Determination of nephroprotective activity of *Sansevieria roxburghiana* Schult. & Schult.f. (Agavaceae) methanolic crude extract in gentamicin-induced nephrotoxicity in male Wistar albino rats

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Jhona Beth P. Aclan, Kay Ann T. Cabungcal,
Apol Clarissa B. Bagon, Daniel Marie M. Portuguese,
Geneveive M. Reyes, Oliver Shane R. Dumaoal,
Carina M. Magtibay, Sheryl Aguila, Omar Villalobos
Pharmacy Department, College of Allied Medical Professions,
Lyceum of the Philippines University-Batangas
cmmagtibay@lpubatangas.edu.ph

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Abstract— *Nephrotoxicity is one of the most common kidney problems and occurs when the bodyis exposed to drugs or toxin that causes damage to the kidneys. This study was undertaken to determine the potential for nephroprotective effect of the crude methanolic extract of Sansevieria roxburghiana (MESR). Gentamicin was used to induce nephrotoxicity due to its ability to generate reactive oxygen species (ROS) in the kidney which then causes oxidative damage leading to renal toxicity. Ascorbic acid (200 mg/kg BW) was used as standard drug acting as an antioxidant. The study was conducted on twenty-five (25) eight-week old male Wistar albino rats weighing 150-250 grams equally grouped into five. The gentamicin-induced rats were treated with MESR 250 mg/kg and 500 mg/kg body weight intraperitoneally once a day for eight days. At the end of the protocol, blood urea nitrogen test, serum creatinine analyses and histopathological examination of the kidneys were performed. Gentamicin at a dose of 100 mg/kg BW caused marked nephrotoxicity when injected for 8 consecutive days, showing significant ($p<0.05$) increase in the levels of blood urea nitrogen (65.2940 + 2.2213 mg/dL) and serum creatinine (0.8780 + 0.0166 mg/dL) as compared to normal control animals (13.8980±0.7776 and 0.2440±0.0264 respectively). The MESR treated groups showed evident nephroprotective effect as seen in the reduction of BUN and serum creatinine levels when compared to gentamicin administered rats. The results showed that the lower dose of MESR (250 mg/kg body weight) significantly reduced the levels of serum creatinine (0.3200 ± 0.0176) and blood urea nitrogen (14.0060 ± 0.9325) to near normal control levels and is comparable to the group given ascorbic acid, 0.3140 ± 0.0087 and 16.6840 ± 1.1245, respectively. It was noted that MESR250 exhibited the highest activity in the reduction of BUN and serum creatinine levels among the treatment groups. The present study provides scientific evidence that the methanolic extract of S. roxburghiana 250 mg/kg BW has nephroprotective effects and is beneficial in decreasing elevated BUN and serum creatinine. Histological analysis of the kidney point out that the extract reduced the damage as compared to the gentamicin group. The findings of the study proves that the MESR has a nephroprotective potential.*

Keywords: *gentamicin, kidney, nephroprotective, reactive oxygen species, Sansevie riaroxburghiana*

INTRODUCTION

Aminoglycosides remain to embody highly effective antimicrobial agents since the time of their introduction in about more than 50 years ago [1]. Although newer and highly potent antibiotics with wide-spectrum were discovered, aminoglycosides continue to be used widely against serious and life-threatening gram-positive and gram-negative aerobic bacterial infections [1],[2].

They possess certain admirable characteristics such as rapid concentration-dependent bactericidal effects, clinical effectiveness, a low rate of true resistance, synergism with other beta lactam antibiotics, and low cost of therapy which is why they are most commonly used worldwide [1] [3]. However, according to a study by Bashan et al. [3], they have been known to induce nephrotoxicity in 10-20% of

patients on therapeutic courses in a dose-dependent mechanism.

Among the aminoglycosides, gentamicin is most commonly used because of its low cost and reliable activity against gram-negative aerobes [2]. In fact, bacterial strains that are resistant to other antibiotics in many conditions found gentamicin as the most powerful therapeutic drug [4]. Gentamicin-induced nephrotoxicity as described in a study by Pai et al. [1] is characterized by increase in plasma creatinine and urea levels and severe proximal renal tubular necrosis, followed by deterioration and renal failure. Since severe nephrotoxicity can result from gentamicin use, it turn out to be the most common substance used to study drug-induced acute renal failure. Nephrotoxicity caused by gentamicin results from an increase in oxidative stress leading to generation of reactive oxygen species (ROS) in the kidney which then causes oxidative damage [5].

Several studies claimed the nephroprotective effects of the antioxidant property of various plant extracts in gentamicin-induced nephrotoxicity [4], [5], [6]. Free radicals generated with gentamicin use may be scavenged by antioxidants. The scavenging ability of antioxidants is mainly attributed to their redox property which allows them to act as hydrogen donors, reducing agents and quenchers of singlet oxygen. However, commonly used antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and tert-butylhydroquinone (TBHQ) are suspected to cause liver damage and carcinogenesis. Therefore, there is an increasing demand in the discovery of newer and safer antioxidants [7].

At the present time, many diseases resort to and find cure with medicinal plants owing to their cheapness, safety and non-toxicity as compared with synthetically produced drugs [8]. *Sansevieria roxburghiana*is an Indian herb used in Ayurvedic medicine for various ailments by traditional healers. Phytochemical studies revealed the presence of carbohydrates, saponin, flavonoids, phenols, alkaloid, anthocyanin and -cyanin, glycosides, proteins and phytosterols [9]. In traditional medicine, *S. roxburghiana* has been used as cardiotonic, expectorant, febrifuge, purgative, tonic in glandular enlargement and rheumatism as mentioned by Haldar, Kar, Bhattacharya, Bala, & Kumar [10] and Roy, Kuddus, Begum, and Hasan [11] on their study. Antibacterial activity was also noted on the leaves of the plant and the whole plant was reported to have analgesic, cytotoxic and antioxidant activity [11]. According to Phillip, Kaleena, &Valivittan [12], the antioxidative power of *S. roxburghiana* leaf extracts could be attributed to the different phytochemical compounds present in the extract. It has been established that the role of flavonoids and phenolic compounds as antioxidants are existent. Methanol extract of leaves also showed the strong presence of alkaloids, glycosides, phytosterol and steroids. The presence of high alkaloids, sterols, flavonoids and saponins found in the methanol extract can be accounted for the antioxidant potential as revealed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) and nitric oxide (NO) radical scavenging [12].

MATERIALS AND METHODS

Collection and identification of plant samples

Leaves of *Sansevieria roxburghiana* were collected from GulodItaas, Batangas City last November 2016. The leaf samples were brought to Bureau of Plant Industry for authentication located at San Andres Street, Malate, Manila.

Figure 1. *Sansevieria roxburghiana* leaves

Reagents

Analytical grade methanol and standard ascorbic acid were purchased from Belman Laboratories, Mandaluyong City, Manila. Gentamicin (Maxigen®) was procured from Batangas Healthcare Hospital Jesus of Nazareth, Barangay GulodItaas, Batangas City, Batangas.

Preparation of extract

Upon authentication, the leaves were washed, shredded and air dried at room temperature. The size was further reduced using a blender yielding a total of 300 grams of dried leaf samples [9]. The samples were immersed in 95% methanol. It was kept in a rotary shaker at 100 rpm overnight and was filtered with Whatman No.1 filter paper. The filtrate was concentrated to dryness using rotary evaporator at 40°C and was further dried in an oven at 40°C until a semi-solid mass was obtained. The dried extract was then weighed and preserved at 4ºC for future use [9].

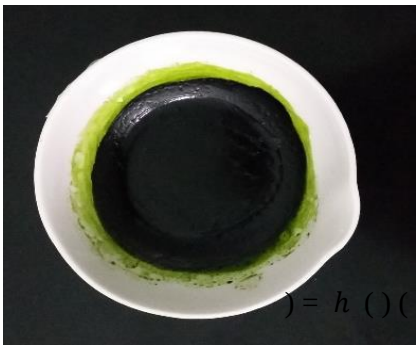

Figure 2. Methanolic extract of *Sansevieria roxburghiana*

Test Animals

To conduct the study, thirty male Wistar albino rats weighing 150-250g were obtained from Lipa Batangas and were certified free from evidence of dangerous communicable animal diseases by Dr. Neil Norman A. Cruz, DVM. The animals were acclimatized for one week in the Lyceum of the Philippines University– Batangas animal house in an improvised cage modeled in a standard polypropylene cage; maintained under a constant 12-hr light and dark cycle with a room temperature of 22-24°C, relative humidity of 30-60%. A standard pellet food and distilled water was given *ad libitum* [6]. The experiment was conducted in accordance to the Amended Animal Welfare Act (R.A 8485 or R.A 10631).

Induction of nephrotoxicity

Gentamicin sulfate 40 mg/ml was used to induce nephrotoxicity and was given 100 mg/kg/day intraperitoneally for eight days [6].

Acute oral toxicity

The acute oral toxicity of methanolic extract of *S. roxburghiana* (MESR) was evaluated according to the method described by the Organization of Economic Cooperation and Development Guideline 423 with a slight modification; the study was conducted beginning at the highest dose. The experimental animals were deprived of food overnight prior to administration of the extract. The MESR was administered orally through oral gavage at a dose of 2000 mg/kg BW on 3 male wistar albino rats that were initially separated into three cages. After administration, food was withheld for another 3-4 hours. Their mortality was observed for 48 hours. The rats were further observed for 14 days. The experimental animals were observed for the following pharmacotoxic signs: salivation, increased motor activity, sedation, restlessness, gasping and sensitivity to sound and touch. They were graded as (-) for no effect; (+) as slightly affected; and (++) if they are strongly affected by the treatment used [13].

Experiment Protocol

After acclimatization, a total of 25 male Wistar albino rats were used in the experiment protocol. The animals were randomly assigned into 5 experimental groups. The extract and the drugs were administered for a total duration of 8 days. The following formula was used to compute for the exact dose of the drugs and extracts to be administered for each rat:

The groups were as follows:

Group 1 (normal control): normal saline(1ml/kg/day, per orem)
Group 2 (disease group): Gentamicin (100mg/kg/day, IP)
Group 3 (MESR250): Gentamicin (100 mg/kg/day,IP) + MESR (250mg/kg/day, per orem)
Group 4 (MESR500): Gentamicin (100 mg/kg/day,IP) + MESR (250 mg/kg/day, per orem)
Group 5 (standard drug): Gentamicin (100mg/kg/day, IP) + Ascorbic Acid (200 mg/kg/day, per orem)

Biochemical Parameters

Twenty-four hours after the last dose was given, blood samples were collected from the test animals via cardiac puncture under ether anesthesia. The serum obtained after centrifugation were forwarded to Hi-Precision Diagnostics Plus at Rosario, Batangas for the conduction of blood urea nitrogen and serum creatinine test.

Histopathological Parameters

Both kidneys of one rat each group was collected and preserved under 10% formalin until it was delivered to Hi-Precision Diagnostics Plus for slide preparation. The kidney slides were forwarded to Dr. Emil Joseph S. Vergara in UP Los Baños for interpretation. Alterations in the kidney tissues of different experimental groups were evaluated depending on the severity of glomerular atrophy, glomerular hypertrophy, tubular degeneration, tubular necrosis, swelling of endothelium, vacuolation of endothelium, leukocytes cell infiltration and perivascular edema. The following findings were graded as follows: 0 if absent, + (mild level) if less than 25% of the total fields examined revealed histopathological alterations, ++ (moderate level) if less than 50% of the total fields examined revealed histopathological alterations and +++ (severe level) if less than 75% of the total fields examined revealed histopathological alterations [14].

Statistical Analysis

The BUN and serum creatinine levels was analyzed and expressed as mean ± Standard Error (SEM). The significance of difference among the

various treated groups and control group was analyzed by means of one-way ANOVA with Post Hoc Analysis (Tukey) as well as Dunnett test. The *p* values of <0.05 were considered as significant [9].

RESULTS AND DISCUSSION

Plant extract

The methanolic extract of S. roxburghiana leaves appeared to have a sticky dark green mass with semi solid consistency and pungent odor and a dark-green color. A percentage yield of 5.43% was obtained.

Acute Oral Toxicity

The acute oral toxicity of MESR was observed and conducted at the dose of 2000 mg/kg BW of the plant extract. The behavioral patterns of the experimental rats were observed after 30 minutes, one hour, two hours, three hours and four hours post-administration. The rats experience side effects such as restlessness, gasping and sensitivity to touch few hours after extract administration. The noted effects may be due to the stress from receiving the oral administration of the extract. Nevertheless, after two days of observation the rats survived, indicating that a dose level of 2000 mg/kg BW MESR is practically safe. Thus, the LD50 of MESR in rats was estimated to be greater than 2000 mg/kg. Gross necropsy examinations of the three rats were conducted. No significant findings were noted from the general observation of specific organs of the rats such as heart, lungs, liver, kidney, intestines, stomach and spleen.

Biochemical Parameter

All the groups' BUN and serum creatinine levels were identified to evaluate the nephroprotective effect of the MESR. In the present study, gentamicin at a dose of 100 mg/kg BW caused marked nephrotoxicity when injected for 8 consecutive days, showing significant (p=0.00) increase in blood urea nitrogen levels (65.2940 + 2.2213 mg/dL) and serum creatinine (0.8780 + 0.0166 mg/dL) as compared to normal control animals. The gentamicin group, as seen in figures 3 and 4, showed higher levels of the parameters measured when compared to other groups. Figures 3 and 4 also shows the multiple comparisons between the levels of serum creatinine and BUN of various study groups. A significant difference was noted when the gentamicin group was compared to all the other groups. On the other hand, no significant difference was observed between the normal control group, ascorbic acid treated and extract treated at a dose level of 250 mg/kg groups. However, a significant difference was recorded when the dose level of the extract at 500 mg/kg was compared with the normal control and the dose level of the extract at 250 mg/kg.

The MESR treated groups (MESR250 and MESR500) showed evident nephroprotective effect as seen in the reduction of BUN and serum creatinine levels when compared to gentamicin administered rats. Moreover, results showed that the lower dose of MESR (250 mg/kg body weight) significantly reduced the levels of serum creatinine (0.3200 $\pm$ 0.0176) and blood urea nitrogen (14.0060 $\pm$ 0.9325) to near normal control levels and is comparable to the group given ascorbic acid, 0.3140 $\pm$ 0.0087 and 16.6840 $\pm$ 1.1245, respectively. MESR 500 mg/kg was also able to improve renal function; however, significant normalization of blood urea nitrogen (28.4020 $\pm$ 3.2733) and serum creatinine (0.3740 $\pm$ 0.0452) levels were better observed with the lower dose 250 mg/kg of MESR. It was noted that MESR250 exhibited the highest activity in the reduction of BUN and serum creatinine levels among the treatment groups.

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The effects of MESR on kidney function test Serum BUN on gentamicin-induced nephrotoxicity in rats

*Data are expressed as means ± SEM (n=5). # (p<0.05) vs. normal control group *(p<0.05) vs. gentamicin group ^(p<0.05) vs. standard drug*

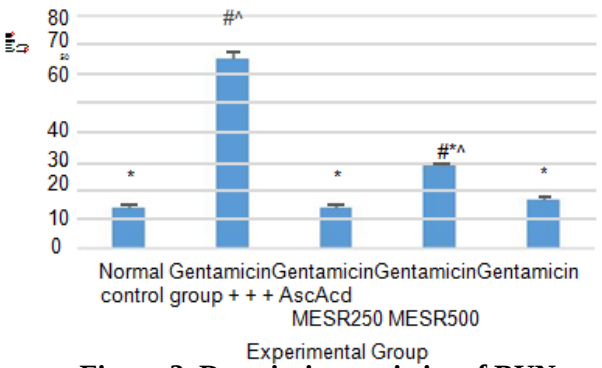

Figure 3. Descriptive statistics of BUN

The effects of MESR on kidney function test Serum Creatinine on gentamicin-induced nephrotoxicity in rats

*Data are expressed as means ± SEM (n=5). # (p<0.05) vs. normal control group *(p<0.05) vs. gentamicin group ^(p<0.05) vs. standard drug*

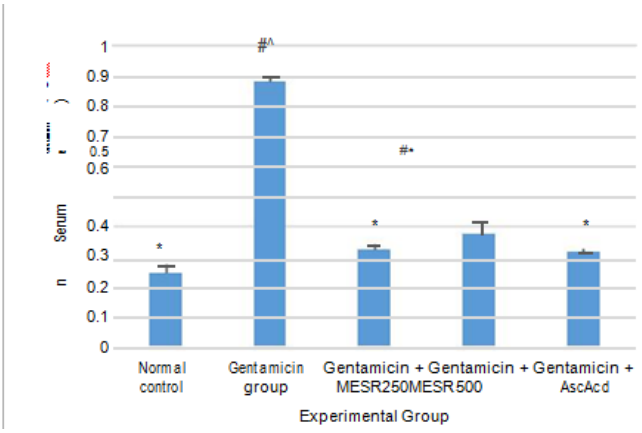

Figure 4. Descriptive statistics of Serum Creatinine

Histopathological parameters

The renal particles and kidney tubules with normal structure were seen in the histopathological examination of the kidney tissues in the normal control group. Gentamicin-induced group showed moderate to severe acute tubular injury with large areas of coagulation necrosis and intratubular nuclear and proteinaceous debris. There is also prominent loss of tubular cells specifically in the region of the proximal tubules. Proliferative glomerulonephritis, as shown by a decrease in the space of the Bowman's capsule, was also a prominent finding. In addition, congestion, marked lymphoplasmocytic infiltration and significant leakage of proteinaceous fluid into the interstitial space were notable. Similar mild to moderate lesions and changes were also observed in the kidneys of rats included in MESR250, MESR500 and Ascorbic Acid group. These deterioration and alterations were more evidently reduced in MESR250 group as compared to other groups.

MESR reduced most of the glomerular and tubular alterations induced by gentamicin. Gentamicin-induced proximal convoluted tubule alterations were significantly reduced and tubular necrosis was prevented by the MESR treatment. At higher doses, MESR also diminished evident tubular alterations but additional lesions can be noted. Marked reduction in histopathological alterations was seen greater with MESR250 compared to its higher dose, MESR500. This reduction also shows no significant difference to that effect of the standard drug, ascorbic acid. The histological alterations produced by gentamicin that are ameliorated by MESR are summarized in Table 3. Data obtained from investigation of 4 histological sections from kidneys of all groups. A minimum of 4 fields for each kidney section were examined and assigned for severity of changes by an observer blinded to the treatments of the animals and graded the severity of changes as seen in table 3.

Table 3. The nephroprotective effects of MESR against histopathological alterations induced by gentamicin (GM) in the kidney tissues of different experimental groups

Histopathological alterations	I	II	III	IV	V
Glomerular atrophy	0	+	+	+	+
Glomerular Hypertrophy	0	++	++	++	++
Tubular Degeneration	0	+++	++	++	++
Tubular necrosis	0	+++	+	+	+
Swelling of endothelium	0	+	+	+	+
Vacuolation of endothelium	0	+	+	+	+
Leukocytes cells infiltration	0	+	+	++	+
Perivascular edema	0	+	++	++	+

I: Normal Control; II: Gentamicin Group; III: Gentamicin + MESR250; IV: Gentamicin + MESR500; V: Gentamicin + Ascorbic Acid. Scoring: 0: absent. +: (mild level) less than 25% of the total fields examined revealed histopathological alterations. ++: (moderate level): less than 50% of the total fields examined revealed histopathological alterations. +++: (severe level): less than 75% of the total fields examined revealed histopathological alteration.

DISCUSSION

Sansevieriaroxburghiana had numerous published studies; however its acute oral toxicity had not previously been identified. Thus, prior to conduction of the experimental protocol, acute oral toxicity of the plant extract was determined. The experimental animals survived fourteen days after extract administration at a dose level of 2000 mg/kg BW. Thus, the LD50 of MESR in rats was estimated to be greater than 2000 mg/kg meaning, it is non-toxic and safe. No significant findings were noted from the general observation of specific organs of the rats such as heart, lungs, liver, kidney, intestines, stomach and spleen which further supports the safety of MESR at 2000 mg/kg BW.

Table 4. Histological appearance of all groups showing different kidney section alteration

Kidney Sections Alterations	Normal control group	Gentamicin group	Gentamicin + MESR250 group	Gentamicin + MESR500 group	Gentamicin + Ascorbic acid
Acute tubular injury	evident brush border cuboidal epithelium lining the proximal convoluted tubules	Moderate to severe with large areas of coagulation necrosis and intratubular nuclear and proteinaceous debris and proliferative glomerulonephritis	Moderate acute tubular injury	Mild to moderate acute tubular injury	Mild to moderate acute tubular injury
Lymphoplasmolytic infiltration/inflammation	Normal architecture of renal glomeruli with intact Bowman's capsule	Prominent loss of tubular cells specifically in the region of the proximal tubules, mild congestion and marked lymphoplasmocytic infiltration in kidneys of the diseased rats	Some loss of tubular cells, mild congestion and some lymphoplasmocytic infiltration	Some loss of tubular cells, mild congestion and moderate lymphoplasmocytic infiltration	Some loss of tubular cells, congestion and marked lymphoplasmocytic infiltration
Leakage of fluids	Normal kidney tissues	Significant leakage of proteinaceous fluid into the interstitial space	Moderate leakage of proteinaceous fluid into the interstitial space	Few leakage of proteinaceous fluid into the interstitial space	Moderate leakage of proteinaceous fluid into the interstitial space

In the study undertaken, twenty-five male Wistar albino rats were randomly divided into five groups. Gentamicin injection at dose level of 100 mg/kg BW has been proven to cause renal toxicity when administered for 8 consecutive days [6]. Results obtained from the study supported the previous statement when a significant rise in serum creatinine and BUN levels were noted in gentamicin treated groups. Direct injury to the tubular cells, resulting in acute tubular necrosis and damage to interstitial cells, which causes acute interstitial nephritis, is viewed as the gentamicin mechanism of toxicity [15]. It can also induce suppression of Na(+)-K(+)-ATPase activity and DNA synthesis in rats' proximal tubules leading to renal injury; this injury may be relevant to reactive oxygen metabolites generated by gentamicin. Toxicity is attributed primarily due to the drug's accumulation and retention in the proximal convoluted tubules which alters the normal function, perfusion and excretion of the nephrons in kidneys [16].

Free radicals generated with gentamicin use may be scavenged by antioxidants. The present study was undertaken to determine if the crude methanolic leaf extract of Sansevieria roxburghiana possesses a nephroprotective effect, owing to its antioxidant activity. From the study, the MESR was able to decrease the levels of serum creatinine and BUN when concomitantly administered with gentamicin due to the presence of flavonoids and phenolic compounds which acts as antioxidants. The extract, MESR did not show concentration dependence in alleviating nephrotoxicity. While improved renal function was observed with MESR 500 mg/kg BW as the BUN and serum creatinine levels were reduced, significant normalization of serum creatinine and BUN levels were measured only with the lower dose of MESR (250 mg/kg BW) and is comparable with ascorbic acid even if it is only a crude extract. This indicates that renal injuries were markedly prevented with MESR 250 mg/kg treatment.

The results of the biochemical analysis of our study were confirmed by the histopathological analysis, where gentamicin treated group showed moderate to severe alterations in the kidney tissues. Gentamicin-induced nephrotoxicity was reduced by the administration of MESR 250 mg/kg BW as demonstrated by both biochemical results and histopathological evidence. The methanolic extract of S. roxburghiana when co-administered with gentamicin had a nephroprotective effect and showed only mild to moderate acute tubular injury with few areas of coagulation necrosis and intratubular nuclear and proteinaceous debris. There is also some loss of tubular cells specifically in the region of the proximal tubules. In addition, minimal congestion, lymphoplasmocytic infiltration and some leakage of proteinaceous fluid into the interstitial space were also noted. The findings of the study proves that the MESR has a nephroprotective potential.

SUMMARY

The current study showed that the leaf extract of S. roxburghiana when administered concomitantly with gentamicin is effective in producing nephroprotective effect because it exhibited a significant decrease in blood urea nitrogen (BUN) and serum creatinine. The treatment with MESR 250mg/kg showed greater effect in protecting the kidneys from the toxic effects of gentamicin compared to that of MESR 500mg/kg. Additionally, the standard drug group, ascorbic acid, showed no significant difference with MESR 250 mg/kg in terms of reducing the BUN and serum creatinine levels which indicates that it is comparable to the control drug.

CONCLUSIONS

The present study provides scientific evidence that the methanolic extract of S. roxburghiana 250 mg/kg BW has nephroprotective effects and is beneficial in decreasing elevated BUN and serum creatinine. Furthermore, histological analysis of the kidney point out that the extract reduced the damage as compared to the gentamicin group.

The researchers highly recommend further studies on the toxicological effect of MESR. Isolation of the active nephroprotective compound of S. roxburghiana and testing their potency in alleviating nephrotoxicity is also recommended. The researchers also recommend additional parameters in determining the changes in the functionality of the kidneys such as the determination of electrolyte levels, 24-hr urine creatinine and determination of oxidative stress biomarkers in renal tissues.

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