

ANTIOXIDANT AND ANTI-INFLAMMATORY EFFECTS OF CURCUMIN CONTRIBUTE INTO ATTENUATION OF ACUTE GENTAMICIN-INDUCED NEPHROTOXICITY IN RATS

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ABSTRACT

Objectives: Nephrotoxicity is a renal-specific situation in which the excretion of toxic metabolites is reduced due to toxic agents and drugs. Gentamicin is an antibiotic belongs to aminoglycoside group which may induce nephrotoxicity due to induction of oxidative stress. Curcumin is a component of traditional medicine with significant nephroprotective effect. Therefore, the objective of the present study was to evaluate the nephroprotective effect of curcumin on gentamicin-induced nephrotoxicity.

Methods: A total of 30 male Sprague-Dawley rats were used which divided into Group 1 (n=10): Rats treated with distilled water 5 ml/kg plus normal saline 5 ml/kg for 12 days, Group 2 (n=10): Rats treated with distilled water 5 ml/kg plus gentamicin 100 mg/kg for 12 days, and Group 3 (n=10): Rats treated with curcumin 100 mg/kg plus gentamicin 100 mg/kg 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 evident by significant elevation in blood urea, serum creatinine, KIM-1, MDA, and cystatin-C sera levels. Curcumin leads to significant reduction of blood urea and serum creatinine compared to gentamicin group, $p < 0.05$. Curcumin also reduced MDA, KIM-1, and cystatin-C sera levels significantly compared to gentamicin group, $p < 0.01$.

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

Keywords: Nephrotoxicity, Gentamicin, Curcumin.

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INTRODUCTION

Nephrotoxicity is a renal-specific condition in which the flow of toxic metabolites does not go resourcefully due to toxic agents and drugs. Approximately 20% of nephrotoxicity is caused by drugs; this fraction is augmented in the elderly due to the rise in the life span [1].

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

Excessive production of reactive oxygen species and free radicals is the chief mechanism for gentamicin-induced nephrotoxicity. Definitely, 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 previously linked to the oxidative stress only.

Chronic and high dose of gentamicin provokes *in vitro* and *in vivo* free radical productions and induction of oxidative stress. Gentamicin triggers mitochondrial superoxide anions causing generation of hydroxyl radicals [1].

Moreover, antioxidant agents demonstrate a renoprotective effect in gentamicin-induced nephrotoxicity. One of these plants called curcumin which is a member of the ginger family. Curcumin is the main curcuminoids present in the turmeric which contains virtually 77% curcumin [4].

Curcumin's effect on free radicals is happened by different mechanism; it scavenges free radicals such as reactive oxygen species and reactive

nitrogen species. As well, curcumin inhibits reactive oxygen species-generating enzymes including lipoxygenase, cyclooxygenase, and xanthine oxidase [5].

Therefore, the aim of the present study was to assess the nephroprotective effect of curcumin on gentamicin-induced nephrotoxicity.

METHODS

A total number of 30 Sprague-Dawley male rats were used, rats age ranges from 3 to 4 months and their body weight ranges from 200 to 400 g. The animals were placed at appropriate temperature of 22–25°C with 12/12hrs, light-dark cycle. This study was permitted by specific Scientific Adjudicators and Ethical Committee in the Medical Board College of Medicine, Al-Mustansiriya, Baghdad, Iraq. Humane care for animals was according to the guide to the care and the use of laboratory animal. The rats were randomly divided into three groups: Group 1 (n=10): Rats treated with distilled water (5 ml/kg, p.o) for 12 days, on day 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 day from 6 to 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 day 6–12, they received gentamicin 100 mg/kg, i.p at an interval of 1 h. On the 13th day, rats were decapitated under light anesthesia and blood samples were centrifuged at 3500 rpm/15 min. The method was according to Singh *et al.* method [6].

All drugs were purchased from private pharmacy gentamicin ampoule (Garamycin 80 mg Schering-Plough, USA) and curcumin tablet (*Curcuma longa* 500 mg tablet 95% curcuminoids, rhizome, VEGGIE CAPS., 04216CUR120, Los Angeles, USA).

Table 1: Renal function and renal injury 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

Data are expressed as mean±SD *p<0.05; p<0.01, unpaired t-test, MDA: Malondialdehyde; KIM-1: Kidney injury molecule-1, Cys-C: Cystatin

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

Data are expressed as mean±SD *p<0.05; p<0.01, unpaired t-test, MDA: Malondialdehyde, KIM-1: Kidney injury molecule-1; Cys-C: Cystatin

Assessment of renal injury biomarkers

Blood urea and serum creatinine were assessed by autoanalyzer. 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 manufacturer.

Statistics

Data of the present study were presented as mean ±SD. Unpaired Student's t-test was used to detect the level of significance between control and treated groups. p value was regarded as statistically significant when it is <0.05.

RESULTS

Blood urea was raised significantly in gentamicin group (56.87±9.33mg/dl) compared to the control (41.83±7.46mg/dl) p=0.007, as well, serum creatinine was increased significantly in gentamicin group (1.08±0.40 mg/dl) compared to control (0.70±0.14 mg/dl), p=0.04.

Regarding the oxidative stress and endogenous antioxidant capacity, there was insignificant increase in the MDA serum levels in gentamicin group (408.11±145.8 ng/ml) compared to the control (289.85±44.18 ng/ml), p=0.08. Moreover, KIM-1 was significantly increased in gentamicin group (354.98±46.38 pg/ml) compared to the control (73.78±16.29), p=0.0001. Certainly, 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 0.028±0.0016 ng/ml in the experimental group, p=0.01 (Table 1).

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

DISCUSSION

Gentamicin is a bactericidal antibiotic used alone or in combination with β-lactam antibiotics for the treatment of different bacterial infections. In spite of these possessions, gentamicin therapy leads to nephrotoxicity in about 30% of treated cases even after precise monitoring [7].

The present study definitely illustrated that gentamicin was proficient to induced experimental nephrotoxicity in rats through significant elevation in blood urea and serum creatinine which correspond with a recent study [8].

It has been established 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 depletion of proximal renal tubules antioxidant potential which subsequently leads to lipid peroxidation and tubular damages [9].

Therefore, serum level of MDA was elevated in different models of gentamicin-induced nephrotoxicity as illustrated by Hajihashemi *et al.* study [10].

The present study as well illustrated significant consequence of gentamicin in rising KIM-1 levels as inconsistency with Luo *et al.* study that demonstrated both KIM-1 and NGAL sera levels are sensitive and specific biomarkers in gentamicin-induced nephrotoxicity. The augmentation in those biomarkers is due to progressive gene expression of KIM-1 and NGAL [11].

Remarkably, the imbalance in the production of free radicals and the shortage to detoxify these free radicals by antioxidants lead to induction of oxidative stress. Curcumin has a higher antioxidant potential against free radicals due to phenolic and flavonoid compounds [12].

Furthermore, Trujillo *et al.* study confirmed that curcumin has a significant nephroprotective effect due to antioxidant and/or preservation of endogenous antioxidant capacity, anti-inflammatory, free radical scavenging effects, as well as preservation of renal mitochondrial redox balance during acute and chronic nephrotoxicity [13].

Recently, Mercantepe *et al.* 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 antioxidant potentials [14].

Besides, curcumin significantly reduces renal tubular injury biomarkers due to significant nephroprotective effect in gentamicin-induced nephrotoxicity as supported by Kim *et al.* study that demonstrated administration of 100 mg/kg/day of curcumin was able to reduced KIM-1 and NGAL sera levels significantly in cadmium-induced nephrotoxicity [15]. As well, Wu *et al.* showed important effect of curcumin in reduction of inflammatory and renal tubular injury biomarkers during glycerol-induced acute nephrotoxicity [16].

Interestingly, the present study proved the protective effect of curcumin on the glomerular function through reduction of cystatin-C serum levels when coadministered with gentamicin. Curcumin significantly reduced 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 intraglomerular pressure and inflammations [17,18].

CONCLUSION

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

AUTHORS' CONTRIBUTIONS

All authors contribute equally in data collection, experimental design, interpretation, statistical analysis, literature review, manuscript preparation, and review.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

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