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Improvement of renal profile in Gentamicin-induced Nephrotoxicity in albino wistar rats by edible macrofungi *Dacryopinax spathularia* and *Schizophyllum commune*

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Abstract
The present work has been taken to assess the pharmacological efficacy of two edible macrofungi *Dacryopinax spathularia* and *Schizophyllum commune* in the improvement of renal profile of Gentamicin-induced nephrotoxicity in albino wistar rats. The intraperitoneal administration of gentamicin 80 mg/Kg Body Weight per day had resulted in alterations in renal function and renal damage which was reflected by abnormal and significant (p=0.05) increase in renal function parameters of blood like Urea, Creatinine, Uric Acid and Blood Urea Nitrogen (BUN). On administration of high dose (500 mg/Kg BW) of *D. Spathularia* extract to the nephrotoxic group of rats the concentration of urea, creatinine, uric acid and BUN significantly decreased from 104.26±7.45 to 76.27±7.24, 1.17±0.43 to 0.68±0.47, 3.68±1.34 to 2.58±0.56 and 48.72±4.36 to 31.14±3.76 respectively, in comparison to the nephrotoxic group of rats. On the other hand, the administration of high dose (500 mg/Kg BW) of *S. commune* extract to the nephrotoxic group of rats resulted into significant (p=0.05) decrease in the concentration of urea, creatinine, uric acid and BUN, from 104.26±7.45 to 51.42±6.15, 1.17±0.43 to 0.62±0.14, 3.68±1.34 to 2.36±0.74 and 48.72±4.36 to 28.65±3.85 respectively, in comparison to the nephrotoxic group of rats. The results also revealed that *S. commune* extract showed comparatively more efficacy in the renal profile improvement of nephrotoxic rats in comparison to the *D. spathularia* extract.

Keywords: *Dacryopinax spathularia*, Gentamicin, Macrofungi, Nephrotoxicity, Oxidative stress, Schizophyllum commune.

INTRODUCTION

Kidneys or Renal organs are paired organs carrying out many vital physiological functions in the body like maintaining the homeostasis, excretion of waste products, maintaining the pH, regulation of blood pressure, secretion of some active compounds etc. Therefore any serious nephropathological condition may cause serious health problems and may prove fatal for the individual. Gentamicin is an aminoglycoside, frequently used as antibiotic drug against gram negative bacterial infections, which may include bone infections, meningitis, pneumonia, urinary tract infections, sepsis etc. (Gilbert, 2005). However, on the other side of its medicinal uses, gentamicin causes dose-dependent serious adverse effects on renal functions and accounts for 10-15% of all cases of acute renal failure (Morales *et al*., 2010; Ramhariya, 2015). Gentamicin binds with the acidic phospholipids of the plasma membrane of the cells of proximal renal tubules and accumulate there (Rodrigues *et al*., 2014). It can enter into the cells of proximal renal tubules and bind with intracellular organelles and also it can alter the mitochondrial respiration (Erdem *et al*., 2000). The gentamicin-induced nephrotoxicity is a complex phenomenon mainly characterized by the abnormal levels of some biochemical parameters of blood plasma like Urea, Creatinine, Uric acid and BUN (Blood Urea Nitrogen), associated with renal tubular necrosis leading to progressive deterioration and renal failure (Cuzzocrea *et al*., 2002). Previous studies have suggested that the gentamicin-

induced nephrotoxicity is associated with the development of oxidative stress by the generation of free radicals like ROS (Reactive Oxygen Species) associated with the depletion of antioxidant molecules in the kidney (Reiter *et al*., 2002; Balakumar *et al*., 2008; Ozbek, 2012). Several studies have suggested the drugs with antioxidant capacity for their application as nephroprotective agents against gentamicin-induced nephrotoxicity (Abdel-Raheem *et al*., 2009; Harlalka *et al*., 2007).

The mushrooms or macrofungi are known to be rich sources of various bioactive substances like tannins, saponins, alkaloids, flavonoids, phenolics, terpenoids etc., which are having various types of significant pharmacological activities including markable antioxidant properties. The therapeutic efficacy of macrofungi have also been extensively reviewed by Lindequist *et al* (2005). *Dacryopinax spathularia* (Schwein) and *Schizophyllum commune* (Fries) are two edible macrofungi belonging to group Basidiomycota and are among the commonly used traditional neutraceutical dietary sources, especially in north-eastern region of India, as antibacterial, anti-inflammatory, anti-diabetic, hepatoprotective and nephroprotective food supplement. The biochemical composition and the antioxidant activity of *D. spathularia* and *S. commune* have been reported by Kumar *et al* (2018). The Hepatoprotective efficacy of the edible macrofungi *D. spathularia* and *S. commune* has also been reported by Kumar *et al* (2019). Keeping in view that the gentamicin-induced nephrotoxicity is being associated with the development of oxidative stress and these two edible macrofungi have significant antioxidant efficacy, the present work was taken to assess the nephroprotective activity of these macrofungi using albino wistar rats as animal model.

MATERIALS AND METHODS

Animals: In the present study, Wistar albino rats were used, weighing about 175-200 g. The animals were maintained under standard laboratory conditions under temperature maintained at 25±5ºC, Dark-Light cycle of 12 hrs., relative humidity of 50±15%, throughout the experimental period of time. The commercial pellet diet was used to fed the animals and water was supplied *ad libitum.* Polypropylene cages were used to house the animals and paddy husk was used as bedding material in a well-ventilated room. The experiment was carried out as per the approval of Ethics committee of Ranchi University, Ranchi.

Acute toxicity studies: The acute toxicity studies has been done according to the OECD guidelines (2004). Two groups of 10 rats each were formed and each group received different doses of one macrofungal extract. The animals were fed the extract orally by using oral feeding tube. Within 48 hrs. no mortality was observed up to the doses of 2000 mg/kg body weight (BW) /day.

Induction of nephrotoxicity and evaluation of improvement in renal profile: After acclimatization, Nephrotoxicity was induced by intraperitoneal administration of 80 mg/Kg BW (Body Weight) per day of Gentamicin for 10 consecutive days. The rats were divided into six groups of six rats each and the experiment was carried out as follows:

Group 1: Control group, received 1 ml of distilled water orally

Group 2: Nephrotoxic group, received intraperitoneal (i.p.) injection of i.p. of Gentamicin 80 mg/Kg BW per day

Group 3: Nephrotoxic, received 250 mg/Kg BW/ day of *D. spathularia* extract (LD) one hour post gentamicin injection; LD= Low Dose

Group 4: Nephrotoxic rats, received 500 mg/Kg BW/day of *D. spathularia* extract (HD) one hour post gentamicin injection; HD= High Dose

Group 5: Nephrotoxic rats, received 250 mg/Kg BW/ day of *S. commune* extract (LD) one hour post gentamicin injection

Group 6: Nephrotoxic rats, received 500 mg/Kg BW/day of *S. commune* extract (HD) one hour post gentamicin injection

Sample collection and assessment of biochemical parameters: The experimental procedure as stated above was continued for 10 consecutive days. After 10 days, the animals were starved overnight and then collection of blood was done by puncturing the retro-orbital plexus under light ether anesthesia without sacrificing the animals. Three blood samples were collected in, randomly from each group. The blood samples were taken in test tubes, allowed to clot for 30 minutes and then centrifuged at 2500 rpm for 10 minutes to get the clear serum for biochemical investigations. The renal activity marker blood parameters like Urea, Uric acid, Creatinine and BUN (Blood Urea Nitrogen) were estimated by Autoanalyser (cobas c311, Roche diagnostics, Japan) with the help of standard kits.

Statistical analysis: All data was taken in triplicate and presented as mean± standard error of mean. The obtained data was statistically analyzed by one way ANOVA, which was followed by student's t-test. The difference of the values was considered significant at $p<0.05$.

RESULTS AND DISCUSSION

Gentamicin-induced nephrotoxicity is associated with increased rate of generation of free radicals like reactive oxygen species such as hydroxyl radicals, super-oxide anions etc. (Parlakpinar *et al*., 2005; Sener *et al*., 2002). The reactive oxygen species can produce cellular injury or necrosis through membrane lipid peroxidation, DNA damage or protein alterations (Arivazhagan and Vimaastalin, 2014). The renal damage or altera-

Table 1. Nephroprotective efficacy of *Dacryopinax spathularia* extract against Gentamicin-induced nephrototoxicity in rats (Data expressed as mean±SE, n=3).

Animal Groups	Urea (mg/dL)	Creatinine (mg/dL)	Uric acid (mg/dL)	BUN (mg/dL)
Group 1 (Control)	46.83±8.61	0.54±0.16	2.14±0.38	22.09±3.89
Group 2 (Gentamicin treated Nephrotoxic)	104.26±7.45[a]	1.17±0.43[a]	3.68±1.34[a]	48.72±4.36[a]
Group 3 (Nephrotoxic + LD of D. Spathularia extract)	88.36±6.34[ab]	0.84±0.52[ab]	2.87±0.64[ab]	38.16±3.14[ab]
Group 4 (Nephrotoxic + HD of D. Spathularia extract)	76.27±7.24[ab]	0.79±0.47[ab]	2.58±0.56[ab]	31.14±3.76[ab]

[a]Statistically significant when compared to control group(p<0.05); [b]Statistically significant when compared to nephrotoxic group(p<0.05).

Table 2. Nephroprotective efficacy of *S. commune* extract against Gentamicin-induced nephrototoxicity in rats (Data expressed as mean±SE, n=3).

Animal Groups	Urea (mg/dL)	Creatinine (mg/dL)	Uric acid (mg/dL)	BUN (mg/dL)
Group 1 (Control)	46.83±8.61	0.54±0.16	2.14±0.38	22.09±3.89
Group 2 (Gentamicin treated Nephrotoxic)	104.26±7.45[a]	1.17±0.43[a]	3.68±1.34[a]	48.72±4.36[a]
Group 3 (Nephrotoxic + LD of *S. commune* extract)	71.36±5.12[ab]	00.73±0.27[ab]	3.06±0.78[ab]	32.57±3.28[ab]
Group 4 (Nephrotoxic + HD of *S. commune* extract)	50.42±6.15[b]	0.62±0.14[b]	2.36±0.74[b]	28.65±3.85[ab]

tion in normal functioning of kidney results in abnormal levels of renal function parameters of blood like Urea, Uric acid, Serum creatinine and BUN (Pragati *et al*., 2018). Many previous workers have reported the nephroprotective efficacy of several natural products of plant or animal origin through their antioxidant activities against Gentamicin-induced nephrotoxicity in albino rats (Saud *et al*., 2012; Nair *et al*., 2018).

Table 1 shows the results of assessment of nephroprotective efficacy of *D. spathularia* extract. The results clearly revealed that the concentration of renal function marker serum biochemical parameters like Urea, Creatinine, Uric acid and Blood Urea Nitrogen (BUN) significantly increased (p=0.05) from the normal levels of 46.83±8.61 to 104.26±7.45, 0.54±0.16 to 1.17±0.43, 2.14±0.38 to 3.68±1.34 and 22.09±5.89 to 48.72±4.36 respectively in the Gentamicin-induced nephrotoxic group of rats (group 2) in comparison to the normal control group of rats (group 1). On administration of low dose (250 mg/Kg BW) of *D. Spathularia* extract to the nephrotoxic group of rats (group 3) the concentration of Urea, Creatinine, Uric acid and BUN significantly decreased from 104.26±7.45 to 88.36±6.34, 1.17±0.43 to 0.78±0.52, 3.68±1.34 to 2.87±0.64 and 48.72±4.36 to 32.16±3.14 respectively. On administration of high dose (500 mg/Kg BW) of *D. Spathularia* extract to the nephrotoxic group of rats (group 4)) the concentration of Urea, Creatinine, Uric acid and BUN significantly decreased from 104.26±7.45 to 76.27±7.24, 1.17±0.43 to 0.68±0.47, 3.68±1.34 to 2.58±0.56 and 48.72±4.36 to 31.14±3.76 respectively, in comparison to the nephrotoxic group of rats.

The results of assessment of nephroprotective activity of *S. commune* extract has been shown in table 2. On administration of low dose (250 mg/Kg BW) of *S. commune* extract to the nephrotoxic group of rats (group 3) the concentration of Urea, Creatinine, Uric acid and BUN significantly decreased from 104.26±7.45 to 71.36±5.12, 1.17±0.43 to 0.73±0.27, 3.68±1.34 to 2.96±0.78 and 48.72±4.36 to 32.57±3.28 respectively. On administration of high dose (500 mg/Kg BW) of *S. commune* extract to the nephrotoxic group of rats (group 4) the concentration of Urea, Creatinine, Uric acid and BUN significantly decreased from 104.26±7.45 to 51.42±6.15, 1.17±0.43 to 0.62±0.14, 3.68±1.34 to 2.36±0.74 and 48.72±4.36 to 28.65±3.85 respectively, in comparison to the nephrotoxic group of rats.

On administration of LD and HD of the macrofungal extract of *D. spathularia*, significant (p<0.05) decrease in the concentration of these renal function parameters was observed, although these concentrations did not get back to their normal values completely but the decrement in the concentrations of renal function parameters was found significant, indicating the improvement in the renal profile of gentamicin-induced nephrotoxic animals.

Table 2 shows the results of assessment of nephroprotective efficacy of *S. commune* extract. On administration of LD and HD of the macrofungal extract of S. commune, significant (p<0.05) decrease in the concentration of renal function parameters was observed towards their normal values (Group 3 and 4), indicating the improvement in the renal profile of nephrotoxic animals. The results also revealed that the decrement of the renal function parameters on administration of *S. commune* extract was significantly more than that in case of administration of *D. spathularia* extract,

indicating that *S. commune* has relatively more efficacy towards improvement of renal profile in gentamicin-induced nephrotoxicity in the present animal model in comparison to *D. spathularia* extract.

The improvement in renal profile in gentamicin–induced nephrotoxicity in the present animal model by the administration of these two experimental edible macrofungi can be attributed to their significant antioxidant capacities against Reactive oxygen species like hydroxyl radical, super oxide ions etc. (Kumar *et al*., 2018). However, further research in this field can include the characterization and isolation of the exact biochemical constituent compounds in the two experimental macrofungi and their molecular mechanism of interactions to describe their role and pathways of their action in the improvement of renal profile of nephrotoxic animals, that has been found in the present work.

Conclusion

The present work revealed that both the experimental macrofungi have significant (p<0.05) efficacy to improve the renal profile in gentamicin-induced nephrotoxic rats. The *S. commune* was found to have more efficacy in improvement of renal profile of gentamicin-induced nephrotoxic rats, in comparison to *D. spathularia* extract, probably due to more antioxidant activities of *S. commune* in comparison to that of *D. spathularia.*

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