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Nephroprotective effect of Curcumin (*Curcuma Longa*) in acute nephrotoxicity in Sprague-Dawley rats

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Objective The objective of this study was to evaluate the nephroprotective effect of curcumin in gentamicin induced-nephrotoxicity.
Methods Thirty male Sprague-Dawley rats were used which was divided into three groups, Group 1 (n = 10): Rats treated with distilled water plus normal saline for 12 days. Group 2 (n = 10): Rats treated with distilled water plus gentamicin for 12 days. Group 3 (n = 10): Rats treated with curcumin plus gentamicin for 12 days. Blood urea, serum creatinine, malondialdehyde (MDA), kidney injury molecule (KIM-1) and cystatin-C were measured in both control and experimental groups.
Results Rats treated with gentamicin showed nephrotoxicity as evidence by significant elevation in serum creatinine, blood urea, KIM-1, MDA, cystatin-C sera levels.
Conclusion Curcumin produced significant nephroprotective effect in gentamicin induced-nephrotoxicity through modulation of oxidative stress and inflammatory biomarkers.
Keywords nephrotoxicity, gentamicin, curcumin

Introduction

Gentamicin is an antibiotic of aminoglycoside group, used for treatment of different bacterial infections, 90% of administrated gentamicin is excreted unchanged in the proximal renal tubules leading to extensive necrosis at a higher dose.[1,2]

Overproduction of reactive oxygen species and free radicals are the main mechanism for gentamicin induced nephrotoxicity. Certainly, gentamicin induces the expression of transporter proteins at proximal renal tubules causing free radical generations.[3] Therefore, gentamicin induced-nephrotoxicity is a multifaceted phenomenon which formerly linked to the oxidative stress only.

Chronic and/or high dose of gentamicin initiates *in vitro* and *in vivo* free radical productions and induction of oxidative stress. Gentamicin triggers mitochondrial superoxide anions cause generation of hydroxyl radicals.[4]

Therefore, antioxidant agents demonstrate a renoprotective outcome on gentamicin induced nephrotoxicity. One of these plants called curcumin which is member of the ginger family. Curcumin is the main curcuminoids present in the turmeric which contains 77% curcumin. Curcumin inhibits peroxidation by scavenging of free radicals.[5]

Curcumin's effect on free radicals is happened by different mechanism, it scavenges various types of free radicals such as reactive oxygen species (ROS), reactive nitrogen species, and also it inhibits ROS generating enzymes including cyclooxygenase, lipoxygenase and xanthine hydrogenase/oxidase.[6]

Therefore, objective of this study was to evaluate the nephroprotective effect of curcumin in gentamicin induced-nephrotoxicity.

Materials and Methods

A total number of 30 Sprague-Dawley male rats were used, rats age ranged from 3 to 4 months and their body weight ranged from 200 to 400 g. The animals were placed at appropriate temperature (22–25°C) with 12/12 light–dark cycle. The rats were randomly divided into three groups, 10 rats in each group. Group 1 (n = 10): Rats treated with distilled water (5 ml/kg, p.o.) for 12 days, on days 6–12 they received an intraperitoneal (i.p.) injection of normal saline (5 ml/kg) daily. Group 2 (n = 10): Rats treated with distilled water (5 ml/kg, p.o.) for 12 days and on days 6–12 they received gentamicin 100 mg/kg, i.p. Group 3 (n = 10): Rats treated with curcumin (100 mg/kg, p.o.) for 12 days and on days 6–12 they gentamicin 100 mg/kg, i.p. at an interval of 1 h. On 12th day rats were decapitated under light anesthesia and blood samples were obtained and serum was taken by centrifugation at 3500 rpm/15 min. The method was according to Singh et al.,[7] method.

Assessment of Renal Injury Biomarkers

Blood urea and serum creatinine were assessed by auto-analyzer. Biomarkers of renal injury including serum of malondialdehyde (MDA), kidney injury molecules (KIM-1) and cystatin-C were measured by ELISA kit methods according to the instruction of the manufacture.

Statistical Analysis

Data of this study was presented as mean ± SD and the variables were tested by using unpaired student t-test between control and treated groups. The P-value was regarded as significant when it is <0.05.

Results

Blood urea was increased significantly in gentamicin group up to (56.87 ± 9.33 mg/dl) compared with the control group (41.83 ± 7.46 mg/dl) (P = 0.007), while; serum creatinine in gentamicin group increased significantly (1.08 ± 0.40 mg/dl) compared with control group (0.70 ± 0.14 mg/dl) (P = 0.04). Regarding the oxidative stress and endogenous anti-oxidant capacity, there were insignificant increase in the MDA serum levels in gentamicin group (408.11 ± 145.8 ng/ml) compared with the control group (289.85 ± 44.18 ng/ml) (P = 0.08).

Moreover, KIM-1 was significantly raised in gentamicin group (354.98 ± 46.38 pg/ml) compared with the control group (73.78 ± 16.29) ($P = 0.0001$).

Definitely, cystatin-C serum level was significantly increased during induction of nephrotoxicity by gentamicin from 0.024 ± 0.0005 ng/ml in the control group to 0.0280 ± 0.0016 ng/ml in the experimental group ($P = 0.01$) (Table 1).

Curcumin leads to significant reduction of blood urea, serum creatinine compared with gentamicin group ($P < 0.05$). Curcumin also reduced MDA, KIM-1 and cystatin-C sera levels significantly compared with gentamicin group ($P < 0.01$) (Table 2).

Discussion

Gentamicin is a bactericidal antibiotic characterized by chemical stability and rapid antibacterial activity, that is extensively used alone or in combination with β-lactam antibiotics for different and serious bacterial infections. In spite of these possessions gentamicin therapy leads to nephrotoxicity in approximately 30% of treated cases even after precise monitoring.[8]

This study definitely illustrated that gentamicin was talented to induced experimental nephrotoxicity in rats though significant elevation in blood urea and serum creatinine which correspond with a recent study.[9]

It has been well known that the production of free radicals and induction of oxidative stress are the main important pathway of gentamicin induced-nephrotoxicity. Overproduction of reactive oxygen species is linked with exhaustion of proximal renal tubules anti-oxidant potential which next developed into lipid peroxidation and tubular damages.[10]

Table 1. **Renal function and renal biomarkers in gentamicin induced-nephrotoxicity**

Variables	Control ($n = 10$)	Gentamicin ($n = 10$)	*P*
Blood urea (mg/dl)	41.83 ± 7.46	56.87 ± 9.33	0.007**
Serum creatinine (mg/dl)	0.70 ± 0.14	1.08 ± 0.40	0.04*
MDA (ng/ml)	289.85 ± 44.18	408.11 ± 145.8	0.08
KIM-1 (pg/ml)	73.78 ± 16.29	354.98 ± 46.38	0.0001**
Cystatin-c (ng/ml)	0.024 ± 0.0005	0.028 ± 0.001	0.0001**

*$P < 0.05$. **$P < 0.01$, unpaired *t*-test. MDA: malondialdehyde, KIM-1: kidney injury molecule-1, Cys-C: cystatin-C.

Table 2. **Effect of curcumin on the biochemical and renal injury biomarkers in gentamicin induced-nephrotoxicity**

Variables	Gentamicin ($n = 10$)	Curcumin ($n = 10$)	*P*
Blood urea (mg/dl)	56.87 ± 9.33	46.25 ± 8.47	0.01*
Serum creatinine (mg/dl)	1.08 ± 0.40	0.77 ± 0.18	0.03*
MDA (ng/ml)	408.11 ± 145.8	208.11 ± 88.8	0.001**
KIM-1 (pg/ml)	354.98 ± 46.38	131.79 ± 31.22	0.0001**
Cystatin-C (ng/ml)	0.028 ± 0.001	0.024 ± 0.0004	0.0001**

*$P < 0.05$. **$P < 0.01$, unpaired *t*-test. MDA: malondialdehyde, KIM-1: kidney injury molecule-1, Cys-C: cystatin-C.

Therefore, serum level of MDA is elevated in different models of gentamicin induced-nephrotoxicity as illustrated by Hajihashemi et al.,[11] study that confirmed the protective effect of hydroalcoholic extract of *Zataria Multiflora* in reduction of MDA with significant effect in rising of anti-oxidant enzyme activities.

This study also illustrated significant effect of gentamicin in increase KIM-1 levels as correspond with Luo et al., study that showed both KIM-1 and NGAL sera level are sensitive and specific biomarkers during gentamicin induced-nephrotoxicity. The rise in those biomarkers is time and dose dependent due to gene expression of KIM-1 and NGAL.[12]

Notably, inequality or imbalance in the generation of free radicals and the deficiency to detoxify these free radicals by anti-oxidants lead to induction of oxidative stress. Curcumin has a higher anti-oxidant potential against free radicals due to phenolic and flavonoid compounds.[13]

Moreover, Trujillo et al.,[14] study confirmed that curcumin has significant nephroprotective effect due to anti-oxidant and/or preservation of endogenous anti-oxidant capacity, anti-inflammatory, and free radical scavenging effects as well as preservation of renal mitochondrial redox balance during acute and chronic nephrotoxicity. In recent times, Mercantepe et al.,[15] illustrated significant nephroprotective effect of curcumin in attenuation of cisplatin induced-nephrotoxicity and acute kidney injury through modulation of reactive oxygen species and augmentation of endogenous anti-oxidant potentials.

Furthermore, curcumin significantly reduced renal tubular injury biomarkers due to significant nephroprotective effect and attenuation of gentamicin induced-nephrotoxicity as supported by Kim et al.,[16] study that demonstrated administration of 25 mg/kg/day of curcumin is able to reduce levels of KIM-1 and NGAL sera levels significantly in cadmium induced-nephrotoxicity due to the protective effect of curcumin on the renal tubules. As well Wu et al.,[17] showed important effect of curcumin in reduction of inflammatory and renal tubular damage biomarkers during glycerol induced acute nephrotoxicity.

Interestingly, this study proved the protective effect of curcumin on the glomerular function via reduction of cystatin-C serum levels when co-administrated with gentamicin. Curcumin significantly reduce cystatin-C serum levels in both acute and chronic renal injury due to significant nephroprotective effect of curcumin through modulation of glomerular blood flow and regulation of intra-glomerular pressure and inflammations.[18,19]

Conclusion

Curcumin produced significant nephroprotective effect in gentamicin induced-nephrotoxicity through modulation of oxidative stress and inflammatory biomarkers.

Funding and Sponsorship

None.

Conflict of Interest

None.

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