Bioactive traditional plant *Cinnamomum zeylanicum* successfully combat against nephrotoxic effects of aminoglycosides
Introduction

*Cinnamomum zeylanicum* belongs to family Lauraceae, widely used as spices and food preservatives in form of oils and extracts (Yu et al., 2007). This traditional plant is extensively used for the treatment of different kidney ailments and due to the sweet bark of plant, it is known as sweet wood (Willis, 1973). The plant may have protective role in alleviating the signs and symptoms of many diseases due to oxidative stress (Ranjbar et al., 2006). The extracts of *Cinnamomum* regularly used as food antioxidants (Mancini-Filho et al., 1998). The plant has also been used for the treatment of several diseases (Senhaji et al., 2007). The usefulness of plant extract in the treatment of gastritis, dyspepsia, disturbances in blood circulation and inflammation has been reported (Wang et al., 2009). The analgesic, antipyretic, antitussive and antiallergenic actions have also been presented (Singh et al., 2008).

The essential oil obtained from the bark *C. zeylanicum* has abundant cinnamaldehyde, which have antimicrobial actions against several pathogenic bacteria and fungi (Mastura et al., 1999). Mishra and coworkers reported that the bark of *C. zeylanicum* contains some antifungal substances (Mishra et al., 2009). Most importantly, the plant possesses antioxidant activities due to its phenolic contents (Tomaino et al., 2005) evaluated by different *in vitro* assays (Lee and Shibamoto, 2002). Because of antioxidant properties the extract obtained from *C. zeylanicum* have beneficial role against free radical damage to the cell membranes (Hasani-Ranjbar et al., 2009). The plant has also been presented to stimulate antioxidant enzymes (Dhuley, 1999). Due to its antioxidant actions it possesses strong wound healing properties (Kamath et al., 2003). The

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**Abstract**

*Cinnamomum zeylanicum* is traditionally used for the treatment of bladder and kidney problems; believed to have kidney tonic effects. The prime objective of the current study was to explore the nephroprotective effects of the plant due to its strong antioxidant properties, to provide experimental facts for their traditional use. Daily dose of 200 mg/kg of plant extract was employed alone and in combination with gentamicin for a period of twenty one days in rabbits. Biochemical kidney functioning parameters were assessed thrice throughout study period. Histopathological examination of the kidneys was performed on the last day of experimental period. Present study showed that *C. zeylanicum* significantly attenuated renal functional and histological changes associated with gentamicin as assessed by urea, creatinine, uric acid, electrolytes, urinary protein, and histopathological examination. The plant extract successfully proved to have strong nephroprotective properties, especially against aminoglycosides induced nephrotoxicities.

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**Bioactive traditional plant *Cinnamomum zeylanicum* successfully combat against nephrotoxic effects of aminoglycosides**

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plant also proved to have insecticidal activity (Abdel Halim, 2006), with effectiveness in allergic rhinitis (Corren et al., 2008).

On the basis of above discussed text; C. zeylanicum comprise a number of remedial properties, particularly determined as antioxidant and free radical scavenging properties may due to strong phenolic contents (Ranjbar et al., 2006; Mancini-Filho et al., 1998; Tomaino et al., 2005; Lee and Shibamoto, 2002; Hasani-Ranjbar et al., 2009; Dhuley, 1999), which has been reported to be responsible for the amelioration of gentamicin induced renal damage (Ali and Mousa, 2001). Most importantly, the powdered bark of C. zeylanicum is used traditionally for the treatment of various kidney problems like kidney stones, renal colic and believed to have a tonic effect on kidney. Consequently the present work was aimed to explore the defensive effect of C. zeylanicum against renal disruption associated with administration of aminoglycosides.

Materials and Methods

Plant material and extraction

Three kilogram of dried bark of C. zeylanicum plant was purchased from local market Abbottabad Pakistan. The voucher specimen number 1024 was deposited after had identified by Umar Farooq, Professor of Botany, Govt. College Abbottabad Pakistan. Powdered plant material was extracted with ethanol for three weeks and evaporated under reduced pressure (Bhukya et al., 2009).

Experimental protocol

Similar weighted male rabbits were acclimatized and maintained at same diet in twelve hours cycles of dark and light after the approval from University Ethical Committee. Twenty four animals were arranged equally into four groups and were treated separately according to dosage schedule (Table I). For estimation of blood urea nitrogen (BUN), serum creatinine, creatinine clearance, serum uric acids, serum electrolytes, urinary urea, urinary creatinine, urinary protein and urinary volume; blood and urine samples were collected trice throughout duration of treatment.

Biochemical assessments

BUN was assessed by following Bertholot’s indophenol assay while serum creatinine was evaluated by following Jaffe reaction. Serum uric acid was estimated by chemistry analyzer with the help of reagent kits (Smith, 1985). Further, serum sodium and serum potassium was measured by flame photometric method while serum calcium by cresolphthalein complexone method (Blosser, 1985).

Histo-pathologic examination of kidney

On last day of experimental period, half of the animals in each experimental group were slaughtered for renal histopathology. Kidneys were secluded and fixed in formalin solution. Tissues were treated with ascending order of ethanol followed by xylene and fixed in wax. Blocks were cut into thin slices with help of rotatory microtome (Micros, Germany). The slides were stained with hematoxylin and eosin and studied with the help of microscope (Germany).

Statistical analysis

Results were tabulated as mean ± SEM and all the experimental groups were compared with gentamicin treated group by using Dunnett t-test subsequent to one-way ANOVA with the help of GraphPad Prism (Version v). p value <0.05 was considered statistically significant.

Results

Mean body weight

Body weight lost significantly in group G (10.8 ± 1.1), when compared with group C (0.2 ± 0.9%). The body weight of animals treated with both gentamicin and C. zeylanicum were found significantly different from group G animals, exactly same as group C (Figure 1A).

Measurement of serum BUN

BUN increased significantly in group G, as 54.2 ± 2.6 mg/dL on last day of study period in comparison with group C (14.1 ± 1.1 mg/dL). Group GC-ze and C-ze were also observed significantly different when compared with group G (14.2 ± 1.2 and 13.7 ± 0.2 mg/dL vs 54.2 ± 2.6 mg/dL; Table II).

Measurement of serum creatinine

Significant increase in serum creatinine was observed in group G, as 4.0 ± 0.1 mg/dL on last day of study period in comparison with group C (0.8 ± 0.1 mg/dL). Group GC-ze and C-ze were also observed significantly different when compared with group G (0.9 ± 0.1 and 0.7 ± 0.1 mg/dL vs 4.0 ± 0.1 mg/dL; (Table II).
Measurement of creatinine clearance
Creatinine clearance significantly decreased in group G, as 0.8 ± 0.1 mL/min on last day of study period in comparison with group C (5.0 ± 1.2 mL/min). Group GC-ze and C-ze were found to be extremely different when compared with group G (3.8 ± 0.6 and 5.4 ± 0.5 mL/min vs 0.8 ± 0.1 mL/min; Table II).

Measurement of serum sodium
No significant fall in serum sodium was observed in group G, as 137.7 ± 1.1 mEq/L on last day of study period in comparison with group C (140.2 ± 1.0 mEq/L). Further serum sodium vel of group GC-ze (141.2 ± 1.1 mEq/L) was found significantly different from group G, while C-ze (140.8 ± 1.5 mEq/L) was same as that of group G.

Measurement of serum potassium
Significant fall in serum potassium level in group G, as 3.4 ± 0.2 mEq/L was observed on last day of study period in comparison with group C (5.1 ± 0.2 mEq/L). Further, group GC-ze and C-ze were also observed to be significantly different from group G (5.1 ± 0.1 and 5.2 ± 0.4 mEq/L vs 3.4 ± 0.2 mEq/L; Table II).

Measurement of serum calcium
Significant fall in serum calcium was observed in group G, as 7.7 ± 0.2 mg/dL on last day of study period in comparison with group C (9.7 ± 0.3 mg/dL). However, group GC-ze and C-ze were found significantly different from group G (7.7 ± 0.2 mg/dL vs 5.3 ± 0.1 and 5.4 ± 0.4 mg/dL; Table II).

Mean ± SEM (n = 6); *considered significant when compared with gentamicin-treated group

| Table I |

| Biochemical kidney functioning parameters on day 0, 11 and 21 of study period |

| Group | Blood urea nitrogen (mg/dL) | Day 0 | Day 11 | Day 21 |
|-------|-----------------------------|-------|--------|--------|
| C     | 13.1 ± 1.2                  | 13.8 ± 1.0 | 14.1 ± 1.1 |
| G     | 12.8 ± 1.1                  | 37.8 ± 2.1 | 54.2 ± 2.6 |
| GC-ze | 13.7 ± 1.2                  | 13.9 ± 1.2 | 14.2 ± 1.2 |
| C-ze  | 13.5 ± 0.2                  | 13.6 ± 0.2 | 13.7 ± 0.2 |

| Group | Serum creatinine (mg/dL) | Day 0 | Day 11 | Day 21 |
|-------|--------------------------|-------|--------|--------|
| C     | 0.7 ± 0.1                 | 0.7 ± 0.1 | 0.8 ± 0.1 |
| G     | 0.5 ± 0.0                 | 2.0 ± 0.1 | 4.0 ± 0.1 |
| GC-ze | 0.6 ± 0.0                 | 0.7 ± 0.0 | 0.9 ± 0.1 |
| C-ze  | 0.7 ± 0.1                 | 0.7 ± 0.1 | 0.7 ± 0.1 |

| Group | Creatinine clearance (mL/min) | Day 0 | Day 11 | Day 21 |
|-------|--------------------------------|-------|--------|--------|
| C     | 5.7 ± 0.6                     | 5.1 ± 0.8 | 5.0 ± 1.2 |
| G     | 5.3 ± 0.5                     | 2.1 ± 0.3 | 0.8 ± 0.1 |
| GC-ze | 5.7 ± 0.7                     | 4.6 ± 0.5 | 3.8 ± 0.6 |
| C-ze  | 6.3 ± 0.6                     | 5.5 ± 0.7 | 5.4 ± 0.5 |

| Group | Serum sodium (mEq/L) | Day 0 | Day 11 | Day 21 |
|-------|----------------------|-------|--------|--------|
| C     | 140.5 ± 1.2          | 139.6 ± 0.6 | 140.2 ± 1.0 |
| G     | 141.2 ± 0.8          | 140.5 ± 0.6 | 137.7 ± 1.1 |
| GC-ze | 141.3 ± 1.1          | 141.3 ± 1.1 | 141.2 ± 1.1 |
| C-ze  | 141.2 ± 1.5          | 140.7 ± 1.6 | 140.8 ± 1.5 |

| Group | Serum potassium (mEq/L) | Day 0 | Day 11 | Day 21 |
|-------|-------------------------|-------|--------|--------|
| C     | 5.3 ± 0.2               | 5.3 ± 0.2 | 5.1 ± 0.2 |
| G     | 5.2 ± 0.2               | 4.0 ± 0.1 | 3.4 ± 0.2 |
| GC-ze | 5.3 ± 0.1               | 5.2 ± 0.1 | 5.1 ± 0.1 |
| C-ze  | 5.4 ± 0.4               | 5.3 ± 0.4 | 5.2 ± 0.4 |

| Group | Serum calcium (mg/dL) | Day 0 | Day 11 | Day 21 |
|-------|-----------------------|-------|--------|--------|
| C     | 10.1 ± 0.2            | 10.0 ± 0.2 | 9.7 ± 0.3 |
| G     | 10.3 ± 0.3            | 8.5 ± 0.3 | 7.7 ± 0.2 |
| GC-ze | 10.3 ± 0.3            | 10.1 ± 0.2 | 10.0 ± 0.2 |
| C-ze  | 10.3 ± 0.2            | 10.3 ± 0.2 | 10.3 ± 0.2 |

| Group | Serum uric acid (mg/dL) | Day 0 | Day 11 | Day 21 |
|-------|-------------------------|-------|--------|--------|
| C     | 1.2 ± 0.1               | 1.4 ± 0.0 | 1.5 ± 0.0 |
| G     | 1.3 ± 0.1               | 1.6 ± 0.1 | 2.3 ± 0.1 |
| GC-ze | 1.3 ± 0.1               | 1.3 ± 0.1 | 1.5 ± 0.1 |
| C-ze  | 1.4 ± 0.1               | 1.4 ± 0.1 | 1.4 ± 0.1 |
different from group G (10.0 ± 0.2 and 10.3 ± 0.2 mg/dL vs 7.7 ± 0.2 mg/dL; Table II).

Measurement of urinary volume

Significant decrease in urinary volume of group G, as 126.0 ± 9.1 mL was observed in comparison with group C (217.0 ± 19.8 mL). Group GC-ze (195.0 ± 17.9 mL) and C-ze (236.0 ± 19.8 mL) were also found significantly different from group G (Figure 1B).

Measurement of urinary protein excretion

Significant rise in the excretion of protein was noted in group G animals as 3.9 ± 0.3 mg/dL on last day of study period in comparison with group C animals as 1.8 ± 0.2 mg/dL. Urinary protein excretion of group GC-ze and C-ze were found significantly different from group G animals (Figure 1C).

Measurement of serum uric acid

Significant increase in group G, as 2.3 ± 0.1 mg/dL was observed on last day of study period in comparison with group C (1.5 ± 0.0 mg/dL). Group GC-ze and C-ze were found significantly different when compared with group G (1.5 ± 0.1 and 1.4 ± 0.1 mg/dL vs 2.3 ± 0.1 mg/dL; Table II).

Histopathologic examination of the kidney

Group C animals presented normal tubules with no hydropic abnormalities. Glomeruli appeared normal with no confirmed identification of necrosis; renal medulla presenting normal distal tubules with a little hazy appearance as shown in Figure 2A-B. However, group G animals presented necrosis of proximal tubules with disrupts cellular structure. Additionally atropic glomeruli with hydropic abnormalities and a number of ruptured tubules were also found; renal medulla showed loss of cellular pattern with large number of ruptured tubules as shown in Figure 3A-B. Further, group GC-ze and C-ze animals presented normal structures, with no common abnormalities, except few ruptured tubules in case of some animals of group GC-ze; renal medulla of both groups presenting normal...
tubules with no proper abnormality except some ruptured tubules in group C-ze, as shown in Figure 4A-B, 5A-B.

Discussion

In the present work we investigated the offset property of *C. zeylanicum* against the nephrotoxic side effects of aminoglycosides due to their antioxidant potentials. These nephrotoxic effects are dependent on dose and its duration of treatment, especially when the drug is used at higher doses (Bennett et al., 1999). Gentamicin as the most important member of aminoglycoside group, used at different doses (40/60/80 mg/kg/day) to produce nephrotoxic effects, followed in the present work at 80 mg/kg/day to generate renal toxicity (Gilbert et al., 1989).

Significant increase in creatinine, BUN and uric acid with a decrease in creatinine clearance was observed in the present exploration in group G animals in comparison with control group animals. Which is in agreement with previous reported findings as, significant fall in creatinine clearance with rise in serum creatinine and BUN was produced after treatment with gentamicin (Moghaddam et al., 2010). Further, animals treated with combine therapy of extract and gentamicin proved safe from nephrotoxicity like group C-ze animals, confirmed the nephroprotectant properties of *C. zeylanicum*.

Body weight progressively decreased in group G animals when compared with group C animals. Further, animals treated with both gentamicin and *C. zeylanicum* were found with no significant loss in their body weight. Gentamicin treated animals were found with fall in urinary volume and rise in excretion of protein, significantly dissimilar to that of group C animals. Further, urinary volume and urinary protein excretion of animals treated with combine administra-

![Figure 3: Microphotographs of Group G (Gentamicin treated); (A) renal cortex presenting glomerular atrophy with hydropic changes, hyaline filled lumina, necrosis and loss of cellular pattern and (B) renal medulla presenting loss of cellular pattern with a number of ruptured and dilated collecting tubules.](image)

![Figure 4: Microphotographs of Group GC-ze (Gentamicin and *C. zeylanicum* treated); (A) renal cortex presenting normal structures with some ruptured tubular cells and (B) renal medulla presenting normal tubules with no proper evidence of abnormality.](image)
tion of gentamicin and C. zeylanicum were found significantly different from gentamicin treated animals. Sodium excretion has been reported to improve with the reduction in re-absorption of potassium by toxic gentamicin treatment (Derakhshanfar et al., 2007). Gentamicin has also been reported to produce hypokalemia at large doses as in present study for group G animals, opposite in case of animals treated with combine gentamicin and C. zeylanicum (Bennett et al., 1999). C. zeylanicum treated animals alone and in combination with gentamicin significantly protect from reduction in serum potassium different from group G animals (Asif et al., 2012). Serum calcium decreased significantly in group G animals in the present work, significantly different from group C and all other treated groups as reported previously (Lambie, 1991). However, in opposition; gentamicin has been presented with no sound effect on serum calcium (Lambie, 1991). Further, in the present work serum sodium was found nearly same in all groups including gentamicin treated group. However, altered serum sodium has been presented previously (Bennett et al., 1999).

Increase in serum creatinine was reported to be linked with necrosis of tubules (Solez, 1983), may because of accumulation of debris in the tubules as like in the present findings necrosis and increase in creatinine are side by side in gentamicin treated animals. In opposition it has been presented that necrosis and other functional parameters are independent to each other (Luft et al., 1977).

The increase excretion of urinary excretion in group G animals in the present study may due to renal casts and hyaline in the tubules, responsible for blocking of tubules causes renal toxicity (Solez, 1983). In addition kidney histology presented group G with necrosis and hydropic abnormalities as reported previously (Bennett et al., 1999). No proper abnormality like hydropic abnormalities, cast cells or necrosis were identified in group C animals and animals treated with both gentamicin and C. zeylanicum, nor in animals treated with C. zeylanicum alone, confirmed the nephroprotectant properties of C. zeylanicum.

Conclusion
C. zeylanicum successfully attenuated renal structural and functional derangements associated with aminoglycosides assessed by histological and biochemical parameters, may due to its strong antioxidant potentials.

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Conflict of Interest
Authors declare no conflict of interest

References
Abdel Halim AS. Efficacy of C. zeylanicum on third stage larvae and adult fecundity of Musca domestica and Anopheles pharoensis. J Egypt Soc Parasitol. 2006; 38: 475-82.
Ali BH, Mousa HM. Effect of dimethyl sulfoxide on gentamicin-induced nephrotoxicity in rats. Hum Exp Toxicol. 2001; 20: 199-203.
Aṣif AH, Rasool ST, Khan TM. Pyridoxal Phosphate a possible intervention to prevent aminoglycoside induced Electrolyte imbalance. J Clinic Res Bioeth. 2012; 3: 124.
Bennett WM, Elzinga LW, Porter GA. Tubulointerstitial disease and toxic nephropathy. In: The Kidney. Brenner BM, Rector FC, eds. 4th ed. Philadelphia, WB Saunders
Bhukya B, Anreddy RNR, William CM, Gottumukkala KM. Analgesic and anti-inflammatory activities of leaf extract of *Kydia calycina* Roxb. Bangladesh J Pharmacol. 2009; 4: 101-04.

Blosser N. Electrolytes. In: Clinical chemistry, principles, procedures, correlations. Bishop ML, Duben-Von Laufen JL, Fody EP, eds. Philadelphia, JB Lippincott, 1985, pp 263-89.

Corren J, Lemay M, Lin Y, Rozga L, Randolph RK. Clinical and biochemical effects of a combination botanical product (Clear Guard) for allergy: A pilot randomized double-blind placebo-controlled trial. Nutr J. 2008; 7: 20.

Dhuley JN. Anti-oxidant effects of cinnamon (*Cinnamomum verum*) bark and greater cardamom (*Amomum subulatum*) seeds in rats fed high fat diet. Indian J Exp Biol. 1999; 37: 238-42.

Gilbert DN, Wood CA, Kohlhepp SJ, Kohnen PW, Houghton DC, Finkbeiner HC, Lindsley J, Bennett WM. Polyaspartic acid prevents experimental aminoglycoside nephrotoxicity. J Infect Dis. 1989; 159: 945-53.

Hasani-Ranjbar S, Larijani B, Abdollahi M. A systematic review of the potential herbal sources of future drugs effective in oxidant-related diseases. Inflamm Allergy Drug Targets. 2009; 8: 2-10.

Johnson AM, Rohlfs EM, Silverman LM. Proteins. In: Tietz textbook of clinical chemistry. Burtis CA, Ashwood ER (eds). 3rd ed. Philadelphia, WB Saunders, 1999, pp 477-540.

Kamath JV, Rana AC, Chowdhury AR. Pro-healing effect of *C. zeylanicum* bark. Phytother Res. 2003; 17: 970-72.

Lambie AT. Disturbances in water, electrolyte and acid-base balance. In: Principles and Practice of Medicine. Edward CRW, Bouchieer IAD, eds. 16th ed. Edinburgh, Churchill Livingstone, 1991, pp 203-28.

Lee KG, Shibamoto T. Determination of anti-oxidant potential of volatile extracts isolated from various herbs and spices. J Agric Food Chem. 2002; 50: 4947-52.

Luft FC, Yum MN, Kleit SA. The effect of concomitant mercuric chloride and gentamicin on kidney function and structure in the rat. J Lab Clin Med. 1977; 89: 622-31.

Mancini-Filho J, Van-Koiij A, Mancini DA, Cozzolino FF, Torres RP. Antioxidant activity of cinnamon (*C. zeylanicum*, Breyn). Boll Chim Farm. 1998; 137: 443-47.

Mastura M, Nor Azah MA, Khozirah S, Mawardi R, Manaf AA. Anticandidal and antidermatophytic activity of *Cinnamomum* species essential oils. Cytobios 1999; 98: 17-23.

Mishra AK, Mishra A, Kehri HK, Sharma B, Pandey AK. Inhibitory activity of Indian spice plant *C. zeylanicum* extracts against *Alternaria solani* and *Curvularia lunata*, the pathogenic dematiaceous moulds. Ann Clin Microbiol Antimicrob. 2009; 8: 9.

Moghaddam AH, Javaheri M, Nabavi SF, Mahdavi MR, Nabavi SM, Ebrahimzadeh MA. Protective role of pleurotus porrigens (Angels wings) against gentamicin-induced nephrotoxicity in mice. Eur Rev Med Pharmacol Sci. 2010; 14: 1011-14.

Ranjbar A, Ghasmeinezhad S, Zamani H, Malekirad AA, Baiaty A, Mohammadirad A, Abdollahi M. Anti-oxidative stress potential of *C. zeylanicum* in humans: A comparative cross-sectional clinical study. Therapy 2006; 3: 113-17.

Senhaji O, Faid M, Kalalou I. Inactivation of *Escherichia coli* O157:H7 by essential oil from *C. zeylanicum*. Braz J Infect Dis. 2007; 11: 234-36.

Singh G, Kapoor IP, Singh P, De Heluani CS, De Lampasona MP, Catalan CA. Chemistry, anti-oxidant and antimicrobial investigations on essential oil and oleoresins of *Zingiber officinale*. Food Chem Toxicol. 2008; 46: 3295-302.

Smith ST. Non protein nitrogen. In: Clinical chemistry, Principles, procedures, correlations. Bishop ML, Duben-Von Laufen JH, Fody EP, eds. Philadelphia, JB Lippincott Company, 1985, pp 411-23.

Solez K. Pathogenesis of acute renal failure. In: International review of experimental pathology. New York, Academic Press, 1983, pp 321-26.

Tomaino A, Cinino F, Zimbalatti V, Venuti V, Sulfaro V, De Pasquale A, Saija A. Influence of heating on anti-oxidant activity and the chemical composition of some spice essential oils. Food Chem. 2005; 89: 549-54.

Wang R, Wang R, Yang B. Extraction of essential oils from five cinnamon leaves and identification of their volatile compound compositions. Innov Food Sci Emerg Technol. 2009; 10: 289-92.

Willis JK. A dictionary of the flowering plants and ferns. 8th ed. Cambridge, Cambridge University Press, 1973.