

## THE POSSIBLE PROTECTIVE EFFECTS OF NIGELLA SATIVA CRUDE SEEDS ON GENTAMICIN INDUCED NEPHROTOXICITY IN UNILATERAL NEPHROECTOMIZED RATS

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### ABSTRACT

*Nigella sativa* seed is widely used as general tonic, it was suggested to have a general protective roles. Twenty four white male albino rats were divided into four equal groups. The first group was exposed to sham operation and received saline through an oro-gastric tube for 15 consecutive days and kept as control. The other groups were subjected to unilateral nephroectomy. The second group was given suspension of crushed seeds of *Nigella sativa*, 2gm / kg B.W. orally daily for 15 consecutive days. The third group was injected intraperitoneally (i.p.) by gentamicin in a dose of 30 mg/kg B.W. daily for the same period. The fourth group was injected (i.p.) by 30 mg/kg B.W. gentamicin i.p., in combination with 2gm /kg B.W. suspension of crushed seed of *Nigella sativa* orally daily for the same period. Changes in blood pressure, heart rate, blood urea and serum creatinine were recorded. The histopathological changes in kidneys were also demonstrated. The results of this study, revealed that, gentamicin alone showed a significant increase in blood pressure, blood urea, and serum creatinine, there is no significant changes in the group given *Nigella sativa* alone. On the other hand, insignificant changes were recorded in the same parameters, in the group given gentamicin in combination with suspension of crushed seeds of *Nigella sativa*. Histopathological studies of the kidney, showed tubular degeneration, tubular necrosis, interstitial haemorrhage and basement membrane distortion with gentamicin. On the other hand no histopathological changes were recorded in gentamicin and *Nigella sativa* treated group. These changes supported our findings. These results suggested that *Nigella sativa* seeds and their constituents did not produce deleterous effects on kidney tissues and function, but prevented the nephrotoxic manifestations of gentamicin.

### INTRODUCTION

Gentamicin is a widely used aminoglycoside antibiotic in the treatment of gram negative bacterial infection (1). Unfortunately the clinical usefulness of this is limited due to the development of gentamicin induced nephrotoxicity (2,3).

*Nigella sativa* crude seed oil is widely used nowadays, not only for protection but also in the treatment of many clinical syndromes. Recently little researches were carried out to study the possible pharmacological actions of *Nigella sativa* crude seed oil.

It has been found that *Nigella sativa* seed oil inhibited the spontaneous movement of rat and guinea pig uterine smooth muscles and reduced the contraction induced by oxytocin (4) *Nigella sativa* seed oil has immunostimulant effect through the enhancement of the production of interleukin<sub>3</sub> by human lymphocytes (5).

Keshri et al., (6) suggested that hexans extract of *Nigella sativa* seeds prevented pregnancy in Sprague Dawley rats treated orally with 2 gm /kg body weight daily on days 1-10 postcoitus and significant antifertility activity, observed in its column fractions and subfractions at a contraceptive dose level. The same authors added that active hexans extract of *Nigella sativa* seeds exhibited only mild uterotrophic activity, which is directly proportional to ethinyloestradiol, but was devoid of any oestrogenic activity in the immature rat bioassay.

Houghton et al., (7) found that crude seed oil of *Nigella sativa* has antiinflammatory activity, possibly through inhibition of eicosanoid generation and membrane lipid peroxidation, or through inhibition of

cyclo-oxygenase and lipooxygenase pathways of arachidonate metabolism. They reported also that other components of crude seed as unsaturated fatty acids may be contributing to its anti-eicosanoid and antioxidant activity. In spite of extensive use of *Nigella sativa* seed and their constituents as general tonics, the exact pharmacological actions is not fully investigated until now.

Therefore, aim of this study is to elucidate the possible protective role of *Nigella sativa* crude seed oil against gentamicin induced nephrotoxicity in unilateral nephroectomized rats.

### MATERIAL AND METHODS

#### Material:

**Gentamicin:** Garamycin ampoules (80 mg) Memphis - Cairo- ARE.

***Nigella sativa*:** Seeds of *Nigella sativa* were obtained from Egyptian Company for Sugar and Integrated Industries.

**Urethane:** Used as powder from Aldrich, Chemical Co. (England).

**Heparin:** Ampoules (5000 IU/ml) Nile Co. (Egypt).

**Saline:** 0.9 % solution from El-Nasr Co. (Egypt).

**Thiopental sodium:** Vials (0.5gm) powder dissolved in distilled water (Biochem. GmbH-Vienna Austria).

**Stains:** - Haematoxylin and eosin (8). Periodic acid-Schiff (PAS) stain to evaluate the integrity of tubular basement membrane (9).

#### Animals:

Twenty four adult male healthy albino rats weighing about  $180 \pm 20$  g were used for performing these experiments. They were randomized into four equal groups.

**Group 1:** Exposed to sham operation and injected by 1ml saline i.p. and received saline 0.5 ml orally and served as control group.

**Group 2:** Exposed to unilateral nephrectomy and given aqueous suspension of crushed seeds of *Nigella sativa* in a dose of 2g/ kgbody weight per day orally for 15 consecutive days. (6).

**Group 3:** Exposed to unilateral nephrectomy and injected i.p. with gentamicin in a dose of 30 mg /kg. for 15 consecutive days (10).

**Group 4:** Exposed to unilateral nephrectomy and injected with gentamicin 30mg /kg B.W. in combination with suspension of crushed seeds of *Nigella sativa* in a dose of 2gm /kg B.W. orally for 15 consecutive days.

Each group was caged separately and rats were left free for normal feeding and water *ad libitum*. After 15 days animals were anaesthetized with urethane (11) for determination blood pressure and heart rate. At the end of each experiment, blood samples from carotid artery, were taken and centrifuged. Sera were kept at -50°C until the assay for blood urea (12) and creatinine (13). The kidneys were excised, kept in 10% formalin processed and embedded in paraffin film. Blocks were stained with H & E and periodic acid-schiff stain to show tubular B.M. and examined microscopically for histopathological evaluation (14).

**Statistical analysis:**

All values are expressed as the mean ± S.E. The significance of the difference between mean values was analysed, using the Student of "t" test for paired observations and the levels were considered to be significant at  $P \leq 0.05$  (15).

**RESULTS**

**1-Pharmacological and biochemical changes :**

Table (1) : The effect of *Nigella sativa* (2 mg/kg orally), gentamicin (30 mg/kg ip.) and their combination on blood pressure and heart rate in unilateral nephrectomized rat .

Parameter		Control group	<i>Nigella sativa</i> treated group	Gentamicin treated group	Gentamicin combined with <i>Nigella sativa</i> treated group
Blood pressure (mmHg)	mean ± SE	88.33±2.19	92.52±2.5	151.33±4.81*	97.5±1.87
	% changes		4.72%	70.99%	10.17%
Heart rate (b/m)	mean ± SE	386.7±4.69	388.6±6.33	381.7±5.42	390±4.61
	% changes		0.49%	1.29%	0.85%

Number of rats in each group (n) = 6 rats

\* Significant ( $P < 0.05$ )

**A- Changes in blood pressure and heart rate :**

In the present study, it was found that, *Nigella sativa* in a dose of 2 gm/Kg orally produced insignificant increase in the mean arterial blood pressure, from 88.33±2.19 to 92.52±2.5 mmHg. Compared with the control group.

Gentamicin given i.p. in a dose of 30mg/kg, produced significant increase in the mean arterial blood pressure, from 88.33 ± 2.19 up to 151.33 ± 4.81 mmHg ( $P < 0.05$ ). as regard to the control group.

The combined administration of *Nigella sativa* in dose of 2 gm/kg and gentamicin in a dose of 30 mg/kg produced a slight increase in the mean arterial blood pressure from 88.33 ± 2.19 to 97.5± 1.87 mmHg as regard to the control group. However it produced significant reduction in blood pressure as regards to gentamicin treated group (151.33±4.81 down to 97.5±1.87 mmHg) ( $P < 0.05$ ).

*Nigella sativa* in a dose of 2gm/kg produced insignificant increase in heart rate, from 386.7 ± 4.69, to 388.6 ± 6.33 b/m (Table 1) Gentamicin in a dose of 30mg/kg, produced insignificant decrease in heart rate, from 386.7 ± 4.69, down to 381.7 ± 5.42 b/m. While combination of *Nigella sativa* 2 gm/kg and gentamicin 30 mg/kg produced insignificant increase in heart rate from 386.7 ± 4.69, up to 390 ± 4.61 b/m Fig. (1,2,3,& 4).

**B- Changes in blood urea :**

As shown in Table (2), *Nigella sativa* in a dose of 2 gm/kg orally, produced insignificant increase in blood urea from 38.33± 2.19 up to 39.54±3.32 mg/dL. Gentamicin in a dose of 30 mg/kg produced increase in blood urea from 38.33 ± 2.19 in control group up to 104.33±4.22 mg/dL. However the concurrent administration on *Nigella sativa* in a dose of 2 gm/kg with gentamicin in a dose of 30 mg/kg, produced insignificant increase in blood urea from 38.33 ± 2.19 mg/dL in control group up to 40.33±3.07 mg / dL.

Table (2) : The effect of Nigella sativa (2 mg/kg orally), gentamicin (30 mg/kg ip.) and their combination on blood urea and serum creatinine in unilateral nephroctomized rats.

Parameter		Control group	Nigella sativa treated group	Gentamicin treated group	Gentamicin combined with Nigella sativa treated group
Blood urea (mg/dL)	mean $\pm$ SE	38.33 $\pm$ 2.19	39.54 $\pm$ 3.32	104.33 $\pm$ 4.22*	40.33 $\pm$ 3.07mg/dL
	% changes		3.2%	170.8%	5.19%
Serum creatinine (mg/dL)	mean $\pm$ SE	0.98 $\pm$ 0.07	1.1 $\pm$ 0.12	2.33 $\pm$ 0.16	1.1 $\pm$ 0.07 mg/dL
	% changes		12.27%	158%	12.24%

Number of rats in each group (n) = 6 rats

\* Significant (P<0.05)

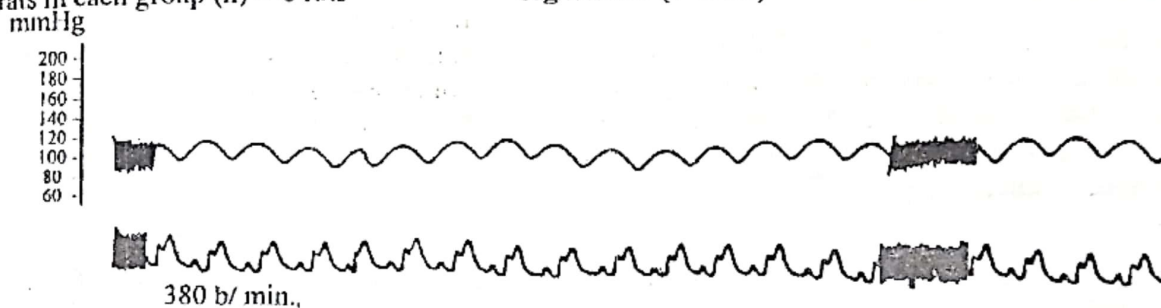


Fig. (1) : Control group



Fig. (2): Nigella sativa treated group

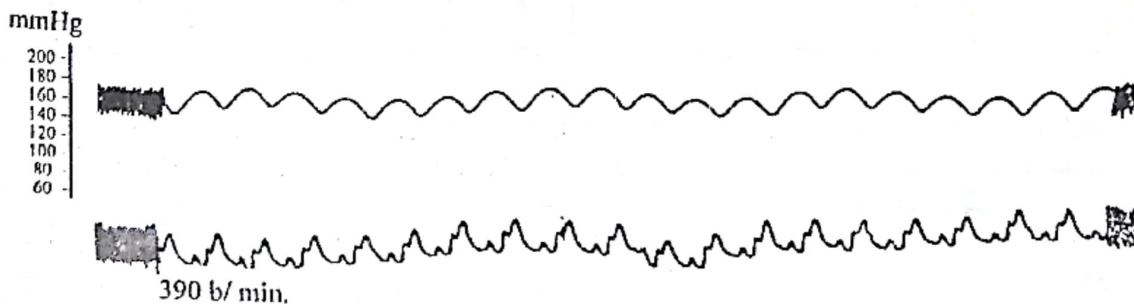


Fig. (3) : Gentamicin treated group

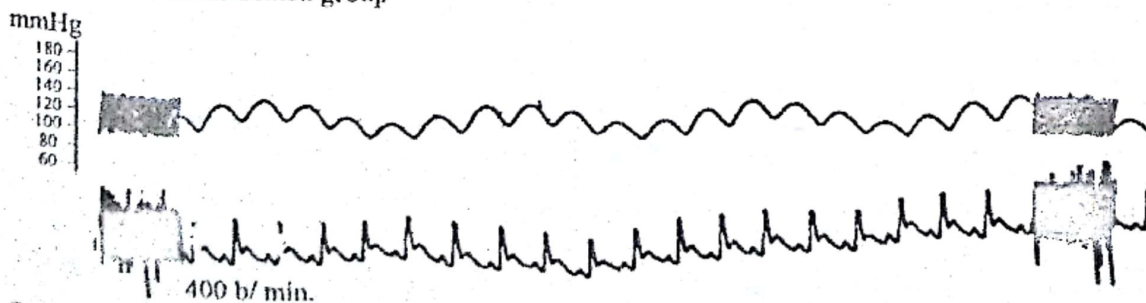


Fig. (4) : Gentamicin combined with Nigella setiva treated group.

The effect of Nigella sativa (2 gm/kg ); gentamicin (30 mg/kg i.p), gentamicin combined with Nigella sativa (2gm/kg orally) on blood pressure and heart rate in unilateral nephroctomized rats.

**C- Changes in serum creatinine:**

*Nigella sativa* in a dose of 2 gm/kg orally produced insignificant increase in serum creatinine from  $0.98 \pm 0.07$  mg/dL in control group, up to  $1.1 \pm 0.12$  mg/dL (Table 2). Gentamicin in a dose of 30 mg/kg produced significant increase in serum creatinine from  $0.98 \pm 0.07$  mg/dL in control group, up to  $2.33 \pm 0.16$  mg/dL. The concurrent administration of *Nigella sativa* in a dose of 2 gm / kg orally and gentamicin in a dose of 30 mg / kg ip. Produced insignificant increase in serum creatinine, from  $0.98 \pm 0.07$  mg / dL in control group, up to  $1.1 \pm 0.07$  mg/dL.

**II- Histopathological studies :**

On the other hand, it was obvious that no histopathological changes were detected in both control and *Nigella sativa* treated group. No significant pathological changes were also detected in the glomeruli of all experimental animals.

Treatment with i p gentamicin 30 mg / kg for 15 consecutive days induced nephrotoxic, tubular vacuolar and granular degeneration, tubular dilatation, peritubular infiltration with mononuclear inflammatory cells mainly lymphocytes and plasma cells and interstitial haemorrhage were detected in all animals (6/6). Tubular basement membrane (by periodic acid-schiff stain) was distorted and/or damaged in 5 animals (5/6), while tubular necrosis was evident in 4 animals (4/6).

In the group given gentamicin with *Nigella sativa*, the histopathological changes were less evident than in gentamicin group. Tubular degeneration, interstitial haemorrhage and distorted basement membrane were found in 2 animals only (2/6), while tubular necrosis was observed in one animal (1/6). Peritubular inflammatory infiltrate of lymphocytes and plasma cells were found in 3 animals (3/6).

Table (3) : Tubular degeneration, necrosis and dilatation in unilateral nephroectomized rats due to the effect of gentamicin and *Nigella sativa*.

Group	Tubular degeneration					Tubular necrosis					Tubular dilatation				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Control group	6	-	-	-	-	6	-	-	-	-	6	-	-	-	-
<i>Nigella sativa</i> treated group	6	-	-	-	-	6	-	-	-	-	6	-	-	-	-
Gentamicin treated group	-	1	2	2	1	2	2	1	1	-	-	2	2	2	-
Gentamicin+ <i>Nigella sativa</i> treated group	4	1	1	-	-	5	1	-	-	-	3	2	1	-	-

Table (4) : Peritubular inflammation , interstitial haemorrhages, and basement membrane integrity in unilateral nephroectomized rats due to the effect of gentamicin and *Nigella sativa* and their combination.

Group	Inflammation peritubular infiltration					Interstitial haemorrhage					Basement membrane integrity (PAS stain)				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Control group	6	-	-	-	-	6	-	-	-	-	6	-	-	-	-
<i>Nigella sativa</i> treated group	5	1	-	-	-	6	-	-	-	-	6	-	-	-	-
Gentamicin treated group	-	2	3	1	-	-	1	3	1	1	1	4	1	-	-
Gentamicin+ <i>Nigella sativa</i> treated group	-	3	-	-	-	4	1	1	-	-	4	2	-	-	-

The extent and distribution of each of these lesions in the kidney of each rat were scored according to **Hottendorf and Gordon (17)** as follows :

Score 0 - No lesion

Score 2 - Lesion represented in 10-50% of the nephrons.

Score 4 - Lesion represented in more than 90 % of the nephrons.

Score 1 - Lesion represented in less than 10% of nephrons

Score 3 - Lesion represented in 50-90% of the nephrons

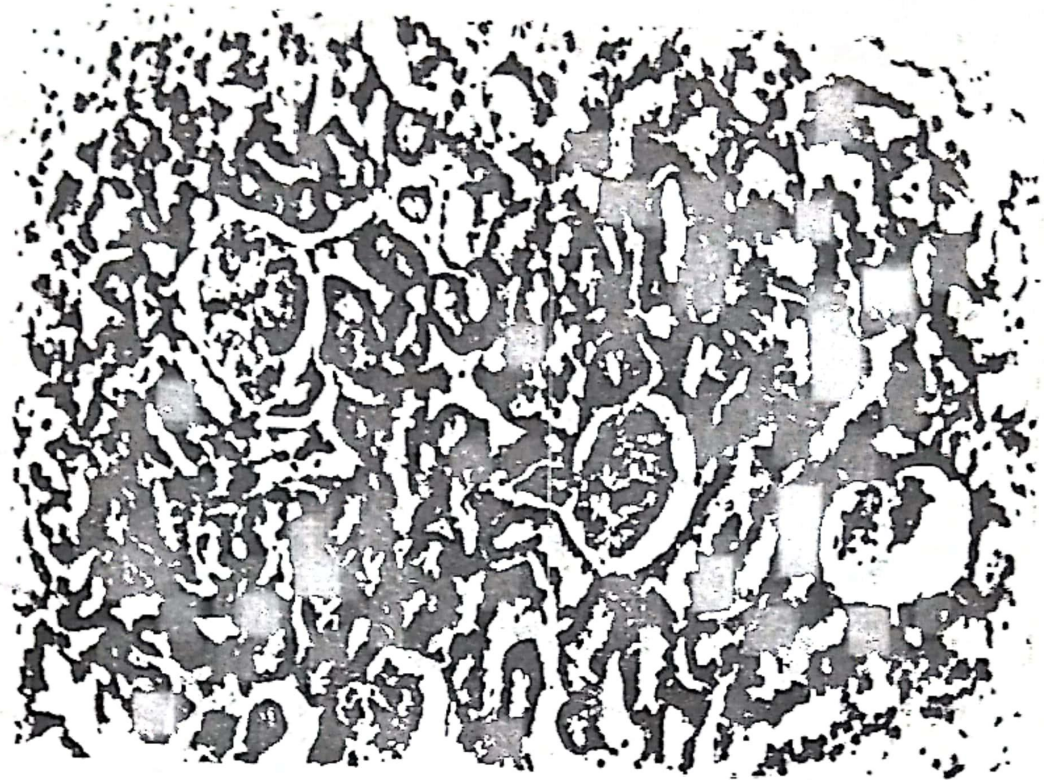


Fig. (5) : Section in kidney of unilateral nephrectomized control rat, showing normal renal tubules, glomeruli and intact basement membranes (H & E x 200).

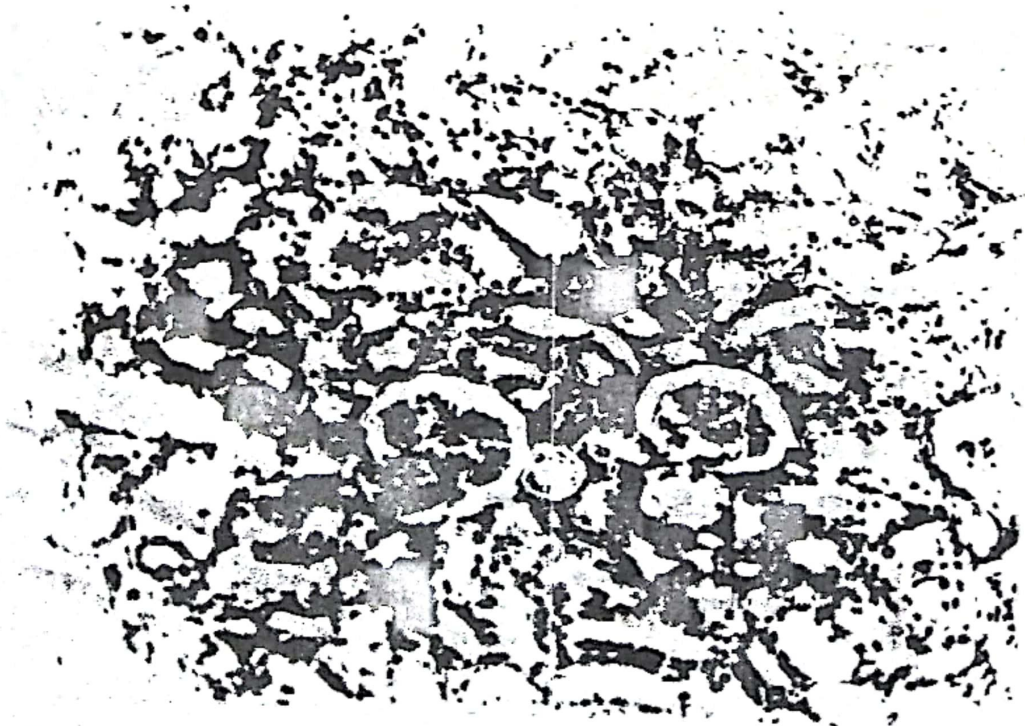


Fig. (6) : Section in kidney of unilateral nephrectomized control rat, that received *Nigella sativa* showing normal tubules, glomeruli and intact basement membranes (H & E x 200).



Fig. (7) : Section in a kidney of unilateral nephrectomized rats that received *Nigella sativa* showing no changes in basement membranes. (PAS  $\times 300$ )

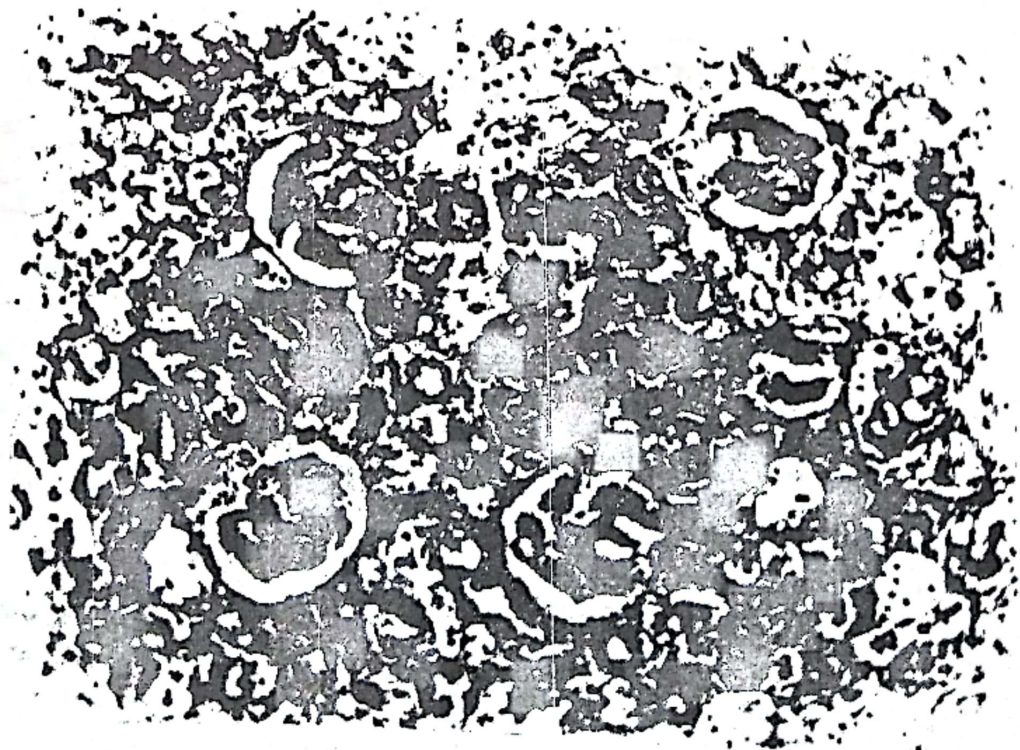


Fig. (8) : Section in a kidney of unilateral nephrectomized rats that received gentamicin, showing degeneration and necrosis of most of renal tubules and interstitial haemorrhage (H&E  $\times 200$ )

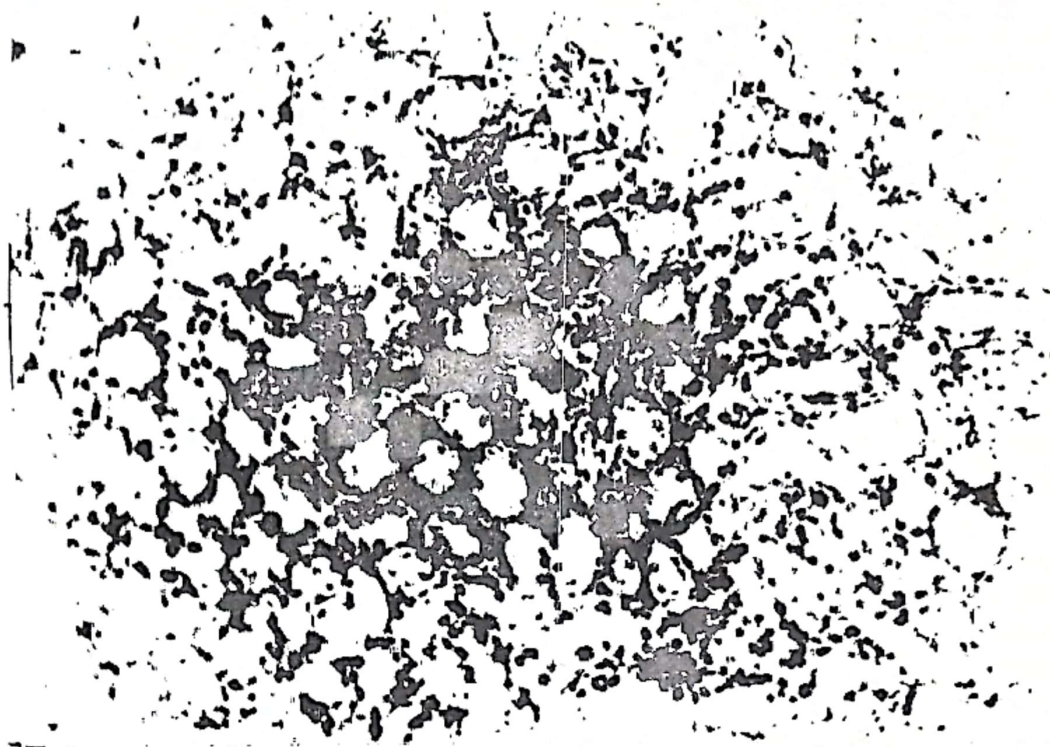


Fig. (9) : Section in a kidney of unilateral nephrectomized rats that received gentamicin showing multiple areas of peritubular lymphocytic and plasma cell infiltration (H & e x 200).

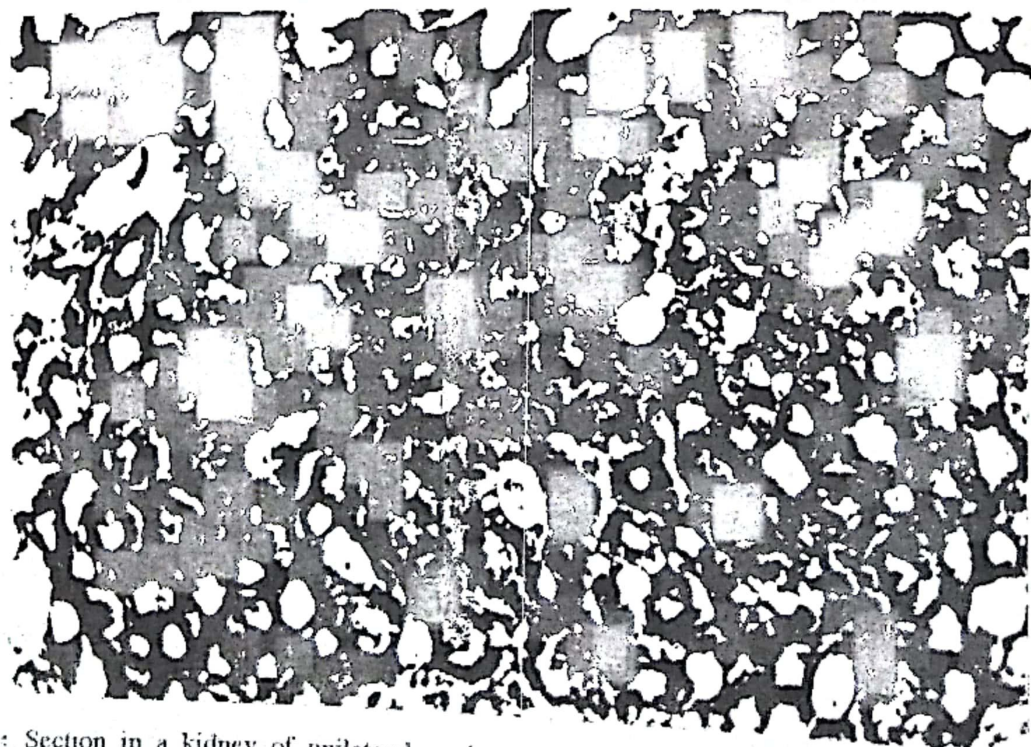


Fig. (10) : Section in a kidney of unilateral nephrectomized rats that received gentamicin, showing distortion, necrosis and interruption of basement membranes (PAS x 300).



Fig. (11) : Section in a kidney of unilateral nephroctomized rats that received *Nigella sativa* and gentamicin showing , regenerated renal tubules, normal glomeruli and slight peritubular lymphocytic infiltration (H & E x 200).

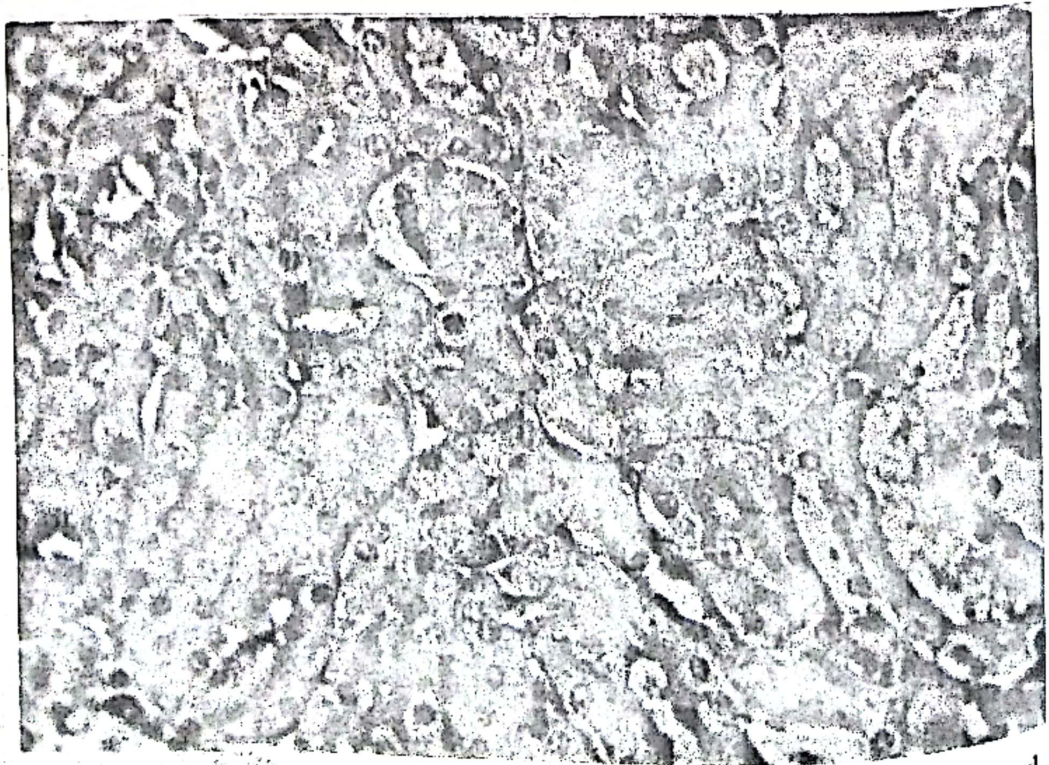


Fig. (12) : Section in a kidney of unilateral nephroctomized rats that received *Nigella sativa* and gentamicin showing , intact and normal basement membranes (PAS x 300).



## DISCUSSION

In the present study, it was found that, gentamicin produced significant increase in blood pressure, increase in blood urea and serum creatinine but did not affect the heart rate. Similar results were recorded before (16), they found that gentamicin nephrotoxicity increased both blood urea and serum creatinine.

Histopathological studies revealed that gentamicin induced renal tissue damage represented by, tubular vacuolar and granular degeneration, tubular dilatation and necrosis, peritubular infiltration with mononuclear inflammatory cells, interstitial haemorrhages and distortion and/or destruction of tubular basement membrane (by PAS stain). These findings were compatible with the results previously, reported (17). They reported that gentamicin nephrotoxicity is represented by vacuolar and/or granular degeneration, tubular necrosis, tubular dilatation and peritubular basophilic infiltration. It has been found that approximately 8 % up to 20 % of patients who received aminoglycosides for more than several days will develop mild renal impairment, that always reversible (1). The renal changes caused by aminoglycosides can be attributed to their selective accumulation in proximal convoluted tubules in human (18, 19) and in experimental animals (20, 21).

It was proved that aminoglycosides gain access to the proximal tubule via brush border (luminal) and basolateral (vascular) membrane surfaces. (22, 23). Patel et al., (24) supported this suggestion and added that, initial damage at this site is manifested by the excretion of enzymes at renal tubular brush border e.g. alanine aminopeptidase and alkaline phosphatase and BD glucosaminidase. The interaction between the aminoglycoside (gentamicin) and renal brush border membranes has been described in rats (25, 26) and rabbit (27, 28), appeared to represent specific binding process. Polycations such as spermine and polysine have been shown to inhibit renal membrane binding (28) and tissue accumulation of gentamicin (29). The previous authors proposed also that the renal membrane binding of aminoglycoside is of positive charge and the renal transport pathway of aminoglycosides is specific for polycations Stations. On the other hand gentamicin nephrotoxicity can be potentiated by certain drugs such as amphotericin B, vancomycin, cisplatin and cyclosporine (30) by more than one mechanism such as volume depletion, potassium wasting, or clearance defects (31).

Our results revealed that *Nigella sativa* did not significantly change the blood pressure, heart rate, blood urea or serum creatinine. Moreover, no pathological changes in kidney parenchymatous tissue in *Nigella*

*sativa* treated group compared to control group. These results are correlated with that observed before (32); they reported that *Nigella sativa* oil produced insignificant changes in blood pressure, serum creatinine or, blood urea,, which also agreed with that noticed before (33), who found that *Nigella sativa* produced insignificant histopathological changes in kidneys.

In the present study, it was obvious that concomitant administration, of *Nigella sativa* with aminoglycosides, *Nigella sativa* prevented the increase in blood pressure, blood urea and serum creatinine. It prevent also the histopathological changes in kidneys that appear more or less as control group, which coincide with results reported before (33). He found that *Nigella sativa* produced insignificant histopathological changes in kidneys in aminoglycoside induced guinea pigs nephrotoxicity due to chelation of DNA under the effect of free radicals.

The exact mechanism /s of renal tissue protection produced by *Nigella sativa* is not clearly obvious until know but it was suggested that *Nigella sativa* can strikingly increase the cAMP content in renal cells (34). This means that *Nigella sativa* can promote the activity of tissue glycometabolic enzymes and enhance cellular glycometabolism. Besides, cAMP as an important physiologic medium in organic cells, also it may plays an important part in regulation of the cardiovascular system through this mechanism (35).

Jarl-stedt and Bugger - sjoba, (36) proved that gentamicin can inhibit protein synthesis in renal cells by decreasing the RNA content of these cells. On other hand, Salami et al., (37) stated that *Nigella sativa* enhances DNA synthesis and protein synthesis. Houghton et al., (7) proved that the unsaturated fatty acid component of *Nigella sativa* may contribute also to its antieicosanoid and antioxidant activity.

From these results, it can be concluded that *Nigella sativa* prevent the gentamicin-induced nephrotoxicity through many mechanisms. Prevent the processes of gentamicin binding with brush borders of renal tubular cells; through it's antioxidant effect, and consequently inhibit gentamicin renal absorption.

Enhancement DNA synthesis and intercellular renal tubular protein synthesis, which may prevent renal tissue damage. Inhibition of cyclo-oxygenase with consequent selective inhibition of prostaglandin synthesis which consequently inhibit renal tissue necrosis, degeneration, inflammation, edema and other pathological kidney changes.

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Received : 24 July , 1997  
Accepted : 17 Sept. , 1997

## دراسة احتمال التأثير الوقائي للبذور المطحونة لحبة البركة على التسمم الكلوي المحدث بعقار

### الجنتاميسين في الجرذان ذات الكلى الواحدة

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يستعمل زيت حبة البركة على نطاق واسع كمقوى عام وأيضاً للوقاية من بعض الامراض على الرغم من عدم توافر المعرفة التامة بخصوصية هذا العشب داخل جسم الانسان. لذلك أجرى هذا البحث لمعرفة التأثير الوقائي لزيت حبة البركة على تسمم الكلى المحدث بعقار الجنتاميسين في الفئران ذات الكلى الواحدة أثبتت نتائج هذا البحث أن معلق حبة البركة المطحون لا يحدث أى تغيرات فارماكولوجية . كيميائية أو باثولوجية في الجرذان ذات الكلى الواحدة. أما حقن الجنتاميسين أحدث تأثير باثولوجيا شديد على الكلى مصحوب بارتفاع شديد في ضغط الدم والبولينا ونسبة الكرياتينين وعلى العكس من ذلك تماماً ، وجد أن المجموعة التى أعطيت الجنتاميسين بالإضافة إلى معلق حبة البركة انطوونه ليس بها أى تغير باثولوجي فى أنسجة الكلى ، وأن معدل ضغط الدم والتبص والبولينا ونسبة الكرياتينين لا تختلف كثيراً عن معدلاتها فى المجموعة الضابطة. يتضح من هذا البحث أن معلق حبة البركة المطحونه له تأثير وقائى من التسمم الكلوي المستحدث بعقار الجنتاميسين فى الجرذان ذات الكلى الواحدة.