

ORIGINAL ARTICLE

A Morphological and Biochemical Study of Ethanolic Fruit Extract of *Berberis Vulgaris* Against Gentamicin Induced Renal Damage in Albino RatsLubna Faisal¹, Tabina Urooj², Zia ul Islam³, Fatima Rehman⁴, Sadia Abdul Qayyum⁵, Aaqiba Rasheed⁶**ABSTRACT**

Objective: To analyze the reno protective potential of berberis vulgaris on renal function by measuring renal biomarkers (serum urea and serum creatinine).

Study Design: Experimental lab-based study.

Place and Duration of Study: Study was done in Baqai Medical & Dental University 4th July 2017 to 3rd Aug 2017.

Materials and Methods: Forty adult healthy male laboratory animals were randomly divided into four groups. Group A was treated as control group. Group B were administered with *Berberis vulgaris* fruit extract 100 mg/kg/body wt. single oral dose for 21 days. Group C were administered with gentamicin 100 mg/kg/day intraperitoneally single dose for 21 days. Group D, animals received gentamicin intraperitoneally 100mg/kg/day along with berberis vulgaris fruit extract orally for 21 days. Both kidneys were dissected, all sections obtained were stained with two dyes hematoxylin and eosin and periodic acid schiff stain for histomorphology. Standard error of mean was used to express results. Numerical data obtained from different groups were analyzed using SPSS version 21. P-value of 0.05 or less than 0.05 was considered statistically significant.

Results: This study revealed that body weight, kidney weight has been reduced in gentamicin group whereas biomarkers and relative weight of kidney have shown significant increase in group D as compared to control group.

Conclusion: *Berberis vulgaris* fruit extract ameliorates functional abnormalities along with biochemical parameters associated with gentamicin induced nephrotoxicity.

Key Words: *Berberis vulgaris*, *Gentamicin*, *Nephrotoxicity*, *Serum creatinine*, *Serum Urea*.

Introduction

Kidneys play an important role for the removal of waste products, for maintenance of balanced body chemical and acid content of the body. Substances produced by different metabolic reactions that occur in the body are excreted through kidneys include ammonia, bilirubin and creatinine in muscles and also drugs and other xenobiotics.¹ Life threatening infections caused by different microorganisms such as *Proteus*, *E.coli*, *Klebsiella*, *Citrobacter* species and

Staphylococcus species is most commonly treated by broad spectrum antibiotic gentamicin.² Clearance of gentamicin first rapidly by renal excretion but partially reabsorbed and accumulation occurred mostly within the proximal convoluted tubules, which are main site for renal toxicity. Therefore, gentamicin has always been a restriction in clinical use for long term. Renal insufficiency including renal end stage disease takes place in 30% of patients treated with gentamicin.³ Aminoglycoside has the potential to generate acute kidney failure due to tubular cell necrosis confined to proximal convoluted tubules by raising serum biomarkers creatinine and urea. Additionally reactive oxygen species (ROS) e.g., hydroxyl radicals (OH), hydrogen peroxide (H₂O₂), and superoxide anion (O₂⁻) which are the most important mediators of tissue damage are produced by gentamicin. Gentamicin renal toxicity also decreases the activity of renal tissue antioxidant agents like catalase, superoxide dismutase content.⁴ Tissue damage induced by gentamicin mainly caused by mitochondrial dysfunction as mitochondria are

^{1,3,4}Department of Anatomy/Forensic Medicine⁵

Liaquat National Hospital & Medical College, Karachi

²Department of Anatomy

Ziauddin Medical University, Karachi

⁶Department of Anatomy

Islam Medical & Dental College, Sialkot

Correspondence:

Dr. Lubna Faisal

Assistant Professor

Department of Anatomy

Liaquat National Hospital & Medical College, Karachi

E-mail: DrLubna.Faisal@lnh.edu.pk

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main sites of ROS production.⁵ It is proved that gentamicin renal accumulation facilitates nephrotoxicity.⁶ Toxicity induced by gentamicin is mainly due to oxidative stress and this condition could be antagonized by dietary antioxidant.⁷

Berberis vulgaris medicinal herb belongs to the family Berberidaceae found abundance in European countries, Northwest Africa and in few Asian regions. Fruit of *Berberis vulgaris* commonly called Barberry, (Zereshk) in local language in Iran are edible, they contain large amount of vitamin C.⁸ Barberry of both types dried and fresh have increased antioxidant activity and are rich in phenolic and anthocyanin compounds, intake of both is recommended.^{9,10} *Berberis vulgaris* also contains large percentage of ascorbic acid which is antioxidant.¹¹ Fruit of *Berberis vulgaris* is approved by FDA and it is safe for humans.¹²

Considering reported therapeutic medicinal uses of *berberis vulgaris* fruit extract, the present study was conducted based on experiments to evaluate the probable protective role of *berberis vulgaris* fruit extract on renal parenchyma and to analyze the ameliorative potentials of *berberis vulgaris* fruit extract on renal function by measuring renal biomarkers (serum urea and serum creatinine).¹³

Materials and Methods

This experimental study was performed at Baqai Medical & Dental University in Anatomy department jointly with Animal house of BM & DU after ethical approval of experimental protocol (Ref: BMU-EC/2016-04) from Board of Advanced Research and Studies (BAS&R) Baqai Medical University 4th July 2017 to 3rd Aug 2017. Inclusion criteria for this study used were forty healthy male adult albino rats aged 10-12 weeks and weighted 180-250gms. Exclusion criteria for this study used were any diseased rat or rat died during study. Total four groups were made for this experimental study each having ten rats (n=10). Group A required laboratory food and water, no drug or treatment was given to this group. Group B animals were given fruit extract of *berberis vulgaris* orally 100mg/kg rat body wt./day for 21 consecutive days. Gentamicin was injected intraperitoneal route to group C at a single dose of 100mg/kg rat body wt./day daily for 21 consecutive days to induce nephrotoxicity. Group D were given gentamicin 100mg/kg rat body wt./day

intraperitoneally daily once as company with *berberis vulgaris* Ethanolic fruit extract 100 mg/kg rat body wt. daily once through gastric gavage for 21 days. Before the commencement of this procedure all animals were weighted by using digital electronic balance, tagged, and kept in segregated cages in animal house of BM&DU and allowed free access for fresh water & concentrated food (pellets) ad libitum. *Berberis vulgaris* was purchased from local herbal market of Karachi and authenticated by pharmacognosy department of Karachi University. *Berberis vulgaris* fruit obtained was dried to make it free from bacteria, fungus then it was chopped into small pieces to make refined powder. The grounded sample was retained in a sealed jar and then reserved for further extraction. Grinded powdered fruit (1000g) was soaked in adequate volume of ethanol: water 70:30 ratio, stirred in a circular shaker at room temperature. The extract was kept for 7 days for further extraction. The decoction then separated from the remainder by filtration through Whatmanno.1 filter paper. The remainder solvent of the concentrate removed by using rotary evaporator¹⁴. After completion of dosing, all animals were anesthetized and then sacrificed. All animals weight was recorded at the beginning and at the time of sacrifice.

Effects of gentamicin related nephrotoxicity in albino rats was measured by kidney weight/100g rat body weight¹⁵, biomarkers serum creatinine and serum urea concentration in rats.

5ml whole blood samples were carefully collected at the end from each experimental rat by intracardiac puncture in a 10 ml capacity bottles for detailed estimation of biomarkers urea and creatinine levels. Abdominal cavities were exposed by giving midline incisions. Kidneys of both sides were obtained and divided into two equal-size length wise halves and were fixed for 24h in 10% formalin (BFN). All fixed specimen of both kidneys were dehydrated with ascending grades of ethanol cleared in xylene solution and embedded in paraffin wax blocks. 5um thick tissue sections were made. The architecture of all four groups slides A to D was observed.

Four randomly selected sections from each kidney were observed under a light microscope at 10 and 40X. Two basic stains routine hematoxylin and eosin (H&E) and periodic acid Schiff (PAS) were used to

notice the overall tissue architecture of both kidneys. Standard error means (SEM) was used to express results. Numerical data obtained from different groups were analyzed using SPSS version 21. P-value of 0.05 or less than 0.05 was considered statistically significant. The obtained data was analyzed by one way ANOVA.

Results

Normal control mean for initial and final body weight were recorded as 207±4.26 and 210 ± 3.09 respectively. Data showed highly significant increased (p-value 0.003) in the mean of final rat body weight of normal control group A (Table I). Berberis received group initial and final body weight were recorded as 196.50± 2.66 and 210.80±2.84 respectively. Significant increase (p-value0.0001) in the mean of final rat body weight of Group B was noticed. (Table I).Group C mean value for initial and final rat body weight were recorded as 196.2±2.26 and 183.8±1.93 respectively. Significant decrease (p-value 0.0001) (Table I) in the mean of final rat body weight of Group C was noticed.

Group D mean value for initial and final body weight were recorded as 203.30 ± and2.07 217.90 ± 2.09 respectively. Data showed significant increase (p-value0.0001) in the mean of final body weight of Group D. (Table I).

The mean value of weight of rat kidneys (gm) in group A and B were .614±.018 and .639±.013 respectively. Mean value of weight of rat kidney (gm) in gentamicin group was .962±.010 and mean value of weight of kidney in gentamicin along with berberis vulgaris treted group was .660±.009 (Table II).

It was noticed in this study data revealed highly significant increament in the mean value of weight of kidneys (p-value 0.00) in gentamicin treated group.962±.010 when compared with normal control group.614±.018.

The data of this study also showed highly significant increas in the mean of rat kidneys in gentamicin group (p-0.00) when compared with berberis group.639±.013.

Experimental data showed significant increment in the mean value of rat kidneys of group C .962 ±.010 (p-0.00) when compared with group D .660 ±.009.

The mean values of relative weight of kidneys in normal group, berberis vulgaris fruit extract group, gentamicin treated group, and gentamicin along

berberis vulgaris group are shown in (Table III A). Significant increase was observed in the mean value of relative kidneys weight (p-0.000) in group C when compared with control normal group A, B and D (Table IIIb).

Interstingly our data showed highly significant increased (p-0.00) in the mean of biochemical parameters serum urea level (mg/dl) of gentamicin treated group in comparision with normal control group A. Additionally gentamicin along with berberis vulgaris treated group showed not much raised level of urea as compared to control group which revealed nephroprotective result of berberis vulgaris fruit extract against nephrotoxic drug gentamicin.(Graph no 1).

Mean value of serum creatinine level (mg/dl) in group A and B were 0.655±.011, mean.635±.007 respectively. Mean of serum creatinine level (mg/dl) in group C and D were 5.35±.186 and .688±.009. respectively (Graph No 2). Results of our study showed significant increament in the mean value of serum creatinine level (p-0.00) in gentamicin group 5.35±.186when compared with normal control group 0.655±.011.(Graph No 2).

The data showed significant increased in the mean value of serum creatinine level (p-0.00) in gentamicingroup C 5.35±.186 when compared with group D.688±.009.

Additionally, highly significant increase was observed in the mean value of serum creatinine level (p-0.00) in comparision with gentamicin group5.35±.186 when compared with berberis group .635±.007.

In contrast, tha data revealed no remarkable change in the mean value of serum creatinine level (p-0.869) in gentamicin treated along with berberis vulgaris fruit extract groupin comparision with control group A.

Table I : Mean Rat Body Weight (Gm) In Different Treated Groups

Groups n=10 in each group	Treatment received	Initial weight	Final weight	P-value
A	No experiment done	207±4.26	216±3.09	0.003*
B	Ethanolic Berberis vulgaris fruit extract (100mg/kg rat	196.5±2.66	210±2.84	0.000*

	body wt/day)for 21 consecutive days orally			
C	Gentamicin (100mg/kg rat body wt /day) single dose i.p for 21days	196.2±2.66	183±1.93	0.000*
D	Gentamicin i.p (100 mg/kg rat body wt /day)+with berberis vulgaris orally for 21 days	203±2.07	217±2.09	0.000*

Table II: Mean Rat Kidney Weight (gm) in Study Groups n=40

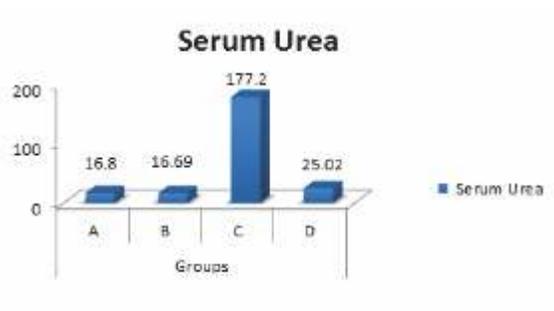
Groups	Treatment Received	Rats' Kidney Weight
A	No experiment done	.614±.018
B	Ethanolic Berberis vulgaris fruit extract (100mg/kg rat body wt/day)for 21 consecutive days orally	.639±.013
C	Gentamicin (100mg/kg rat body wt /day) single dose i.p for 21days	.962±.010
D	Gentamicin i.p (100 mg/kg rat body wt /day)+with berberis vulgaris orally for 21 days	.660±.009

Table III a : Mean Relative Weight of Kidney In Different Groups

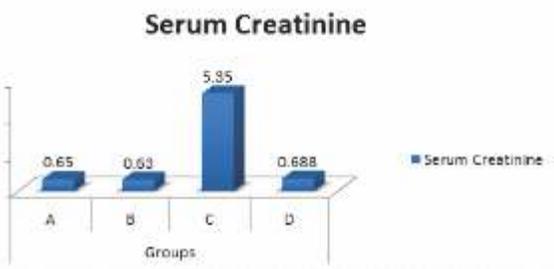
Groups	Treatment received	Relative weight of kidneys
A	No experiment done.	2.13±.063
B	Ethanolic Berberis vulgaris fruit extract (100mg/kg rat body wt /day)for 21 consecutive days orally	2.22±.067
C	Gentamicin (100mg/kg rat body wt /day)single dose i.p for 21 consecutive days	3.34±.064
D	Gentamicin i.p (100 mg/kg rat body wt /day)+with berberis vulgaris orally for 21 consecutive days	2.29±.069

Table III b Analysis of Differences in Relative Weight of Kidneys between Different Groups.

Comparison of groups.	Difference between treated groups	P-VALUE
A and B	-.086±.093	.361
A and C	-1.209±.093	.000
A and D	-.156±.093	.104
B and C	-1.12±.093	.000
B and D	-.096±.093	.464
D and C	-1.052±.093	.000



Graph No 1. Serum Urea Mean Values Comparison of Different Experimental Groups.



Graph No 2. Serum Creatinine Mean Values Comparison of Different Experimental Groups.

Discussion

Aminoglycoside brand Gentamicin is one of an important and effective antibiotic due to its strong bactericidal properties, lower resistance rate and cost effectiveness. Aminoglycosides accounts for 10%-20% of nephrotoxicity which is its one of major complication.¹⁶

Gentamicin can be used both in humans as well as for animals in treating gram negative bacterial infections.¹⁷ Gentamicin induced nephrotoxicity is commonly used to study acute kidney failure in animal model for research based experiments.¹⁸ Gentamicin induced nephrotoxicity results in acute kidney failure.¹⁹ AKF is a complex series of event indicated by elevated serum creatinine level and blood urea including proximal tubular cell necrosis resulting in renal failure.²⁰ Production of ROS in mitochondria is directly increased by gentamicin as a result cellular damage occurred, decreased production of ATP, apoptosis stimulating factor released from mitochondria, lipid per oxidation all these lead to cell hypertrophy and cell death by apoptosis thus resulting in decreased body weight. Sawardekar et al.²¹ showed same results which was observed in this study. Berberis vulgaris fruit (BVF) can be used as an alternative medicine or as additive supplement food against nephrotoxicity generated

by gentamicin.

Berberis vulgaris (BV) and its important compound berberine have been used since for a long period in indigenous medicine. Antioxidant results of *berberis vulgaris* are greater due to synergy of phenols and berberine compounds.²²

The most specific indicator for measuring adverse effects of divergent xenobiotics is the body weight, therefore it is considered as a principle parameter to test toxicity. Significant decline in rat body weight gain was noted in group C. Renal failure leads to acidosis, accompanied by anorexia and decreased food intake which later on results in body weight loss by gentamicin induced nephrotoxicity. Similar findings have been stated by Erdem et al.²³ In this study it was noted in *berberis vulgaris* protected group increase to some extent in body weight as compared to gentamicin treated group.²⁴ Tamilarasan et al also confirmed these findings.²⁵ Same energy levels were found in Group D animals when compared with normal group. This is because *Berberis vulgaris* fruit extract which has a potential to reduce oxidative stress, results in decline of free radicals scavenging activity. *Berberis vulgaris* possess strong antioxidant effects which help to improve physical strength consequently increased body weight. This was in accordance with previously done study by Laamech et al.²⁶ Marked increase in relative weight of kidney was observed in gentamicin treated group C as compared to control group due to decreased prostaglandin E2 production which causes sodium retention resulting in renal hypertrophy and interstitial edema produced by gentamicin induced tubular necrosis resulted in significant increased kidney weight as similar to Noorani et al.²⁷

Prominent increased level of serum urea and creatinine concentrations are good signs of concentrated glomerular filtration and significant kidney failure. Significant rise in levels of serum urea and creatinine concentrations resulted in powerful renal destruction produced by gentamicin nephrotoxicity.²⁸ Serum creatinine is more authentic biomarker in the mechanism of pathogenesis of renal disease as compared to urea.²⁹ Further more concentration of urea starts to develop right after injury of renal parenchyma. Antioxidant properties of tissue are decreased by gentamicin which is revealed by prominent decrease in enzymatic

activity of superoxide dismutase and marked increase in per oxidation of lipids. Due to this it generates oxidative stress to different organs. Antioxidant agent can alter majority of the modifications in histological tissue sections of renal parenchyma generated by gentamicin related nephrotoxicity.

The mechanism due to which serum urea and creatinine levels raised are because of the reason that gentamicin causes the Ca²⁺ to enter more into the mesangial cells resulting in decreased glomerular filtration rate.³⁰ Similar finding was observed by W Hozayen et al.³¹

It was clearly evident through results of our study that gentamicin at a dose of 100 mg/kg rat body wt/day generates nephrotoxic effects which was obvious by marked increase in p-value (0.000) in serum urea and blood creatinine level as compared to normal control group.

Berberis vulgaris fruit extract has strong antioxidant potential leading to nephroprotective effects (Jyothilakshmi et al., 2013).³² No significant increase in serum urea and blood creatinine concentration was found in *Berberis vulgaris* treated group when compared with normal control group. In the light of above statistical analysis, figures, and facts.

Conclusion

It is concluded that Gentamicin produces oxidative nephrotoxic effects on renal parenchyma which can be limited and prevented by protective antioxidative effect of *Berberis vulgaris* that restored histomorphological changes in renal tissue induced by gentamicin toxicity.

Limitations of Study

There will be no doubt if herbs will be used in future that will significantly benefit human beings. However sample size of this study is too small, animal studies are time consuming and there will be chance of high failure in development of new drug.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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