



Research Article

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ATTENUATION OF GENTAMICIN INDUCED NEPHROTOXICITY IN RATS BY AQUEOUS EXTRACT OF *TRIGONELLA FOENUM GRACEUM* SEEDS

Harneet Kaur, Amarjeet Singh, Sachin Kumar Singh, Amit Bhatia, Bimlesh Kumar *
School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar, Punjab, India

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*Corresponding author

E-mail: bimlesh.12474@lpu.co.in

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ABSTRACT

The present study was conducted to examine the protective effect of aqueous extract of *Trigonella foenum graceum* (Fenugreek) on gentamicin-induced nephrotoxicity in rats. Aqueous extract of *T. foenum graecum* was evaluated for its antioxidant property using DPPH and H₂O₂ scavenging assay. The nephroprotective effect of plant extract (200, 400 and 800mg/kg p.o.) was tested against gentamicin induced renal injury (100 mg/kg/d i.p.). After 8 days of respective treatment, 24-hour urine was collected for renal biochemical alterations and blood sample was collected to determine serum creatinine, blood urea nitrogen and serum protein. Kidneys were isolated for antioxidant enzyme estimations and histopathological analysis. Aqueous extract of *T. foenum graecum* showed antioxidant activity of 77.61 and 71.07% (at 80 µg/ml) in DPPH and H₂O₂ scavenging assay respectively. Co-administration of plant extract with gentamicin markedly improved all the parameters of nephrotoxicity induced by gentamicin in rats. There was a significant reduction in lipid peroxidation and rise in GSH levels with extract treatment. Histopathological reports showed reduction in the kidney damage in the animals treated with the plant extract. As a conclusion, the aqueous extract of *Trigonella foenum graceum* seeds may provide a cushion for a prolonged therapeutic option against gentamicin.

Keywords: Gentamicin, nephrotoxicity, *Trigonella foenum graceum*.

INTRODUCTION

Gentamicin (GM), an aminoglycoside, is an antibiotic commonly used in the treatment of life-threatening gram-negative bacterial infections. However, 30% of the patients treated with GM for more than 7 days show signs of nephrotoxicity^{1,2} because a small sizable proportion of the administered dose is retained in the epithelial cell lining of proximal tubules after glomerular filtration³ which increases serum creatinine and blood urea concentration as well as induces severe proximal renal tubular necrosis followed by deterioration and renal failure.⁴ Although the pathophysiology of GM induced nephrotoxicity is multi-factorial, generation of oxygen-free radicals is thought to be a major factor in its production.⁵ The role of antioxidants during drug induced toxicity was estimated, if they can protect the oxidative stress induced by reactive intermediates produced by various chemicals and drugs.³ GM generates hydrogen peroxide as well as reactive oxygen species (ROS) in renal cortex mitochondria and induces cellular injury and necrosis via several mechanisms including peroxidation of membrane lipids, protein denaturation and DNA damage.⁶

Trigonella foenum graecum (family- Fabaceae), common name Fenugreek, is known for its multiple pharmacological effects including antidiabetic, antineoplastic, anti-inflammatory, antiulcer, antipyretic, antitumor and immunomodulatory effects. In India, it is commonly known as Methi and has been used in various kidney diseases in order to tonify kidneys and to alleviate pain.⁷⁻⁹ The active components of fenugreek seeds behind most of the properties have been described as polyphenolic flavonoids, steroid saponins (steroidal sapogenins), polysaccharides mainly galactomannans and 4-hydroxyisoleucine.^{10,11} Treatment with *Trigonella foenum graceum* has been found to decrease calcium oxalate deposition, one of the major cause of nephrotoxicity, inside kidneys and

therefore it could have nephroprotective activity.^{12,13} Since, the role of fenugreek seeds against GM induced renal injury has not so far been considered, the present study aimed to examine the protective effect of aqueous extract of *Trigonella foenum graceum* on gentamicin-induced nephrotoxicity in rats.

MATERIALS AND METHODS

Procurement of plant material

The aqueous extract of *Trigonella foenum graceum* seeds (AETFG) was collected from Herbo Nutra Pvt. Ltd., New Delhi having batch no HN-110622.

Procurement of chemicals

GM was collected from Medipol Pvt. Ltd. Baddi, H.P., India. All the other chemicals used in the study were of analytical grade and purchased from local chemical agencies.

Procurement of animals

Wistar rats (160–180 g) were procured from NIPER, Mohali, India. Animals were divided into groups randomly and maintained at temperature 22±2°C and humidity at >40% with a 12-h light/dark cycle and provided the pellet diet and water ad libitum. The study protocol was approved by the Animal Ethics Committee (954/ac/06/CPCSEA/11/09), School of Pharmaceutical Sciences, Lovely Professional University, India. All animal procedures were performed in accordance with the standards set forth in the Guidelines for the Care and Use of experimental Animals by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

In vitro antioxidant activity

DPPH free radical scavenging assay

The free radical scavenging activity of the extract was measured in terms of hydrogen donating ability using DPPH as described by Mon et al. (2011)¹⁴ and Singh et al. (2015)¹⁵ using ascorbic acid (ASA) as standard. The absorbance of the samples was measured at 518nm.

Scavenging of H₂O₂

The ability of the extracts to scavenge hydrogen peroxide was determined as described by Ebrahimzadeh et al. (2010)¹⁶ and Chowdhary et al. 2014.¹⁷ The absorbance of the H₂O₂ was measured at 230nm.

Experimental design

Evaluation of *in vivo* nephroprotective activity

Animals were divided into 5 groups (n=6). Group I served as normal control and received saline orally. Group II received GM injection (100 mg/kg/d) through i.p. route for 8 days. Group III, IV and V received oral dose of AETFG at 200, 400 and 800 mg/kg/d respectively for 8 days. After 1 hour of respective

extract treatment, group III, IV and V were injected with GM everyday through i.p. route.^{18,19} After the last injection of GM, 24-hour urine was collected and evaluated for creatinine content. At the end of the study, animals were sacrificed and blood samples were collected for the determination of serum creatinine, blood urea nitrogen (BUN) and serum protein.²⁰ Furthermore, kidneys were isolated, weighed and were processed to estimate GSH,²¹ Catalase²² and lipid peroxidation level.²³

Histopathological evaluation

The kidney specimens obtained from all the animals were fixed in 10% formalin (24 h), and then stained with haematoxylin-eosin for microscopic evaluation of degenerative changes in renal parenchyma and renal tubules.²⁴

Statistical analysis

Results were reported as mean ± SEM (Standard error of mean). The obtained data was analysed by one-way analysis of variance (ANOVA) followed by Dunnett's test using Graph pad prism software. Statistical significance was set at P ≤ 0.05.

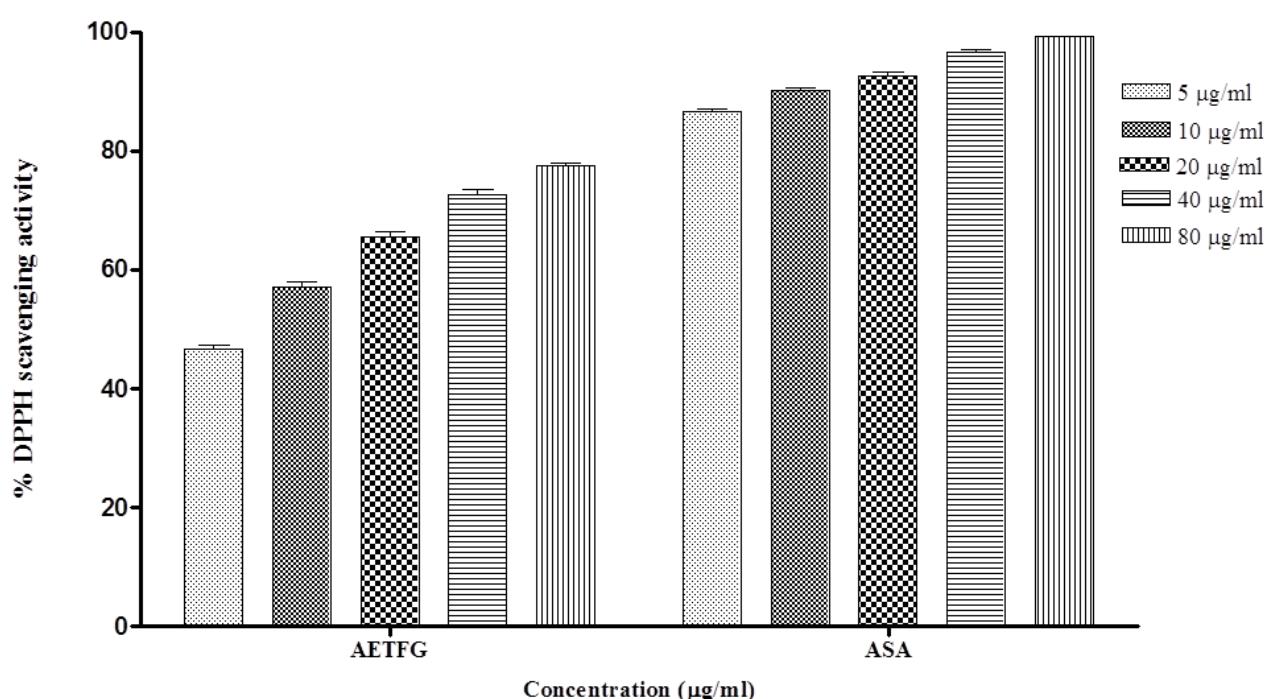


Figure 1: DPPH free radical scavenging activity of AETFG. ASA=ascorbic acid, AETFG=aqueous extract of *Trigonella foenum graceum*.

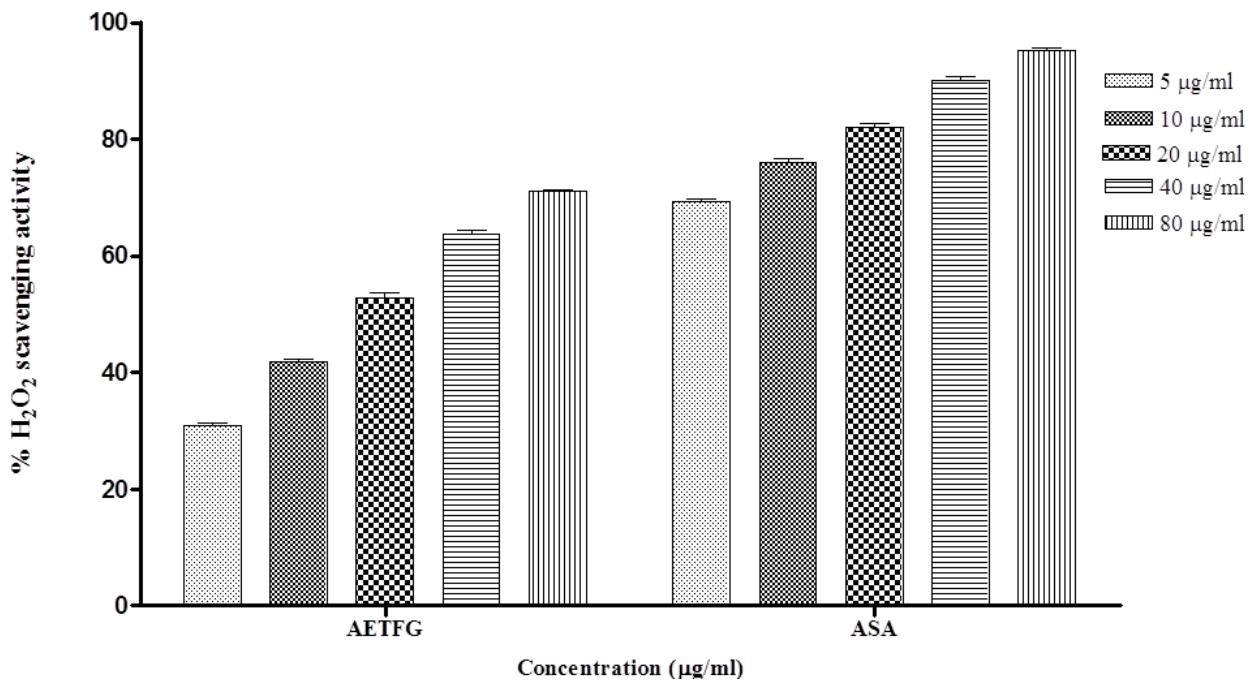


Figure 2: H_2O_2 scavenging activity of AETFG. ASA=ascorbic acid, AETFG=aqueous extract of *Trigonella foenum graceum*.

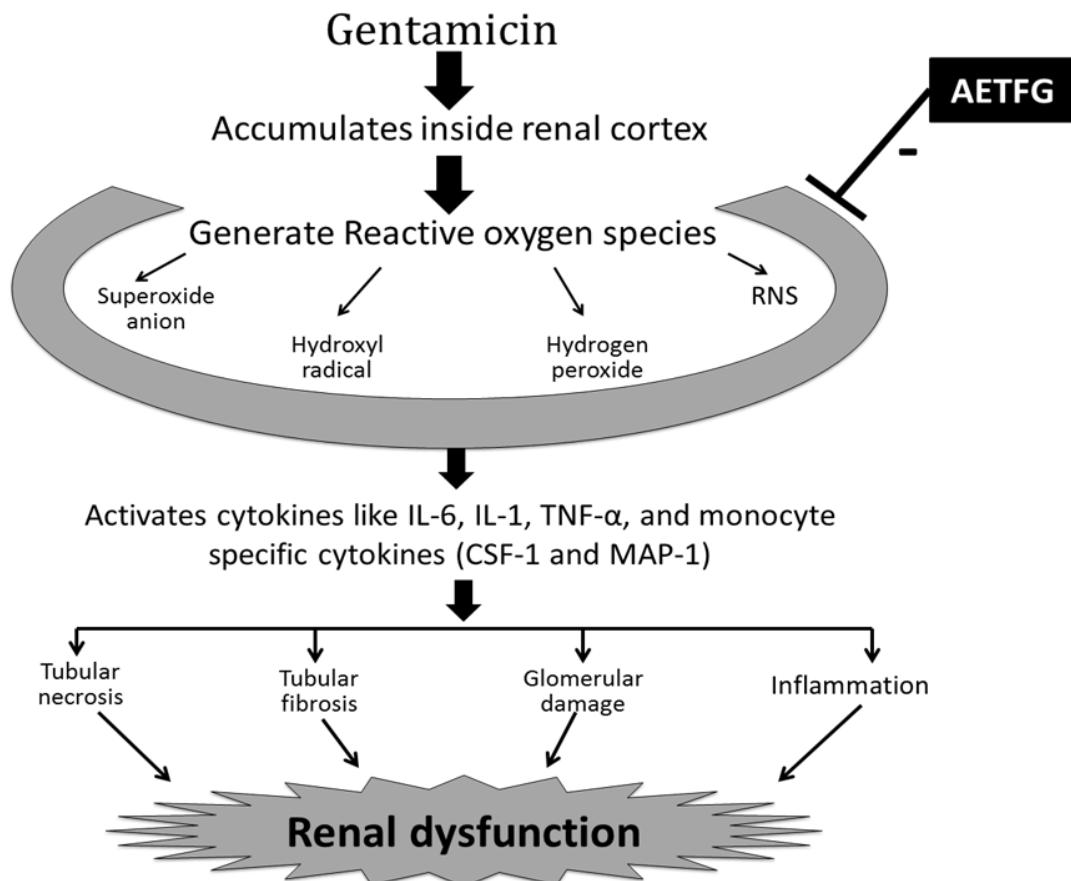


Figure 3: Schematic representation of GM induced nephrotoxicity. GM causes oxidative stress and generates reactive oxygen species and activates different types of cytokines via NF- κ B. This results in insult of nephron as tubular necrosis, fibrosis, inflammation and damage of glomerulus (renal dysfunction). AETFG exhibits nephroprotective activity due to its antioxidant potential. GM=gentamycin, AETFG=aqueous extract of *Trigonella foenum graceum*, RNS=reactive nitrogen species.

Figure 4: Histopathological study of kidneys. GM=gentamycin, AETFG=aqueous extract of *Trigonella foenum graceum*.

Table 1: Effect of AETFG on body weight, urine volume, and kidney weight against GM-induced nephrotoxicity

Groups (n=6)	Treatment (mg/kg)	Change in body weight (ml)	Urine volume (ml)	Kidney weight (g)
I	Normal	8.42±0.37	7.78±0.13	0.80±0.04
II	Toxic control (GM) (100)	-7.14 ±0.81	3.05±0.04	1.15±0.01
III	AETFG (200)	-4.34±0.21**	4.37±0.05**	0.98±0.03**
IV	AETFG (400)	-3.22±0.34**	5.22±0.04**	0.92±0.03**
V	AETFG (800)	-1.89±0.21**	6.22±0.05**	0.86±0.03**

Values are expressed as mean±SEM (n=6); **P<0.01; compared with toxic control group; GM= gentamycin; AETFG= aqueous extract of *Trigonella foenum graceum*.

Table 2: Effect of AETFG on serum parameters (urea, creatinine and total protein) against GM-induced nephrotoxicity

Groups (n=6)	Treatment (mg/kg)	Urea (mg/dl)	Creatinine (mg/dl)	Total protein (g/dl)
I	Normal	16.27±0.40	1.11±0.03	7.31±0.17
II	Toxic control (GM) (100)	38.53±0.51	7.35±0.36	3.20±0.01
III	AETFG (200)	31.66±0.36**	5.65±0.26**	4.71±0.28**
IV	AETFG (400)	26.89±0.30**	3.72±0.18**	5.88±0.28**
V	AETFG (800)	20.23±0.33**	1.92±0.19**	6.86±0.12**

Values are expressed as mean±SEM (n=6); **P<0.01; compared with toxic control group; GM= gentamycin; AETFG= aqueous extract of *Trigonella foenum graceum*.

Table 3: Effect of AETFG on CAT, GSH and MDA level

Groups (n=6)	Treatment (mg/kg)	Catalase (μmol H ₂ O ₂ /min/100mg protein)	GSH (μmol/100mg)	MDA (nmol/mg)
I	Normal	55.05±0.24	379.59±5.26	22.10±0.42
II	Toxic control (GM) (100)	4.12±0.06	63.26±4.21	184.52±0.23
III	AETFG (200)	17.71±0.14**	153.96±2.86**	116.04±0.93**
IV	AETFG (400)	25.11±0.15**	209.29±8.54**	62.28±0.60**
V	AETFG (800)	47.12±0.14**	345.35±7.58**	33.57±0.48**

Values are expressed as mean±SEM (n=6); **P<0.01; compared with toxic control group; GM= gentamycin; AETFG= aqueous extract of *Trigonella foenum graceum*.

RESULTS AND DISCUSSION

In vitro antioxidant assay

DPPH free radical scavenging assay

The freshly prepared DPPH solution exhibits purple color. When an electron or hydrogen radical is exposed to DPPH, it reduces to a stable diamagnetic molecule diphenylpicrylhydrazine with a decrease in the intensity of color.^{25,26} AETFG and ASA demonstrated a dose dependent antioxidant activity (Figure 1) and possess highest DPPH scavenging activity of 77.61% and 99.21% respectively at 80 μg/ml.

The DPPH radical is lipophilic and relatively stable nitrogen centered free radical. It easily accepts an electron or hydrogen radical to become a stable diamagnetic molecule. DPPH radical reacts with suitable reducing agents, as a result of which the electrons become paired off forming the corresponding hydrazine. The solution therefore loses colour stoichiometrically depending on the number of electrons received.²⁷ The degree of discoloration indicates the hydrogen donating ability of the extract which is a measure of its free radical scavenging potential.¹⁴ From the obtained results it is evident that the

Scavenging of hydrogen peroxide

H₂O₂ is a weak oxidizing agent that inactivates many enzymes directly, usually by oxidation of essential thiol (-SH) groups.²⁸ It also causes cytotoxicity by giving rise to hydroxyl radicals.^{17,29} AETFG and ASA were capable of scavenging H₂O₂ with the increase in concentration as shown in Figure 2. The maximum hydrogen peroxide scavenging activity shown by AETFG and ASA was 71.07% and 95.11% respectively, at 80 μg/ml.

Antioxidants act as inhibitors of the oxidation process at a very small concentration and thereby eliminate the threat of pathological states. Fenugreek seeds are in fact rich in polyphenolic flavonoids (>100 mg/g) including quercetin.^{30,31} In the present study, we hypothesized that AETFG would prevent GM-induced nephrotoxicity due to its intrinsic biochemical and antioxidant properties that would lead to improved metabolism and antioxidant defense mechanism in the kidney.

Evaluation of *in vivo* nephroprotective activity

Effect of AETFG on change in body weight, urine volume, and kidney weight

Although GM has a proven usefulness in the treatment of gram-negative infections, its nephrotoxic effect limits widely its use.

AETFG is acting as donor of hydrogen and thus able to scavenge DPPH free radical.

In fact, it has been estimated that approximately 30% of the patients treated with GM are associated with renal dysfunction³² that is why, GM-induced nephrotoxicity has been widely used as an animal model to study acute kidney failure in experimental research.³³

Administration of GM in the toxic control group led to a decrease in the body weight and urine output whereas treatment with AETFG was found to protect the rats from such effects (Table 1). GM causes loss of appetite and increased catabolism resulting in acidosis which is accompanied by anorexia.^{34,35} The observed improvement in body weight by AETFG may be due to an increase in the appetite, as the appetizer effect of AETFG.³⁶ There was a significant ($p<0.01$) increase in the urine volume of the rats treated with AETFG (200, 400 and 800 mg/kg p.o.). Kidney weight of the rats treated with AETFG was reduced (Table 1). The increase in the kidney weight by GM probably resulted from oedema that is caused by drug-induced acute tubular necrosis. This was confirmed histopathologically in the study of Erdem et al. (2000).³⁴

Effect of AETFG on serum parameters

As represented in Table 2, single i.p. injection of GM at 100 mg/kg/d for 8 days induced significant rise in serum creatinine and blood urea levels and a fall in total protein content as compared to normal rats indicating renal dysfunction. However, these changes were significantly attenuated by AETFG pretreatment in dose dependent fashion. The exact mechanism by which GM induces renal damage is unknown, however, evidences suggest a role of ROS in this damage, since it has been found that O_2^- , hydrogen peroxide and hydroxyl radical increases with GM-treatment.³²

This study showed that GM induces renal dysfunction as revealed by more than 2 fold increase in serum urea, 7 fold increase in creatinine and around 50% fall in total protein content. Increase in urea and serum creatinine has been recognized as biomarker of glomerular damage. AETFG prevented these changes of nephrotoxicity in blood in a dose dependent manner.

Effect of AETFG on CAT, GSH and MDA level

There was a significant decrease in the catalase activity and reduced glutathione level in the toxic control group as compared to normal group (Table 3). However, a significant increase in the catalase activity and reduced glutathione level was observed in the extract treated groups, as compared to the toxic control group which may be due to the antioxidant property of the plant extract. Furthermore, MDA level in the GM treated group was much higher than other groups, indicating a higher degree of lipid peroxidation being occurred. However, administration of extract prevented the lipid peroxidation to a greater extent, which is evident from a significant decrease in the MDA level in the extract treated animals.

Several reports have suggested the association of GM induced nephrotoxicity with oxidative stress.^{37,38} After getting accumulated in renal proximal tubules, GM induces oxidative stress by enhancing hydrogen peroxide generation by the mitochondria.^{38,39} ROS generation leads to tubular necrosis and decrease of glomerular filtration rate as summarized in Figure 3. Reactive oxygen species activates nuclear factor kappa-B that plays a key role in the inception of inflammatory process.³³ In consistent with the previous findings, the present study also showed enhanced oxidative stress in GM-treated animals

indicated by an increase in MDA level and decrease in total thiol content causing tissue damage and renal functional failure. The results also revealed that AETFG possessed significant protective effect against GM-induced nephrotoxicity and the effect was found to be in a dose dependent manner.

Histological studies

Animals treated with saline showed normal glomerular and tubular histology, while those treated with GM showed swelling, vacuolization and necrosis in the proximal tubular epithelial cells (Figure 4). Concurrent treatment with the extracts was found to reduce such degenerative changes in kidney histology as found in GM intoxicated rats.

CONCLUSION

The results obtained in this study suggested that AETFG has an overall protective effect against GM-induced nephrotoxicity in rat model. The *in vitro* and *in vivo* antioxidant effect of AETFG may be attributed, at least in part, to its protective effect in GM-induced nephrotoxicity. The potential ability of AETFG to reduce GM-induced nephrotoxicity in patients remains to be established. Further studies are required to isolate the active phytoconstituents and also to elucidate the possible mechanisms for nephroprotection.

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