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ORIGINAL ARTICLE

Anti-Tuberculosis Drug-Induced Oxidative Stress in Kidneys: Role of Brahmi as an Antioxidant Supplement

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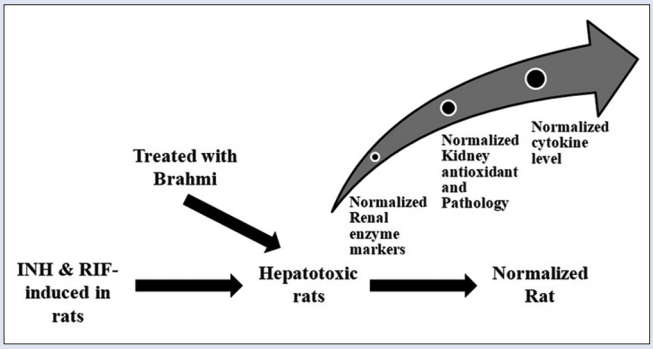
ABSTRACT

Purpose: Nephrotoxicity is a known, but rare complication of anti-tuberculosis (TB) therapy and is known to be due to induction of oxidative stress and immune reaction to the drugs. In the current study, we have made an attempt to evaluate the effect of Brahmi in attenuating the oxidative stress caused by isoniazid (INH) and rifampicin (RIF) in the kidneys of Wistar rats. **Materials and Methods:** The animals were administered INH and RIF with concomitant supplementation of Brahmi for 28 days. The levels of urea, uric acid, creatinine, and acid phosphatase were measured to evaluate kidney function along with catalase, superoxide dismutase, glutathione peroxidase, glutathione-S-transferase, and lipid peroxidation to assess the kidney antioxidant status. In addition, the levels of cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, and the cytokine tumor necrosis factor (TNF-α) were also measured. The protective efficacy of Brahmi was compared to that of Silymarin. **Results:** Brahmi caused a statistically significant ($P < 0.05$) restoration of kidney function along with an increase in the antioxidant status. This was accompanied by a reduction of TNF-α level to near normal. A histopathological study of the kidney tissues confirmed the protective effect of Brahmi against INH- and RIF-induced oxidative stress in the kidneys. **Conclusion:** It is evident that Brahmi plays a protective role against anti-TB drug-induced oxidative stress in the kidneys.

Key words: Antioxidants, Brahmi, nephrotoxicity, oxidative stress, tumor necrosis factor-α

SUMMARY

- Renal damage is one of the common factors of anti-tuberculosis drug-induced toxicity. The current research was to evaluate the nephroprotective effect of Brahmi against Isoniazid (INH) and Rifampicin (RIF)-induced toxicity in Wistar albino rats. The total study duration was 28 days in which the rate was divided into five groups. Group 1 was normal control group, Group 2 was INH, and RIF-induced rats, Group 3 and Group 4 were INH- and RIF-include rats treated with Brahmin and silymarin and Group 5 was Brahmi alone treated group. After sacrifice, the rats were analyzed for renal enzyme markers, kidney antioxidant, kidney histopathology, and tumor necrosis factor-α. It was observed to show that Brahmin treated rats was able to normalize the toxicity caused by INH and RIF which was similar to the standard group. The study found that Brahmi was able to treat the toxicity caused by INH and RIF on Wistar albino rats.



Abbreviations used: INH: Isoniazid; RIF: Rifampicin; CAT: Catalase; SOD: Superoxide dismutase; GPx: Glutathione peroxidase; GST: Glutathione-S-transferase; LPO: Lipid peroxidation; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TNF-α: Tumor necrosis factor; TB: Tuberculosis; HIV: Human immunodeficiency virus; ARF: Acute renal failure; GSH: Reduced glutathione; EDTA: Ethylene diamine tetraacetic acid; PBS: Phosphate buffered saline; TG: Triglyceride; ELISA: Enzyme-linked immunosorbent assay; ANOVA: Analysis of variance.

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INTRODUCTION

Mycobacterium tuberculosis causes tuberculosis (TB), one of the most widespread infectious diseases in human history. It typically infects the lungs but also presents as an extra-pulmonary infection. It is the second leading cause of death worldwide due to an infectious agent after the human immunodeficiency virus. In 2014, 9.6 million people were infected with TB, and 1.5 million died from the disease. TB in its drug-susceptible form is commonly treated with a 6 months course of the four antimicrobial drugs isoniazid (INH), rifampicin (RIF), pyrazinamide, and ethambutol. Anti-TB therapy with INH and RIF has been documented to cause nephrotoxic effects in rare and isolated cases.[1] There have been many reports that implicate RIF in causing tubular and interstitial lesions that are characteristic of glomerulonephritis leading to acute renal failure (ARF). The report also showed that intermittent or interrupted treatment with RIF caused hemolytic anemia and thrombocytopenia along with the presence of RIF-antibody complexes.[2] RIF is also known to cause the production of reactive oxygen species that affect the renal oxidant/antioxidant balance.

The negative effects of anti-TB therapy on the liver and kidneys can be balanced by concomitant administration of supplements that

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boost the antioxidant levels of the body. Herbal products that can be administered for long terms with minimal adverse effects have found use as effective nutritional supplements that can fulfill this role. Brahmi (*Bacopa monnieri*) an important medicinal plant is widely used in treating epilepsy, neurodegenerative diseases, and in enhancing memory.[3-5] Along with its neuroprotective role it is also used in treating ulcers, tumors, and other inflammatory conditions.[6,7] The medicinal roles of *B. monnieri* are established to be partly due to the antioxidant potential in its active components. *B. monnieri* as a standalone drug and in combination with other herbs has been administered for long terms in human populations with no known adverse effects.[8] Therefore, in this study, we have tried to evaluate *B. monnieri* as a potential protective supplement against the oxidative stress induced in kidneys during INH and RIF administration to a rat model.

MATERIALS AND METHODS

Animals

Wistar Albino Rats (Female) were obtained from the Animal House, VIT University, Vellore, Tamil Nadu, India with an average weight between 170 and 190 g. The rats were kept under a temperature of 27°C with 12-h dark-light cycles and fed with commercial pelleted feed (Hindustan Lever Ltd., Mumbai, India) along with water that was provided *ad libitum*. The experiment was approved by the Ethical Committee of VIT University, Vellore, India.

Drugs and chemicals

INH and RIF were obtained from LUPIN Ltd, Aurangabad, Maharashtra, India. Commercially available Brahmi (*B. monnieri*) capsules were obtained from Himalaya Pvt., Ltd., India. These were administered at a dosage of 500 mg/kg b. w. found to be effective in previous studies. Since Silymarin is known to have antioxidant functions, it was selected as a standard drug and was obtained from Micro Labs Ltd., Solan, Himachal Pradesh. Suspensions of Silymarin were made in double distilled water. Standard laboratory reagents of analytical grade were used for the experiments and obtained from SD Chemicals, India.

Experimental procedure for animal studies

The rats were divided into five groups for varying treatments with each group containing six animals. Group I was used as normal control; Group II received INH-RIF (50 mg/kg b. w.); Group 3 was given INH-RIF (50 mg/kg b. w.) with concomitant administration of Brahmi (500 mg/kg b. w.); Group 4 was given INH-RIF (50 mg/kg b. w.) along with Silymarin (25 mg/kg b. w.); and Group 5 was administered Brahmi (500 mg/kg b. w.). The treatment was continued for 28 days after which the animals were sacrificed. Blood was collected from the trunk and the kidneys excised for biochemical and histopathological analyses.

Preparation of samples

The trunk blood collected was allowed to clot and centrifuged at 3000 rpm for 10 min at 4°C for serum separation. The kidneys were homogenized in 5% Phosphate buffered saline and centrifuged at 3000 rpm for 10 min at 4°C. The supernatant collected was used for the estimation of antioxidant enzymes, reduced glutathione (GSH) and lipid peroxidation (LPO). A portion of the kidneys was fixed in formalin for further histopathological studies.

Biochemical studies

The levels of superoxide dismutase (SOD),[9] catalase (CAT),[10] glutathione-S-transferase (GST),[11] glutathione peroxidase (GPx),[12] total GSH,[13] LPO[14] and total protein[15] were measured in the supernatant of the kidney tissue homogenate. Commercially available kits were used to measure the levels of urea, uric acid, creatinine and acid phosphatase in serum to evaluate kidney function. Serum total cholesterol, high-density lipoprotein (HDL), and triglyceride (TG) levels were also determined using commercially available kits. The levels of low-density lipoprotein (LDL) were calculated using Friedwald's formula:

LDL = Total Cholesterol – HDL – (TGL/5) mg/dl

Assessment of tumor necrosis factor-α levels

The levels of tumor necrosis factor (TNF-α) was measured in serum by enzyme-linked immunosorbent assay according to the manufacturer's protocol (Krishgen, Biosystems, India). TNF-α levels were expressed in pg/ml.

Histopathological studies

The kidney samples that were fixed in formalin were washed and dehydrated using varying grades of isopropanol, rinsed with xylene, embedded in molten paraffin wax following which 5-µm thick sections were cut. The sections were evaluated after staining with hematoxylin and eosin.

Statistical analysis

One-way analysis of variance was used to analyze the results for statistically significant differences between the treatments, in which Graph pad software was used.

RESULTS AND DISCUSSION

Effect of Brahmi on body weight

Table 1 displays the body weights of the animals undergoing various treatments. Group II that was administered INH and RIF showed a statistically significant ($P < 0.05$) decrease in the body weight with a simultaneous increase in the kidney weights of the rats in comparison to the control group. This was in contrast to Brahmi treated rats that had their body and kidney weights closer to the control group. Although the liver is the primary site for the biotransformation of drugs, the kidneys

Table 1: Body weight of normal and experimental group of animal

Experimental groups	BW 0th day	5th day	10th day	15th day	20th day	25th day
Group I (normal control)	191.17±2.42	188.00±1.47	189.83±3.65	187.84±1.96	188.00±3.71	187.00±2.74
Group II (INH and RIF 50 mg/kg BW)	162.33±2.16^{a,*}	159.33±3.82^{a,*}	168.33±1.63^{a,*}	149.00±2.74^{a,*}	139.19±1.86^{a,*}	130.00±2.73^{b,*}
Group III (INH and RIF treated with brahmi 500 mg/kg)	197.17±3.79^{b,*}	189.00±3.71^{b,*}	181.67±1.27^{b,*}	183.33±2.32^{b,*}	179.04±1.03^{b,*}	164.83±3.72^{b,*}
Group IV (INH and RIF treated with silymarin 25 mg/kg BW)	195.17±4.63^{b,*}	181.67±3.15^{b,*}	182.83±1.71^{b,*}	182.29±2.97^{b,*}	183.00±3.76^{b,*}	160.17±3.71^{b,*}
Group V (Brahmi alone 500 mg/kg)	183.00±6.16^{b,*}	184.33±4.32^{b,*}	185.00±3.74^{b,*}	177.08±^{b,*}	187.00±3.74^{b,*}	163.33±5.38^{b,*}

Each value represents the mean±SD of six rats. Comparisons were made as follows: ^{a}Group I versus Groups II, III, IV, V; ^{b}Group II versus Group III, IV, V; ^{c}Group III versus Groups IV, V; ^{d}Groups IV versus Group V. The symbol represents statistical significance at $^{*}P<0.05$. Statistical analysis was calculated by one-way ANOVA followed by the Student–Newman–Keul's test. INH: Isoniazid; RIF: Rifampicin; SD: Standard deviation; BW: Body weight; ANOVA: Analysis of variance

also play a role that is not far behind the liver in the disposition of drugs. Similarly, the toxic metabolites of drugs also have an adverse effect on the kidneys. The kidneys constitute only 0.4% of the body mass, whereas almost 20%–35% of the cardiac output passes through it. In addition, the pH and concentration of the urine produced also affect the degree of toxicity to which the intra-tubular cells and epithelial cells are exposed. In our study, the experimental procedure was not carried for isoniazid alone and rifampicin alone as these drugs are known to cause toxicity by its own on liver and kidney in rats. Isoniazid is known to cause liver damage at the dosage of 200 mg/kg b. w. and 400 mg/kg b. w. for 7 days.[16,17] Rifampicin at the dosage of 9 mg/kg b. w. for 3 months was known to cause kidney damages in rats.[18]

Effects of Brahmi on biochemical parameters

Urea, uric acid, and creatinine were used to evaluate abnormalities in renal function [Table 2]. The results obtained showed a statistically significant ($P < 0.05$) increase in these levels among the rats treated with INH and RIF compared to the control group. Brahmi imposed a protective effect and lowered these parameters to near normal levels. This was comparable to the protective effect shown by Silymarin [Table 2]. The levels of cholesterol, TGs, and LDL were elevated by the antibiotic treatment, whereas the level of HDL was decreased indicating a negative effect on the balance of lipids in the body. This adverse effect was corrected to near normal levels by the administration of Brahmi [Table 3]. The study has shown that there is an elevation in the levels of markers that indicated impairment of renal function. This is indicated by the reduced clearance of creatinine, urea, and uric acid among the INH and RIF treated rats. These levels were reverted to normal levels among the rats treated with Brahmi and silymarin. It is known that reduced renal function affects the lipid metabolism and causes negative changes in lipid levels of the plasma and tissues. Reduced renal function affects the levels of HDL and also causes an increase in oxidative stress that may lead to oxidation of lipoproteins with impairment of HDL maturation, antioxidant, and anti-inflammatory function.[19,20] These changes have been reflected in the lipid levels of rats treated with INH and RIF indicating that reduced renal function and oxidative stress affect the lipid metabolism in the model animals. Brahmi showed a reversal of these lipid changes indicating its medicinal and protective effects.

Changes in kidney antioxidant enzymes in kidney

The protective effects of Brahmi on INH and RIF induced oxidative stress in the kidneys were assessed. The levels of CAT and LPO were significantly increased in INH and RIF treated rats as compared to

Table 2: Effect of Brahmi on the levels of kidney functional markers in the serum of isoniazid and rifampicin toxicant group

Parameters	Group I (normal control)	Group II (INH and RIF induced)	Group III (INH and RIF + brahmi)	Group IV (INH and RIF + silymarin)	Group V (brahmi alone)
Urea (mg/dl)	13.33±4.32	66.33±6.12^{a,*}	66.33±6.12^{a,*}	15.00±4.85^{b,*}	15.16±4.57^{b,*}
Uric acid (mg/dl)	8.46±0.79	12.06±0.36^{a,*}	8.91±0.61^{b,*}	9.23±0.92^{b,*}	8.60±0.59^{b,*}
Creatinine (mg/dl)	0.72±0.18	3.55±0.22^{a,*}	1.35±0.21^{a,*,b,*}	1.29±0.17^{a,*b,*}	0.81±0.14^{b,*c,*d,*}
Acid phosphate (mg/dl)	0.35±0.04	0.61±0.01^{a,*}	0.28±0.05^{b,*}	0.33±0.06^{b,*}	0.27±0.06^{b*}

Each value represents the mean±SD of six rats. Comparisons were made as follows: [a]Group I versus Groups II, III, IV, V; [b]Group II versus group III, IV, V; [c]Group III versus groups IV, V; [d]Groups IV versus Group V. The symbol represents statistical significance at *P<0.05>. Statistical analysis was calculated by one-way ANOVA followed by the Student–Newman–Keul's test. INH: Isoniazid; RIF: Rifampicin; SD: Standard deviation; ANOVA: Analysis of variance

Table 3: Effect of Brahmi on serum lipid profile of isoniazid and rifampicin toxicant group

Parameters	Group I (normal control)	Group II (INH and RIF induced)	Group III (INH and RIF + Brahmi)	Group IV (INH and RIF + silymarin)	Group V (Brahmi alone)
Cholesterol (mg/dl)	71.66±5.27	111.67±4.63^{a,*}	83.00±5.47^{a,*,b,*}	81.00±3.74^{a,*,b,*}	85.66±4.63^{a,*,b,*}
Triglycerides	144.67±5.16	177.33±7.09^{a,*}	139.00±3.74^{b,*}	139.67±4.67^{b,*}	141.00±3.74^{b,*}
HDL	35.00±3.74	15.00±3.76^{a,*}	39.0±3.72^{b,*}	41.0±3.71^{b,*}	37.0±3.70^{b,*}
LDL	25.15±2.38	29.92±2.66^{a,*}	23.85±1.25^{b,*}	21.49±1.76^{b,*}	24.03±2.63^{b,*}

Each value represents the mean±SD of six rats. Comparisons were made as follows: [a]Group I versus groups II, III, IV, V; [b]Group II versus group III, IV, V. [c]Group III versus groups IV, V; [d]Groups IV versus group V. The symbol represents statistical significance at *P<0.05>Statistical analysis was calculated by one-way ANOVA followed by the Student–Newman–Keul's test. INH: Isoniazid; RIF: Rifampicin; SD: Standard deviation; ANOVA: Analysis of variance; HDL: High-density lipoprotein; LDL: Low-density lipoprotein

Table 4: Effects of Brahmi on the activities of anti-oxidant enzyme the kidney tissue homogenate of isoniazid and rifampicin toxicant group

Parameters	Group I (normal control)	Group II (INH and RIF induced)	Group III (INH and RIF + Brahmi)	Group IV (INH and RIF + silymarin)	Group V (Brahmi alone)
SOD (Units/mg protein)	209.00±3.74	97.66±5.27^{a,*}	205.00±3.74^{b,*}	207.00±3.74^{b,*}	202.00±2.16^{b,*}
CAT (µmol of H_2O_2 consumed/min/mg protein)	10.48±0.98	3.49±0.83^{a,*}	9.79±0.58^{b,*}	10.78±0.46^{b,*}	11.05±0.76^{b,*}
Lipid peroxidase (mM TBARS/100 g of wet tissue)	0.39±0.05	0.99±0.05^{a,*}	0.45±0.04^{b,*}	0.47±0.06^{b,*}	0.40±0.05^{b,*}
GST (nmol/min mg protein)	18.00±0.047	9.03±0.03^{a,*}	18.06±0.07^{b,*}	17.56±0.59^{b,*}	17.58±0.24^{b,*}
Reduced glutathione (µmol/mg protein)	8.23±0.03	5.19±0.06^{a,*}	8.14±0.03^{b,*}	8.20±0.04^{b,*}	8.20±0.07^{b,*}
Glutathione peroxidase (mol/min mg protein)	6.05±0.06	3.07±0.03^{a,*}	6.05±0.09^{b,*}	6.07±0.95^{b,*}	6.07±0.11^{b,*}

Each value represents the mean±SD of six rats. Comparisons were made as follows: [a]Group I versus groups II, III, IV, V; [b]Group II versus group III, IV, V; [c]Group III versus groups IV, V; [d]Groups IV versus Group V. The symbol represents statistical significance at *P<0.05>. Statistical analysis was calculated by one-way ANOVA followed by the Student–Newman–Keul's test. INH: Isoniazid; RIF: Rifampicin; SD: Standard deviation; ANOVA: Analysis of variance; SOD: Superoxide dismutase; CAT: Catalase; GST: Glutathione-S-transferase

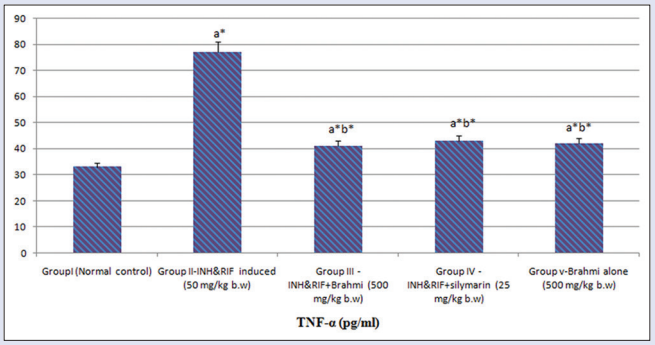

Figure 1: Level of tumor necrosis factor-α in experimental rats. Each value represents the mean ± standard deviation of six rats. Comparisons were made as follows: a-group I versus Groups II, III, IV, V; b-Group II versus Group III, IV, V. c-Group III versus Groups IV, V; d-Groups IV versus group V. The symbol represents statistical significance at *($P < 0.05$). Statistical analysis was calculated by one-way analysis of variance followed by the Student–Newman–Keul's test

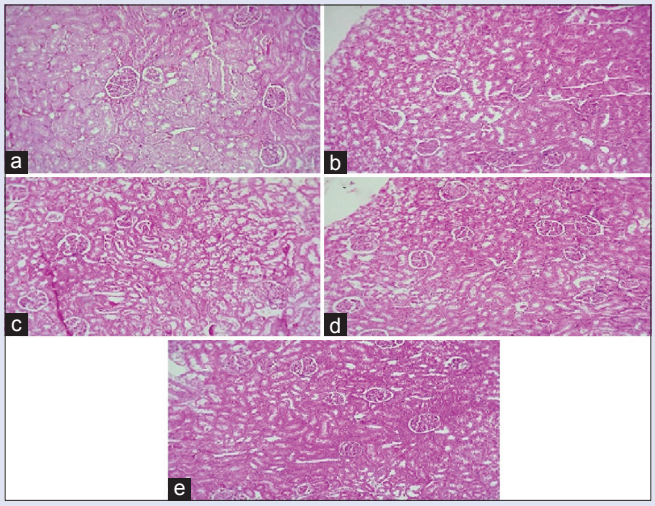

Figure 2: Kidney histopathology of experimental rats. (a-e): Kidney section (Stained with H and E) from rats (a) Control groups shows normal morphology (H and E, ×100), (b) Toxin group (isoniazid and rifampicin 50 mg/kg B. W) shows normal to decreased cellularity of glomerulus, renal tubules showing cell swelling with increase in eosinophilia of the cytoplasm with karyolysis in few of the cells. (c) Group 3 (isoniazid and RI 50 mg/kg b. w + Brahmi 500 mg/kg b. w) normal morphology. (d) Group 4 (isoniazid and rifampicin 50 mg/kg B. W + silymarin 25 mg/kg b. w) shows normal morphology (e) Group 5 Brahmi alone (500 mg/kg b. w) shows normal morphology (H and E, ×100)

the control group. The antibiotics also caused a significant decrease in the levels of SOD, GST, GSH, and GPx. These effects were countered by the concomitant administration of Brahmi and were comparable to the effect of the standard drug silymarin [Table 4]. RIF is known to have the most negative effect of all the anti-TB drugs on the kidney antioxidant levels. The renal toxicity of RIF has been reported periodically with frequent presentations of ARF.[21] RIF-induced renal toxicity presents histologically as tubule interstitial nephritis or tubular necrosis.[22] An intermittent regimen of RIF is known to induce acute tubular necrosis through the production of RIF-dependent antibodies, while continuous administration of RIF induces a higher degree of interstitial inflammation compared to acute tubular necrosis.[23]

Changes in the levels of tumor necrosis factor-α

The levels of TNF-α was increased indicating inflammation in the rats that were treated with INH and RIF. These levels were kept close to normal when the rats were simultaneously administered Brahmi and were comparable to the effect on silymarin treated rats [Figure 1]. The levels of TNF-α among the rats that were treated with Brahmi alone also remained unchanged. There are a number of renal enzymes that become affected by toxic metabolites that are coupled with–SH groups. This makes the kidneys vulnerable to the toxic metabolites of drugs. Around 75%–90% of INH that is ingested has been shown to be excreted via the kidneys while for RIF the percentage that is excreted through the kidneys is very less at around 15%. Although such a low percentage of the ingested RIF finds its way through the kidneys, it is known that RIF is the biggest inducer of nephrotoxicity among the anti-TB drugs. The mechanism of RIF induced kidney injury is not well established. A number of studies have suggested that it is due to a type II or type III hypersensitivity induced by RIF antigens.

Kidney histopathology

The control group of rats displayed normal renal histological architecture. This was in contrast to the effect of INH and RIF treatment (Group II) which showed decreased cellularity of the glomerulus, inflammation of renal tubules, eosinophilic changes in the cytoplasm, and karyolysis in few cells. These changes were reversed by treatment with Brahmi (Group III) and silymarin (Group IV), respectively. Rats treated with Brahmi alone (Group V) also showed normal histological architecture [Figure 2].[21,24,25]

CONCLUSION

The current study shows that co-administration of INH and RIF induce similar renal symptoms to humans in the model animal and that these symptoms are efficiently attenuated by the co-administration of Brahmi a commonly used herb with antioxidant properties. Further studies are needed to enhance our comprehension of the exact mechanism of INH- and RIF-induced renal toxicity which is a rare but highly threatening drug-induced complication among TB patients.

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Conflicts of interest

There are no conflicts of interest.

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