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Ameliorative Synergistic Anti-Oxidative, and Nephroprotective Effects of Quercetin and Gallic Acid against Gentamicin-Induced Renal Injury in Rats

Khaled Abo-EL-Sooud*, Sama El Mokadem, Sama Essam Ali, Alaa Mohammed Hashim and Mirna Akram Labib

Department of Pharmacology, Faculty of Veterinary Medicine, Cairo University, Giza 12211, Egypt

Abstract

THE research was planned to assess the protective antioxidant potential of quercetin (QC) and gallic acid (GA) alone or in combination against well-established oxidative nephrotoxicity by gentamicin (GM) in Sprague–Dawley female rats. Rats were weighed and divided into five groups of 5 rats each: the 1st group was kept as control received vehicle (1 ml/kg body weight BW), rats of the 2nd group were injected GM (100 mg/kg BW) intraperitoneally (IP) once daily to induce nephrotoxicity the 3rd and 4th groups were administered QC and GA (100 mg/kg BW) respectively, orally 30 min before the GM injection. The 5th group received both QC and GA concurrently at 50 mg/kg BW, orally, 30 min before the GM injection, respectively. All treatments were administered daily for 8 consecutive days. Serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, uric acid, and creatinine were estimated. The renal oxidative stress biomarkers catalase (CAT), superoxide dismutase (SOD), and, malondialdehyde (MDA), were also evaluated. Finally, the histopathological findings in renal tissues were assessed. Significant increases in the levels of transaminases, urea, uric acid, and creatinine in serum were observed in GM-treated rats. While high doses of QC and GA significantly restored the levels of all these parameters ($p < 0.01$) but the restoration to normal levels was found to be more significant ($p < 0.001$) when QC was administered concurrently with GA at half doses. Gentamicin significantly reduced the renal levels of CAT and SOD ($p < 0.01$) nevertheless, it induces a significant rise in oxidative radical (MDA) level ($p < 0.01$). QC and/or GA significantly improved the antioxidant figures as compared to GM-exposed groups. Our results established that QC with GA at half-recommended doses acts synergistically against acute nephrotoxicity induced by GM by modifying the consequence of renal oxidative stress. Consequently, it will be proper to recommend this combination as a promising nephroprotective agent in renal damage.

Keywords: Gentamicin, Quercetin, Gallic acid, Synergism, Nephrotoxicity, Oxidative stress.

Introduction

Aminoglycosides are considered the 1st choice bactericidal therapy against Gram-negative pathogenic bacteria [1]. The most significant therapeutic restriction of aminoglycosides is nephrotoxicity crises, especially with GM [2]. Gentamicin-induced nephrotoxicity through the existence of reactive oxygen species (ROS), accompanied by degeneration in the convoluted tubule linings, and so acute renal damage occurred [3]. GM intoxication elevated serum creatinine, blood urea nitrogen (BUN), urea, and oxidative pro-inflammatory cytokines. Alternatively, the antioxidant tissue CAT and SOD levels were significantly reduced after seven days from the 1st dose of aminoglycoside remedy [4, 5]. Quercetin is a distinctive flavonoid, universally found in fruits and vegetables, and it has potent antioxidant and anti-inflammatory actions [6]. The strong protective effects of QC against chemical and drug toxicity have been given increased consideration [7–9]. Quercetin can prevent oxidative stress through scavenging oxygen free radicals, potentiating cellular antioxidant status, and inhibiting cell death [10]. Additionally, QC significantly reduces the elevated hepatic enzymes and lessens the hepatic injury, and it could be a natural candidate to protect the vital organs against environmental toxicity [11]. Gallic acid is a natural phenolic structure found in many

*Corresponding authors: Khaled Abo-El-Sooud, E-mail: kasooud@cu.edu.eg, Tel.: +201066756870
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herbs and has respected antioxidant properties via neutralizing free oxidative radicals [12]. It has a polyphenolic moiety that scavenges ROS and modifies them to a safe quinone [13]. In addition, GA modulated the signaling pathways of cytokines and the antioxidant mechanism [14]. Gallic acid is a promising protective agent of normal renal function and reduces the levels of ROS, cytokines, and apoptotic patterns in kidneys [15]. The protective antioxidant effects of QN and GA against oxidative stress produced by di-butyl phthalate in the kidneys of rats were compared alone. Furthermore, single QC treatment showed more promising results than GA on the collected *quantitative analysis* [16]. An earlier study assessed the concurrent synergism between both antioxidants, GA and curcumin, and it postulated that one strengthened the effect of the other [17].

However, the effects of coadministration of QC and GA on GM-induced oxidative renal damage have not been studied. We evaluated the synergistic antioxidative and nephroprotective effects of QC with GA against GM-induced renal injury in rats.

Materials and Methods

Chemicals and reagents

QC (C_{15} H_{10} O_7, $2H_2O$, M.W. = 338.27) and GA (C_7 H_6 O_5. H_2O, MW = 188.14) from Alpha Chemika in Cairo, Egypt, dissolved in dimethyl sulfoxide (DMSO) in distilled water at a molar ratio of 1 DMSO: 2 H_2O [18]. Gentamicin sulfate was obtained as Garamycin® ampoules from the Egyptian branch of Merck, MSD, under the license of Schering-Plough.

Experimental plan

Twenty-five adult Sprague Dawley female rats (BW range 180.33±6.50 g) were obtained from the National Research Center breeding division (Giza, Egypt). All rats were observed in clean, stainless-steel mesh cages with a light-dark cycle and relative humidity of 60%. For the experiment, rats were acclimatized with free access to water and rodent food for 14 days.

Faculty of Veterinary Medicine at Cairo University's research committee authorized the experimental protocol on the ethics of animal use, which followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals in Scientific Investigations. All efforts were made to treat the animals with compassion and to resolve ethical issues.

One IP injection of GM (100 mg/kg) was administered daily for 8 successive days to induce nephropathy. To observe the effects of alone or in combination doses of QC and GA treatment on gentamicin-induced nephrotoxicity was administered orally 30 min before the GM injection for 8 consecutive days [5], respectively.

The rats were weighed and divided randomly into five groups (n = 5) as follows:

Group 1 (the normal group) received 1 mL of solvent (distilled water with DMSO)/rat once daily.

Group 2 (the intoxicated group) received GM at 100 mg/kg, IP [19] for 8 consecutive days.

Group 3 and Group 4 (the co-administered groups at recommended doses separately) received QC and GA (100 mg/kg) [20, 21], respectively, orally 30 min before the GM injection at 100 mg/kg, IP, for 8 consecutive days.

Group 5 received both QC and GA (the co-administered group at half-recommended doses concurrently) (50 mg/kg), orally, 30 min before the GM injection at 100 mg/kg, IP, for 8 consecutive days.

Both QC and GA were dissolved in DMSO in distilled water at a molar ratio of 1 DMSO: 2 H_2O (solvent) [18].

Sampling

On the 9th day, all groups were fasted to allow precise body and kidney weights and consistent evaluation of the biochemical parameters [40]. After that, the rats were weighed, anesthetized, and euthanized by cervical dislocation. To collect blood samples, a sterile glass capillary tube was used to penetrate the rat's retro-orbital venous plexus. Blood was taken into a standard centrifuge tube, permitted to clot, centrifuged for 15 min at 500×g, and the obtained serum was kept at -20 ◦C for further analysis. Immediately following the decapitation, the kidneys were removed, cleaned of fat, washed with physiological saline, and weighed. The kidney specimens were divided into two portions. The first part was fixed in a 10% buffered neutral formalin solution for histopathological examination. The second one was homogenizing for the antioxidant analysis defined below.

Body and renosomatic index weight

The body weights were measured to evaluate the change in body weight. Both kidneys were excised and weighed, and the absolute and relative kidney weights were estimated in all groups.

Estimation of biochemical markers

Biodiagnostic kits (Giza, Egypt) were used to determine ALT and AST levels with the method of Bergmeyer et al. [22]. According to Coulombe and Favreau [23], Watts [24], and Fossati et al. [25], urea, uric acid, and creatinine levels were respectively, estimated.

Oxidative and antioxidant levels in kidney homogenate

The renal tissue homogenate was prepared following the Nyimanu et al. [26] method. Part of the kidney tissue was homogenized in phosphate buffer saline (0.1 M PBS with pH 7.4). After that, the homogenates were centrifuged for 30 min at 4 ◦C at 500×g, and the supernatants were kept at -70 ◦C until analysis. Biodiagnostic kits, for diagnostic and research reagents in Egypt, were utilized to estimate renal malondialdehyde (MDA) concentration via a colorimetric assay according to the Ohkawa et al. [27] method. Catalase (CAT), and superoxide dismutase (SOD), levels in kidney homogenates were determined spectrophotometrically according to Sinha [28], and Nishikimi, et al. [29] assays, respectively.

Histopathological examination

Each rat's kidney samples were dissected and fixed in a 10% buffered neutral formalin solution. Then, renal tissues were dehydrated with ascending alcohol concentrations, cleared in xylene, embedded, and blocked in paraffin. 4 μm sections were taken, stained with Hematoxylin and Eosin (H & E), and processed according to the Bancroft and Layton [30] procedure. A conventional microscope (Olympus, Tokyo, Japan) was utilized at different magnification powers. Specimens of all rats were randomly examined with a light microscope at different magnifications.

The lesions were scored in blind mode by counting several fields and magnification, and the lesion scores were graded with a semi-quantitative scale from 0 to 3 as follows: 0 (absent), 1 (mild), 2 (moderate), and 3 (severe).

Statistical analysis

Differences between obtained values (mean ± SEM) were compared with one-way analysis of variance (ANOVA) through SPSS version 14 (SPSS, Chicago, IL, USA) with post hoc Tukey's (multiple comparison test).

Results

Effect of body and renosomatic index weight

Gentamicin significantly reduced the absolute BW ($p < 0.001$) in comparison to normal rats. However, the BW was found to be amended significantly in QC and GA (100 mg/kg) as compared to GM-treated rats. Moreover, at the half doses, QC with GA acts synergistically to increase body weight more than both agents independently. Contrary to that, the kidney weight and the renosomatic index of GM-treated rats increased significantly when compared to normal rats. On the other hand, both parameters were significantly improved in all treated groups in comparison to GM rats (Table 1).

Effect on blood biochemical markers

Serum transaminases, urea, uric acid, and creatinine were assessed as markers for evaluating hepato-renal function in toxicological crises. These biochemical parameters were recorded in Table 2. The activities of AST and ALT, which are indices of hepatic function, were significantly higher in the GM-treated rats than in the control group. No significant alteration in the levels of these liver markers was found in the serum between QC and GA-treated rats and the control group. The activity of transaminases was significantly lower in the co-administered group (Table 2). Significant increases in the level of urea, uric acid, and creatinine in serum were observed in GM-treated rats when compared with the normal group. High doses of QC and GA (100 mg/kg) along with GM significantly restored the levels of all these parameters when compared with GM-alone-treated rats. The restoration to normal levels was found to be more significant ($p < 0.001$) when QC was administered concurrently with GA at the half doses (50 mg/kg) with GM.

Assessment of oxidative stress markers

As illustrated in Figures 1, and 2 the renal tissues CAT and SOD levels of GM-treated rats were reduced significantly when compared with the normal non-treated rats. The levels of both antioxidant biomarkers were improved significantly when QC and GA were administered concurrently alone or together, when compared with GM rats alone. Conversely, GM induced a significant elevation in the renal MDA level when compared with the normal rats. Nevertheless, the MDA levels were ameliorated significantly ($p < 0.01$; $p < 0.001$) when QC and GA were administered concurrently alone or together with GM-treated rats when compared with GM rats alone (Figure 3).

Histopathological evaluation

The histopathological findings of kidney sections stained with H and E x100 showed normal glomeruli and surrounding tubules that are lined by intact epithelium in normal control rats (Fig. 4A). The kidney sections of GM-treated rats showed dilated renal tubules lined by thin degenerated and apoptotic epithelium (Fig. 4B1) with interstitial non-specific mononuclear lymphoplasmacytic inflammatory infiltrate (Fig. 4B2); Moderate pathological alterations were observed in both groups treated with QC (100 mg/kg)+GM (Fig. 4C) and D: GA (100 mg/kg) + GM (Fig. 4D) in some tubules that showed hyaline casts with focal affection in the renal tubules lined by thin apoptotic epithelium cells. A complete histological restoration of kidney structure, with preserved glomeruli and intact tubular epithelium with no histopathological damages, was observed in

rats that received QC (50 mg/kg) + GA (50 mg/kg) with GM (Fig. 4E). The lesion scores in renal tissues from all groups were presented in Table 3.

Discussion

Gentamicin is associated with an induction of renal damage via cellular necrosis, Bowman's capsule congestion, and perivascular inflammation, which eventually leads to the mechanism of renal failure [31]. Oxidative stress has been linked to both acute and chronic kidney diseases in GM therapy through the generation of ROS that are also associated with renal damage [32]. The oxidative strain with mitochondrial dysfunction constitutes the main cause of the pathogenesis of renal failure [33]. Nowadays, botanical alternatives are preferred in cases of disease conditions due to their slight side effects.

The IP administration of GM for eight days resulted in a significant decline in absolute and relative body weight. Conversely, the renosomatic mass was increased, which may be associated with renal damage due to disturbance of water and electrolytes reabsorption associated with dehydration, and loss of body weight due to reduced food consumption. These results were also supported by earlier studies on GM-induced nephrotoxicity [5, 34].

Impaired renal function in GM-treated rats was confirmed by significant abnormal elevation of blood creatinine, urea, and uric acid, respectively, when compared to the normal control group. The treatment of rats with 100 mg/kg of QC and GA with GM confirmed a lessening of the degree of renal injury. The restoration to normal levels was found when QC was administered concurrently with GA at half doses (50 mg/kg). Simultaneous administration of QC and GA ameliorated GM nephrotoxic effects, as histopathological changes and serum parameters were normal [35, 36].

The potent antioxidant enzymes in the vital organs are CAT, and SOD which protect tissues from ROS effects [37]. The antioxidant activity of phenolic compounds is mainly due to their reduction reaction with hydrogen donors and vest O_2 sources. Consequently, there has been a lot of interest in the use of natural antioxidants like flavonoids to protect against xenobiotics [38].

Gentamicin-induced nephrotoxicity is characterized by increases in the ROS levels in convoluted tubular apoptosis and induces quick kidney damage [39]. The significant increase in MDA level as well as decreased activity of CAT, and SOD (antioxidant biomarkers) in the renal tissues revealed that oxidative stress contributes to GM-induced nephrotoxicity. Both QC and GA have potential nephroprotective mechanisms against GM, either alone or concurrently, by reducing oxidative stress in rats. Also, the antioxidant activity was superior when both natural agents were used concomitantly, directly by scavenging ROS or indirectly by augmenting antioxidant efficacy and expression [40]. Quercetin can prevent oxidative damage by decreasing lipid peroxidation, modulating intracellular antioxidant status, and preventing cellular apoptosis [41].

Additionally, our biochemical findings were confirmed by histopathological assessment, which revealed dilated renal tubules lined by thin, degenerated, and apoptotic epithelium with an interstitial nonspecific mononuclear lymphoplasmacytic inflammatory infiltrate in GM-intoxicated rats. Whereas, normal and synergistic QC and GA groups did not have significant renal lesions, confirming that the GM administration was the source of histological alterations. Some pathological changes were observed in both groups treated with QC (100 mg/kg) and GA (100 mg/kg) separately, with GM in renal tubules that showed hyaline casts with focal affection in the renal tubules lined by thin apoptotic epithelial cells. Earlier studies stated that GM administration for 8 days affected the renal cortex more than the medulla due to a higher concentration of GM reaching the cortex via the central compartment than that in the medulla [19, 42].

Conclusion

The present study compares the antioxidant efficacy of QC and GA against GM-acute nephrotoxicity. Both natural compounds have potent antioxidant activity by modifying the consequences of renal oxidative stress. Stimulatingly, QC and GA at low doses act synergistically, and this combination is a promising potent antioxidant activity, as each of them strengthens the effect of the other. Consequently, it will be appropriate to recommend this combination as a promising nephroprotective agent in renal damage.

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Declaration of interest

The authors declare that there is no conflict of interest

Ethical approval

Faculty of Veterinary Medicine at Cairo University's research committee authorized the experimental protocol on the ethics of animal use, which followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals in Scientific Investigations.

TABLE 1. Effect of QC and/or GA on body and renosomatic weights (g) in GM-induced nephrotoxicity in rats for 8 days

Estimated parameters	Experimental groups				
	Control	GM	GM+QCN	GM+GA	GM+QC+GA
Initial Body weight (g)	179.80±0.71	180.80±3.79	183.20±3.14	181.67±4.62	183.00±2.82
Final body weight (g)	207.20±2.55	192.33$^{\#\#}$±2.20	210.00**±3.63	209.25**±1.65	215.37**±2.36
Body weight change (g)	27.40 ±3.08	11.53$^{\#\#}$±2.10	26.80** ±2.17	27.58**±2.08	32.37***±2.13
Kidney weight (g)	1.46±0.15	2.24$^{\#\#}$±0.18	1.51**±0.10	1.48**±0.09	1.53**±0.08
Renosomatic index (%)	0.71 ±0.09	1.16$^{\#\#}$±0.08	0.72** ±0.10	0.71**±0.07	0.71**±0.06

Data expressed as Mean ± SEM (n = 5). $^{\#\#}p < 0.01$ as compared to control rats and $^{**}p < 0.01$ and $^{**}p < 0.001$ as compared to the GM group

TABLE 2. Effect of QC and/or GA on serum levels of biochemical analysis in GM-induced nephrotoxicity in rats for 8 days

Estimated parameters	Experimental groups				
	Control	GM	GM+QCN	GM+GA	GM+QC+GA
AST(U/L)	140.00±2.63	197.00$^{\#\#}$±2.82	155.33***±3.93	163.67**±3.62	147.33***±2.32
ALT (U/L)	42.50±2.58	92.12$^{\#\#}$±4.59	52.67***±2.86	63.67**±4.61	51.00***±3.04
Urea (mg/dL)	44.08±2.66	102.80$^{\#\#}$±5.11	72.50**±4.01	71.20**±3.19	52.23***±2.91
Uric acid (mg/dL)	1.08±0.26	2.92$^{\#\#}$±0.13	1.62**±0.11	1.70**±0.12	1.57***±0.08
Creatinine (mg/dL)	0.82±0.10	4.75$^{\#\#}$±0.44	2.42**±0.17	2.86**±0.21	1.58***±0.11

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase
Data are expressed as Mean ± SE. (n = 5). $^{\#\#}p < 0.01$ as compared to control rats and $^{*}p < 0.01$, $^{**}p < 0.001$compared to GM rats

TABLE 3. Effect of QC and/or GA on the renal histopathological scoring (0-3) of GM-induced nephrotoxicity in rats for 8 days

Estimated parameters	Experimental groups				
	Control	GM	GM+QCN	GM+GA	GM+QC+GA
Glomerular membrane thickening	0	3	1	2	0
Tubular dilation	0	3	2	2	0
Tubular degeneration and apoptosis	0	3	1	2	0
Inflammatory infiltration	0	3	1	2	1

The scoring was graded with a semi-quantitative scale from 0 to 3 as follows: 0 (absent), 1 (mild), 2 (moderate), and 3 (severe).

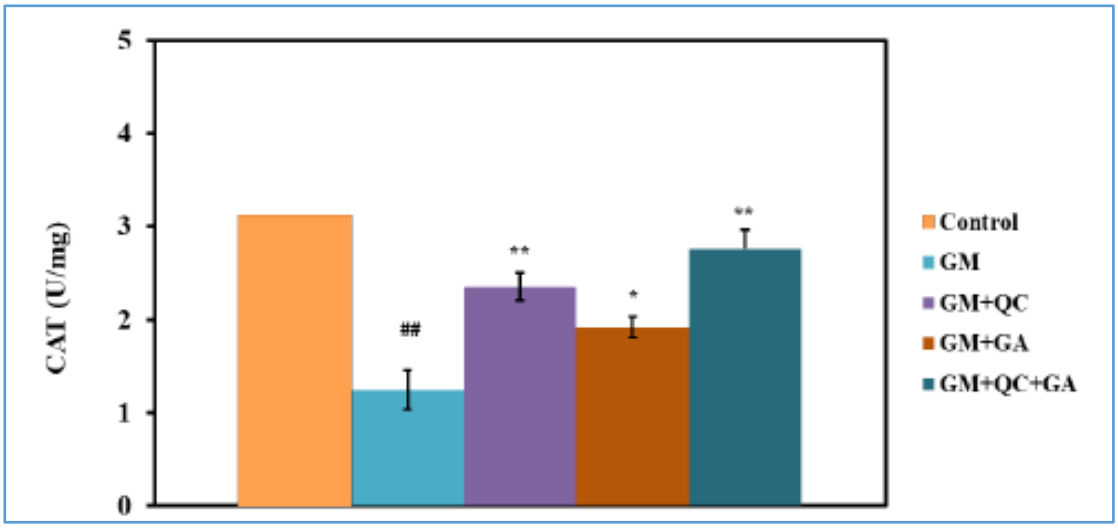

Fig. 1. Effect of QC and/or GA on CAT levels in GM-induced renal damage in rats. Values expressed as mean ± SE (n = 5). ##p < 0.001 as compared to control rats and *p < 0.01, **p < 0.01 compared to the GM group

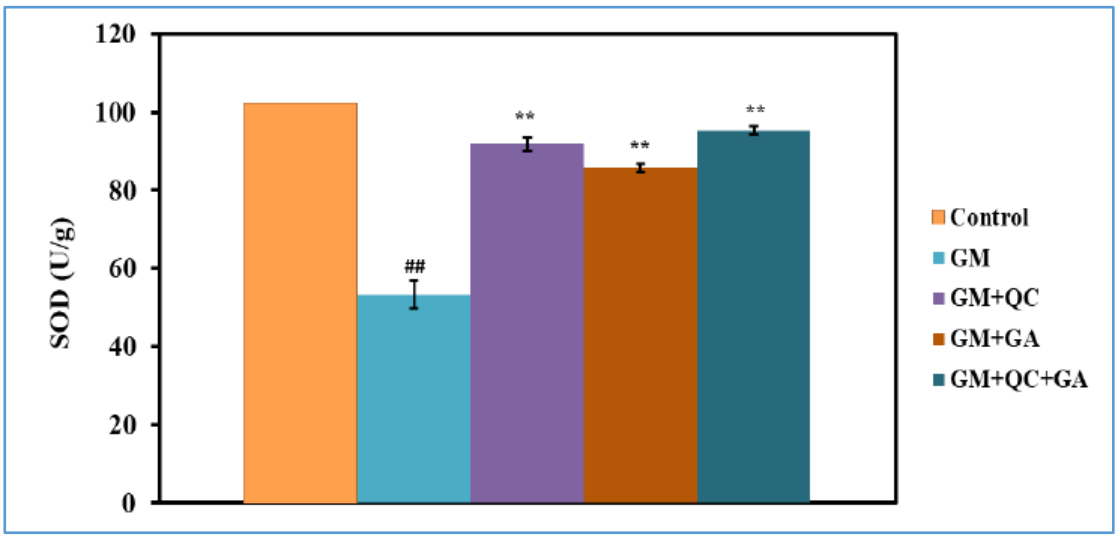

Fig. 2. Effect of QC and/or GA on SOD levels in GM induced renal damage in rats. Values expressed as mean ± SE (n = 5) ##p < 0.001 compared to control rat and **p < 0.01 compared to the GM group

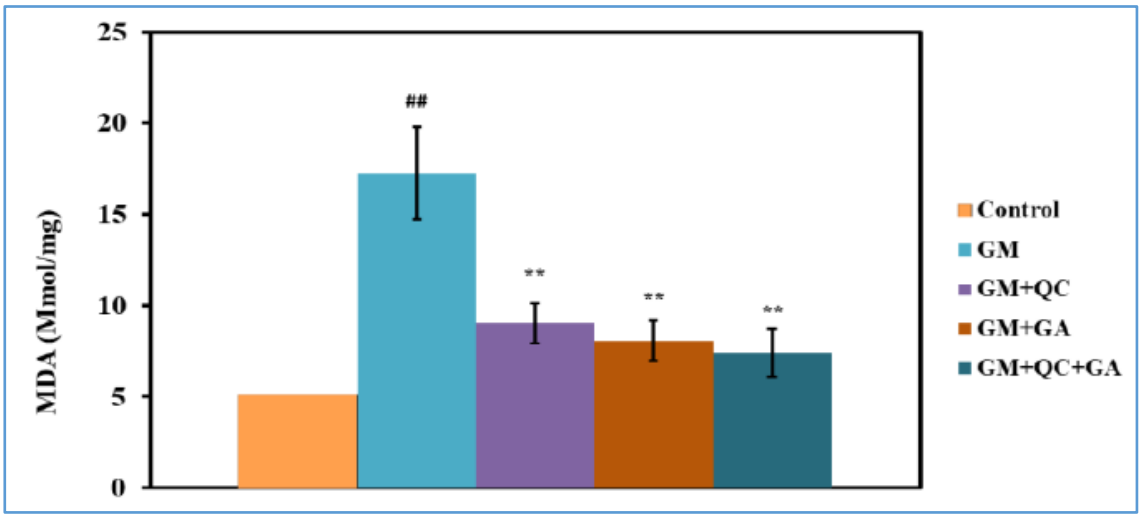

Fig. 3. Effect of QC and/or GA on MDA levels in GM-induced renal damage in rats. Values expressed as mean ± standard error (n = 5) ##p < 0.001 compared to control mice and **p < 0.01 compared to the GM group

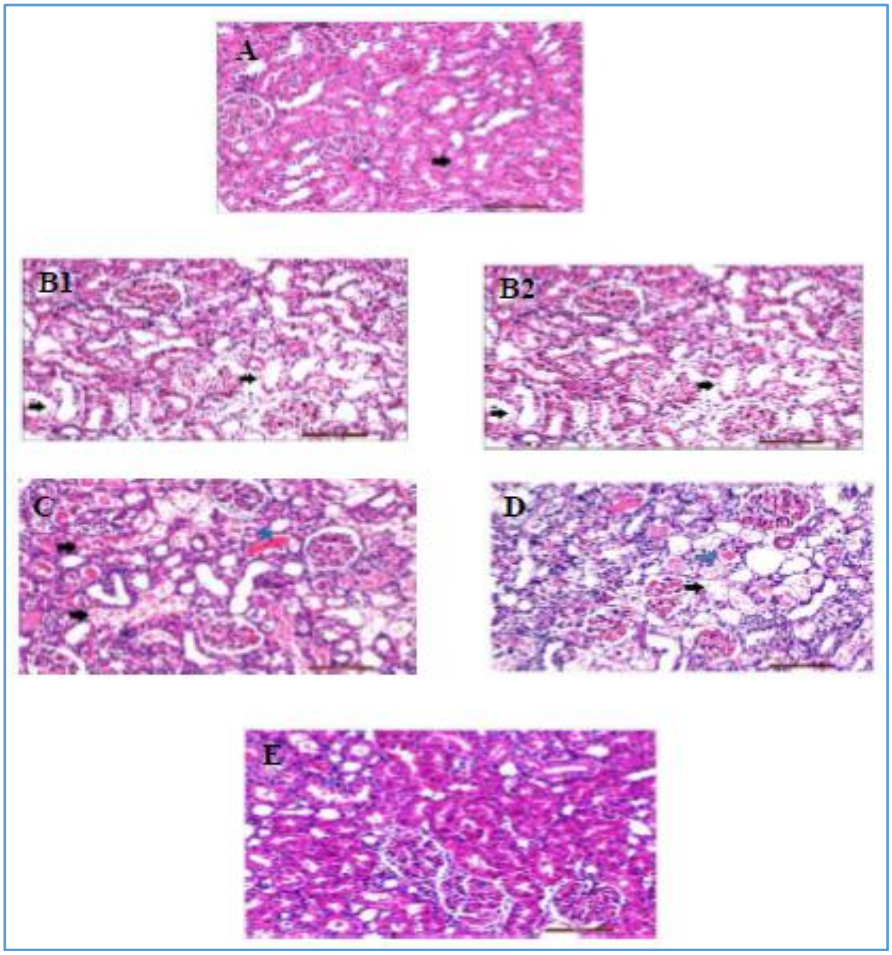

Fig. 4. Histopathological findings of kidney sections stained with H and E x100 A: Control group with normal glomeruli and surrounding tubules that are lined by intact epithelium (black arrow). Group B1: GM-treated rats with dilated renal tubules lined by degenerated and apoptotic epithelium (black arrow). B2 GM-treated rats with interstitial non specific mononuclear lymphoplasmacytic inflammatory infiltrate (black arrow). C: QC (100 mg/kg) +GM and D, GA (100 mg/kg) + GM both groups showed dilated renal tubules (focal affection) lined by thin degenerated and apoptotic epithelium (black arrow) with some tubules show hyaline casts (blue arrow). E: QC (50 mg/kg) + GA (50 mg/kg) +GM showed near complete histological restoration of kidney structure, with preserved glomeruli and intact tubular epithelium

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التأثيرات التآزرية المضادة للأكسدة والحماية الكلوية للكيرسيتين وحمض الجاليك ضد إصابة الكلى الناجمة عن الجنتاميسين في الفئران

خالد أبو السعود* و سما المقدم و سما عصام على و ءالاء محمد هاشم و مرنا أكرم لبيب

قسم الأدوية، كلية الطب البيطرى، جامعة القاهرة، الجيزة، مصر.

الملخص

صُممت هذه الدراسة لتقييم الدور التحسيني المحتمل للكيرسيتين (QC) وحمض الجاليك (GA)، سواءً بمفردهما أو بالاشتراك معاً، ضد السمية الكلوية التأكسدية التي يسببها الجنتاميسين (GM) لدى إناث فئران سبراغ-داولي البالغة. وُزنت الفئران ووُزِّعت على خمس مجموعات، كل مجموعة تتكون من خمسة فئران: كانت فئران المجموعة الأولى مجموعة ضابطة، وأعطيت مذيبًا (1 مل/كجم). حُقنت فئران المجموعة الثانية بالجنتاميسين (100 ملجم/كجم) داخل الغشاء البريتونى (IP) مرة واحدة يوميًا لتحفيز السمية الكلوية. أُعطيت المجموعتان الثالثة والرابعة الكيرسيتين وحمض الجاليك (100 ملجم/كجم) على التوالي، عن طريق الفم قبل 30 دقيقة من حقن الجنتاميسين. أما المجموعة الخامسة، فقد تلقت الكيرسيتين وحمض الجاليك معًا بجرعة 50 ملجم/كجم، عن طريق الفم قبل 30 دقيقة من حقن الجنتاميسين، على التوالي. أُعطيت جميع العلاجات يوميًا لمدة 8 أيام متتالية. في نهاية التجربة، قُدِّرت مستويات إنزيم ألانين أمينوترانسفيراز (ALT)، وأسبارتات أمينوترانسفيراز (AST)، والبولينا، وحمض البوليك، والكرياتينين في مصل الدم. كما قُيِّمت المؤشرات الحيوية للإجهاد التأكسدي الكلوي، مثل الكاتالاز (CAT)، وفوق أكسيد ديسميوتاز (SOD)، والمالونديالدهيد (MDA). وأخيرًا، قُيِّمت النتائج النسيجية المرضية في أنسجة الكلى. تبين أن الجنتاميسين يسبب ارتفاعًا ملحوظًا في مستويات المالونديالدهيد (MDA)، ويُغيِّر بشكل كبير المعايير الكيميائية الحيوية للكبد والكلى؛ ومع ذلك، فقد خفَّض كلٌّ من الكيرسيتين وحمض الجاليك مستويات المالونديالدهيد (MDA) بشكل ملحوظ مع استعادة المستويات الطبيعية عند إعطاء الكريستين بالتزامن مع حمض الجاليك بنصف جرعات (50 ملغ/كغ) مع GM. و أثبتت النتائج أن الكريستين مع حمض الجليك بجرعة منخفضة يعملان تآزريًا ضد السمية الكلوية الحادة للجنتاميسين في الفئران، وذلك بخفض الإجهاد التأكسدي الكلوي و رفع مستويات مضادات الأكسدة الطبعية فى الكلى. وبالتالي يُنصح باستخدامهما معا كعامل واعد في حماية الكلى و خاصة فى حالات التسمم الكلوى.

الكلمات الدالة: الجنتاميسين و الكيرسيتين وحمض الجاليك و السمية الكلوية و التأزر.