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Original Research Article

Amelioration of Amikacin Induced Nephrotoxicity by Nigella Sativa Oil: An in Vivo Study in Rats

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Abstract

The objective of this study is to evaluate the nephroprotective role and antioxidant effects of *Nigella sativa oil* against Amikacin-induced nephrotoxicity in rats.We divide Healthy adult albino rats of either sex (100-200 g) randomly and equally into six groups of five animals each. Group I animals (normal control) were administered distilled water intra peritoneally for 14 days. Group II animals (LNSO) were administered low dose nigella sativa oil 1ml/kg orally for 16 days. Group III animals (HNSO) were administered High dose nigella sativa oil 2ml/kg orally for 16 days. Group IV animals (ANCG)Amikacin negative control group. were administered Amikacin (300mg/kg) From day 1-14 Intra-peritoneally. Group V animals (ALNSO) were administred Low dose of Nigella sativa oil (1ml/kg) orally (From day 1-16) + Amikacin (300mg/kg) (From day 3-16) Intra-peritoneally.Group VI animals (AHNSO) were administered high dose Nigella sativa oil.(2ml/kg) orally (From day 1-16) + Amikacin (300mg/kg) (From day 3-16) intra-peritoneally. On the 16 th day (14th day for normal control group), blood was collected for biochemical tests and the rats were sacrificed. The kidney was removed for histology and lipid peroxidation-antioxidant test. Amikacin caused nephrotoxicity as evidenced by elevated BUN, blood urea and serum creatinine. Co-administration of Nigella sativa oil at doses of 1ml/kg and 2ml/kg in Group V and Group VI caused a dose-dependant reduction in the elevated levels of BUN, blood urea and serum creatinine as compared to Group IV (amikacin negative control group).There was increased catalase and glutathione and decreased malondialdehyde levels in Group IV, while Group V (ALNSO) and Group VI(AHNSO) treatment with low dose and high dose of Nigella sativa oil significantly reversed the changes toward normal values. Histological examination of the kidney shows nephroprotection in Group V and Group VI compared with Group IV. It is seen that Nigella sativa oil has a nephroprotective role against Amikacin-induced nephrotoxicity in rats as is evident from biochemical parameters of blood samples, oxidative stress studies and histopatholgical examinations of tissue samples.

Keywords: Nigella sativa oil, Ameliorate, Nephroprotectivity, nephrotoxicity; aminoglycosides, amikacin, oxidative stress, histopathology, animal study, rats.

Introduction

Aminoglycosides: The aminoglycoside group includes gentamicin, tobramycin, amikacin, netilmicin, kanamycin, streptomycin, paromomycin, and neomycin. The most widely used semisynthetic aminoglycoside is amikacin, which is refractory to most aminoglycoside modifying enzymes. Amikacin was synthesized by acylation with the L-(−)-γ-amino-α-hydroxybutyryl side chain at the C-1 amino group of the deoxystreptamine moiety of kanamycin A. This antibiotic is also essential in the treatment of life-threatening infections in neonates. (Ramirez M *et al* 2017). Amikacin is mostly used for treatment of severe, hospital-acquired infections with multidrug resistant Gram negative bacteria such as Pseudomonas aeruginosa, Acinetobacter, and Enterobacter. Amikacin is not more and not less ototoxic or nephrotoxic than gentamicin (Langhendries, J.P., *et al*.1993). Aminoglycoside are taken up by renal proximal tubular cells and remain there for an extended period this leads to renal damage in the form of structural and functional impairment of the plasma membrane, mitochondria and lysosome (Mingeot-Leclerq MP *et al* 1999). Histopathological studies strongly support the concept that tubular necrosis (and related phenomena) is the primary cause of functional toxicity [1].

Nephroprotection aims at early detection and subsequent prevention of progression of kidney disease, mainly through lifestyle adjustment and the use of new pharmacological agents (Lameire N *et al*.,2005). As Amikacin is used frequently in treatment for cases of microbes resistant to other antibiotics moreover traditional medicinal plants may offer a suitable alternative for nephroprotection having very few if any toxic side effects,wherefore this study was carried out. Nephrotoxicity is one of the main concerns with the use of amikacin. The risk of nephrotoxicity higher in patients with impaired renal function, and in patients of normal renal function who treated at higher doses and/or for duration longer than those recommended.(Polat M *et al* 2017) [2-4].

Despite rigorous patient monitoring, nephrotoxicity appears in 10–25% of therapeutic courses. (Lopez-Novoa JM *et al* 2011).

The ability of the kidney to concentrate the tubular fluid contents is a hallmark of renal function.Any nephrotoxic or potentially nephrotoxic compound present in the tubular fluid would be concentrated in a similar manner.(William O Berndt 1998) .The large surface area of tubular epithelium provides sites for toxin interaction and uptake, specific transport mechanism which are responsible for cellular uptake and the normal concentrating mechanisms of the kidney can increase the concentration of the toxin. (Weinberg J.M *et al*., 1991) [5-8].

Nephrotoxicity due to administration of aminoglycoside is characterized functionally by an increase of serum creatinine, blood urea nitrogen, and decrease in glomerular filtration rate (Romero F *et al* 2009), which morphologically characterized by proximal tubule epithelial desquamation, tubular necrosis, tubular fibrosis, epithelial edema and glomerular hypertrophy (Lakshmi BVS *et al* 2010) [8].

Nigella sativa seed has a long history as a diversely beneficial herb, In Egypt society, the rich golden (Nigella sativa)oil was named

'pharaohs oil (Zohary *et al*, 2000).An authentic saying of the Prophet Muhammad (Peace Be Upon Him) about black seed Allah's Apostle (peace be upon him) said "Use the black seed, which is a healing for all diseases except 'As-Sam" and As-Sam is Death (Al-Bukhari). In Ayurveda system of medicine it is also considered a great metabolic enhancer. Ayurveda utilizes Black seed for its ability to heal nervous disorders, anorexia, and gynaecological problems and also uses this herb to heighten mood, stimulate metabolism, and provide the harmonizing benefits of an overall body tonic. Saleem U *et al* observed the nephro-protective effect of vitamin C and N. sativa oil against gentamicin induced nephrotoxicity in rabbits. [9,10].

Materials and methods

Plant material Nigella sativa oil – Nigella sativa oil (Kalonji oil, Mohammedia products, Aamirnagar, Shah Sahab Mohalla, Karimnagar – 505001, A.P., India) was procured from local market at Aligarh. As per manufacturer's information, it was prepared by steam distillation.

Experimental animals: Healthy adult albino rats weighing 100-200g of either sex were procured from Central Animal House, J.N. Medical College, AMU, Aligarh. The animals were placed in polypropylene cages bedded with paper strips. They were maintained at a temprature of 27°C ± 2°C ,also, the animals were kept under 12 hours dark-light cycle and were fed with standard pellet diet and water ad libitum. The paper strips were changed every day to maintain proper hygiene and comfort for animals. The animals were acclimatized for one week under laboratory conditions before experimentation.

Ethical clearance for experimental study of the animals was obtained from the Institutional animal ethical committee, JNMC, AMU, Aligarh before commencement of the experiments.

IAEC Approval : The study protocol was approved by the Institutional Animal Ethics Registration no.: 401/RO/C/2001/CPCSEA. All animal experiments were carried out as per the rules and regulations of IAEC & CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) under the "Guidelines for Care and Use of Animals in Scientific Research" (INSA 1992 & 2000) [11-14].

Experimental models

I) Amikacin induced nephrotoxicity: Nephrotoxicity was induced by Amikacin in the dose of 300mg/kg/day (Rankin *et al*. 1979) through i.p route daily for 14 days.

II) Nigella sativa Nephroprotectivity model

Nigella sativa oil was administered in two different doses in the study i) low dose 1ml/kg body weight/day and ii) high dose 2ml/kg body weight/day for evaluating the nephroprotective role of the Nigella sativa oil (Hafez 2013, Ali 2004, Danladi 2013) [15,16].

Experimental design. Healthy adult albino wistar rats of either sex weighing 100-200gm were randomly divided into 6 groups of 5 rats each as follows: (n = number of rats in each group).

Table 1: Experimental models

Groups	Treatment and Duration	Route of Drug Administration.
Group I (normal control) : (n=5)	Distilled water 1ml/kg (From day 1-14)	Intra-peritoneally
Group II (normal control) : (n=5)	Nigella sativa oil – 1ml/kg (From day 1-16)	Oral
Group III (normal control) : (n=5)	Nigella sativa oil – 2ml/kg	Oral

	(From day 1-16)	
Group IV : (n=5) (Amikacin negative control)	Amikacin(300mg/kg). (From day 1-14)	Intra-peritoneal
Group V : (n=5) (Amikacin and low dose- -nigella sativa oil treatment group)	Low dose Nigella sativa oil.(1ml/kg). (From day 1-16) + Amikacin(300mg/kg)(From day 3-16)	Oral Intra-peritoneal
Group VI : (n=5) (Amikacin and high dose- nigella sativa oil treatment group)	High dose Nigella sativa oil.(2ml/kg) (From day 1-16) + Amikacin(300mg/kg) (from Day 3-16)	Oral Intra-peritoneal

Administration of Nigella sativa oil was started two days prior in groups V and GroupVI in which Amikacin was co-administered(Ali BH 2004).

Twenty four hours after the last dose in respective treatment group was administered following procedures were carried out:

1. Blood samples were collected for measurement of following biochemical parameters:
2. Blood urea nitrogen (BUN). 2) Blood urea 3) Serum creatinine
3. Animals were dissected and sacrificed (under pentobarbitone sodium 50mg/kg i.p.
   anaethesia). The kidneys were dissected out for histopathological examination
4. Oxidative stress studies were carried out on renal tissue samples from rats of all groups for following parameters 1) Malondialdehyde (MDA) 2) Catalase 3) Reduced glutathione (GSH) [17-20].

Histological examination

All the kidney tissue specimens were preserved in 10% Formalin and processed in the Neuroanatomy & Histology Research Laboratory, Department of Anatomy, J.N. Medical College, A.M.U., Aligarh.

Statistical analysis

The results are presented as Mean ± Standard Deviation (SD). The groups were compared by one-way Analysis of Variance (ANOVA) followed by post hoc "Dunnett's Multiple comparison test" to analyze statistical significance. A "p" value of less than 0.05 ($p<0.05$) was considered to be significant.

Biochemical parameters

Effect of Nigella Sativa oil low dose (1ml/kg) and Nigella sativa oil high dose (2ml/kg): Administration of Nigella sativa oil alone in low dose (1ml/kg p.o) and high dose (2ml/kg p.o) for 16 days produced no significant change in BUN, Blood urea and Serum creatinine levels as compared to normal control.

Table 2: Biochemical parameters

S. No.	Groups	BUN (mg/dl)	Blood Urea mg/dl)	Serum creatinine (mg/dl)
I.	Normal Control	19.14 ± 1.02	40.96 ± 2.19	0.61 ± 0.03
II.	LNSO	18.64 ± 2.54	39.88 ± 7.68	0.57 ± 0.08
III.	HNSO	19.04 ± 1.76	40.74 ± 5.32	0.59 ± 0.05

The values are expressed as Mean ± Standard Deviation (SD). LNSO = Low dose (1ml/kg) Nigellasativa oil. HNSO = High dose (2ml/kg) Nigella sativa oil

Amikacin Induced Nephrotoxicity Model

In the normal control group, which was given only distilled water: BUN, Blood urea and Serum creatinine were within normal range. In the animals treated with amikacinthe levels of BUN, Blood urea and Serum creatinine were significantly elevated ($p<.001$). Administration of N. sativa oil in doses of 1ml/kg and 2ml/kg led to decrease in the level of BUN ,Blood Urea and Serum creatinine as compared with thenegative control (amikacin) group (group VI) which were significant ($p<0.001$).

Table 3: Amikacin Induced Nephrotoxicity Model

S. No.	Groups	BUN (mg/dl)	Blood Urea (mg/dl)	Serum creatinine (mg/dl)
I.	Normal Control	19.14 ± 1.02	40.96 ± 2.19	0.61 ± 0.03
II.	ANCG	40.39 ± 2.50$^{\#}$	86.44 ± 5.36$^{\#}$	1.35 ± 0.05$^{\#}$
III.	ALNSO	35.56 ± 2.78^{c}	76.09 ± 5.95^{c}	1.11 ± 0.06^{c}
IV.	AHNSO	21.56 ± 2.09^{c}	46.14 ± 4.48^{c}	0.79 ± 0.05^{c}

The values are expressed as Mean ± Standard deviation (SD) where "c" is $p<0.001$ when compared with the Amikacin negative control group. Also "#" is $p<0.001$ when comparison is made with Normal control group. ANCG = Amikacin negative control group. ALNSO= Amikacin + Low dose (1ml/kg) N. sativa oil. AHNSO = Amikacin + High dose (2ml/kg) N. sativa oil.

Parameters of oxidative stress

Effect of Nigella Sativa oil low dose (1ml/kg) and Nigella sativa oil high dose (2ml/kg): Administration of Nigella sativa oil alone in low dose 1ml/kg and high dose 2ml/kg did not show much deviation in parameters MDA, Catalase and GSH from normal control. The values were statistically similar to normal control ($p>0.05$).

Table 4: Parameters of oxidative stress

S. No.	Groups	MDA (nmoles/g wet tissue wt.)	Catalase (nmoles H_2O_2consumed/min /mg protein)	GSH (nmoles/mg protein)
I.	Normal Control	48.5 ± 1.57	131.19 ± 2.36	18.35 ± 0.45
II.	LNSO	46.15 ± 2.10	135.57 ± 2.65	18.90 ± 1.07
III.	HNSO	46.80 ± 1.40	133.21 ± 3.80	18.75 ± 0.84

Amikacin Induced Nephrotoxicity Model

In the normal control group, which was given only distilled water the parameters MDA, Catalase and GSH were measured. In the animals treated with amikacin, the level of MDA were significantly elevated, whereas Catalase and GSH levels were significantly decreased ($p<.001$) as compared with normal control group. Administration of amikacin along with Nigella sativa oil in doses of 1ml/kg(low dose) and 2ml/kg(high dose) led to decrease in the level of MDA which was highly significant when compared with the levels of MDA in negative (amikacin) control group (group VII). The levels of Catalase increased with low dose and high dose Nigella sativa oil co-administered with amikacin. This increase was highly significant ($p<0.001$) as compared with the

negative (amikacin) control group (group VII). While comparing the levels of GSH in the negative (amikacin) control group and treatment groups which received Nigella sativa oil in low dose and high dose along with amikacin it was seen that increase in levels of GSH in low dose group was significant upto $p<0.01$ whereas in high dose group the increase was significant upto $p<0.001$.

Histopathological grading

Table 4: Effect of N.sativa oil on Amikacin induced nephrotoxicity in rats

Histopathological features	Normal control Group	ANCG	ALNSO	AHNSO
Glomerular and tubular congestion,	-	++++	++	+
Interstitial oedema	-	+++	++	++
Inflammatory cells infiltration	-	+++	++	+
Tubular necrosis	-	+++	++	+
Tubular casts(hyaline)	-	++	-	-

"+" = Mild ; "++" = Moderate ; "+++" = Severe ; "++++" = Very severe. ANCG = Amikacin negative control group. ALNSO= Amikacin+ Low dose(1ml/kg) Nigella sativa oil. AHNSO= Amikacin + High dose(2ml/kg) Nigella sativa oil.

Discussion

Nephrotoxicity is one of the major adverse effect of aminoglycosides. Major portion of the injected drug is excreted via urine. Results have indicated that receptor-mediated endocytosis is the process by which aminoglycosides are taken up following the binding of aminoglycosides to the brush-border membrane (Baylis *et al* 1977). Many synthetic compounds Drugs Procedures and medicinal plants have been studied and researched over past few decades for search of nephroprotective agent. Like dexpanthenol against nephrotoxic effect of amikacin (Doğan EE *et al* 2017), haemodialysis as a protective technique for preventing high daily dose amikacin nephrotoxicity (Pouzot-Nevoret C *et al* 2017). Aminoglycoside tubular reuptake inhibitors, excretion inducers and calcium channel blockers also showed a promising and rather homogeneous class tendency towards nephroprotection. (Vicente-Vicente L *et al* 2017), Isorientin found in several plants such as *Phyllostachs pubescens, Gentiana patrinia* and in the tubers of *Pueraria tuberosa* lowered renal impairment biomarkers((Fan *et al*., 2020). kaempferol was able to ameliorate renal injury caused by cisplatin (Wang *et al*., 2020). Honey (Abd Ali 2012), Allium sativum (Abdelaziz *et al* 2011) and more have been tested for their role in improving renal function or in offering nephroprotection in various studies [21].

In this study Nigella sativa oil was selected as very few studies have been conducted on the oil obtained from seeds of Nigella sativa in regards to nephroprotective activity against nephrotoxicity induced by amikacin and other aminoglycosides .In the present study it was found that Amikacin treated animals show increase in BUN, Blood urea and S. creatinine as compared with the normal control group. Similar results were obtained in previous studies conducted to evaluate nephrotoxic effects of amikacin (Rankin *et al* 1979, Abdelaziz *et al* 2011 and Abd Ali *et al* 2012) [17, 19].

It was seen that the administration of Nigella sativa oil alone in low dose 1ml/kg body

weight and a high dose 2ml/kg body weight did not show much deviation in values of biochemical parameters and oxidative stress markers and histopathological effects as compared to normal control.

Effects on levels of biochemical parameters: BUN, blood urea and S.Creatinine due to co-administeration of Nigella Sativa oil and amikacin

Administration of Nigella sativa oil along with amikacin led to dose dependant decrease in BUN, Blod urea and S. creatinine as compared to group treated with amikacin alone. Low dose (1ml/kg) and high dose (2ml/kg) of N. sativa oil along with amikacin showed decrease in level of BUN, Blood Urea and S.creatinine, the decrease in values was significant ($P<0.001$) as compared to group receiving Amikacin only.

Effects on levels of oxidative stress markers: MDA, catalase and gsh due to administeration of Nigella Sativa oil concurrently with amikacin.

In the animals treated with amikacin alone, the level of MDA were significantly elevated, whereas Catalase and GSH levels were significantly decreased ($p<.001$) as compared with normal control group. Administration of N. sativa oil in doses of 1ml/kg and 2ml/kg led to dose dependant decrease in the level of MDA, whereas levels of Catalase and GSH showed a dose dependant increase as compared with the negative (amikacin) control group (group VII) which were significant. The decrease in the level of MDA was significant ($p<0.001$) in Nigella sativa oil treated groups and this decrease was more in groups treated with higher dose of Nigella sativa oil. The increase in levels of catalase was significant ($p<0.001$) in groups treated with Nigella sativa oil and the increase was more with higer dose of Nigella sativa oil. The increase in GSH levels was significant ($p<0.001$) in groups receiving Nigella sativa oil in low dose and high dose. The increase in levels of GSH was greater in higher dose treated groups.

Histopathological examination

Histopathological examination revealed that there was damage to the nephrons of cortical region, mainly in PCT due to administration of amikacin. Further it was seen that injury caused by administration of Nigella sativa oil in low dose and in high dose along with amikacin was lesser as compared with the group receiving amikacin only with more reduction in damage observed with high dose of Nigella sativa oil.

In groups receiving only Nigella sativa oil in low dose and high dose it was observed that the histopathological appearance of these samples were similar to those of the normal control group similar to results of Zaoui *et al* (2002) [22].

Nephroprotective role of nigella sativa

Salama *et al* (2011) who reported that the beneficial effects of the use of the N. sativa seeds and thymoquinone (one of its constituent) might be related to their cytoprotective and antioxidant actions. Yaman *et al* (2010) attributed the nephroprotective effect of Nigella sativa oil to it's ability to attenuate oxidative stressthrough attenuation of lipid peroxidation.

Several studies have shown nephroprotective activity of Nigella sativa. In the present study Nigella sativa oil administration was seen to have a nephroprotective role on the basis of observations obtained from biochemical analysis and histopathological examination [20-23].

Conclusion

The present study entitled "Amelioration of amikacin induced nephrotoxicity by Nigella Sativa oil: an in vivo study in rats" is conducted on thirty rats which are randomly divided in 6 groups of 5 animals each. The work was carried out in Department of

Pharmacology and Department of Anatomy J.N. Medical College, AMU, Aligarh. In the present study the amikacin namely was used to induce nephrotoxicity in rats.

It was evident from biochemical parameters, quantification of oxidative stress markers and histopathological examination of renal tissues of sacrificed animals that amikacin is a nephrotoxic drug.

Nigella sativa oil used for studying its nephroprotective found to be nephroprotective as it ameliorates nephrotoxicity induced by amikacin. Neproprotective effect may be attributed to it's ability to decrease oxidative stress, which is thought to be the main mechanism involved in causing nephrotoxicity upon aminoglycoside administration.

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