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Original Article

Nephroprotective Effect of Aqueous Extract of *Pimpinella anisum* in Gentamicin Induced Nephrotoxicity in Wistar Rats

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ABSTRACT

Background: *Pimpinella anisum* known for its various medicinal properties is also a natural antioxidant and a free radical scavenger with no documented evidence as a nephroprotective agent. **Objective:** To evaluate the nephroprotective activity of aqueous extract of *Pimpinella anisum* seeds in a rodent model of gentamicin induced nephrotoxicity. **Materials and Methods:** Wistar albino rats of either sex, weighing 150–200 g was divided into 5 groups; normal saline, gentamicin 80mg/kg, intraperitoneally for 8 days, aqueous extract of *Pimpinella anisum* seeds at 1, 2, and 4g/kg, per oral for 8 days, the test extract administered 3 days prior and concurrently with gentamicin for 5 days. Blood urea, serum creatinine, uric acid and blood urea nitrogen analyses and microscopic examination of kidney were performed. **Results:** Gentamicin treatment caused nephrotoxicity as evidenced by marked elevation in serum urea, serum uric acid, serum creatinine and blood urea nitrogen (107.5±16.92mg/dl, 0.8±0.09 mg/dl, 3.05±0.29 mg/dl, 47.8±9.07 mg/dl) respectively when compared to the saline treated groups. Co-administration of *Pimpinella anisum* extract with gentamicin decreased the rise in these parameters in a dose dependent manner. Histopathological analysis revealed epithelial loss with intense granular degeneration in gentamicin treated rats, whereas aqueous extract of *Pimpinella anisum* mitigated the severity of gentamicin-induced renal damage. **Conclusion:** To conclude, our data suggest that aqueous extract of *Pimpinella anisum* exhibits renoprotective effect in gentamicin induced renal damage and further studies on its mechanism of action are warranted.

Key words: Aniseed, Gentamicin, Nephroprotective, *Pimpinella anisum,* Drug induced nephrotoxicity.

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INTRODUCTION

Recognition of drug-induced nephrotoxicity as a significant contributor to kidney disease including acute kidney injury (AKI) and chronic kidney disease (CKD) has gained increasing momentum in recent times. Nephrotoxicity constitute a whole gamut of disorders reflecting damage to different nephron segments as a consequence of individual drug mechanisms. Consequences of drug toxicity might include both glomerular and tubular injuries leading to acute or chronic functional changes.[1] The frequency of drug-induced nephrotoxicity is approximately 14-26% in adult populations as detailed in previous prospective cohort studies.[2] Aminoglycosides, a commonly used group of antibiotics top the causality chart in drug induced nephrotoxicity.

Aminoglycosides constitute an important part of our arsenal against many life threatening infections especially against gram negative bacterial infections.[3,4] They have survived against all odds despite the introduction of highly potent, wide spectrum antibiotics because of certain properties such as rapid concentration dependent bactericidal effects, clinical effectiveness, a low rate of true resistance, synergism with other beta lactam antibiotics and low cost of therapy.[5,6] However, nephrotoxicity induced by them continue to be a challenge as it results in kidney damage by a direct dose dependent mechanism.[7,8] Gentamicin induced acute renal failure has proved to be an excellent working animal model for exploring the pathogenesis of drug induced acute renal failure and has resulted in an impetus to develop therapeutic approaches to minimize or prevent its harmful effects in humans.[9]

Renal toxicity caused by gentamicin is an elaborate phenomenon, the key features of which include an increase in plasma creatinine and urea levels with severe proximal renal tubular necrosis, with progressive deterioration and renal failure.[10,11] Generation of reactive oxygen species (ROS) in the kidney have been implicated as the culprits for nephrotoxicity induced by aminoglycosides.[11,12] The cellular antioxidant status plays an important role in determining the susceptibility to oxidative damage which might alter in response to oxidative stress.[13] Several studies have claimed antioxidant property of drugs as crucial for their nephroprotective effects in gentamicin induced renal damage.[14,15,16,17]

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Pimpinella anisum L. (anise, aniseed), a plant belonging to the umbelliferae family, is an age old medicinal plant.[18] Aniseed, a native of the Eastern Mediterranean region, is grown to a small extent in India as a culinary herb.[19] They are also used as an important raw material for pharmaceutics, perfumery, food and cosmetic industries.[20] It has been reported that essential oil and extracts of *Pimpinella anisum* have a wide range of biological activities.[21] In folk medicine, pimpinella species have been used as appetizing, hypnotic, expectorant, hepatoprotective, carminative, aromatic, disinfectant, and galactagogue.[18,22] Various other pharmacological properties attributed to this plant include antimicrobial, antifungal, antiviral, antioxidant, muscle relaxant, anticonvulsant, hypoglycemic, hypolipedaemic as well as different effects on gastrointestinal system.[18] In recent years much attention has been devoted to natural antioxidants and their association with health benefits. Plants are a large source of new bioactive molecules with therapeutic potentials.[23] Studies have shown that many dietary polyphenolic constituents derived from plants are more effective antioxidants *in vitro* than vitamins E or C, and thus might contribute significantly to the protective effects *in vivo*.[24] Aniseed is shown to have great health benefits due to the presence of considerable amounts of phenolic compounds that possess varying degrees of antioxidant activity.[25] However literature research revealed that the nephroprotective activity of *Pimpinella anisum* seeds has not been established and its probable role has only been postulated with no positive evidence. Hence with this background we decided to explore the nephroprotective role of *Pimpinella anisum* in a murine model of gentamicin-induced renal damage.

MATERIALS AND METHODS

This study was done as per the guidelines set by the Committee for the Purpose of Control and Supervision of Experiments on Animals. The study was undertaken after obtaining the approval by the Institutional Animal Ethics Committee.

Experimental Animals

Adult Wistar albino rats of either sex, weighing 150-200g, inbred in the institutional animal house were used for the study. Animals were housed in polypropylene cages in a controlled environmental condition (22± 3^0C, 55 ± 5% humidity and a 12 h light/ dark cycle). The animals were fed with standard rodent diet and water *ad libitum*. They were allowed to acclimatize to these conditions for one week.

Drugs

Gentamicin sulfate injection (Piramal Health Care Ltd) was used to induce renal damage.

Plant material and preparation of extracts

Pimpinella anisum seeds were procured from the local market, authenticated by a local botanist and a voucher specimen of the plant (F.5860175) is being maintained in the herbarium of Department of Botany, St Aloysius, College, Mangalore. The seeds were cleaned and dried in shade and powdered by a mechanical grinder. For the aqueous extract, the seed powder (100 g) was added to 1000 mL of hot water, boiled for 15 min and filtered. The filtrate was evaporated to dryness under reduced pressure to afford a viscous residue. The residue was dissolved in normal saline for oral administration.[26]

Experimental procedure

After acclimatization, the animals were divided randomly into five groups of 6 animals each and placed in separate cages. The test drug, the aqueous extract of *Pimpinella anisum* seeds and gentamicin were administered for a total duration of 8 days. The test drug was started 3 days prior to the commencement of the study. The animals were grouped accordingly as follows: Group one served as control group and received normal saline (1ml/kg intraperitoneal) throughout the course of the experiment. Group two received daily intraperitoneal injections of gentamicin (80 mg/ kg).[14] Group three, four and five received the test drug, aqueous extract of *Pimpinella anisum* orally at 1, 2 and 4g/kg respectively.[26] Animals of group three, four and five were administered 80 mg/kg of gentamicin intraperitoneal along with test drug for 8 days.

Sample collection and biochemical assays

Twenty-four hour after the last injection the rats were anesthetized with ketamine (60 mg/kg) and xylazine (5mg/kg) intraperitoneally [27] and blood samples were collected by cardiac puncture. The serum was rapidly separated and processed for determination of serum creatinine, serum urea, serum uric acid and blood urea nitrogen (BUN) as an indicator of kidney damage, using commercially available kits from Aspen Diagnostics Private Ltd (Liquid stable biochemistry kits). The animals were sacrificed and both kidneys were isolated. The kidneys from all the groups were weighed and processed for histopathological examination.

Histopathological examination

The kidneys fixed in 10% neutral buffered formalin were processed and embedded in paraffin wax and sections were taken using a microtome. Sections (5 microns) were then stained with haematoxylin and eosin and examined under light microscope. They were evaluated and assigned scores as follows:[14]

Score 0 = Normal

Score 1 = Areas of focal granulovacuolar epithelial cell degeneration and granular debris in tubular lumens with or without evidence of tubular epithelial cell desquamation of small foci (<1% of total tubule population)

Score 2 = Tubular epithelial necrosis and desquamation easily seen but involving less than half of cortical tubules

Score 3 = More than half of proximal tubules showing desquamation of necrosis but involved tubules easily found

Score 4 = Complete or almost complete tubular necrosis

Statistical analysis

Data were expressed as mean ± standard error of mean (SEM). Statistical evaluation was done using SPSS (version 20). Kruskal-Wallis test was performed to find whether or not values of different groups differ significantly. To test intergroup significant difference, Mann-Whitney test was performed. A value of $p<0.05$ was considered statistically significant.

RESULTS

Effect on biochemical parameters

In the present study, gentamicin (80mg/kg) when injected for eight consecutive days caused marked nephrotoxicity as is evident from Table 1, showing significant ($p< 0.05$) increase in serum urea (107.5±16.92mg/dl), serum creatinine (0.8±0.09mg/dl), serum uric acid (3.05±0.29mg/dl) and blood urea nitrogen (47.8±9.07mg/dl) as compared to normal control animals. The test drug, aqueous extract of *Pimpinella anisum* depicted protective effects at doses 1, 2 and 4g/kg body weight by reducing the levels of serum urea, creatinine, uric acid and blood urea nitrogen as compared to gentamicin treated group but not in a dose dependent manner. There was a significant nephroprotective effect at doses 1 and 2g/kg body weight of the test drug as evidenced by a significant decrease in serum urea, creatinine, uric acid and blood urea nitrogen ($p<0.05$) as compared to gentamicin treated group.

Histopathological changes

The histological changes in the kidney of all the groups were graded and the results are expressed in Table 2. It was noted that the microscopic study of the kidney sections of the rats which were treated with normal

Table 1: Effects of gentamicin and aqueous extract of *Pimpinella anisum* on serum urea, creatinine, uric acid and blood urea nitrogen (BUN).

Group	Treatment	Parameters			
		Urea (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)	BUN (mg/dl)
1	Normal control (1ml/kg, i.p)	53.8±18.6	0.5±0.06	1.7±0.34	25.09±8.69
2	Gentamicin (80mg/kg, i.p)	107.5±16.92*	0.8±0.09*	3.05±0.29*	47.8±9.07*
3	*Pimpinella anisum* (1g/kg, oral) + gentamicin (80mg/kg, i.p)	55±8.68**	0.6±0.07**	1.96±0.15**	25.4±3.88**
4	*Pimpinella anisum* (2g/kg, oral) + gentamicin (80mg/kg, i.p)	29.3±2.38**	0.58±0.04**	2.4±0.61**	13.4±1.04**
5	*Pimpinella anisum* (4g/kg, oral) + gentamicin (80mg/kg, i.p)	93.16±21.5	0.7±0.07	2.6±0.24	43.5±9.78

Values are expressed as mean ± SEM.

*$p < 0.05$ when compared to normal control group.

**$p < 0.05$ when compared to gentamicin treated group.

Table 2: Semi quantitative comparison and scores of the histopathological renal damage of rats of different treatment groups.

Histopathological feature	Normal control	Gentamicin	*Pimpinella anisum* (1g/kg)	*Pimpinella anisum* (2g/kg)	*Pimpinella anisum* (4g/kg)
Glomerular infiltration	_	+++	++	+	_
Interstitial congestion	_	+++	++	++	_
Interstitial infiltration	_	+++	++	+	Sparse, scattered
Tubular regeneration	_	_	_	_	+++
Average score	0	3	2	1.7	0.6

saline appeared histologically normal with the score of 0. The kidney sections of the gentamicin treated group showed extensive tubular necrosis involving most of the renal cortex with an average score of 3. The observed changes included dilated tubules with denuded epithelium, intracytoplasmic vacuolation, blebs, interstitial and glomerular congestion, stromal inflammation and granular casts as depicted in Figure 1. The histomorphology of the kidney sections in rats treated with aqueous extract of *Pimpinella anisum* at doses 1 and 2 g/kg showed moderate tubular epithelial degeneration with dilated tubules and luminal granular necrotic casts with an average score of 2 and 1.7 respectively, as depicted in Figure 2. The dose at 4g/kg of *Pimpinella anisum* showed significant histological changes with presence of regenerating tubules illustrating protection against the gentamicin induced damage with an average score of 0.6, as in Figure 3.

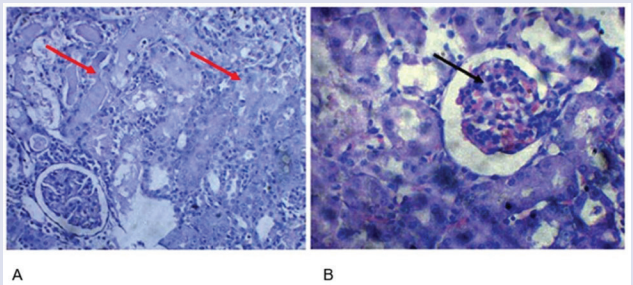

Figure 1: Photomicrograph of kidney sections of gentamicin treated group: showing extensive necrosis (red arrow), glomerular congestion (black arrow), interstitial congestion and inflammatory cell infiltration (40 X, H &E).

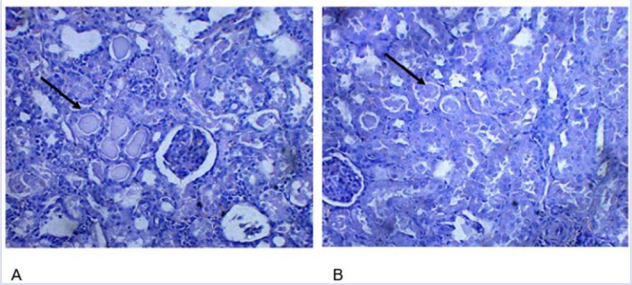

Figure 2: Photomicrograph of kidney sections treated with aqueous extract of *Pimpinella anisum* at doses 1 and 2 g/kg: showing granular casts (black arrow) and degenerated tubular epithelium (40X, H &E).

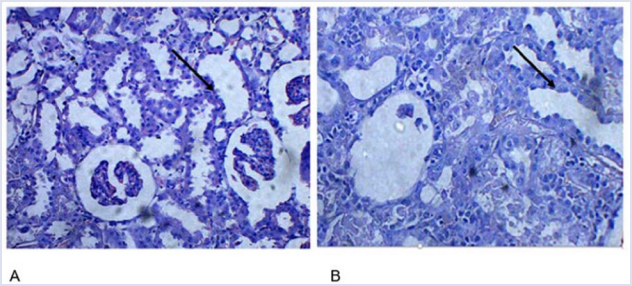

Figure 3: Photomicrograph of kidney sections treated with aqueous extract of *Pimpinella anisum* at dose 4g/kg: showing dilated tubules with flattened epithelium in the regenerative phase after tubular injury (black arrow), shedding of necrotic cells (40X, H &E).

DISCUSSION

Drug-induced nephrotoxicity is increasingly recognized as a harbinger to kidney disease including acute kidney injury and chronic kidney disease. The renal toxicity of aminoglycosides, especially gentamicin is now a well-established fact.[4] Agents ameliorating aminoglycoside nephrotoxicity would offer a distinct clinical advantage in therapeutics employing gentamicin. In view of this the present study was aimed to evaluate the nephroprotective action of the aqueous extract of *Pimpinella anisum* in gentamicin induced acute renal failure in a murine model.

Results of this study confirmed that gentamicin at a dose of 80mg/kg produces significant nephrotoxicity as evidenced by histological changes of the kidneys that include tubular necrosis, dilatation of tubules, degeneration of tubular epithelial cells with casts in the tubular lumen, cell infiltration in interstitium, marked congestion of the glomeruli and extensive necrosis with alteration of corresponding biochemical parameters as shown by increase in serum urea, creatinine, uric acid, blood urea nitrogen. The present histological and biochemical findings in gentamicin treated group correlate with previous reports.[11-17]

Pretreatment with aqueous extract of *Pimpinella anisum* provided marked nephroprotection against gentamicin induced renal damage in rats as evidenced by significant reduction in biochemical parameters. This is supported by histopathological evaluation; concurrent administration of *Pimpinella anisum* appeared to mitigate the severity of the gentamicin-induced renal necrosis, resulting in the preservation of the tubular histology by significantly reducing the scores of histopathological damages compared to gentamicin treated group. The signs of regeneration of tubules were also seen, which was prominent at highest dose. Restoration of the structure of glomerulus and renal tubules in *Pimpinella anisum* pretreated group provides a direct evidence for nephroprotective activity of this extract.

Recent studies have demonstrated an accumulating body of evidence to support the pre-concept of participation of reactive oxygen metabolites including free radicals in renal tissue injury. A clear relationship between oxidative stress and nephrotoxicity has been hypothesized and proved in many experimental animal models.[28,29] Gentamicin enhances the generation of hydrogen peroxide and oxygen free radicals. Reactive oxygen species (ROS) may produce cellular injury and necrosis via, several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage.[28] It has also been considered that gentamicin alters the basolateral membrane and mitochondria enhancing production of free radicals and lipid peroxidation of renal cortex.[30] Gentamicin is well-known to reduce the activities of catalase, glutathione peroxidase and the levels of reduced glutathione. Consumption of foods rich in polyphenolic compounds which delay or prevent the oxidation of cellular oxidizable substrates by direct radical scavenging action or indirect antioxidant action, such as inhibition of ROS producing enzymes (xanthine oxidase, lipoxygenase etc.) provides a logical strategy to minimize these health risks and balance these ROS.[31] Moreover, this has been adequately tried and tested in previous studies which have shown considerable renoprotection by pretreating rats with hydroxyl radical scavengers.[13]

Several experimental studies have shown antioxidant potential of *Pimpinella anisum*.[19,31,32] Phytochemical screening of aniseed has revealed polyphenolic compounds like flavonoids, tannins, and phenolic acids as major components. These are very vital for the free-radical scavenging and antioxidant activities of plants as they act as hydrogen donors and thus neutralize the free-radicals[32] as assessed by DPPH and ABTS radical scavenging activity assays. This radical scavenging potential of aniseed extract can also be supported by significantly decreased lipid peroxidation in the *in vitro* models.[19] Moreover, its antioxidant activity has also been partially held responsible for its preventive and therapeutic effects on acute hepatic injury in rats.[33]

Because of the above properties aniseed can protect biomolecules like proteins, nucleic acids, poly unsaturated fatty acids in membranes and prevent most of the biological molecules from oxidation, thus decreasing the rate of the lipid peroxidation.[19] Further studies are required to explore and associate the antioxidant effect to nephroprotection afforded by *Pimpinella anisum* which might help better characterize its mechanism in attenuating gentamicin induced renal damage.

CONCLUSION

To conclude, this study provides scientific evidence of the nephroprotective effects of orally administered aqueous extract of *Pimpinella anisum* in gentamicin induced renal damage.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUMMARY

The present study provides evidence that pre-treatment and co-administration of *Pimpinella anisum* along with gentamicin prevents both functional and histological renal changes induced by gentamicin in rats.

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