allowed to clot at room temperature before the serum was separated by centrifuging the tubes for ten minutes at 3000 r.p.m. Serum was thoroughly extracted, placed into sterile cuvette tubes, and frozen at -20°C for biochemical analysis for biochemical analysis as described by [15]. The following parameters were determined by analysis of all samples:

In accordance with [16], the body weight gain (BWG) and feed efficiency ratio (FER) were calculated. Using an enzymatic technique, serum urea and creatinine were measured in according with [17] and [18]. While the method of [19] was used to test serum uric acid using a colorimeter. Also, creatinine clearance was measured according to [20] Creatinine clearance= (creatinine in urine × volume of urine)/ (creatinine in serum ×

1440). The methods given by [21] were used to determine the serum alkaline phosphatase (ALP), [22] for serum aspartate aminotransferase (AST), and serum alanine aminotransferase (ALT). In order to measure serum total cholesterol, the colorimetric technique described by [23], serum triglycerides were measured in accordance with [24]. The method described by [25] is used to measure HDL-c. According to [26] the VLDL-c and LDL-c were calculated using the following formulas: VLDL-c= TG / 5; LDL-c = T.C– (HDL-c + VLDL-c). CBC included WBCs, HB, RBCs and PLT were measured according to [27]. Sodium and potassium was determined according to [28]. Total protein was carried out according to [29]. Immunoglobulins (IgM, IgG and IgA) levels were determined by single radial immunodiffusion [30]. According to [31], glucose was measured using an enzymatic test and chemical kits.

### 2.2.8. Histopathological examination:

All experimental groups' kidneys were broken down into small specimens, which were then preserved in 10% neutral buffered formalin, dried in increasing ethanol concentrations (70, 80, and 90%), cleaned in xylene, and embedded in paraffin. Hematoxylin and Eosin was used to create sections with a thickness of (4-6) µm according to [32].

### 2.2.9. Statistical analysis

According to [33], a significant main impact was identified by statistical analysis utilizing the Costate computer program, and the means were separated using the student new Mankeuls test. Differences between treatments of ($p \leq 0.05$) were deemed significant.

## Results and Discussion

The effects of ARP, ARAEx, and AREEx on feed intake (FI), body weight gain (BWG), and feed efficiency ratio of nephrotoxic rats are displayed in Table (1). It was observed that control (-) group mean feed intake was more than the control (+) group came at 14.87±0.66 and 10.74±0.38 (g/day) respectively. When comparing group (8), of nephrotoxic rats treated with AREEx (400 mg/kg of B.W) to control (+), the group for increasing FI was determined. Based on the same data, it was clearly that the control (-) group's mean body weight gain was 0.53±0.028, while the control (+) group was 0.26±0.002 (g\day\rat). Meanwhile, nephrotoxic rats fed with group (8) AREEx (400 mg/kg of B.W) had the best results and the largest rise in body weight gain when compared to control (+). Additionally, table (1) data indicated that the control (-) group mean feed efficiency ratio was greater than the control (+) group the values were 0.036±0.0011 and 0.024±0.0003, respectively. Comparison with control (+), nephrotoxic rats fed on group (8) AREEx (400 mg/kg of B.W) showed the greatest increase in feed efficiency ratio. This result is agreed with [34], who found that ashwagandha roots powder (ARP) at doses 2.5 and 5 % was highest in FI and BWG % on diabetic rats. Also, [35] reported that ashwagandha

roots powder and aqueous extract at levels (2.5 and 5%) increased feed intake, body weight gain and feed efficiency ratio in hyperglycemic rats.

Table (1): The influence of various doses of ashwagandha roots, aqueous and ethanolic extract on (FI), (BWG) and (FER) of nephrotoxic rats.

| Parameter / Groups | FI (g/d) Mean ± SD | BWG (g/d/rat) Mean ± SD | FER Mean ± SD |
|---|---|---|---|
| G1: (– ve) | 14.87±0.66a | 0.53±0.028a | 0.036±0.0011a |
| G2: (+ ve) | 10.74±0.38f | 0.26±0.002g | 0.024±0.0003d |
| G3:ARP 2% | 12.55±0.002de | 0.37± 0.016e | 0.029±0.0005c |
| G4:ARP 4% | 12.69±0.111d | 0.41±0.004d | 0.032±0.0025b |
| G5: ARAEx 200mg\kg of B.W | 12.02±0.06e | 0.30±0.008f | 0.025 ±0.0006d |
| G6: ARAEx 400mg\kg of B.W | 12.21±0.028de | 0.35±0.013e | 0.029±0.0013c |
| G7: AREEx 200mg\kg of B.W | 13.39±0.15c | 0.42±0.002c | 0.031±0.0009bc |
| G8: AREEx 400mg\kg of B.W | 13.88±0.009b | 0.49±0.021b | 0.035±0.0001a |
| LSD | 0.48 | 0.026 | 0.002 |

*The values that differ by a letter in each column are statistically different (P≤0.05). *ARP: Ashwagandha roots powder, ARAEx: Ashwagandha roots aqueous extract, AREEx: Ashwagandha roots ethanolic extract, B.W: Body weight, FI: Feed intake, BWG: Body weight gain and FER: Feed efficiency ratio.*

Tables (2) illustrate the effect of ARP, ARAEx and AREEx on kidney functions (urea, uric acid, creatinine & creatinine clearance) and urine creatinine of nephrotoxic rats. A serum creatinine level in the positive control group was 1.41±0.008 which was higher than negative control group 0.68±0.025 mg/dl. Group 8 AREEx (400 mg/kg of B.W) noticed the lowest serum creatinine of all the treated groups as compared to control (+).The serum urea value of the positive control group was considerably (P≤0.05) greater than that of the negative control group, according to the data; the respective mean values were 34.36±1.12 and 70.40±1.29 mg/dl. When compared to the control (+) group, the nephrotoxic group of rats fed on AREEx (400 mg/kg of B.W) obtained the lowest value and was the best group. Table (2) data showed that the control (+) group means serum uric acid value was greater than the control (-) group, at 6.50±0.045 and 3.06±0.0001 respectively. Serum uric acid levels in nephrotoxic rats fed with group (8) AREEx (400 mg/kg of B.W) were highest in comparison to control (+). Urine creatinine analysis revealed that the negative control group had higher mean values (90±1.11) than the positive control group (52±1.43) mg/dl. When compared to the control (+) group of rats, the nephrotoxic group of rats administered AREEx (400 mg/kg of B.W) had the greatest increase in urine creatinine. Also, data from the previous table indicated that the control (-) group mean creatinine clearance was higher than the control (+) group, at 0.183±0.0009 and 0.051±0.0025, respectively. When compared to the control (+), group 8

AREEx (400 mg/kg of B.W) had the highest creatinine clearance. These findings were consistent with those of [36], who discovered that ashwagandha root extract (500 mg/kg/ B.W orally) decreased serum urea and creatinine in rats given gentamicin injections by enhancing glomerular filtration. This effect may have been caused by the extract's ability to inhibit the production and scavenging of free radicals due to its active ingredients, which include flavonoids like sitoindosides VII and withaferin A as well as phenolic compounds. The administration of W. somnifera orally at doses (250 and 500 mg/kg) was found to decrease serum creatinine, urea, and uric acid and increase urine creatinine, which in turn caused nephrotoxicity and mitochondrial oxidative stress in rats. This may be because some of the plant's active ingredients, such as sitoinosides, alkaloids, and steroidal lactones, are involved [37]. [38], who found that oral administration of ashwagandha powder and aqueous extract decreased renal functions (urea, uric acid, and creatinine) on male rats.

Table (2): The influence of various doses of ashwagandha roots, aqueous and ethanolic extract on kidney functions and urine creatinine of nephrotoxic rats.

| Parameter / Groups | Serum creatinine (mg/dl) Mean±SD | Serum urea (mg/dl) Mean±SD | Serum uric acid (mg/dl) Mean±SD | Urine Creatinine (mg/dl) Mean±SD | Creatinine clearance (ml/hour) Mean±SD |
|---|---|---|---|---|---|
| G1: (– ve) | 0.68±0.025g | 34.36±1.12f | 3.06±0.001h | 90±1.11a | 0.183±0.0009a |
| G2: (+ ve) | 1.41±0.008a | 70.40±1.29a | 6.50±0.045a | 52±1.43g | 0.051±0.0025h |
| G3:ARP 2% | 1.04±0.11d | 41.6±0.99cd | 4.84±0.002e | 73±1.23d | 0.097±0.0013e |
| G4:ARP 4% | 0.94±0.033e | 39.6±1.74de | 4.50±0.005d | 76±1.31c | 0.112±0.0001d |
| G5: ARAEx 200mg\kg of B.W | 1.30±0.007b | 48.45±1.67b | 5.88±0.011b | 63±1.63f | 0.067±0.0036g |
| G6: ARAEx 400mg\kg of B.W | 1.19±0.009c | 43.58±1.34c | 5.20±0.023c | 67±1.74e | 0.078±0.0007f |
| G7: AREEx 200mg\kg of B.W | 0.81±0.072f | 38.55±0.76e | 4.11±0.004f | 83±1.65b | 0.142±0.0002c |
| G8: AREEx 400mg\kg of B.W | 0.70±0.006g | 31.68±0.55g | 3.80±0.008g | 85±1.25b | 0.169±0.0144b |
| LSD | 0.085 | 2.15 | 0.032 | 2.48 | 0.009 |

*The values that differ by a letter in each column are statistically different (P≤0.05). *ARP: Ashwagandha roots powder, ARAEx: Ashwagandha roots aqueous extract, AREEx: Ashwagandha roots ethanolic extract and B.W: Body weight.*

The data in table (3) showed how ARP, ARAEx, and AREEx affected on levels of serum sodium, urine sodium, serum potassium and urine potassium of nephrotoxic rats. Serum sodium levels in the positive and negative control groups were found to be substantially different, at 140±1.14 and 110±0.36 mmol/l, respectively. Nephrotoxic rats given AREEx (400 mg/kg of B.W) indicated the lowest serum sodium levels as compared to the control group (+).The negative control group serum sodium level was found to be substantially greater than that

of the positive control group, at 142.2±0.11 and 119.9±1.03 mmol/l, respectively for urine sodium. Nephrotoxic rats administered AREEx (400 mg/kg of B.W) reported the greatest urinary sodium levels as compared to the control group (+). According to the same table, the positive control group and negative control group levels serum potassium levels were 3.42±0.2 mmol/l and 5.35±0.16 mmol/l, respectively. Comparing with control (+), AREEx (400 mg/kg of B.W) was the best results observed. Furthermore, the positive control group urine potassium level was higher than that of the negative control group which was 55±1.14 and 35±1.01 mmol/l, respectively. When compared to control (+), nephrotoxic rats fed on AREEx (400 mg/kg of B.W) noticed the highest group of urine potassium. This study is consistent with [39], who found that, as compared to a control group treated with gentamicin, the oral administration of ashwagandha root extract (500 mg/kg B.W) for 22 days resulted in an increase in serum potassium and a slight reduction in serum sodium levels. [40], who proposed that the presence of active components such withanolides may be in charge of ashwagandha diuretic effect by preventing renal tubules from reabsorbing sodium ions. Also, research conducted by [9], revealed that the alcoholic extract of W. somnifera raised serum potassium and decreased serum sodium due to the presence of biologically active compounds called withanolides, which may one day prove to be a novel therapeutic molecule for renal disorders and improve electrolyte abnormalities in rats intoxicated with gentamicin.

**Table (3): Influence of various doses of ashwagandha roots, aqueous and ethanolic extract on serum sodium, urine sodium, serum potassium and urine potassium of nephrotoxic rats.**

| Parameter / Groups | Serum sodium (mmol/L) Mean ± SD | Urine sodium (mmol/L) Mean ± SD | Serum potassium (mmol/L) Mean ± SD | Urine potassium (mmol/L) Mean ± SD |
|---|---|---|---|---|
| G1: (– ve) | 110±0.36g | 142.2±0.11a | 5.35±0.16a | 35±1.01g |
| G2: (+ ve) | 140±1.14a | 119.9±1.03g | 3.42±0.2f | 55±1.14a |
| G3:ARP 2% | 129±0.66c | 134.4±0.32d | 4.51±0.001cd | 49±0.25c |
| G4:ARP 4% | 127±0.45d | 137.4±0.42c | 4.68±0.303c | 47±0.99d |
| G5: ARAEx 200mg\kg of B.W | 132±0.84b | 130.5±0.99f | 3.99±0.025e | 51±0.42b |
| G6: ARAEx 400mg\kg of B.W | 130±0.99c | 132.6±0.25e | 4.36±0.006d | 52±0.36b |
| G7: AREEx 200mg\kg of B.W | 125±0.5e | 140.0±0.13b | 5.01±0.009b | 42±1.65e |
| G8: AREEx 400mg\kg of B.W | 120±1.83f | 141.3±0.56a | 5.10±0.007b | 39±1.67f |
| LSD | 1.66 | 1.21 | 0.24 | 1.85 |

*The values that differ by a letter in each column are statistically different (P≤0.05). *ARP: Ashwagandha roots powder, ARAEx: Ashwagandha roots aqueous extract, AREEx: Ashwagandha roots ethanolic extract and B.W: Body weight*

The effect of ARP, ARAEx, and AREEx on the liver enzymes (AST, ALT, and ALP) of nephrotoxic rats were shown by the data in Table (4). The ALT liver enzyme levels in the positive and negative control groups were clearly different, ranging from 183.53±1.12 to 35.63±0.25 U/L, respectively. When compared to control (+), the nephrotoxic group of rats administered with AREEx (400 mg/kg of B.W) showed the best serum ALT results. The liver enzyme AST levels in the negative and positive control groups were 84.02±1.21 and 163.67±2.25 U/L, respectively, and the data indicated significant differences (P≤0.05). When comparing group 8 AREEx (400 mg/kg of B.W) to control (+), the lowest serum AST was indicated. It is clear that there were notable variations in the ALP liver enzyme levels between the positive and negative control groups being 184.48±1.48 and 380.57±1.03 U/L, respectively. Nephrotoxic rats fed on AREEx (400 mg/kg of B.W) noticed the lowest ALP enzyme of all treated groups as compared to control (+), and it was the best group. This result supports the findings of [41], who demonstrated that giving ashwagandha root extract (500 mg/kg B.W orally) for 22 straight days reduced serum AST and ALT in rats intoxicated with gentamicin. This may be because the extract has the ability to scavenge free radicals, which is indicative of its hepatoprotective effect. Additionally, because the extract contains withanolides, which have anti-inflammatory properties, it may also help prevent liver damage [42]. This data is also in line with the findings of [43], who proposed that ashwagandha roots, through their antioxidant mechanism and phenolic contents, protected liver functions and histology by reducing serum AST, ALT, and ALP in obese rats.

Table (4): The influence of various levels of ashwagandha roots, aqueous and ethanolic extract on liver enzymes of nephrotoxic rats.

| Parameter / Groups | ALT (U/L) Mean ± SD | AST (U/L) Mean ± SD | ALP (U/L) Mean ± SD |
|---|---|---|---|
| G1: (– ve) | 35.63±0.25h | 84.02±1.21h | 184.48±1.48h |
| G2: (+ ve) | 138.53±1.12a | 163.67± 2.25a | 380.57±1.03a |
| G3: ARP 2% | 92.69±0.66d | 142.42± 1.34d | 250.05±1.26d |
| G4: ARP 4% | 89.08±0.34e | 136.72±1.19e | 241.11± 1.19e |
| G5: ARAEx 200mg\kg of B.W | 110.83±0.98b | 149.30±0.36b | 270.40±1.36b |
| G6: ARAEx 400mg\kg of B.W | 103.79±0.51c | 146.38±1.24c | 265.41±1.4c |
| G7: AREEx 200mg\kg of B.W | 81.62±0.49f | 130.11±1.28f | 231.67±0.25f |
| G8: AREEx 400mg\kg of B.W | 79.79±0.68g | 112.94±1.88g | 229.60±0.43g |
| LSD | 1.23 | 2.49 | 1.97 |

*The values that differ by a letter in each column are statistically different (P≤0.05). *ARP: Ashwagandha roots powder, ARAEx: Ashwagandha roots aqueous extract, AREEx: Ashwagandha roots ethanolic extract, B.W: Body weight, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase and ALP: Alkaline Phosphates.*

The effects of ARP, ARAEx, and AREEx on total protein in serum and urine of nephrotoxic rats were presented in Table (5). The table's data revealed that there were notable differences in serum total protein levels between the positive and negative control groups. The average values were 5.69±0.031 and 7.00±0.3 (mg/dl), respectively. When compared to control (+), group 8 nephrotoxic rats administered with AREEx (400 mg/kg of B.W) showed the best serum total protein. Urine total protein levels in the positive and negative control groups were found to be markedly different, at 280±2.66 and 50±1.13 (mg/dl), respectively. Nephrotoxic rats given AREEx (400 mg/kg of B.W) had the decreased serum urine total protein levels as compared to the control (+) group. These outcomes agreed with those of [44], who discovered that giving ashwaganda root and leaf extracts orally increased the amount of total protein in the serum in rats that were diabetic.

Table (5): Influence of various doses of ashwagandha roots, aqueous and ethanolic extract on total protein in serum and urine of nephrotoxic rats.

| Parameter / Groups | Serum total protein (mg/dl) Mean ± SD | Urine total protein (mg/dl ) Mean ± SD |
|---|---|---|
| G1: (– ve) | 7.00±0.3c | 50±1.13h |
| G2: (+ ve) | 5.69±0.031f | 280±2.66a |
| G3: ARP 2% | 6.41±0.004e | 95±1.25d |
| G4: ARP 4% | 6.66±0.034d | 90±1.19e |
| G5: ARAEx 200mg\kg of B.W | 6.31±0.009e | 110±1.34b |
| G6: ARAEx 400mg\kg of B.W | 6.37±0.002e | 100±1.53c |
| G7: AREEx 200mg\kg of B.W | 7.22±0.019b | 85±1.41f |
| G8: AREEx 400mg\kg of B.W | 7.55±0.099a | 80±1.69g |
| LSD | 0.19 | 2.76 |

*The values that differ by a letter in each column are statistically different (P≤0.05).*ARP: Ashwagandha roots powder, ARAEx: Ashwagandha roots aqueous extract, AREEx: Ashwagandha roots ethanolic extract and B.W: Body weight.*

Table (6) showed the effect of ARP, ARAEx, and AREEx on the lipid profile of nephrotoxic rats. It is evident that the control group total cholesterol levels 170±1.29 was greater than those of the control group (-) 111±1.1 mg/dl, respectively. Rats from the nephrotoxic group fed on AREEx (400 mg/kg of B.W) observed the best therapy of all the groups as compared to the control (+).The results revealed that the serum triglyceride levels of the positive control group and the negative control group differed significantly (P≤0.05). The averages were 79±0.66 and 142±0.52 mg/dl, respectively. AREEx (400 mg/kg of B.W) offered the best results when compared to control (+).The results that were obtained indicated that the levels of HDL-c in the positive control group (40±0.25) and negative control group (50±0.9) mg/d, differed significantly

(P≤0.05). In comparison to the control (+), the rats in the nephrotoxic group administered with AREEx (400 mg/kg of B.W) reported the most elevated levels of HDL-c. Based on the results, the LDL-c values in the positive control group were 101.6±1.32, whereas those in the negative control group were 45.2±1.1 mg/dl. Nephrotoxic rats given AREEx (400 mg/kg of B.W) displayed the lowest serum LDL-c in comparison to control (+) and it was the best outcome. Additionally, the negative and positive control groups for VLDL-c, at 15.8±0.05 and 28.4±0.25 mg/dl, respectively, found significant differences (P≤0.05). Comparing AREEx (400 mg/kg of B.W) to control (+), the best results was observed. The results align with the findings of [45], that the oral administration of an ethanolic extract derived from two plants, Withania somnifera Dunal (also known as ashwagandha) and Commiphora wightii (Arnott.), was found to reduce serum T.C, T.G, LDL, and increase HDL in hyperlipidemic wistar rats induced by a high-fat diet. The antioxidant properties of W. somnifera contribute to the lipid lowering activity, as well as decrease lipid peroxides, xanthine oxidase, and increase superoxide dismutase. It has been discovered that W. somnifera can increase thyroxin production, which explains how they reduce cholesterol. Furthermore, [46] demonstrated that in experimental rats, a high-cholesterol diet (HCD) combined with Withaferin-A (WA) 10 mg/kg B.W of ashwagandha lowered serum total cholesterol, triglycerides and LDL, while increasing HDL, RNS, inflammatory mediators, oxidative stress, and apoptosis.

**Table (6): The influence of various levels of ashwagandha roots, aqueous and ethanolic extract on lipid profile of nephrotoxic rats.**

| Parameter / Groups | T.C (mg/dl) Mean ± SD | T.G (mg/dl) Mean ± SD | HDL (mg/dl) Mean ± SD | LDL (mg/dl) Mean ± SD | VLDL (mg/dl) Mean ± SD |
|---|---|---|---|---|---|
| G1: (– ve) | 111±1.1h | 79±0.66h | 50±0.9a | 45.2±1.1g | 15.8±0.05g |
| G2: (+ ve) | 170±1.29a | 142±0.52a | 40±0.25g | 101.6±1.32a | 28.4±0.25a |
| G3: ARP 2% | 135±1.8d | 98±0.33d | 44±0.05de | 71.4±1.05c | 19.6±0.09d |
| G4: ARP 4% | 128±1.46e | 92±0.49e | 45±0.85cd | 64.6±1.29d | 18.4±0.11e |
| G5: ARAEx 200mg\kg of B.W | 143±1.39b | 126±0.73b | 42±0.4f | 75.8±1.51b | 25.2±0.19b |
| G6: ARAEx 400mg\kg of B.W | 139±1.6c | 124±0.59c | 43±0.44ef | 71.2±1.11c | 24.8±0.08c |
| G7: AREEx 200mg\kg of B.W | 122±1.26f | 86±0.19f | 46±0.08c | 58.8±0.75e | 17.2±0.99f |
| G8: AREEx 400mg\kg of B.W | 118±1.71g | 83±0.82g | 48±0.99b | 53.4±1.24f | 16.6±0.08f |
| LSD | 2.54 | 0.96 | 1.05 | 2.06 | 0.65 |

*The values that differ by a letter in each column are statistically different (P≤0.05).*ARP: Ashwagandha roots powder, ARAEx: Ashwagandha roots aqueous extract, AREEx: Ashwagandha roots ethanolic extract, B.W: Body weight, T.C: Total cholesterol, TG: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein and VLDL: Very low density lipoprotein.*

The impacts of ARP, ARAEx, and AREEx on HB%, RBCs, WBCs and PLT of nephrotoxic rats are illustrated in Table (7). The mean HB% of the control (-) group

was found to be greater than that of the control (+) group, at 15.75±0.022 and 10.40±0.001 (g\dl), respectively. When compared to the control group (+), nephrotoxic rats fed on group (8) AREEx (400 mg/kg of B.W.) exhibited the greatest increase in HB% and yielded the best outcome. It was seen that the control (-) group mean RBCs value was 6.30±0.003 and the control (+) group was 3.74±0.007 (106/µL), respectively. When comparing group (8) treated with AREEx (400 mg/kg of B.W) to control (+), the most effective group for raising RBCs was identified. In accordance to the results, the control (-) group WBCs mean value was greater than the control (+) group, coming in at 9.34±0.25 and 4.21±0.25 (103/µL), respectively. In comparison to control (+), AREEx (400 mg/kg of B.W) provided the best treatment for WBCs. Due to, the same tables data suggested that the control (-) group's mean PLT value was larger than the control (+) group's, at 614.5±2.11 and 160±1.25 (103/µL), respectively. When compared to control (+), nephrotoxic rats given AREEx (400 mg/kg of B.W.) had the best PLT result. According to [47], ashwaganda 300 mg/kg B.W given orally increased the total count of white blood cells (WBC) and platelets after treatment; however, there was no statistically significant changes in the RBCs count observed in any group during the study against toxicity in rats because Withania somnifera root extract has been demonstrated to have beneficial properties like anti-inflammatory, anti-arthritic, anti-oxidant, and immunomodulatory activities. Furthermore, ethanolic extracts of Withania somnifera (EEWS) were shown to be an efficient immuno-regulatory agent, as evidenced by an increase in RBCs, WBCs, and HB as hematological parameters in male albino rats [48].

**Table (7): The influence of various doses of ashwagandha roots, aqueous and ethanolic extract on HB%, RBCs, WBCs and PLT of nephrotoxic rats.**

| Parameter / Groups | HB% (g/dl) Mean ± SD | RBCs (106/µL) Mean ± SD | WBCs (103/µL) Mean ± SD | PLT (103/µL) Mean ± SD |
|---|---|---|---|---|
| G1 (– ve) | 15.75±0.022a | 6.30±0.003a | 9.34±0.25a | 614.5±2.11a |
| G2 (+ ve) | 10.40±0.001h | 3.74±0.007f | 4.21±0.002d | 160±1.25h |
| G3: ARP 2% | 12.15±0.003e | 5.45±0.45c | 6.99±0.012c | 485±2.01e |
| G4: ARP 4% | 12.20±0.025d | 5.51±0.222c | 7.09±0.005c | 495.5±1.32d |
| G5: AEAR 200mg\kg | 11.11±0.034g | 4.61±0.063e | 6.50±0.022c | 402±1.99g |
| G6: AEAR 400mg\kg | 11.35±0.046f | 4.78±0.008d | 6.90±0.009c | 438±2.5f |
| G7: EEAR 200mg\kg | 13.45±0.006c | 5.62±0.003c | 8.63±0.004b | 523.5±2.78c |
| G8:EEAR 400mg\kg | 14.20±0.003b | 5.94±0.088b | 8.80±0.888ab | 610.6±2.83b |
| LSD | 0.041 | 0.15 | 0.56 | 3.76 |

*The values that differ by a letter in each column are statistically different (P≤0.05). *ARP: Ashwagandha roots powder, ARAEx: Ahwagandha roots aqueous extract, AREEx: Ashwagandha roots ethanolic extract, B.W: Body weight, HB: Hemoglobin, RBCs: Red blood cell, WBCs: White blood cell and PLT: Platelet count.*

The effect of ARP, ARAEx, and AREEx on IgG, IgA, and IgM of nephrotoxic rats are displayed in the following Table (8). The data collected showed that the control (-) group mean IgG value was 456.4±2.2, while the control (+) group mean value was 167.75±1.58 ng/ml. When compared with the control (+), Group 8 AREEx (400 mg/kg of B.W), got the best IgG levels. The remainder of the table (8) indicates the value of IgA of control (+) 1213.5±3.99 while control (-) was 311.1±2.59, respectively and IgM value of control (+) greater than control (-) which were 496.4±1.9 and 260.1±1.28 (ng/ml) respectively. When comparing to control (+), AREEx fed on (400 mg/kg B.W.) reported the least amount of IgG and IgM reduction. These findings were in parallel to those of [49], who found that an aqueous extract of ashwagandha root (5 mg/rat/day) enhanced IgG against So2 in rats because of the active components' antistress and antioxidative qualities, which hasten hematopoiesis and promote antibody formation. As part of innate immunity, WS (Withania somnifera) root and leaf extract optimized for withanolide glycosides (withanoglycosides) has also been shown to raise immunoglobulin, as well as IFN-gamma and T-cells CD3+ and CD4+ in humans [50]. These findings implied a significant role in maintaining human innate and adaptive immunity, which is essential for identifying and reacting correctly to prevalent bacteria, viruses, and allergens.

Table (8): Influence of various levels of ashwagandha roots, aqueous and ethanolic extract on immunoglobulins IgG, IgA and IgM of nephrotoxic rats.

| Parameter / Groups | IgG (ng/mll) Mean ± SD | IgA (ng/ml) Mean ± SD | IgM (ng/ml) Mean ± SD |
|---|---|---|---|
| G1 (– ve) | 456.4±2.2a | 311.1±2.59h | 260.1±1.28h |
| G2 (+ ve) | 167.75±1.58h | 1213.5±3.99a | 496.4±1.9a |
| G3: ARP 2% | 251.15±2.03e | 411.40±3.6d | 382.2±1.5d |
| G4: ARP 4% | 284.4±2.44d | 390.41±2.32e | 333.4±1.06e |
| G5: AEAR 200mg\kg | 184.48±2.83g | 686.4±3.14b | 411.5±1.89b |
| G6: AEAR 400mg\kg | 223.34±2f | 434.5±2.34c | 394.4±1.4c |
| G7: EEAR 200mg\kg | 341.14±2.99c | 350.11±2.16f | 270.4±1.19f |
| G8:EEAR 400mg\kg | 382.2±3.15b | 330.01±2.84g | 265.1±1.89g |
| LSD | 4.25 | 5.08 | 2.68 |

*The values that differ by a letter in each column are statistically different (P≤0.05). *ARP: Ashwagandha roots powder, ARAEx: Ashwagandha roots aqueous extract, AREEx: Ashwagandha roots ethanolic extract and B.W: Body weight.*

The effect of ARP, ARAEx and AREEx on serum blood glucose levels in nephrotoxic rats is shown in Table (9). Significant differences (P≤0.05) were seen in the mean serum glucose results of the control (-) group, which were 456.4±2.2, whereas the control (+) group results were 167.75±1.58 mg/dl. Rats in the nephrotoxic group that were administered with AREEx (400 mg/kg of

B.W) saw the lowest amount of blood glucose comparison with control (+) group. These results are in the same line with those of [51], who determined that by lowering inflammatory markers and increasing insulin sensitivity, Withania somnifera root (WS) decreased serum glucose in rats. Withaferin A appears to be the principal active ingredient in charge of these effects. Furthermore, [52] proved that Withaferin A has strong therapeutic promise since it can effectively regulate type 1diabetes in rats that has been created by modulating Nrf2/NFκB signaling.

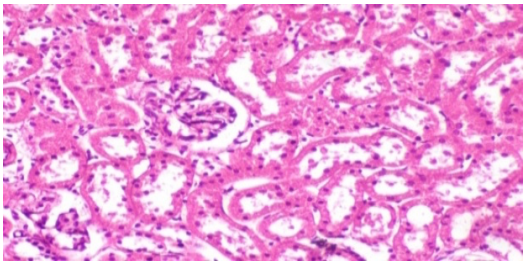
**Table (9): Serum glucose of nephrotoxic rats affected by feeding on ashwaganda roots, aqueous and ethanolic extract.**

| Groups | Glucose (mg/dl) Mean ± SD |
|---|---|
| G1 (– ve) | 122±1.11g |
| G2 (+ ve) | 247±1.23a |
| G3: ARP 2% | 184±1.41c |
| G4: ARP 4% | 177±1.63d |
| G5: ARAEx 200mg\kg of B.W | 201± 1.25b |
| G6: ARAEx 400mg\kg of B.W | 186±1.06c |
| G7: AREEx 200mg\kg of B.W | 160±1.54e |
| G8: AREEx 400mg\kg of B.W | 150±1.92f |
| LSD | 2.46 |

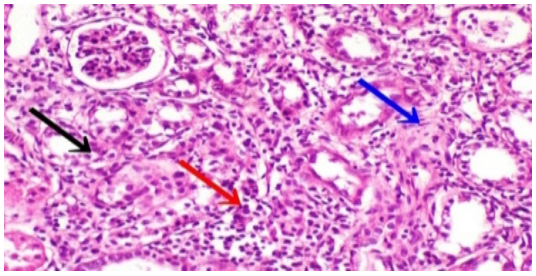
*Values in each column with different letters are significantly different (P≤0.05). *ARP: Ashwagandha roots powder, ARAEx: Ashwagandha roots aqueous extract, AREEx: Ashwagandha roots ethanolic extract and B.W: Body weight.*

4. Kidney histopathological examination:

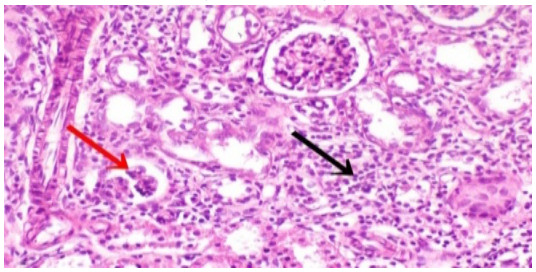
Rats from group 1 (negative) showed normal renal parenchyma, renal cortex, and renal medulla histological structure under a microscope (Pic 1). In adverse, rats from group 2 (positive) showed kidneys with notable histological lesions in the unfavorable phase. These lesions included vacuolar degeneration of the renal tubule epithelium, interstitial nephritis, interstitial fibroplasia, and atrophy of the glomerular tuft (Pic 2&3). Meanwhile, rats from group 3 (powdered ashwaganda roots, 2%) had renal tissue that displayed vacuolar degradation of the renal tubule lining (Pic 4) and per tubular infiltration of a few inflammatory cells (Pic 5). However, the kidneys of the rats in group 4 (powder made from 4% ashwagandha roots) showed vacuolar degeneration of the epithelium lining some renal tubules (Photo 6), bowman's space and the lumen of certain renal tubules contain proteinaceous eosinophilia materials (Pic 7). Similarly, the renal tubules lining in groups 5 and 6 (aqueous extract 200 and 400 mg/kg) displayed vacuolar degeneration of the epithelium (Pic 8). Rats from group 7&8 (ethanolic extract 400 mg/kg) showing normal histological structure of renal parenchyma (Pic 9) except the vacuolar degeneration of certain renal tubules' epithelial lining (Pic 10).



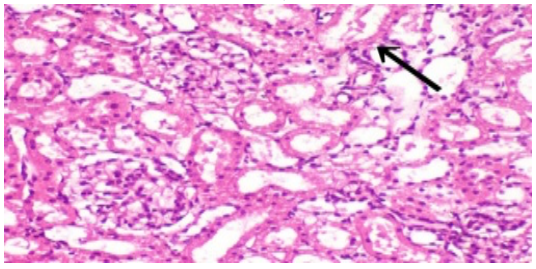
Pic (1): Photomicrograph of group 1 (negative) showed normal renal parenchyma, renal cortex, and renal medulla histological structure (H & E X 400).



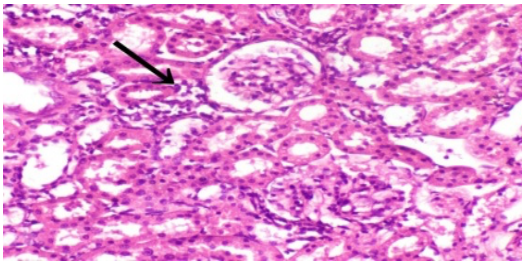
Pic (2): Photomicrograph of kidney of rat from group 2 (positive) demonstrating interstitial fibroplasia (blue arrow), interstitial nephritis (red arrow), and vacuolar degeneration of the epithelium lining renal tubules (black arrow) (H & E X 400). (H & E X 400).



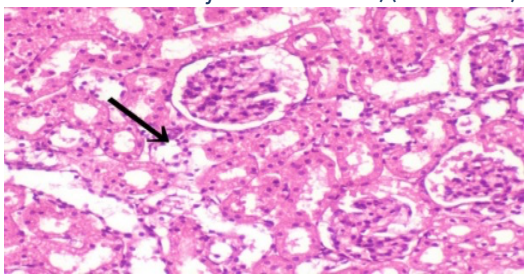
Pic (3): Photomicrograph of kidney of rat from group 2 (positive) showing demonstrating atrophy of the glomerular tuft (red arrow) and interstitial nephritis (black arrow) (H & E X 400).



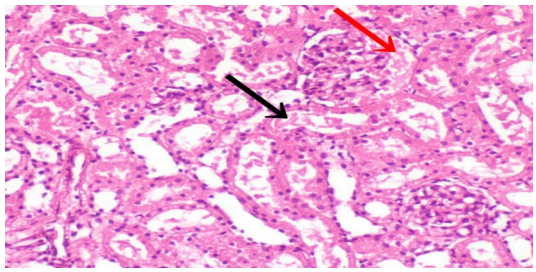
Pic (4): Photomicrograph of kidney of rat from group 3 (ashwaganda roots powder) showing renal tissue that displayed vacuolar degradation of the renal tubule lining (black arrow) (H & E X 400).



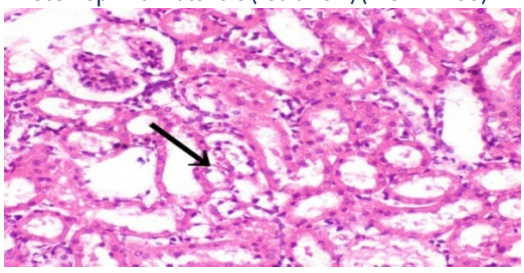
Pic (5): Photomicrograph of kidney of rat from group 3 (ashwaganda roots powder) showing per tubular infiltration of a few inflammatory cells black arrow) (H & E X 400).



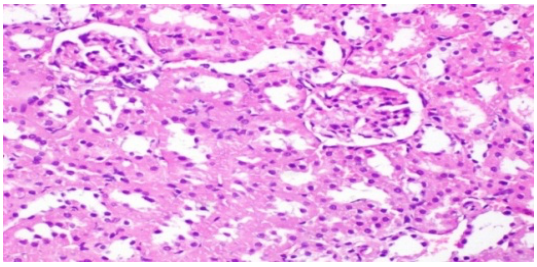
Pic (6): Photomicrograph of kidney of rat from group 4 (ashwagandha roots powder) showing vacuolar degeneration of the epithelium lining some renal tubules (black arrow) (H & E X 400).



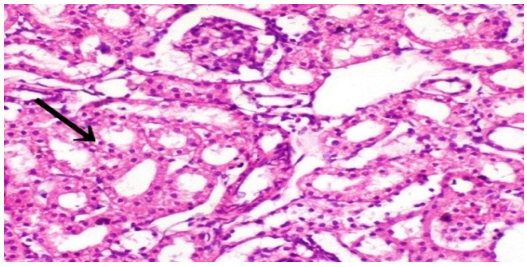
Pic (7): Photomicrograph of kidney of rat from group 4 (ashwaganda roots powder) showing bowman's space and the lumen of certain renal tubules contain proteinaceous eosinophilia materials (red arrow) (H & E X 400).



Pic (8): Photomicrograph of kidney of rat from group 5&6 (aqueous extract 200 & 400 mg/kg) displayed vacuolar degeneration of the epithelium (black arrow) (H & E X 400)..



Pic (9): Photomicrograph of kidney of rat from group 7&8 (ethanolic extract200&400mg/kg) showing normal histological structure of renal parenchyma (H & E X 400)



Pic (10): Photomicrograph of kidney of rat from group 7&8 (ethanolic extract 200& 400mg/kg) showing the vacuolar degeneration of certain renal tubules' epithelial lining (black arrow) (H & E X 400).

## CONCLUSION

Based on these findings, it is possible that the antioxidant and anti-inflammatory properties of ethanolic ashwaganda root extract can serve as an efficient preventive against kidney injury. We therefore advise using it as a functional food to prevent or treat nephrotoxicity in conjunction with other treatments.

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التغذية وعلوم الاطعمة

# التأثيرات الكيموحيوية والتغذوية لجذور الأشواجندا على خلل وظائف الكلي ونشاط التوازن المناعى في الفئران

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**الملخص العربى:**

لقد ثبت بالفعل أن العديد من النباتات ومستخلصاتها لها تأثيرات إيجابية كبيرة على الالتهاب والتليف بالإضافة إلى تحسين الخلل الكلوي من خلال عملها كمضادات للأكسدة. يهدف هذا العمل إلى دراسة تأثير جذور الأشواجندا والمستخلص المائي و الايثانولي على السمية الكلوية للفئران.تم تقسيم أربعين ذكرًا بالغًا من فئران الألبينو إلى مجموعتين رئيسيتين؛ المجموعة الرئيسية الأولى (5 فئران) كمجموعة سالبة تتغذي على نظام الغذاء الاساسى والمجموعة الرئيسية الثانية (35 فأر) والتى تم حقنها بالجنتاميسين لاحداث السمية الكلوية وقسمت الى سبع مجموعات (خمسة فئران في كل مجموعة): المجموعة الثانية كمجموعة موجبة والتي تتغذي على نظام الغذاء الاساسي, المجموعات (3-4) والتى تتغذي على نظام غذائي يحتوي على (2&4% من مسحوق جذور الأشواجندا), المجموعات (5-6) (7-8) والتى تتغذي على نظام غذائي يحتوي على المستخلص المائى والمستخلص الايثانولى من جذور الاشواجندا (200 و 400 ملجم/كجم من وزن الجسم) عن طريق الفم على التوالى. فى نهاية التجربة، تم تحليل سيرم الدم لوظائف الكلى , وظائف الكبد , دهون الدم , والصوديوم والبوتاسيوم, عدد كريات الدم البيضاء والحمراء والهيموجلوبين والصفائح الدموية ,الجلوكوز وتم جمع البول لمدة 24 ساعة لتقدير الصوديوم والبوتاسيوم والبروتين الكلى والكرياتينين وتم تقدير ايضا الجلوبيولينات المناعية (IgG-IgA-IgM). وفقا للنتائج: تم تحسين وظاف الكلى والكبد فى الدم والجلوبيولينات المناعية ودهون الدم بشكل أفضل مع المستخلص الإيثانولى عن طريق الفم لجذور أشواجندا (400 مجم / كغم من وزن الجسم). الخلاصة: أظهرت الفئران المعالجة بالمستخلص الإيثانولى لجذور الأشواجندا (400 مجم/كجم من وزن الجسم) عن طريق الفم تحسنًا فى وظائف الكلى والنشاط المناعى والبنية النسيجية للكلى وذالك من خلال الشقوق الحرة والنشاط المضاد للأكسدة.

الكلمات الكاشفة: السمية الكلوية، المناعة،جذور الأشواجندا, الجنتاميسين , الويثانوليدات و ويثافيرين-أ