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Research Article
Nephroprotective Effect of Camel Milk and *Spirulina platensis* in Gentamicin-Induced Nephrotoxicity in Rats

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Abstract

Background and Objective: The increasing number of patients with chronic kidney disease throughout the world has shifted global attention towards prevention of renal disease. Therefore, the aim of the present study was to investigate the nephroprotective effect of both camel milk and aqueous extract of *Spirulina platensis* against gentamicin-induced nephrotoxicity in rats. **Materials and Methods:** About 30 male wistar rats were randomly divided into 5 groups. One group served as normal control (NC), while the other four groups were injected intraperitoneally with 80 mg kg^{-1}/day gentamicin (GM). One of these 4 groups was kept as injury control (IC) and the remaining three groups received orally spirulina extract (SP), camel milk (CM) or combination of spirulina extract and camel milk (SPCM) for 28 days. **Results:** Administration of GM increased urea, creatinine and malondialdehyde (MDA) levels and decreased glutathione (GSH) levels. Histological examination of kidney sections showed extensive tubular necrosis due to administration of GM. Administration of CM, SP and their combination (SPCM) resulted in a significant improvement ($p<0.05$) in kidney ratio and oxidative stress markers (MDA, GSH). These positive effects were more pronounced when rats were given a combination of camel milk and spirulina (SPCM). In addition, SPCM showed a normal histological appearance better than that of SP or CM alone. **Conclusion:** Induced nephrotoxicity in rats can be ameliorated by camel milk and spirulina.

Key words: Spirulina, camel milk, gentamicin, nephroprotective, oxidative stress

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Chronic kidney disease (CKD) is a health problem that is growing significantly due to its association with a substantial burden of illness and mortality throughout the world. Globally, it is estimated that over 2 million patients receiving treatments for CKD[1]. The incidence of CKD in the Arab world is higher than that of elsewhere. For example the prevalence of CKD is 483 and 463 patient per million population in Egypt and Saudi Arabia, respectively[2,3]. There is a global attention towards prevention and management of CKD. In this respect, diet manipulations as well as lifestyle modifications can be effective for protection from CKD[4].

Camel milk (CM) has been used for centuries by people who live in the desert. It is known for its medicinal characteristics in folk systems of medicine in various countries like Saudi Arabia and Egypt[5]. Compared to the milk of other ruminants, CM contains low levels of lactose and cholesterol but contains higher quantity of protective proteins such as immunoglobulins, lysozyme and lactoferrin[6]. There are several reports about health benefits of CM. It is believed that CM can be used against gastrointestinal disorders, diabetes, food allergy, hepatitis C and cancer[7-9]. In addition to the reported positive effects of CM such as protection from toxicity of lead and cadmium[5], it also improves liver and kidney functions[10].

Due to their minimal side effects and low cost, different herbal plants are used for management and treatment of various health issues[11]. Spirulina (SP) is blue-green algae that have been used as food supplements for both human and animals. It contains high amount of different nutrients such as protein that contains all essential amino acids, essential fatty acids, vitamins and minerals[12]. Several *in vitro* and *in vivo* studies have shown biological activities and health benefits of SP such as antioxidant potential[13], anti-inflammatory[14], immunostimulatory[15] and anticancer[16].

The present study was designed to explore the protective effect of both CM and aqueous extracts of SP (*Spirulina platensis*) against nephrotoxicity induced by gentamicin in rats. The effect of oral administration of CM and SP on renal functions, oxidative stress markers as well as histopathological examination of kidneys of rats was investigated.

MATERIALS AND METHODS

Materials

Experimental material: Spirulina (*Spirulina platensis*) biomass was obtained from The Algae Biotechnology Unit, National research center, Cairo, Egypt. Camel milk samples were obtained from healthy lactating animals at the Agricultural Research Station, Qassim University, Buraidah, Saudi Arabia.

Chemicals: Pure reagents were purchased from Sigma (Sigma-Aldrich, St. Louis, MO, USA) and Roche Diagnostics (Roche Professional Diagnostics, Rotkreuz, Switzerland Commercial kits used for determining urea and creatinine were purchased from Bio-Merieux Laboratory Reagents and Products, France and kits from Nubenco Enterprises INC. Paramus, New Jersey, USA.

Experimental animals: About 30 male wistar rats (140±10 g body weight) were obtained from the experimental animal unit, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. Animals were housed in control housing unit (Department of Food Science and Human Nutrition, College of Agriculture and Veterinary Medicine, Qassim University, Saudi Arabia) and were kept under standard conditions of temperature and humidity (temperature at 25°C, 55% humidity and in a 12:12 h light:dark cycle) in an experimental animal house. The animals were fed on basal diet according to AIN-93 guidelines[17] and were provided with water *ad libitum* during the experimental period. This experiment has been conducted during November, 2015 to May, 2016.

Preparation of aqueous extract of spirulina: Aqueous extract of Spirulina (*Spirulina platensis*) biomass were prepared according to the method described by Abdel-Salam *et al*.[5,18,19]. Briefly, *Spirulina platensis* materials (6% total dry matter) were pulverized and then extracted with 1000 mL hot distilled water in an electric blender for 15 min. The suspension was left at room temperature for 1 h, then filtered through cheesecloth (50% cotton/50% polyester) and then filtered through Whatman No.2 filter paper. The clear aqueous extract was preserved in sterile dark bottles (100 mL) at -20°C until further used.

Methods of analysis

Biological experiment procedure: Rats were randomly divided into 5 groups with 6 rats in each group. Group I served as normal control (NC). The animals in the other 4 groups were administrated intraperitoneally (IP) with gentamicin (Parkin Remedies, India) 80 mg kg^{-1}/day. Group II was kept as injury control (IC), group III received orally aqueous extract of *spirulina platensis* (SP), group IV received orally camel milk (CM) and group V received orally a combination of *spirulina*

platensis aqueous extract and camel milk (SPCM) for 28 days. The changes in body weight were recorded weekly. At the end of the experimental period, blood samples were taken from the retro-orbital plexus of the eyes from all animals of each group in heparinized tubes .The animals were anesthetized with ether and rapidly decapitated. The kidneys were collected immediately after dissection and weighted. Plasma was obtained from blood samples by centrifugation at 1500 rpm/15 min at an ambient temperature for analysis. Animal procedures were performed in accordance with the ethics committee of Qassim University and according to the guide for the care and use of Laboratory Animals of the National Institute of Health.

Biochemical investigation

Evaluation of kidney function: Enzymatic colorimetric determination of urea was carried out according to the method of Searcy *el al.*,[20]. Kinetic determination of creatinine was carried out according to the method of Henry[21].

Determination of oxidative stress marker: Lipid peroxidation was determined by measuring the thiobarbituric acid reactive substances (TBARS) and the last product in lipid peroxidation pathway (malondialdehyde, MDA) was measured in plasma at 534 nm according to Ohkawa *et al.*,[22]. The reduced glutathione (GSH) in plasma was estimated by its reaction with dithio-bis-2-nitrobenzoic acid (DTNB) according to the method described by Beutler *et al.*,[23].

Histopathological investigation: Autopsy samples were taken from the kidneys of the sacrificed rats of the different groups and fixed in 10% formal saline solution. Washing was done in tap water then serial dilutions of ethyl alcohol were used for dehydration. Specimens were cleared in xylene and embedded in paraffin at 56°C in hot air oven for 24 h. Paraffin wax tissue blocks were sectioned at 4 µm thickness by sledge microtome. The sections were collected on the glass slides, deparaffinized and stained with hematoxylin and eosin stain for routine examination by the light electric microscope[24].

Statistical analysis: Descriptive values of data were represented as means±standard errors. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test with $p \leq 0.05$ being considered statistically significant Steel *et al.*[25]. Statistical analysis was conducted with SAS program[26].

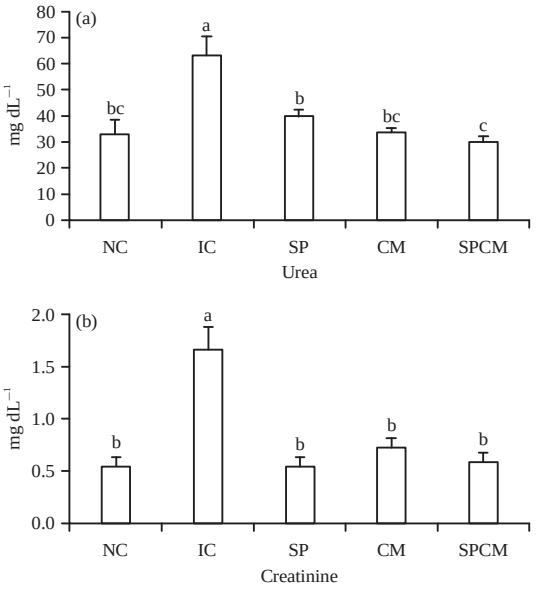

Fig. 1: Effect of camel milk (CM), aqueous extract of *Spirulina platensis* (SP) and their mixture (SPCM) on kidneys' functions in normal and gentamicin-treated rats

Table 1: Effect of camel milk, aqueous extract of *Spirulina platensis* and their mixture on body weight gain and relative kidneys weight in normal and gentamicin-treated rats

Groups	Initial BW (g)	Final BW (g)	Kidneys ratio (g/100 g)
NC	340±60^{a}	405±39^{a}	0.59±0.06^{b}
IC	334±32^{a}	404±40^{a}	0.90±0.08^{a}
SP	342±52^{a}	405±65^{a}	0.67±0.10^{b}
CM	336±38^{a}	435±79^{a}	0.63±0.11^{b}
SPCM	337±41^{a}	431±44^{a}	0.58±0.07^{b}

Means having different superscripts in the same row are significantly different ($p \leq 0.05$), NC: Normal control, IC: Injury control, SP: *Spirulina platensis* group, CM: Camel milk group, SPCM: Combination of camel milk and *Spirulina platensis* group

RESULTS

Body weight gain and relative kidney weight in rats: As shown in Table 1, there was no significant differences in initial and final body weights of all groups ($p>0.05$). However, there was a significant difference in kidneys ratio to the body weight between groups ($p<0.05$). Treated rats with gentamicin (IC group) resulted in an increase in the kidney ratio (increased 52.5% vs NC, $p<0.05$). Oral administration of spirulina extract (SP), camel milk (CM) or their combination (SPCM) lowered kidneys ratio effectively ($p<0.05$) by 25.6, 30 and 35.6%, respectively, when compared with IC group.

Kidney functions and oxidative stress markers: Results of kidney functions are presented in Fig. 1. It is obvious that

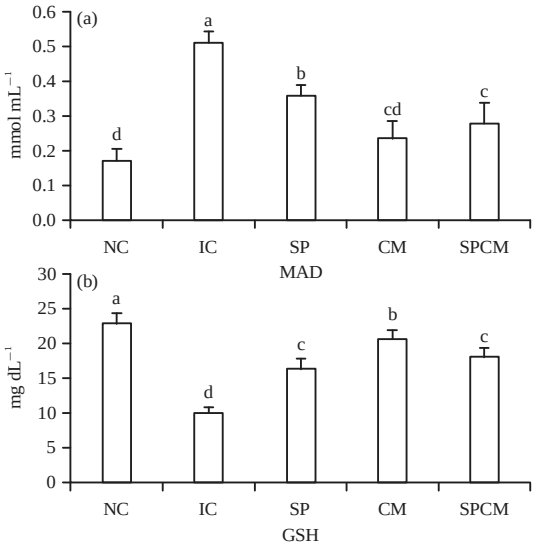

Fig. 2: Effect of camel milk (CM), aqueous extract of *Spirulina platensis* (SP) and their mixture (SPCM) on oxidative stress parameters in normal and gentamicin-treated rats

injection of gentamicin significantly elevated blood levels of urea and creatinine in rats (IC group), when compared with NC group. However, oral administration of SP, CM or their combination improved blood levels of urea and creatinine. The obtained levels were similar to the levels in NC group ($p>0.05$). It worth mentioning that, the reduction on blood urea levels was more pronounced in rats given a combination of camel milk and spirulina (SPCM vs SP, $p<0.05$).

Levels of glutathione (GSH) and malondialdehyde (MDA) as oxidative stress markers are illustrated in Fig. 2. It can be seen that injection of gentamicin (IC group) was associated with a significant increase in the levels of MDA and reduction in levels of GSH that indicates a high oxidative stress. Giving rats spirulina improved MDA levels, but still higher than that of the NC group ($p<0.05$). It is obvious that effect of camel milk on MDA was more pronounced than that of spirulina alone (SP vs CM, $p<0.05$). However, effect of spirulina on MDA was increased when combined with camel milk (SPCM vs SP, $p<0.05$). On the other hand, blood levels of GSH were increased when rats were given CM, SP or their combination ($p<0.05$). Although, all treatments significantly increased levels of GSH, this improvement was not high enough to reach levels state in normal rats.

Histopathological examination: Kidney injury was evaluated by histopathological approach in Fig. 3 and Table 2. The normal control group (NC) showed a normal histological structure of the glomeruli and tubules at the cortex and tubules at the corticomedullary as well as the medullary portions. The kidney sections obtained from animals treated with gentamicin (IC) showed focal inflammatory cells aggregation in between the degenerated tubules and glomeruli at the cortex associated with congestion in the blood vessels.

The kidney sections obtained from animals treated with gentamicin+aqueous extract of *spirulina platensis* (SP) showed congestion in the cortical blood vessels. The kidney sections obtained from animals treated with gentamicin+camel milk (CM) showed coagulative necrosis in some individual tubules at the cortex. No histopathological alterations were noticed in the kidney sections obtained from animals treated with gentamicin+mixture of aqueous extract of *spirulina platensis* and camel milk (SPCM).

The histopathological changes (Table 2) in pretreated groups with aqueous extract of *spirulina platensis*, camel milk and their combination as compared to that induced with gentamicin alone (IC) indicated marked protective effects of these substances.

DISCUSSION

The aim of the present study was to evaluate nephroprotective effect of combination (SPCM) of both camel milk and *Spirulina platensis*. Results showed that SPCM lowered kidneys ratio effectively (by 35.6% compared with injury control group, $p<0.05$). In addition, SPCM reduced blood urea levels and malondialdehyde more pronounced than camel milk or spirulina alone. All biochemical results was associated with the histopathological examination in which no histopathological alterations were noticed in the kidney sections obtained from animals of SPCM group (Table 2, Fig. 3). There are many published reports about the physiologically active ingredients in foods from both plants and animal origins that could reduce risk of chronic disease[27]. To the best of our knowledge, it is the 1st report to evaluate the effect of combination of CM and SP on gentamicin-induced nephrotoxicity in rats.

In the present study, injection of gentamicin (GM) was associated with a significant kidney dysfunction as manifested by elevation of urea and creatinine in serum of rats (Fig. 1) as well as histopathological changes in the kidney (Fig. 3 and Table 2). This effect of GM on kidney function was associated with elevation in lipid peroxidation and oxidative stress (Fig. 2). However, GM is known to cause nephrotoxicity due to its accumulation in the renal proximal convoluted tubules[28]. In the present study, CM, SP and their combination showed a marked nephroprotective effect against gentamicin-induced

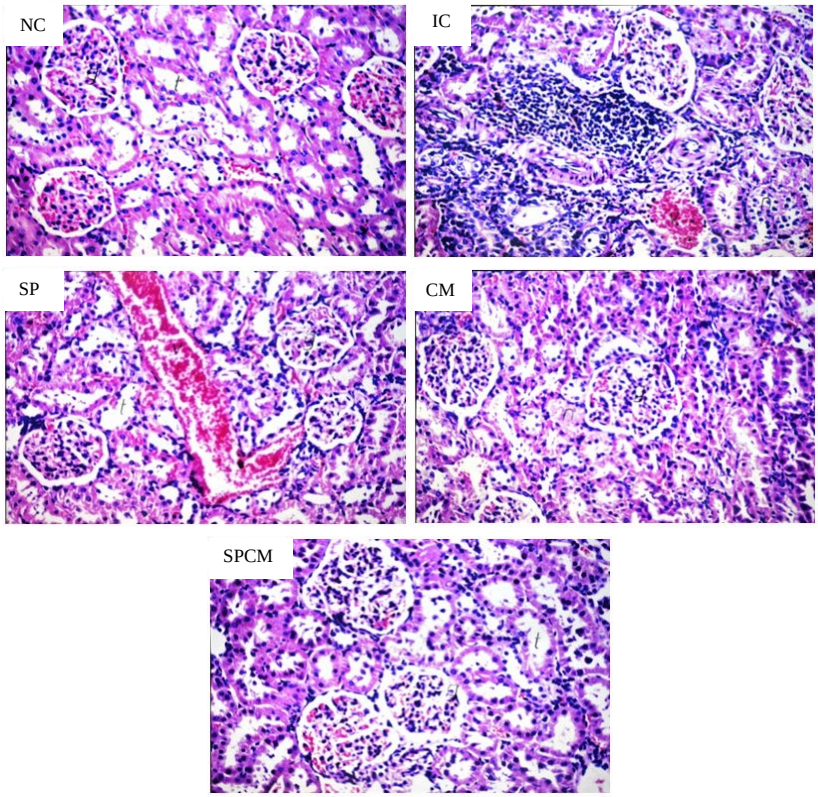

Fig. 3: Effect of camel milk (CM), aqueous extract of *Spirulina platensis* (SP) and their mixture (SPCM) on the histopathology of kidneys from normal and gentamicin-treated rats

Table 2: Effect of camel milk, aqueous extract of *spirulina platensis* and their mixture on gentamicin induced histopathological changes in rat kidney

	Treatments				
Histopathological alteration	Normal control (NC)	Gentamicin Injury control (IC)	Gentamicin+SP	Gentamicin+CM	Gentamicin+SPCM
Focal acute interstitial nephritis	-	+++	-	-	-
Nephrosis in tubules	-	++	-	-	-
Congestion on blood vessels	-	++	+	-	-
Tubular necrosis	-	-	-	+	-

-: Nil, +: Mild, ++: Moderate, +++: Severe effect, SP: *Spirulina platensis* group, CM: Camel milk group, SPCM: Combination of camel milk and *Spirulina platensis* group

nephrotoxicity in rats. This nephroprotective effect was more pronounced when rats were given a combination of CM and SP.

Malondialdehyde (MDA) is a stable lipid hydroperoxide that is used as a marker of lipid peroxidation[29,30]. Lower lipid peroxidation and lower MDA levels is protecting kidney cells from injury by GM. In the present study, both SP and CM reduced lipid peroxidation as shown by a reduction in the serum levels of MDA. This lipid peroxidation lowering effect might be due to the natural antioxidant content and free radical scavenging properties of both SP and CM. Several reports confirmed the potent antioxidant activity of SP[13,31]. Recently, fermented camel milk showed a high scavenging activity[5]. Camel milk lactoferrin was shown to have a high antioxidant activity[32].

Glutathione (GSH) is a tripeptide and an important non-enzymatic antioxidant that is essential for integrity of cells against oxidative stress. Nephrotoxicity induced by GM is associated with depletion of serum levels of GSH due to elevation of lipid peroxides and oxidative stress[28]. In the present investigation, both SP, CM and their combination significantly reduced MDA and increased GSH levels (Fig. 2)

when compared with the injury control group ($p<0.05$). The lowering effect of CM on lipid peroxides was more pronounced than that of SP as the lowest MDA levels were observed in both CM and SPCM groups. The levels of MDA were lowered by 29.4, 45.1, 52.9% in SP, CM and SPCM groups, respectively, compared with IC group (Fig. 2). Similarly, the improvement in GSH levels in rats were much higher in groups containing CM than SP group. These findings indicates a higher ability of camel milk to restore the level of endogenous antioxidants in the kidney to almost normal levels when compared with spirulina. This effect of camel milk might be due to its higher antioxidant properties. Recently, fermented camel milk showed a significant higher scavenging activity (84.03%) than that shown by spirulina (71.09%) and this activity was increased by addition of water extracts of spirulina to camel milk (98.32%)[5]. In addition, previous studies have reported that spirulina alone increased GSH levels and reduced MDA levels[33]. Therefore, reduction of negative effects of gentamicin-induced nephrotoxicity by administration of SP probably by inhibiting a free radical mediated process[33].

The obtained biochemical results correlated well with the histological examination of kidney of rats (Fig. 3). All treatments improved the extensive and marked tubular necrosis due to nephrotoxicity induced by GM. It can be observed from the histological examination that combination of camel milk and spirulina showed a normal histological appearance than that of each of them alone. Therefore, no histopathological alteration was noticed in the kidney sections of SPCM group.

CONCLUSION

Oral administration of camel milk, spirulina and their mixture significantly improved kidney ratio, kidney function and oxidative stress complications in rats. In addition, histopathological examinations of the kidney confirmed protective ability of these treatments. These positive effects were more pronounced when rats were given a combination of camel milk and spirulina than each of them alone. In summary, a combination of camel milk and spirulina (*Spirulina platensis*) could be used for protection from kidney damage.

SIGNIFICANCE STATEMENT

This study discovers the synergistic effect of camel milk (CM) and aqueous extracts of spirulina (SP) combination that can attenuate nephrotoxicity induced in rats by gentamicin. The combination of CM and SP restore function of kidneys throughout lowering of parameters of oxidative stress (reduced glutathione and malondialdehyde). This study will help research to formulate a new functional food that could be produced to protect from kidney damage.

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