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RESEARCH ARTICLE

Nephroprotective Potential of *Rosa damascena* Mill Flowers, *Cichorium intybus* Linn Roots and Their Mixtures on Gentamicin-Induced Toxicity in Albino Rabbits

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ABSTRACT

Gentamicin is an aminoglycoside antibiotic comprised of a mixture of related gentamicin components and fractions and is used to treat many types of bacterial infections, particularly those caused by Gram-negative organisms. Herbal plants can be used for the prevention and treatment of kidney damage. Therefore, the nephroprotective activity of aqueous extract of *Rosa damascena* (250 and 500 mg/kg), *Cichorium intybus* (250 and 500mg/kg) and their mixture (250 and 500 mg/kg) was evaluated on gentamicin (80 mg/kg) induced toxicity in albino rabbits by using the standard drug silymarin (200 mg/kg). The study period was from 0-21 days and blood samples were collected at 0, 7th, 14th and 21st day. The biochemical analysis was done by using the standard protocols and kit methods. Serum urea and creatinine are the reliable markers to access the renal function. The results were subjected to two way analysis of variance and Duncan Multiple Range test as applicable. The gentamicin caused a significant ($P \leq 0.01$) increase in levels of serum urea, creatinine and blood urea nitrogen and decrease in levels of serum albumin. Statistically significant decrease in levels of serum urea, creatinine and blood urea nitrogen and statistically significant increase in the levels of albumin was observed for both plants and their mixture in dose dependent manner as compared to untreated, gentamicin treated and silymarin treated control groups. All results were supported by significantly improved renal cortical histopathology and kidney weight observations. The findings suggested that aqueous extract of both plants and their mixture have marked nephroprotective activity in dose dependent manner which could be due to the inherent antioxidant and free radical scavenging capacity contained in both plants.

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INTRODUCTION

Kidney is a major excretory organ and plays an important role in regulating water and electrolyte balance and conservation of necessary products according to body needs (Hall, 2011). Kidneys are poised to sense plasma concentrations of amino acids, creatinine, and glucose; they are important regulators of blood pressure, glucose metabolism and erythropoiesis (Shimmi *et al*., 2011). Gentamicin (GM) is an aminoglycoside and is mostly used in patients with severe gram negative bacilli infection. The specificity of gentamicin for renal toxicity is related to its ability to facilitate the production of reactive oxygen species (ROS) in mitochondria in the renal proximal convulated tubules where it leads to characteristic tubular necrosis which ultimately causes acute renal failure (Javed *et al.,* 2013).

Nephropathy is often recognized only when filtration is affected due to which a rise in the blood urea nitrogen, serum urea and serum creatinine. The nephrotoxicity due to gentamicin is a complex process which is characterized by an increase in serum levels of urea, creatinine, BUN and uric acid (Al-Majed *et al*., 2002). Now-a-days extracts of several natural products have been reported for having their protective effects against drug induced nephrotoxicity due to their antioxidant, diuretic, anti-inflammatory, antispasmodic properties. (Rasikh *et al.*, 2012). *Rosa damascena* Mill(*R. damascena*) has been

used as cardiotonic, mild laxative, anti-inflammatory, cough suppressant, anti-leptic, anti-diabetic and also used for the treatment of menstrual bleeding and digestive problems (Boskabady *et al*., 2013). *R. damascene* also has antioxidant potential (Shahriari *et al*., 2007). Recent studies demonstrated the anti-HIV, antibacterial, anti-tussive, respiratory smooth muscle relaxant, analgesic and anti-inflammatory effects of *Rosa damascena* (Hajhashemi *et al*., 2010).

Cichorium intybus Linn (*C. intybus*) is commonly known as Chicory used as hepatoprotective, hypoglycemic, anti-hyperlipidemic, anti-cancerous, anti-hepatotoxic and hypoglycemic agent (Mulabagal *et al*., 2009). A number of studies had been conducted to determine the antioxidant potential of *Cichorium intybus* (Hassan and Yousef, 2010). It has also been reported to act as a diuretic, treatment for anti-testicular toxicity and also has some immune-modulatory activities (Grieshop *et al*., 2004). The objective of present study was to evaluate the nephroprotective activity of *Rosa damascena* flowers, *Cichorium intybus* roots and their mixture against gentamicin-induced kidney injury in rabbits.

MATERIALS AND METHODS

Drugs and plant material: Drugs used were Inj. Gentacin® (Gentamicin sulphate, 80mg/2ml) manufactured by Abbott Laboratories Pakistan Ltd. and Tab. Silliver® (Silymarin, 200mg) manufactured by Searl Pakistan (SPL) Ltd. Flowers of *R. damascena* and roots of *C. intybus* were purchased from the local herbal market of Faisalabad and were identified and authenticated from the Department of Botany, University of Agriculture Faisalabad, Pakistan. A 500g dried powder of flower of *R. damascena* and root of *C. intybus* was taken and aqueous extraction was done by following the process of maceration. The weight of the resultant residue after lyophilization by freeze drying apparatus (Christ, Germany model # Alpha 1-4LSC) was 700 mg/5 ml of *R. damascena* and 237 mg/5 ml of *C. intybus* was recorded and percentage yield was calculated. The extract was stored at 4°C till analysis. The aqueous extract of mixture was simply prepared by mixing the equal amounts of aqueous extracts of both plants for both doses (250 and 500 mg/kg).

Experimental protocol: Fifty four healthy male albino rabbits were purchased from local market of Faisalabad and were kept at 25±5°C under 12 hour light and dark cycle in ventilated animal house of Department of Physiology and Pharmacology, UAF, Pakistan. Rabbits were given seasonal fodder and water *ad libitum*. These rabbits were divided in nine equal groups having six rats in each group. Group 1 was given only the vehicle. All rest of eight groups was given gentamicin at dose rate of 80 mg/kg intraperitoneal. Group 3 was given additionally silymain at dose rate of 200 mg/kg. Group 4 was given aqueous extract of *R. damascena* flowers at dose rate of 250 mg/kg, group 5 was given aqueous extract of *C. intybus* roots at dose rate of 250mg/kg, group 6 was given aqueous extract of *mixture of R. damascene* flowers and *C. intybus* roots at dose rate of 250 mg/kg, group 7 was given aqueous extract of *R. damascena* flowers at dose rate of 500 mg/kg, group 8 was given aqueous extract of *C. intybus* roots at dose rate of 500mg/kg while group 9 was given extract of *mixture of R. damascene* flowers and *C. intybus* roots at dose rate of 500 mg//kg additionally. All aqueous extracts were given orally.

Phytochemical analysis: Test for phenols and Carbohydrates was performed by using the method of Sofowora (1993). Terpenoids, saponins and steroids were identified by following the method of Edeoga *et al*. (2005). Flavonoids and Alkaloids were identified by using the method of Harborne (1998). Kellar-Kiliani test was performed to identify Glycosides by using the method of Parekh and Chanda (2007). Tannins were identified by using the method of Kumar *et al*. (2007).

Biochemical analysis: Serum urea (mg/dl), creatinine (mg/dl) and albumin (g/dl) level were determined at 0, 7th, 14th and 21st day of experiment by commercially available kit by Merck(Private) Limited, DiaSys Diagnostic System Gmbh, Holzheim, Germany. Blood urea nitrogen (BUN) is calculated by applying a conversion factor on the results which were obtained from serum urea calculations which is: BUN (mg/dl) = Urea (mg/dl)/2.14.

Histopathological examination: At the end of experimental procedure, rabbits were euthanized with ketamine and kidney were excised and fixed in formalin and further biopsies were processed through graded concentrations of ethanol and embedded in paraffin blocks. The sections of kidney were oriented perpendicular to the plane of section in the block and 6 micrometer thick transverse sections were cut and mounted on glass slides and stained with hematoxylin and eosin (Weiss *et al.*, 20110).

Statistical analysis: The results of all parameters were represented as mean±SE for all nine groups. Data was analyzed by two way analysis of variance under factorial complete random design (FCRD) by using a computer program of SPSS (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA) and M-Stat to test for any differences between the mean values of all groups. In case of significant difference among groups, days and groups × days interaction Duncan Multiple Range Test (DMRT) was applied. A $P \leq 0.01$ or $P \leq 0.05$ was considered to be significant.

RESULTS

Experimental data and results have been systematized and reviewed as follows: A preliminary phytochemical analysis was done for the screening of the pharmacologically active constituents in the flowers of *R. damascena* and roots of *C. intybus* (Table 1). Analysis of variance of serum urea, serum BUN, serum creatinine and serum albumin was significant at $P \leq 0.01$ for all days, groups and days × groups. In the present study serum urea and serum creatinine in gentamicin treated group significantly increased ($P \leq 0.01$) as compared to untreated and silymarin treated control groups showing kidney damage. The administration of silymarin significantly ($P \leq 0.01$) counteracted the effects of gentamicin, as

Table 1: Preliminary phytochemical analysis to identify pharmacologically active constituents in *R. damascena* flowers and *C. intybus* root

Pharmacologically active constituents	Plants	
	Rosa damascena	*Cichorium intybus*
Phenols	++	++
Flavoniods	++	++
Terpenoids	+	++
Saponins	++	-
Tannins	++	++
Glycosides	++	+
Alkaloids	+	++
Carbohydrates	++	++
Ascorbic Acid	+	++
Steroids	++	+

Strongly positive=++, Positive=+, Negative=-

Table 2: Effect of *R. damascena* flowers and *C. intybus* roots and their mixture on the average kidney weight and gross kidney examination in gentamicin induced toxicity in albino rabbits

Group	Urea (mg/dl)	BUN (mg/dl)	Creatinine (mg/dl)	Albumin (g/dl)	Kidney weight (g)
A	32±1.04	14.94±0.49	0.56±0.03	6.21±0.11	3.43±0.11
B	100.5±9.08	46.95±4.24	2.65±0.26	2.11±0.36	4.07±0.14
C	40±2.56	18.69±1.19	0.75±0.05	0.23±0.23	3.56±0.11
D	80±8.37	37.38±3.91	1.95±0.17	0.30±0.30	3.80±0.13
E	72.01±7.64	33.65±3.57	1.75±0.15	0.24±0.24	3.73±0.11
F	64±5.72	29.91±2.67	1.57±0.12	0.23±0.23	3.71±0.12
G	56±4.59	26.17±2.14	1.13±0.10	0.19±0.19	3.60±0.11
H	64±5.79	29.91±2.70	1.35±0.10	0.26±0.26	3.65±0.14
I	48±4.39	22.43±2.05	0.95±0.10	0.27±0.27	3.53±0.14

Table 3: Histopathological features as seen in the kidney in the gentamicin model

Histopathological Features	Groups								
	A	B	C	D	E	F	G	H	I
Glomerular congestion	_	+++	+	++	+	+	+	+	+
Peritubular congestion	_	+++	_	+	++	_	_	+	+
Epithelial desquamation	_	++	_	+	_	_	_	+	_
Blood vessel congestion	_	+++	_	_	_	_	+	_	_
Inflammatory cells	_	+++	_	++	++	+	_	+	_
Necrosis	_	+++	+	++	+	+	+	+	+
Connective tissue proliferation	_	+++	_	++	+	+	_	_	_
Peritubular dilation	_	++	_	++	+	+	+	++	_

*(-): normal; (+): little effect; (++): appreciable effect; (+++): severe effect

expected. At the dose rate of 250mg/kg the mixture of both plants responded relatively better to decrease the serum urea and creatinine levels as compared to individual one when compared with control group. At the dose rate of 500mg/kg *R. damascena* responded better as compared to *C. intybus* to decrease serum urea and creatinine levels. However, a highest decrease in serum urea and serum creatinine levels was observed by the mixture at dosage rate of 500mg/kg as compared to all other experimental groups against increased serum urea and serum creatinine due to gentamicin as shown in Table 2. Exactly the same results were observed for serum BUN as that of serum urea (Table 2).

In the present study serum albumin in gentamicin treated group significantly decreased as compared to untreated control, showing renal damage. The administration of silymarin significantly ($P \leq 0.01$) brought back the serum albumin level to the normal in comparison to GM treated group. At the dosage rate of 250mg/kg the mixture of both plants responded better to increase in serum level of albumin as compared to mixture at dosage rate of 500 mg/kg. On individual basis *C. intybus* responded better to increase in serum level of albumin as compared to *R. damascene* both at 250 mg/kg and 500 mg/kg. However, a highest decrease ($P \leq 0.01$) in serum level of albumin was observed by the mixture at dose rate of 500 mg/kg as compared to all other experimental groups (Table 2). The overall mean values for kidney weight showed that gentamicin leads to increase in kidney weight of rabbits as compared to untreated control. The overall mean values for silymarin treated group and all other experimental study groups did decrease in the kidney weight as compared to GM treated group (Table 2).

Histopathological examination: Histopathological examination of kidney tissues was done and the results were in consistence with the results of biochemical analysis. Establishment of acute and repeated dose gentamicin nephrotoxicity was also corroborated by the histological findings which showed glomeruli with loss of surrounding Bowman's capsule and varying degrees of tubular necrosis when compared to untreated control group (Fig. 1). The silymarin treated control group offered nephroprotection in comparison to gentamicin treated control group. Highest protection was offered by the aqueous extract of mixture (500mg/kg) in comparison to gentamicin treated group (Fig. 1).

DISCUSSION

Gentamicin-induced nephrotoxicity model is commonly used to analyze the in vivo nephroprotective activity of natural plants as reported by many researchers (Raju *et al*., 2011). The production of ROS is considered as the major mechanism of GM induced toxicity because it leads to denaturation of proteins and severe necrosis due to lipid peroxidation (Javed *et al.*, 2013). Various studies reported the GM-induced renal toxicity characterized by increased apoptosis which could be a reason of GM-induced tubular necrosis (Jovanovic *et al*., 2005).

Plants are good source of antioxidants and various studies have claimed antioxidant property of plants for their nephroprotective effects in gentamicin induced renal damage (Yaman and Balikci, 2010). The phytochemical analysis of *R. damascena* and *C. intybus* revealed the presence of terpenoids, glycosides, saponins, flavonoids, phenols, steroids and ascorbic acid which are given in Table 1. Flavonoids and phenols are considered to provide nephroprotection by their antioxidant potential (Marzouk *et al*., 2011).

The increased level of serum urea and creatinine could be good indicator of renal toxicity. In the present study, GM caused nephrotoxicity as it increased the serum level urea and creatinine as previously reported by Nitha and Janardhanan (2008). The increased level of serum creatinine and urea are due to accumulation of GM where it is actively transported into proximal tubules after glomerular filtration and results in proximal tubular injury and alters the renal circulation that leads to reduced GFR (Varzi *et al*., 2007).

The mechanism behind the decreased glomerular filtration rate (GFR) due to GM administration might be due to enhanced production of hydrogen peroxide (H_2O_2) which leads to contraction of mesangial cells, modifying the filtration surface area and ultimately reducing the GFR

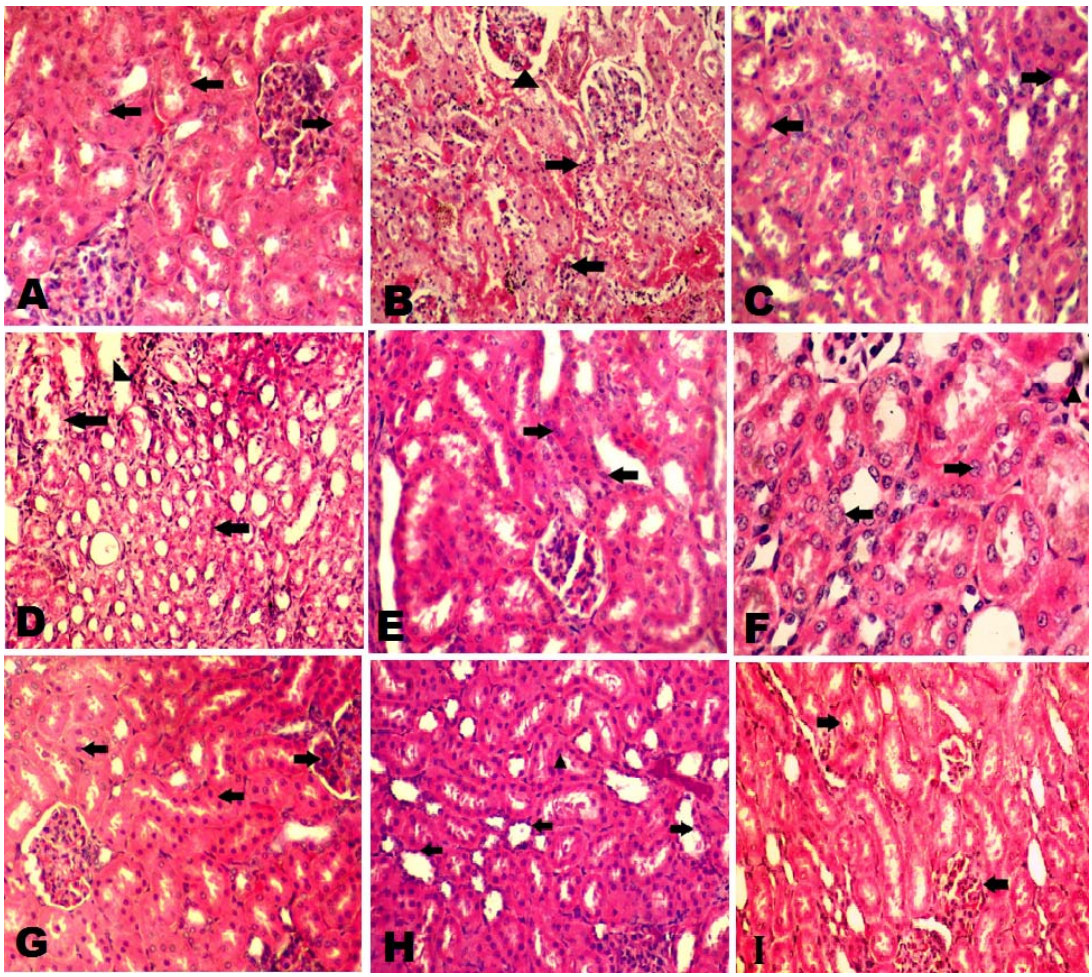

Fig. 1: Photomicrographs of kidneys (X-200, X-400; H & E). A: Group1 showing normal tubular epithelium; B: Group 2 with necrotic changes in tubular epithelial cells, nuclei are pyknotic and hyperchromatic (arrow), marked dilation of the capillaries (arrow head); C: Group 3 exhibiting mild coagulative necrosis; D: Group 4 showing mild necrosis, desquamation (arrow) and mononuclear cell infiltration (arrow head); E: Group 5 showing regeneration of tubular epithelial cells (arrow) and mild necrotic changes in the proximal convulated tubules; F: Group 6 showing the normal intact nucleus with prominent nuclei (arrow) along with mild necrosis; G: Group 7 showing mild necrotic changes (arrow) in glomerular and tubular region; H: Group 8 showing tubular dilation of lumen (arrow), mononuclear cell infiltration (arrow head) and regenerative changes (arrow head) and I: Group 9 exhibiting normal epithelial cells.

(Hussain *et al*., 2012). Another reason of reduced GFR might be due to the enhanced activity of platelet activation factor which leads to local vasoconstriction and thus restricts the renal blood flow due to GM (Al-Majed *et al*., 2002).

It could be concluded that the mechanism of GM toxicity might be due to production of ROS and generation of free radicals which causes oxidative stress and cause the induction of oxidative damage at the cellular level of the renal tubule (Safa *et al*., 2010). *Silybum marianum* (silymarin) have the potential to attenuate the effect of nephrotoxic drugs due to its anti-inflammatory, antioxidant and anti-apoptotic properties (Dashti-Khavidaki *et al*., 2012; Hashmi *et al*., 2013; Gad *et al*., 2014). In present study it decreased the levels of serum urea and creatinine in comparison with GM, similar finding as reported by Marzouk *et al*. (2011).

The lower levels of serum urea and creatinine due to aqueous extracts of *R. damascena* flowers, *Cichorium intybus* roots and their mixture was recorded in present study as compared to GM treated group (Table 2). This protective effect supported by proximal tubular histpathological examination which was in favor of results for Silymarin, *R. damascena* flowers, *Cichorium intybus* roots and their mixture (Fig.1; Table 3).

Albumin is the most abundant serum binding protein made by the liver and is essential for maintaining the osmotic pressure between intravascular compartments and body tissues. In case of renal toxicity the urinary protein excretion is increased and it deals with the integrity of the vascular system (Farrugia, 2010). GM induced decrease in albumin level are due to decreased production of albumin by the liver and excretion of albumin through the kidney (Safa *et al*., 2010; Jain and Singhai, 2010). The decrease of total protein content in GM treated group could be due to increased free radical production or because of defective protein synthesis and protein catabolism (Abdel-Raheem *et al*., 2010).

In present study, a lower level of albumin due to GM treated control group was observed as shown in Table 2. The increased level of serum albumin was noted for standard drug silymarin in comparison with GM reported by some other researchers (Marzouk *et al*., 2011). A significantly ($P \leq 0.01$) higher levels of albumin for both

plants and their mixture were in accordance with the results of Natarajan *et al*. (2006).

That increased kidney weight in GM treated group might be due to the accumulation of GM in kidney tubules (Erdem *et al*., 2000). Histopathological examination of GM revealed varying degrees of severe necrosis of kidney tubules, glomeruli with loss of surrounding Bowman's capsule, severe congestion of peritubules and glomeruli of kidney, severe peritubular infiltration and accumulation of fluid in renal tissues (Ahmed, 2009). In present study, on histopathological examination the kidneys of gentamicin treated rabbits displayed severe necrosis of the tubular epithelial cells in renal cortex, mitochondrial swelling and cytoplasmic degeneration (Fig. 1; Table 3). The anti-inflammatory and the antioxidant properties of plants prevent the GM induced histopathological degenerations. Therefore, similarly in current study, experimental groups showed marked histological protection and decreased kidney weight against GM induced toxicity.

Conclusion: Overall results of study suggests that aqueous extract of *R. damascena* flowers, *C. intybus* roots and their mixture possesses nephroprotective potential supported by significantly improved renal cortical histopathology in comparison to untreated and treated controls which might due to the inherent antioxidant and free radical scavenging principles contained in both plants. At dosage rate of 250mg/kg aqueous extract of *C. intybus* roots responded better in mitigating the biochemical changes induced by gentamicin while at the dosage rate of 500mg/kg aqueous extract of *R. damascena* flowers responded better. The nephroprotection was more evident in the mixture of both plants as compared to individual plant extracts in dose dependent manner.

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