

## Nephroprotective Effect of Khar-E-Khasak Khurd (*Tribulus terrestris* Linn) on Gentamicin-Induced Experimental Nephrotoxicity in Rats

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### Authors' contributions

This work was carried out in collaboration among all authors. Author FA conceived and conducted the experiment. Author MUA help in conceiving the idea, designed the study and final manuscript preparation. Author MA guided in the experiment and help in calculation. Author KJ designed the final data, tables and graphs, and article planning. All authors read and approved the final manuscript.

### Article Information

#### Editor(s):

(1) Dr. Rodolfo Valtuille, Salvador University, Argentina.

(2) Dr. P. Kiranmayi, GITAM University, India.

#### Reviewers:

(1) Ankit Kumar Singh, Rajasthan University of Veterinary and Animal Sciences, India.

(2) Samira Asgharzade, Shahrekord University of Medical Sciences, Iran.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/60704>

Original Research Article

Received 20 July 2020  
Accepted 24 September 2020  
Published 10 October 2020

### ABSTRACT

**Background:** Aminoglycoside-Gentamicin is an effective antibiotic against Gram-negative bacterial infections and used in allopathic clinical practice. But its nephrotoxicity limits its frequent clinical use. Unani system of Medicine (USM) has a unique description for tonic (Muqawwiyyat) of many vital organs e.g. heart, brain, eye, kidney, and liver. In Unani classics many nephroprotective drugs have been mentioned by the scholars, Khar-e-Khasak Khurd (KKK) is one of them. This study was designed to evaluate the nephroprotective effect of KKK powder on gentamicin-induced nephrotoxicity in rats.

**Methods:** Albino rats of Wistar strain of either sex were divided into four groups, each having six animals. Nephrotoxicity was induced by giving gentamicin 100-mg/kg b.w/day/subcutaneous in neck region for four days. Gentamicin-administered rats were treated with powder of KKK (840 and 1680 mg/kg/Day) the treatment was started 3 days before the administration of gentamicin while it was continued for 14 days from the day of gentamicin administration.

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**Results:** Administration of gentamicin significantly increased the Blood Urea nitrogen (BUN)-155% serum creatinine (SC)-187% and Serum Uric Acid (SUA)-123% levels. The oral administration of KKK (840 mg/kg) inhibited the rise in blood urea (47.09%), serum creatinine (95.93%) and uric acid (51.41%). There were 70.79% inhibition in the rise of BUN, 72.35% inhibition in the rise of serum creatinine and 79.35% inhibition in the rise of uric acid with 1680mg (KKK).

**Conclusion:** KKK powder has a potential to prevent gentamicin-induced experimental nephrotoxicity in dose dependent manner. The kidney protective effect of KKK powder against gentamicin-induced nephrotoxicity proved the claims of Unani physicians.

**Keywords:** Khar-e-Khasak Khurd; gentamicin; nephroprotection; unani medicine; Muqawwi-e-kulya.

## 1. INTRODUCTION

Kidneys are the vital organs of the body that remove metabolic wastes through urine. Our body is exposed routinely to a variety of diverse chemicals that harm the kidneys. Medications, natural products, industrial chemicals, environmental pollutants, pesticides, etc., cause damage to different organs of the body at various levels [1].

Aminoglycosides (Gentamicin) are the most frequently used class of antibiotics, especially active against Gram-ve infection. A major complication of the use of these drugs especially gentamicin (GM) is nephrotoxicity. It produces acute renal failure of the dose-related cytotoxicity significantly. Investigators who have used well-defined measure of nephrotoxicity indicate an incidence rate of 7 to 36%. Various studies indicated that the average incidence of GM nephrotoxicity is around 15% [2-3]. One of the most clinical manifestations is the presence of non-oliguric renal failure with elevation of serum creatinine (SC) concentration. Impaired urine concentrating ability will be present and enzyuria with N-acetylglucosaminidase, proteinuria with  $\beta_2$  microglobulin and lysozymuria observed [4-6]. It is a well-known fact today that due to the narrow therapeutic toxicity ratio most patients on aminoglycoside therapy will manifest some evidence of renal toxicity [1].

The most common and earliest indication of this increased urinary excretion of proteins [7] and of lysosomal and brush border membrane enzymes [8]. These changes can be detected as early as the first 24 hours of initiating the drug therapy. The dose and the duration of therapy determine the magnitude and frequency of these changes, which indicate the onset of proximal tubular cell necrosis.

The next manifestation of this nephrotoxicity is the increased urinary excretion of tubular cell casts, epithelial cells and white blood cells. This stage signifies a more profound necrosis and advanced cell injury [7].

A relatively late manifestation of GM nephrotoxicity is the depression of GRF. It requires 5 to 7 days Gentamicin therapy in humans for the depression of GRF to occur [9]. Histopathologic lesions may be observed even in the absence of a recordable decline in whole kidney GRF [10].

Baylis et al reported no ultra structural alterations of the glomerular capillaries [11] while Luft et al reported dose dependent decrease in size, density and area of glomerular endothelium of rats treated with gentamicin [12]. Several other theories have been proposed by different worker implicating tubular [13] (Neugarten et al 1983) and increased backleak as a pathogenic factor causing depression of GRF in late GM nephrotoxicity [14].

KKK *Tribulus terrestris* L. is a trailing plant commonly grows in sandy soil. Tribulus species are usually branching prostrate herbs, usually silky with white or yellow flowers and spinous or tuberculate fruits. The powder is of a characteristic light yellow colour slightly acidic in taste and faintly aromatic odour. Microscopic examination of the powder, after clearing with 75% chloral hydrate, reveals that it contains abundance of fibers, epidermal trichomes, xylem elements and few large thin – walled parenchyma cells [15].

In unani classical literature the action of KKK *Tribulus terrestris* L. are mentioned as: Muqawwi-e-Kulya (nephrotonic), Muqawwi-e-Bah (aphrodisiac), Musakkin-e-Alam (analgesic) Muhallil-e-Auram (anti-inflammatory), Tiryaaq (antidote) Daf-e-Tauffun (antiseptic), Mushtahi-e-Tuam (appetizer), Mulayyan (laxative), Musaffi-e-

Dam (blood purifier), Kasir-e-Riyah (carminative), Mubarrid (cooling), Munzij (concoctic), Jali (detergent), Mujaffif (desiccant), Muhafiz-e-kulya (nephroprotective), Mudir-e-Baul (diuretic), Mudir-e-Haiz (emmenagogue), Mufattit-e-Hisat (lithotriptic), Radae (divergent), Moghalliz-e-Mani (semen inspissant), Muqawwi-e-Meda (stomachic), Muqawwi-e-Aam (general tonic) [16].

## 1.1 Objective of Study

The objective of this study was taken to evaluate the efficacy of the crude power of Khar-e-khasak khurd (KKK) *Tribulus terrestris* against gentamicin-induced nephrotoxicity in wistar albino rats.

## 2. MATERIALS AND METHODS

### 2.1 Materials

#### 2.1.1 Animals

Twenty four (24) albino wistar rats of both sexes of weighing between 150 g–200 g were taken from Animal House facility of Jamia hamdard, New Delhi in this study. All the animals were kept under standard laboratory condition in polypropylene cages at 25±1°C temperature and feed with standard diet supplied by New Maharashtra Chakan oil mills LTD, Mumbai.

### 2.2 Methods

All the experimental animals were randomly divided into four (4) groups with six (6) rats in each group. The rats were allowed to acclimatize for one week on normal rat feed.

#### 2.2.1 Induction of nephrotoxicity

Nephrotoxicity was induced by subcutaneous injection 100 mg/kg body weight for four days to the animals of group-II, III & IV [1]. This injection was given from day three to seven of the treatment protocol. After injection all the animals were observed for one hours for the behavior.

#### 2.2.2 Test drug (powder of KKK) and rout of administration

The test drug under the name of Khar-e-Khasak Khurd (KKK) was procured from M/s Mohammad Hussain and Ajmal Hussain, Khari baoli, Delhi, 110006. The botanical authenticity of the drug

was established as *Tribulus terrestris* Linn. by the taxonomist working in NISCOM (National Institute of Science Communication), Dr. K.S. Krishna marg, near Pusa Gate, New Delhi. The specimen sample was also submitted in Department of Ilmu Advia, Faculty of Medicine (U), Jamia Hamdard, New Delhi. The drug was grinded and sieved with 120 no mesh to get the fine powder.

The fine powder of Khar-e-Khasak Khurd (KKK) *Tribulus terrestris* Linn. was administered through the oral route at a low and high dose of 840 mg/kg and 1680 mg/kg body weight in two group-III and Group-IV of the rats for 14 days.

#### 2.2.3 Treatment protocol

Twenty four (24) albino wistar rats grouped into four with six rats in each group was treated as follow;

Group-I served as Normal control and given subcutaneous injection in neck region of distilled from day four to seven and feed with normal saline through oral tube for 14 days.

Group-II served as negative control and treated with subcutaneous injection of gentamicin 100 mg/kg body weight in neck region from day four to seven and feed with normal saline through oral tube for 14 days.

Group-III served test group of low dose and treated with gentamicin same to group-II and given KKK in 840 mg/kg body weight daily using intra-gastric tube for 14 days.

Group-IV served as test group of high dose and treated with gentamicin same to group-II and feed with test drug in a dose of 1680 mg/kg body weight similar to group III.

#### 2.2.4 Experimental parameters and methods

On completion of protocol therapy period of 14 days, next day all the animals were sacrificed by decapitation after anaesthesia and blood samples were collected for analysis of Urea, uric acid, and creatinine and were carried out using appropriate methods as follows.

Blood Urea Nitrogen (BUN) was estimated by diacetyl monoxime method, Serum creatinine by alkaline picrate method and Serum uric acid by phosphotungstic acid reagent method mentioned by Godkar 2003 [17].

### 2.3 Statistical Analysis

Data were expressed as mean $\pm$ S.E.M and analyzed by one- way analysis of variance (ANOVA) followed by Dunnett's 't' test. The probability level less than 5% considered to be significant.

## 3. RESULTS

### 3.1 Effect of KKK (*Tribulus terrestris* L) on BUN in Gentamicin Induced Nephrotoxicity in Rat Model

Animals received subcutaneous injection of gentamicin 100 mg/kg body weight in neck region for four days caused nephrotoxicity as evidenced by marked elevation in blood urea concentration, a 55% increase in comparison to the control group was observed. This increase was significant  $P<0.01$  and assumed as 100% increase in toxic group. Low dose of KKK in 680 mg/kg body weight significantly decrease the rise of BUN 83.30% in compare to toxicant and control group with a significant of  $P<0.01$ , while the high decrease BUN 70.80% in comparisons to toxicant and control as shown in Table 1.

### 3.2 Effects of KKK (*Tribulus terrestris* L) on SC in Gentamicin Induced Nephrotoxicity in Rat Model

Subcutaneous injection of gentamicin in the dose of 100 mg/kg body weight for four days. There is significantly increase the level of SC 87.23% in toxicant group in comparison to control. This increase is significant  $P<0.01$  and assumed as 100% increase in toxic group. The low dose of KKK significantly inhibited the rise of SC 95.93% while in high dose the percentage of inhibition was 72.36% in compare to toxicant and control group as shown in Table 2.

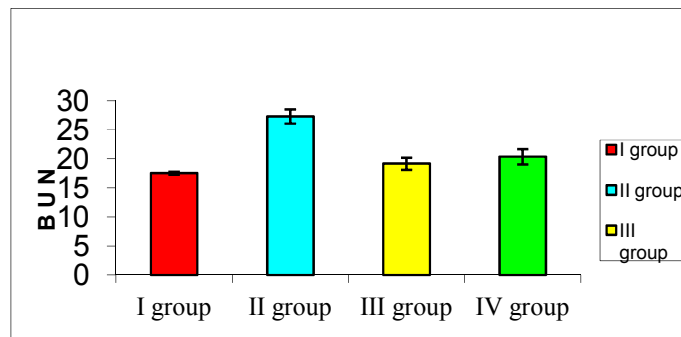
### 3.3 Effects of KKK (*Tribulus terrestris* L) on SUA in Gentamicin Induced Nephrotoxicity in Rat Model

There was 23.21% increase in SUA level in toxicant group in comparison to control group. This increase is assumed 100% change in toxicant group in comparison to control. The test drug KKK reduces the level significantly in comparison to toxicant group. There were 148% and 120.67% inhibition observed in low and high dose comparatively as shown in Table 3.

**Table 1. Effects of powder of KKK (*Tribulus terrestris* L) on BUN in gentamicin induced nephrotoxicity in rat model (oral treatment period –14 days)**

Groups	Treatment	Dose	BUN level (mg/dl) (MEAN $\pm$ S.E.M.)	% of change	% of inhibition
I	Control (vehicle)	10 ml/Kg	17.54 $\pm$ 0.24	-	-
II	Gentamicin	100 mg/Kg/day	27.30 $\pm$ 1.22 <sup>a*</sup>	100	-
III	KKK+Genta	840+100 mg/Kg/day	19.17 $\pm$ 1.03 <sup>b*</sup>	16.70	83.30
IV	KKK+Genta	1680+100 mg/Kg/day	20.39 $\pm$ 1.33 <sup>b*</sup>	29.20	70.80

BUN = Blood urea nitrogen, <sup>a</sup>Statistically significant, <sup>a</sup>in comparison with control, <sup>b</sup>in comparison with toxicant, \*  $P<0.01$

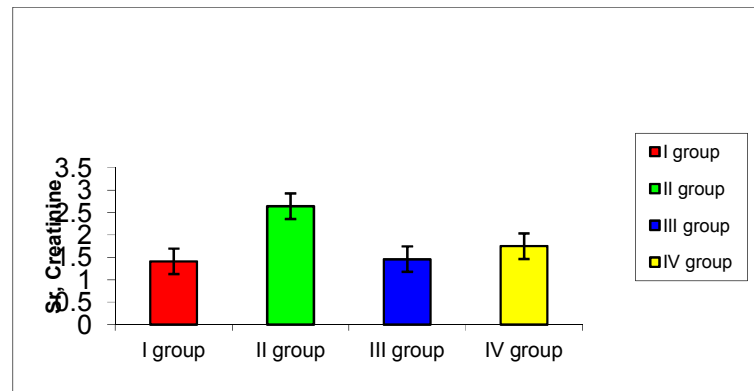


**Fig. 1. Effects of powder of KKK (*Tribulus terrestris* L) on BUN in Gentamicin induced nephrotoxicity in rat model**

**Table 2. Effects of powder of KKK (*Tribulus terrestris* L) on SC in Gentamicin induced nephrotoxicity in rat model (Oral treatment period –14 days)**

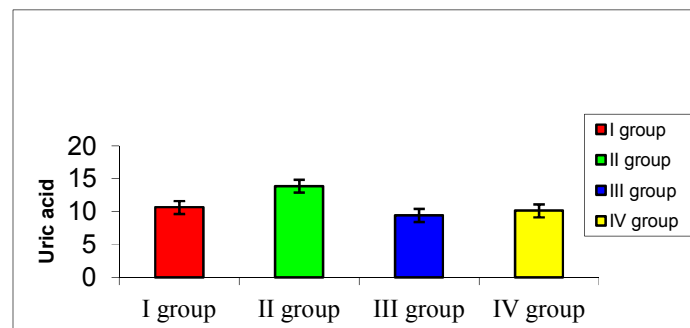
Groups	Treatment	Dose	SC level (mg/dl) (MEAN±S.E.M.)	% of change	% of inhibition
I	Control (vehicle)	10ml/Kg	1.41±0.10	-	-
II	Gentamicin	100mg/Kg/day	2.64±0.20 <sup>a*</sup>	100	-
III	KKK+Genta	840+100mg/Kg/day	1.46±0.07 <sup>b*</sup>	4.0	95.93
IV	KKK+Genta	1680+100mg/Kg/day	1.75±0.06 <sup>b*</sup>	27.6	72.36

SC = Serum creatinine, \*Statistically significant, <sup>a</sup>in comparison with control, <sup>b</sup>in comparison with toxicant, \*P<0.01

**Fig. 2. Effects of powder of KKK (*Tribulus terrestris*) on SC in Gentamicin induced nephrotoxicity in rat model****Table 3. Effects of powder of KKK (*Tribulus terrestris* L) on SUA in Gentamicin induced nephrotoxicity in rat model (Oral treatment period –14 days)**

Groups	Treatment	Dose	SUA level (mg/dl) (MEAN±S.E.M.)	% of change	% of inhibition
I	Control (vehicle)	10ml/Kg	10.64±0.31	-	-
II	Gentamicin	100mg/Kg/day	13.11±0.99 <sup>a*</sup>	100	-
III	KKK+Genta	840+100mg/Kg/day	9.44±0.28 <sup>b*</sup>	-48.00	148%
IV	KKK+Genta	1680+100mg/Kg/day	10.13±0.36 <sup>b*</sup>	-20.67	120.67

UA=Uric acid, \*Statistically significant, <sup>a</sup>in comparison with control, <sup>b</sup>in comparison with toxicant, \*P<0.01

**Fig. 3. Effects of powder of KKK (*Tribulus terrestris* L) on SUA in Gentamicin induced nephrotoxicity in rat model**

#### 4. DISCUSSION

Aqueous extract of TT successfully decrease BUN, S. creatinine in oxidative stress nephropathy in rats [18-19]. 50% methanol showed renoprotective activity in obesity-related glomerulopathy [20]. Hydroalcoholic extract of TT fruit showed nephroprotection against the cisplatin [21] and mercuric chloride [22] induced toxicity in the mice. Ethanol extract of *T. terrestris* showed nephroprotective activity in cadmium induced toxicity in rats [23]. Oral administration of *Tribulus terrestris* extract decreased kidney functional disturbance, oxidative stress, and cellular damages against acute kidney injury induced by reperfusion injury in rats [24].

This nephroprotection may be due to the variety of chemical compounds e.g. saponins, flavonoids, alkaloids, etc present in the plant. Among all the phyto-constituents steroidal saponins and flavonoids are considered to be the most important with diverse bioactivities [16]. Other components isolated from KKK includes organic acids, amino acids etc. Organic acids isolated from TT are benzoic acid, vanillic acid, 2-methyl benzoic acid, ferulic acid, succinic acid, palmitic acid monoglyceride, succinic acid, docosanoic acid, Tribulus acid and others. In addition, KKK also contains 4-ketopinonesinol, uracil nucleic acid, coumarin, emodin, and physcion [16].

Some other different extracts of Unani herbal drugs have also showed nephroprotective activity against gentamicin e.g. Bisehri Booti (*Aerva lanata*) [25]; Kundur (*Boswellia serrata*) [26]; habbul Qilt (*Macrotyloma uniflorum* (Lam) Verd.) [27]; Kakoda / Baqla-e-Yahoodia (*Momordica dioica* Roxb.) [28]; Sahajna (*Moringa oleifera*) [29]; Khajoor (*Phoenix dactylifera*. L) [30]; Bhui amla (*Phyllanthus amarus* Schum) [31]; Biskhapra (*Trianthema portulacastrum* Linn) [32]. Crude powder of TT has significantly reduces the elevated biomarkers by gentamicin induced nephropathy in albino rats. The reduction is may be due to the various biological active compounds presents in the plant e.g. saponins, flavonoids, alkaloids etc. There is long list of Unani herbal plants having nephroprotective activity against different chemicals e.g. Waj-e-Turki (*Acorus calamus*), Aaksaar /Bisehri Booti (*Aerva lanata*), Kachnal/Kachnar (*Bauhinia variegata* Linn.), Shaljum (*Brassica rapa*), Kharnoob-e-Shami (*Ceratonia siliqua* Linn.),

Daoodi/Gul-e-Daoodi (*Chrysanthemum indicum* Linn.), Revand Hindi/Rhubarb (*Rheum emodi*), Zanjabeel (*Zingiber officinale* Roscoe) against cisplatin; Habbul qil qil (*Cardiospermum halicacabum* Linn.), bhui amla (*Phyllanthus amarus* Schum), against acetaminophen; Papita (*Carica papaya* Linn.), Kharnoob-e-Shami (*Ceratonia siliqua* Linn.) against carbon tetrachloride; Kheyaar shanbar (*Cassia fistula* Linn.) against bromobenzene; Baqlat-ul-Khatateef (*Curcuma longa*) against sodium fluoride; Dudhi khurd (*Euphorbia hirta* Linn.) against nitrobenzene induced nephropathy in experimental models [33].

#### 5. CONCLUSION

Loss of function of kidney leading to the retention of nitrogenous waste products of metabolism in blood, failure of regulation of fluid, and electrolyte balance along with endocrine dysfunction. This condition happens when the structural and functional damage is 25% of normal functioning nephrons. This may occurs due to various exogenous and endogenous agents, e.g. cyclosporins, antibiotics like aminoglycosides, chemotherapeutic agents, organic solvents, acetaminophen, and illegal abortifacients [1,34]. Gentamicin causes nephrotoxicity in almost 69% of cases of acute renal failure due to damage to the parenchyma of kidney [35]. Gentamicin is a cationic drug binds to the anionic phosphoinositides receptors located on the apical membrane of proximal tubular cells. It interferes with the catabolism of receptor by directly inhibiting phospholipase C, by modifying substrate-enzyme affinity or by raising the intralysosomal pH above the effective range of enzyme. Resultant the significant reduction in whole kidney adenosine triphosphate levels, adenosine diphosphate dependent.

The results of this experiment also showed a good nephroprotective response by reduction in BUN by 83.30% and 70.80%, Serum creatinine by 95.93% and 72.36%, and Serum uric acid by 148% and 120.67% through low and high doses of powder of KKK respectively. This reduction of biomarkers may be due to the biological compounds present in the plant. It is also proved the claims of Unani scholars mentioned it for treatment of renal failure [16]. Further human clinical trials may be designed to prove its efficacy in cases of chronic kidney diseases as potential nephroprotective drug in clinical practice.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

The protocol has been approved by University Animal Ethics Committee and Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed during the study.

## ACKNOWLEDGEMENTS

The authors are thankful to the Honorable Vice Chancellor, Jamia Hamdard and Hamdard National Foundation, New Delhi for providing excellent facilities of academics and research to carry out this research work.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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