Evaluation of nephroprotective activity of *Musa paradisiaca* L. in gentamicin-induced nephrotoxicity

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Abstract: The objective of the study was to investigate the nephroprotective activity of methanolic extract of different morphological parts (bract, flower, trachea and tracheal fluid) of *Musa paradisiaca* L. (Family: Musaceae) against gentamicin-induced nephrotoxicity in mice. Gentamicin produced significant changes in biochemical (increased levels of blood urea nitrogen level, blood urea, and serum creatinine), and histological parameters in mice. Treatment with methanolic extract of bract (100 and 250mg/kg, b.w) and flowering stalk (trachea) (250 and 500mg/kg, b.w) significantly prevented biochemical and histological changes produced by gentamicin toxicity. The extracts of *M. paradisiaca*(bract and flowering stalk) could contribute a lead to discovery of a new drug for the treatment of drug-induced nephrotoxicity.

Keywords: *Musa paradisiaca* L., Histopathology, Gentamicin, Renal function.

INTRODUCTION

Major health problem in the world are due to liver and kidney diseases which occur due to oxidative stress caused by toxic chemicals, xenobiotics, alcohol consumption, malnutrition, medications and some therapeutic agents such as aminoglycoside antibiotics, chemotherapeutic agents, NSAIDS, chemical agents such as ethylene glycol, carbon tetra chloride, sodium oxalate and heavy metals like lead, mercury, arsenic and cadmium adversely affect the kidney and results in acute renal failure, chronic interstitial nephritis and nephritic syndrome. Nephrotoxicity is the common kidney problems that occur due to exposure to drug or toxin and body become unable to remove excess urine and wastes material and increases the level of blood electrolytes and considered as significant factor for the development of new drug as kidney is important target for toxicity of drugs, xenobiotics and oxidative stress (Alqasoumi 2014; Kanchan *et al*., 2012; Moghaddam *et al*., 2010). Gentamicin sulfate is one of the members of amino glycoside that causes nephrotoxicity in 30% of patients that was treated with gentamicin for more than seven day (Hussain *et al.*, 2012; Kang *et al*., 2013). Itis a bactericidal antibiotic that rapidly excreted by glomerular filtration and reabsorbed by the proximal tubules of kidney (El-Ashmawy *et al*., 2006), enter and binds to 30s ribosomes, induces suppression of Na/KATP-ase activity and blocks bacterial protein synthesis (Salih, 2015). It also provoke superoxide anions, hydroxyl radical production, H_2O_2 generation, lipoperoxidation, increase in concentration ofnitro-tyrosine, protein carbonyl and decrease the reduced glutathione in renal corte (El-Ashmawy *et al*., 2006; Subramanian *et al*., 2015).Some macromolecules are damaged due to abnormal production of reactive oxygen species (ROS), cause necrosis and cellular injury by different mechanisms such as per-oxidation of membrane lipids, protein denaturation and DNA damage. It also acts as iron chelator and form iron–gentamicin complex which is potent catalyst of radical generation (Nitha and Janardhanan, 2008). Morphologically GS nephrotoxicity is characterized by proximal tubule epithelial desquamation, tubular necrosis, tubular fibrosis, epithelial edema, glomerular hypertrophy, increase in serum creatinine and blood urea nitrogen (Kang *et al*., 2013), degeneration, vacuolization of proximal tubules, increased number of hyaline casts in renal tubules, marginal localization of chromatin in the nuclei, mononuclear cell infiltration, inter tubular hemorrhage, picnosis, atrophied glomeruli, and obliterative arteriolepathy in renal tissues (Subramanian *et al*., 2015).GS-induced nephrotoxicity can be prevented or ameliorated by use of synthetic anti-oxidants and natural plant extracts that have antioxidant properties (Kang *et al*., 2013). Utilization of synthetic anti-oxidants is prohibited due to their carcinogenicity therefore there is an imperative need of naturally occurring antioxidant and potent anti-nephrotoxic drug against renal disorders. Therefore a relationship has established between dietary supplementation of vegetables and plants and the reduction of toxic effects of different toxicants, environmental agents, carcinogens and heavy metals (Paliwal *et al*., 2011). Many medicinal plants that are used in traditional medicine have significant role in decreasing the progression of chronic kidney diseases (Alqasoumi, 2014).

Musa paradisiaca L. belongs to family Musaceae that consists of two genera and 42 different species, grows along the road side, areas with compacted soil, near paths. In Pakistan locally it is known as kela, kadali, kadalamu

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and valeiin different local languages (Sanjeev *et al*., 2012; Jawla *et al*., 2012). Used as laxative, demulcent, emollient, antiulcerogenic, antidepressant, antibacterial, antihypertensive, antihelminthic, antivenomic, antifungal agent, analgesic, to remove constipation, wound healing, fevers, burns, diarrhea and inflammation, rheumatism, gripe, diabetes, hypertension, asthma, burns, ulcers and warts are also treated by plantain (Sundaram *et al*., 2014; Hussain *et al*., 2010).The aim is to investigate the pharmacological effect of *M. paradisiaca* bract, flower, flowering stalk (trachea) and tracheal fluid on kidney to find out the economically affordable and easily available drug for kidney problem.

MATERIALS AND METHODS

Collection of plant material

M. paradisiaca plant was collected from District Muzaffar-Garh, (Punjab) Pakistan and authenticated by Dr. Mansoor Hameed Associate Professor, Taxonomic Laboratory, Department of Botany, University of Agriculture Faisalabad. Specimen of each part of plant material was also deposited in the herbal museum Department of Pharmacognosy, Faculty of Pharmacy, University of Karachi. The parts of *Musa paradisiaca* L. [bracts, flower and flowering stalk (trachea)] were separated and dried in shade at room temperature for about one month.

Extraction of plant material

Extraction of bract, flower and flowering stalk was carried out separately by maceration using methanol (Merck) in glass aspirator for seven days with occasional shaking at room temperature then filtration was carried out by using Whatman filter No.1. The filtrate were evaporated to dryness in rotary vacuum evaporator (Rotavapor R-200, Buchi) at temperature 50^0C with rotation 3rpm and pressure 0.07MPA or 20 in Hg .The dried material were weighed, labeled and stored in refrigerator (Sanyo biomedical freezer, MDF-U333, Japan). The fluid obtained from floral stalk (tracheal fluid) after cutting the bunch of fruit is lyophilized at -65 to -60^0Cwith vacuum of 30-40 milibar in alpha 1-4LSC Christ Germany lyophilizer. The dried material were weighed, labeled and stored in refrigerator for experiment.

Animals

Swiss albino mice of either sex were maintained free from pathogens in well cross ventilated animal house of Faculty of Pharmaceutical sciences Government College University Faisalabad. Mice of 8-10 week old of either sex having weight of 25-32g were used in experiment. These animals were allowed one week to acclimate to the facilities prior to usein any experiments. The animals have free access to standard pellet diet and water ad libitum during the entire course of experiment. Temperature (20-23^{o}C), and humidity (40-55%) were kept in control with a light/dark cycle (on 12.00 h, off 12.00 h). This study was carried out according to animal experimental regulations issued by ethical committee for animal handling of Government college University Faisalabad (Ref. No. Pharm/14/1928).

Chemicals

Gentamicin sulphate in form of injection with brand name of Genticyn, batch No 131745 manufactured by Ray pharmaceutical (Pvt) limited Karachi. Chloroform (Sigma Chemical Co., St. Louis, U.S. A), Mayer hematoxylin and eosin (H andE) stain, methanol and all chemical solvents were of analytical grade Ureal and CREJ2 commercial diagnostic kit (Roche Pakistan limited), Cell pack easy Lyte Na/K/Cl/HCO_3 analyzer (Medonic).

Nephroprotective activity

Effect of methanolic extracts of different parts of *Musa paradisiaca* L.(bract, flower, trachea and tracheal fluid)on kidney was performed by the method Okokon*et al*. (2011) with slight modification. Seventy (70) mice either male or female were weighed and divided into 14 groups of five animals each and treated as follows: Group 1 (negative control group) was receiving10 ml/kg distilled water only. Group 2 (positive control group) was receiving 100mg/kg gentamicin sulphate (i.p). Group 3 to 14 (Test group) was administered with 100, 250 and 500mg/kg (orally) methanolic extract of bract, flower, trachea and tracheal fluid of *Musa paradisiaca* daily for eight days orally respectively. Gentamicin was administered daily to all the groups except Group 1concomitantly with the above treatments for 8 days having the dosage of 100mg/kg (Okokon *et al*., 2011).

Collection of sample

At the end of the study period mice in each group were kept in metabolic cages having free access to water and food and were fasted overnight. Then animals were sacrificed under chloroform anesthesia blood samples for kidney markers were collected and centrifuged at 3000 r/min for 10 min to obtain the serum. The serum was stored at 20^0C until usefor biochemical determinations. Kidney of animals were surgically excised and fixed in 10% buffered formalin for subsequent morphological and histological analysis (Okokon *et al*., 2011).

Serum markers of nephrotoxicity

Various biochemical parameters such as blood urea was determined by using diagnostic kit have brand name Urea of Roche Pakistan limited with batch number of 612303-01. Serum creatinine was measured with diagnostic kit CREJ2 of Roche Pakistan limited with batch number 0061103-2. Na, K, HCO3 and Cl ion was determined by cell pack easy Lyte Na/K/Cl/HCO3 analyzer of Medonic company with batch no 14269-1.

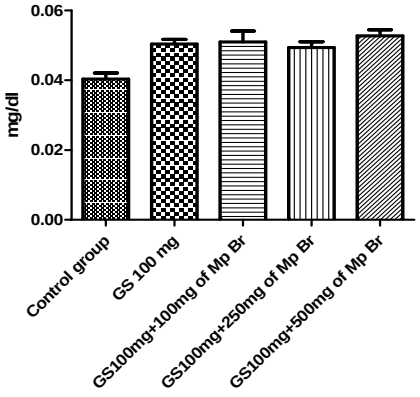

Fig. 1(a): Mp B effect on serum creatinine

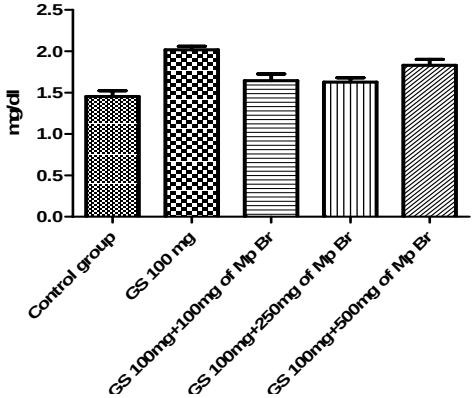

Fig. 1(b): Mp B effect on serum urea

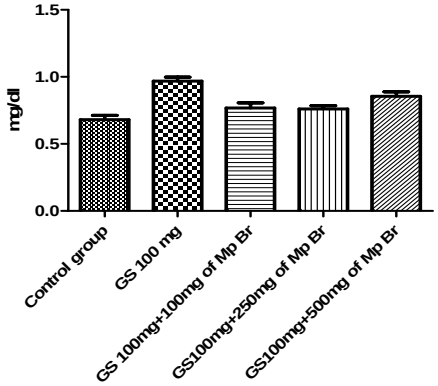

Fig. 1(c): Mp B effect on serum BUN.

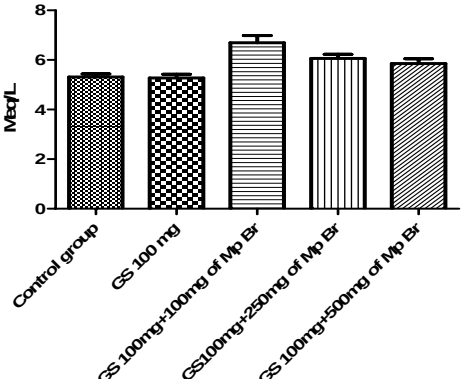

Fig. 1(d): Mp B effect on sodium ion

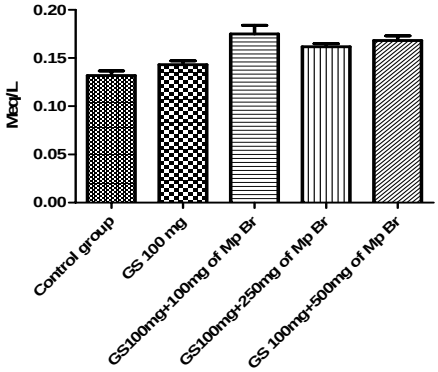

Fig. 1(e): Mp B effect on potassium ion

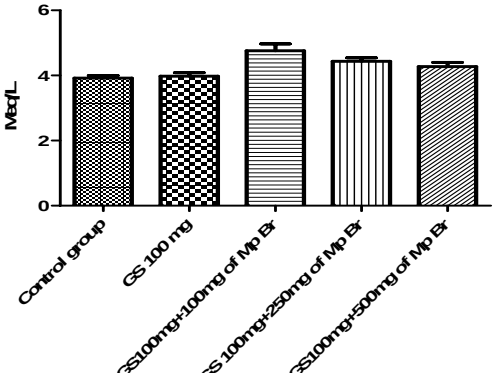

Fig. 1(f): Mp B effect on chloride ion

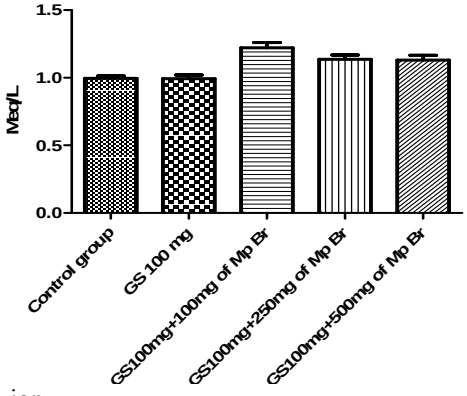

Fig. 1(g): Mp B effect on bicarbonate ion

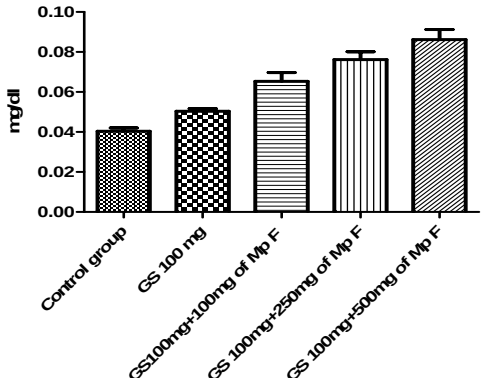

Fig. 2(a): Mp F effect on serum creatinine

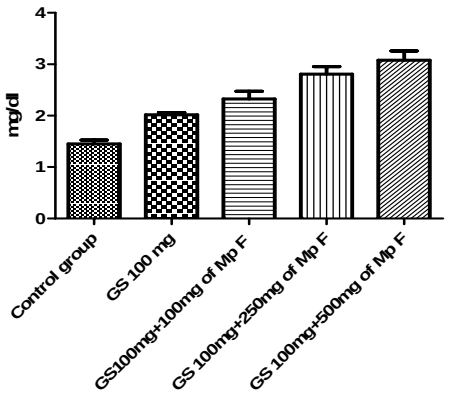

Fig. 2(b): Mp F effect on serum urea

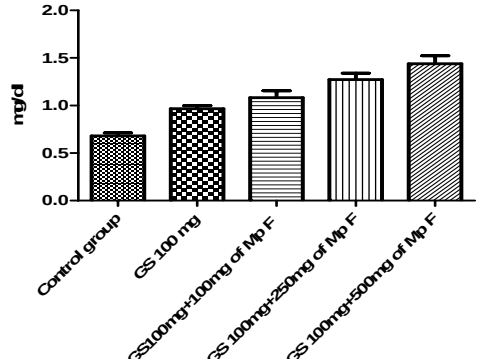

Fig. 2(c): Mp F effect on serum BUN

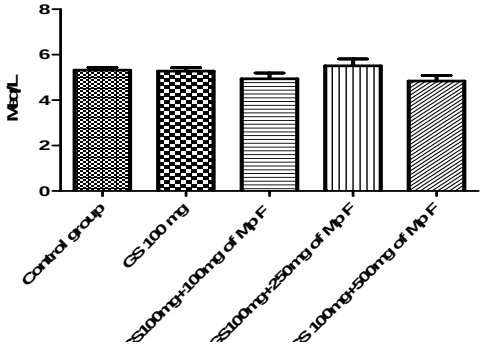

Fig. 2(d): Mp F effect on sodium ion

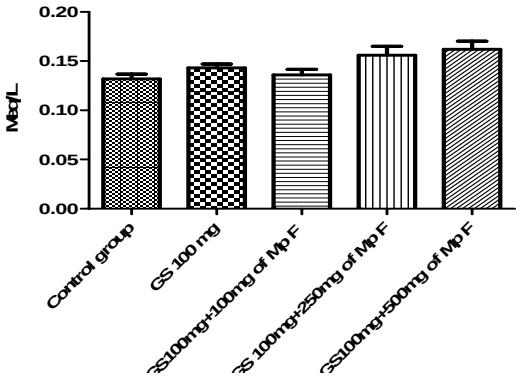

Fig. 2(e): Mp F effect on potassium ion

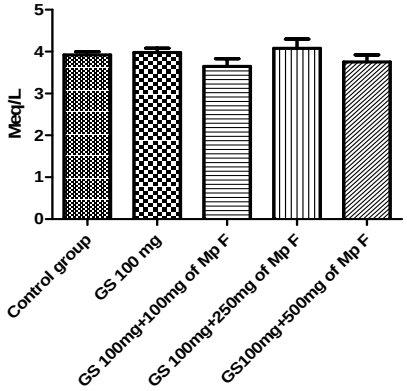

Fig. 2(f): Mp F effect on chloride ion

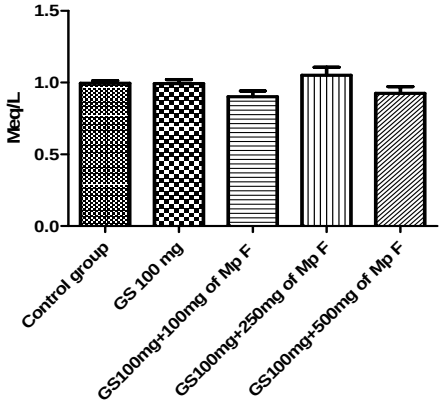

Fig. 2(g): Mp F effect on bicarbonate ion

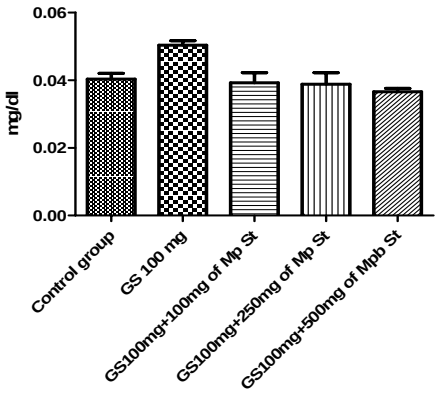

Fig. 3(a): MpT effect on serum creatinine

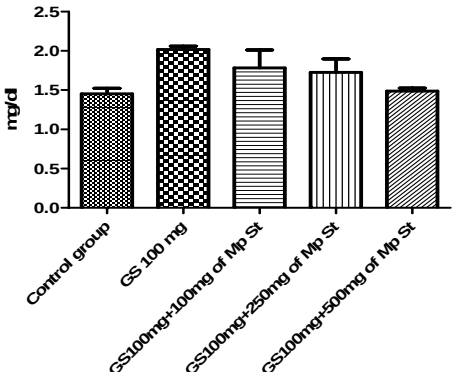

Fig. 3(b): MpT effect on serum urea

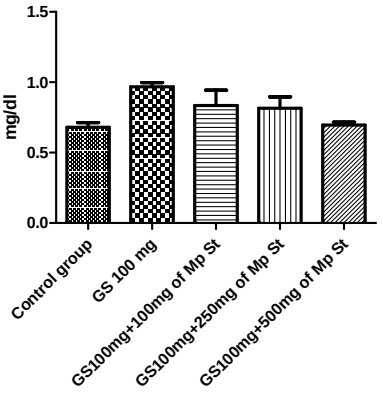

Fig. 3(c): MpT effect on BUN

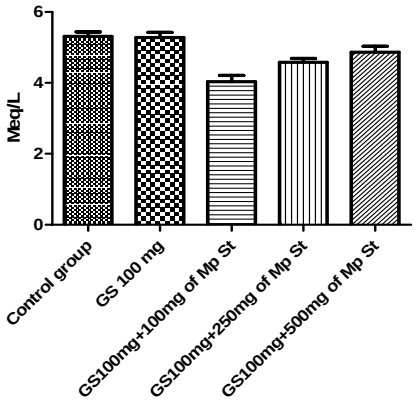

Fig. 3(d): MpT effect on sodium ion

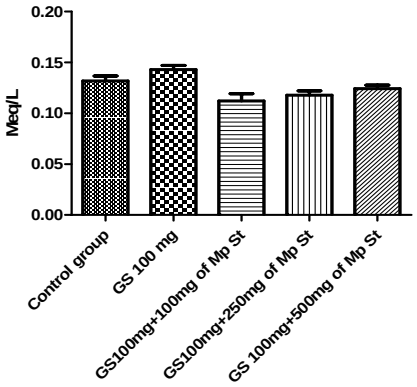

Fig. 3(e): MpT effect on potassium ion

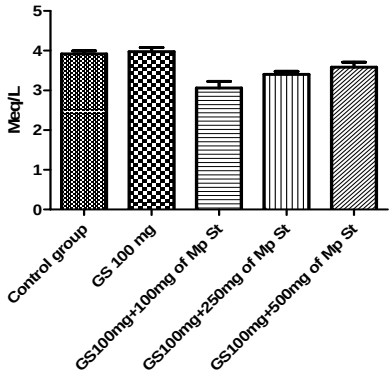

Fig. 3(f): MpT effect on serum chloride ion

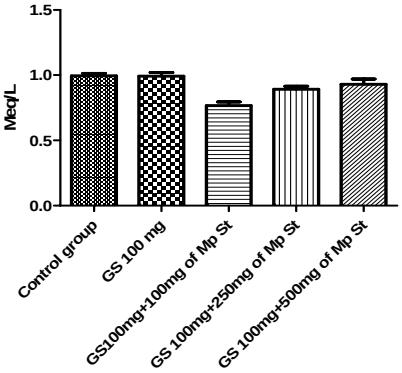

Fig. 3(g): MpT effect on bicarbonate ion

Histological investigations

For histopathological examination the kidneys from mice was fixed immediately in 10% neutral buffered formalin for a period of 24 h and then dehydrated in graded alcohol (30%-100%).After dehydration they were embedded in paraffin and cut into slices of 2X2 mm to 1X2 cm and thickness of 3mm with the help of Sakura Accu-cut: SRM 200cw and stained with Mayerhematoxylin and eosin (H and E) stain. Slides were coded with different names and were examined under microscope for the protective and/ or pathological changes of nephrotoxicity (Lee, 1968).

STATISTICAL ANALYSIS

All of the data are shown as the mean ± SD. Statistical analysis was performed by using one-way analysis of variance (ANOVA) followed by Tukey's test. $P>0.05$ was considered statistically significant.

RESULTS

Biochemical parameters

In the present research work we observed that serum creatinine, blood urea nitrogen level and blood urea were high in the blood sample of mice that was treated with gentamicin as compared to the normal control group. In gentamicin treated group disintegrated cells with coagulated protein was present in lumen of renal tubule. Tubular structures were lost with disruption and disintegration of cells. Necrotic changes were present in more than 70% of tubules. On administration of 100mg/kg dose of methanolic extract of bract of *Musa paradisiaca* to gentamicin intoxicated mice slightly decreases the blood urea, blood urea nitrogen and serum creatinine level. As the dose increases to 250mg/kg there was markedly decrease in the level of kidney function parameters such as blood urea, blood urea nitrogen and serum creatinine. It suggested that methanolic extract of bract have dose dependent nephroprotective effect but as dose was increased to 500mg/kg these parameters have started to increase again which indicate that at the dose of 500mg/kg the methanolic extract of bract of *Musa paradisiaca* is slightly nephrotoxic (fig. 1a, 1b and 1c).

When the methanolic extract of flower of *M. paradisiaca* at the dose of 100 mg/kg was administered to the group of mice that was intoxicated with gentamicin elevates the level of blood urea, blood urea nitrogen and serum creatinine as compared to gentamicin treated group. As the dose increases to the 250mg/kg and 500mg/kg the level of these indicators also elevated respectively which indicates that methanolic extract of flower of *Musa paradisiaca* is nephrotoxic (fig. 2a, 2b and 2c).

The flowering stalk (trachea) on administration at the dose of 100mg/kg to the gentamicin intoxicated mice showed slight decrease in the serum creatinine, blood urea and blood urea nitrogen as compared with gentamicin control group which indicated that dose of 100mg/kg have very low nephroprotective effect. Experiment data showed that 250mg/kg dose have more nephroprotective effect as compared to 100mg/kg. but when the dose was increases to 500mg/kg it was found that it surprisingly decrease the kidney function markers to almost normal which shows that stalk of *M. paradisiaca* possess nephroprotective effect at high dose in gentamicin intoxicated mice (fig. 3a, 3b and 3c).

Tracheal fluid at the dose of 100mg/kg caused the slight increase in blood urea, blood urea nitrogen and serum creatinine level as compared to gentamicin that indicate that tracheal fluid have slightly nephrotoxicity. As the dose were increases to 250mg/kg and 500mg/kg the indicator of renal function increase which were the indication that the tracheal fluid is dose dependent nephrotoxic (fig. 4a, 4b and 4c).

Histological investigations

Histological investigation showed that the group of mice which were receiving 100mg/kg of methanolic extract of *Musa paradisiaca* bract with gentamicin showed necrotic changes in tubular epithelial cells with disruption and disintegration of cells along with some tubular structure also lost. These changes were present in more than 50% of tubules. Disintegrated cells along with protein in coagulated form were present in lumen of renal tubule. Congestion in blood vessel were also evident but to a lesser degree whereas the group of mice that were receiving 250 mg/kg bract extract of *M. paradisiaca* with gentamicin showed necrotic changes in 20-30% of renal tubule and the mice that were administered with 500 mg/kg dose of *M. paradisiaca* bract extract showed congestion in tubules. The renal epithelial cells are showing necrotic changes. These changes were present in about 30-40% of renal tubule other renal tubule are appear to be normal. These finding supports the results that were obtained through the blood serum (fig. 5).

The animals that were treated with 100mg/kg methanolic extract of flower of *Musa paradisiaca* showed mild changes in majority of tubule and glomeruli were appeared to be normal. Mild degenerative changes and severe necrotic changes were present in some of renal tubule whereas group of animals that were administered with the dose of 250mg/kg methanolic extract of flower shows severe changes in majority of renal tubule. Atrophied glomerular and necrotic cells in most of epithelial cells. Animals that were administered with 500mg/kg of extract represent necrotic changes in most epithelial cells of renal tubule. The nucleus is absent in some of cells and is pyknotic in most of cells of renal tubule. The necrotic cells appear detached from basement membrane and fallen in the lumen of renal tubule (fig. 6).

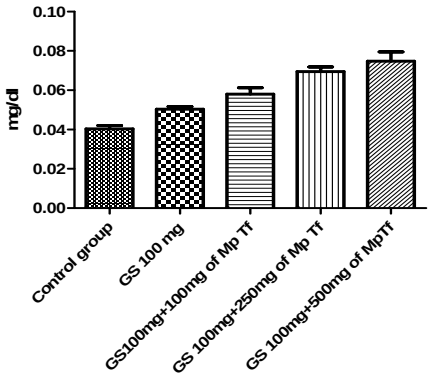

Fig. 4(a): MpTf effect on serum creatinine

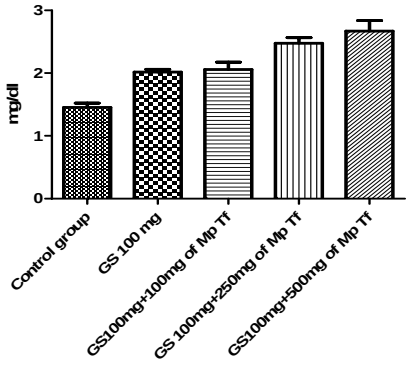

Fig. 4(b): MpTf effect on serum urea

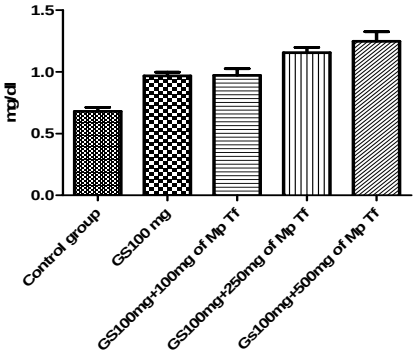

Fig. 4(c): MpTf effect on serum BUN

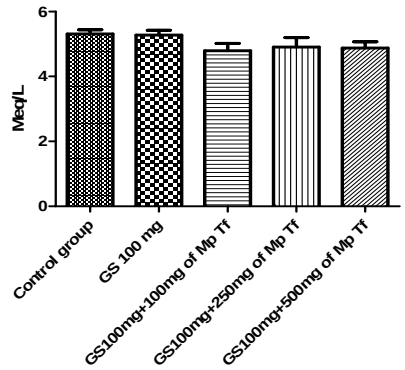

Fig. 4(d): MpTf effect on sodium ion

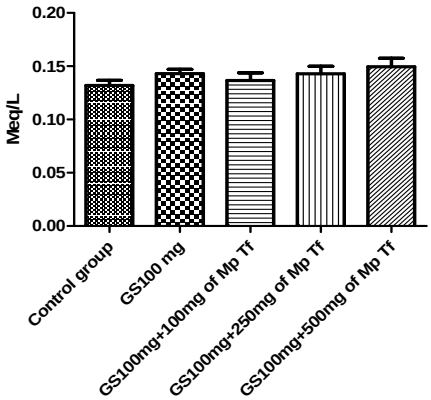

Fig. 4(e): MpTf effect on potassium ion

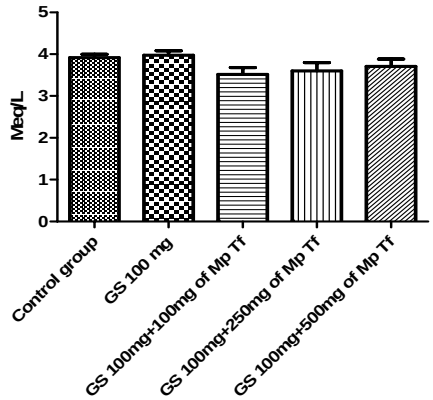

Fig. 4(f): Effect MpTf effect on chloride ion

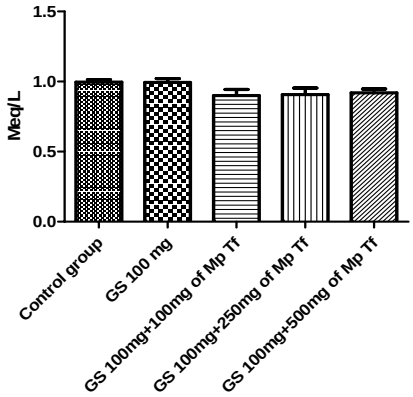

Fig. 4(g): MpTf effect on bicarbonate ion

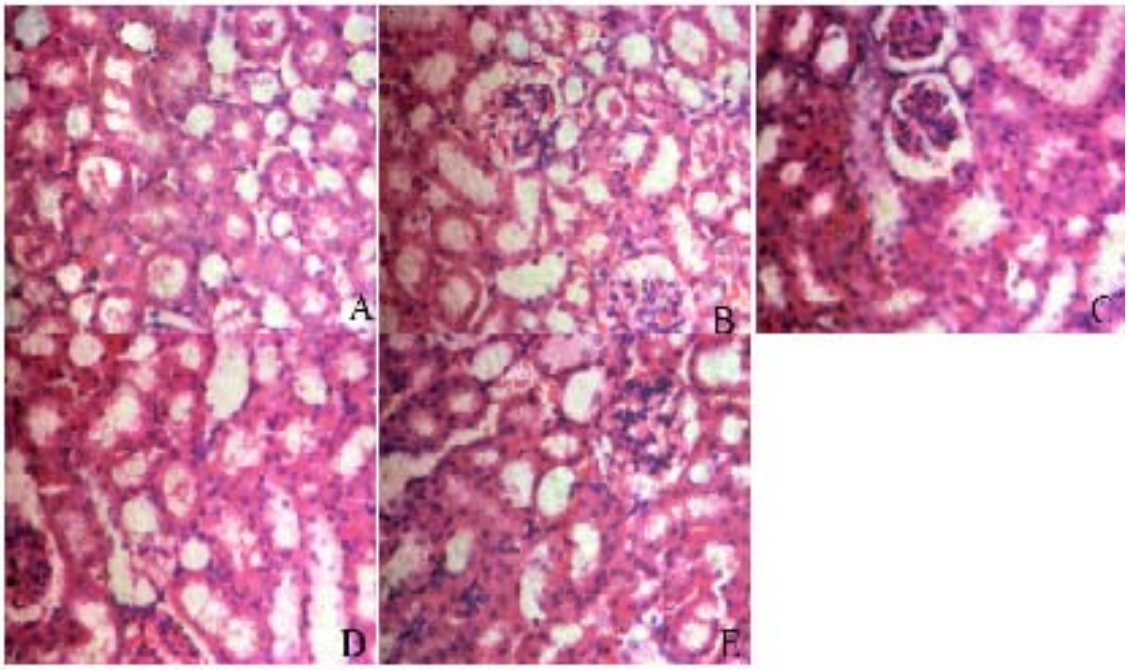

Fig. 5: Photomicrographs showing the effect of control group, gentamicin and different doses of *Musa paradisiaca* L. bract extract on kidney of mice. A: Normal control group; B: gentamicin (100mg/kg) treated group; C: methanolic extract of bract (100 mg/kg) and gentamicin treated group D: methanolic extract of bract (250mg/kg) and gentamicin treated group; E: methanolic extract of bract (500mg/kg) and gentamicin treated group (magnification x10).

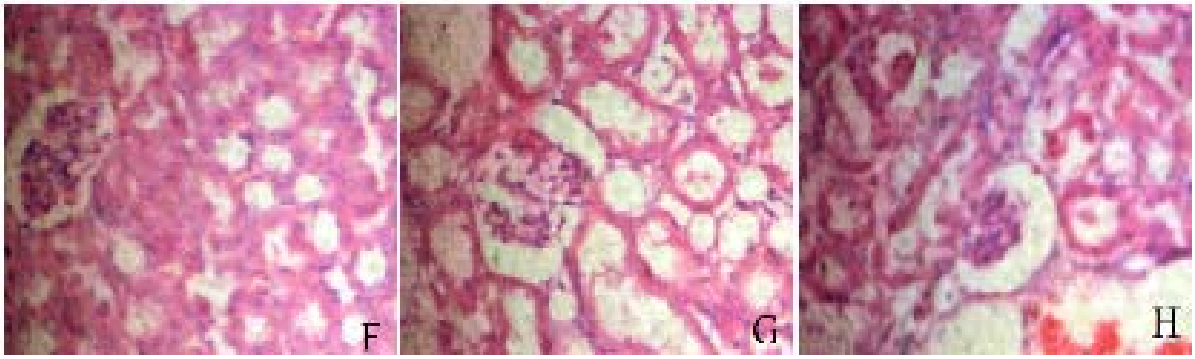

Fig. 6: Photomicrographs showing the effect of different doses of *Musa paradisiaca* L flower extract on kidney of mice. F: methanolic extract off lower (100 mg/kg) and gentamicin treated group G: methanolic extract of flower (250mg/kg) and gentamicin treated group H: methanolic extract of flower (500mg/kg) and gentamicin treated group (magnification x10).

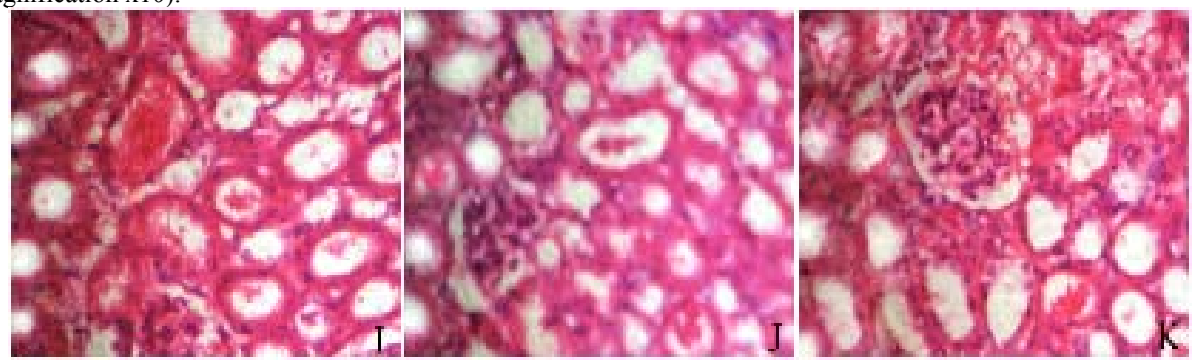

Fig. 7: Photomicrographs showing the effect of different doses of *Musa paradisiaca* L trachea extract on kidney of mice. I: methanolic extract of trachea (100 mg/kg) and gentamicin treated group J: methanolic extract of trachea (250mg/kg) and gentamicin treated group K: methanolic extract of trachea (500mg/kg) and gentamicin treated group (magnification x10).

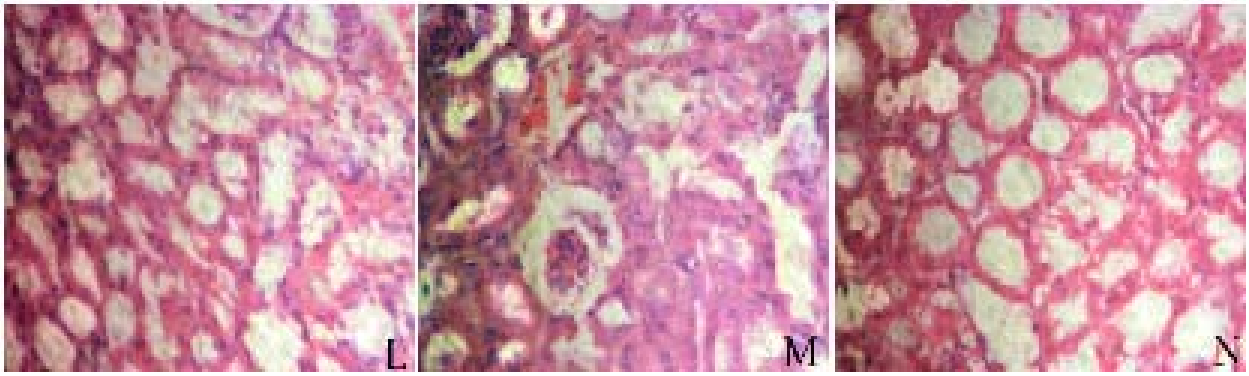

Fig. 8: Photomicrographs showing the effect of different doses of *Musa paradisiaca* L. tracheal fluid extract on kidney of mice. L: methanolic extract of tracheal fluid (100 mg/kg) and gentamicin treated group M: methanolic extract of tracheal fluid (250mg/kg) and gentamicin treated group N: methanolic extract of tracheal fluid (500mg/kg) and gentamicin treated group (magnification x10).

The dose of 100mg/kg of flowering stalk (trachea) shows more severe necrotic changes that were present in more than 70% of renal tubules. Whereas 250mg/kg dose showed mild changes in renal tubules with necrosis in more than 40% of renal tubules. 500mg/kg dose showed minor necrotic changes in renal tubule and some renal tubule are appeared to be normal (fig. 7).

Tracheal fluid at the dose of 100mg/kg represents mild changes in majority of tubule and glomeruli were normal. Mild degenerative changes are present in some of renal tubule and severe necrotic changes are also present in some of renal tubule. Dose of 250mg/kg showed moderate changes in renal tubule whereas 500mg/kg dose causes moderate to severe necrotic changes in most of renal tubule with disappearance of nucleus in most of cells (fig.8).

DISCUSSION

Drugs and drug metabolites are taken up selectively and concentrated into the urine, so high intracellular concentrations are reached, mainly in the renal medulla which has comparatively little vasculature as compare to the cortex. Therefore, direct toxic damage happen and affecting the renal tubular cells and renal papillae. Many groups of drugs can cause nephrotoxicity including allopurinol, cimetidine, carbamazepine, erythromycin and getamincin (Asiiley, 2014). Currently medicinal plants are used to prevent nephrotoxicity not only in animal model but also in human subjects. For that reason, in the present study, the nephroprotective activity of *M. paradisiaca* on gentamicin-induced mice was evaluated. The gentamicin treatment developed major kidney dysfunction with increased level of serum creatinine, blood urea as well as blood urea nitrogen level. Supplementation of *M. paradisiaca* to gentamicin intoxicated mice brings back these changes.

Gentamicin accumulates in the renal cortex and causes the cell damage and death (Kang *et al*., 2013) because it increases the production of super oxide anions and hydroxyl radicals from renal cortical mitochondria and these oxygen free radicals play an important role in pathogenesis of nephrotoxicity. It considerably increased the serum urea, creatinine and blood urea nitrogen (El-Ashmawy *et al*., 2006). Protein catabolism end product is the urea which filtered by the glomerulus, passively reabsorbed in proximal and distal nephron and excreted through urine. The level of serum urea is employed as an indicator of kidney function. Muscle catabolism end product is creatinine that is removed by the kidneys. The serum creatinine concentration is commonly used to measure renal function in clinical medicine. The level of creatinine is the blood rises in the absence of proper functioning of kidney. Acid, bases and salts collectively called as electrolytes and their imbalance leads to critical consequences as these electrolytes aid the body cells to maintain the internal balance in spite of changes in the external environment. Sodium, potassium, chloride and bicarbonate are commonly measured electrolytes as they are good indicators of kidneys function (Suji and Vimalastalin, 2014). The nephroprotective activity of *M. paradisiaca* bract and flowering stalk (trachea) may be due to the phytochemical constituents present in it.

CONCLUSION

It was concluded that the methanolic extract of bract (100 and 250mg/kg, b.w) and flowering stalk (trachea) (250 and 500mg/kg, b.w) significantly prevented biochemical and histological changes produced by gentamicin toxicity. While flower and tracheal fluid observed as nephrotoxic.

ACKNOWLEDGEMENTS

The authors are grateful for the support and facility provided by Prof. Dr M. Tariq Javed, Department of Pathology, University of agriculture Faisalabad to carry out this research work.

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