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Bee venom ameliorates gentamicin-induced kidney injury by restoring renal aquaporins and enhancing antioxidant and anti-inflammatory activities in rats

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Introduction: Gentamicin (GM) is a frequently used aminoglycoside for managing serious illnesses; nonetheless, renal complications limit its use. Bee venom (BV) is a biological toxin that exhibits anti-inflammatory and antioxidant activities. This study was designed to explore the mitigating effect of BV remediation on GM induced renal injury.

Methods: Twenty male rats were divided into four groups (five rats each), namely, control (saline subcutaneously); BV group (1 mg/kg S/C twice weekly for 1 month); GM group (100 mg/kg i. p. for 1 week); and GM-BV group (the same aforementioned dosages of GM and BV, with GM administered in the last week for 4 weeks).

Results and discussion: BV mitigated the GM-inflicted kidney damage, as evidenced by a substantial improvement in the renal function and oxidative state. In addition, a downregulation in the expression of inflammatory biomarkers (Casp-1, IL-6, TNF-α, and NF-κB/P65/P50) and an upregulation of

oxidative stress marker expression (NRF2) were noticed. BV upregulated the expression of aquaporins (AQPs) and renal water channel proteins (AQP1 and AQP2), which are useful for the early detection of renal injury. Additionally, BV exposure exerted a mitigating effect on the apoptotic cascade, as evidenced by the downregulation of cleaved Caspase-3 (Casp-3) and cytochrome c (Cyto c). BV administration also led to an improvement in RBC, WBC, and platelet counts, along with enhanced Hb levels. Interestingly, BV could protect against GM triggered nephrotoxicity.

KEYWORDS

ethnopharmacology, aminoglycoside, bee venom, aquaporins, oxidative stress, renal pharmacology

1 Introduction

Gentamicin (GM) is a well-known, affordable aminoglycoside, with low resistance and high efficacy against potentially lethal infections caused by gram-negative pathogens (Elgazzar et al., 2022). Notwithstanding its extensive therapeutic uses, it is widely recognized for producing considerable nephrotoxic consequences that seriously limit its use (Udupa and Prakash, 2019). The pathophysiology of GM-induced renal damage is multi-factorial. GM accumulates in the proximal convoluted tubules, resulting in glomerular congestion, tubular necrosis, and eventually renal failure (Abouzed et al., 2021). However, a key contributor to GM-mediated nephrotoxicity is the overabundance of deleterious free radicals and consequent oxidative harm (Abdeen et al., 2021). Reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\bullet -}$), and hydroxyl radical ($OH^{\bullet}$), have been proven to be produced by GM, causing severe damage to various cellular molecules, including proteins, lipids, DNA, ultimately leading to apoptosis (Abdeen et al., 2021; Abdelnaby et al., 2022). Inflammatory processes are demonstrated to be a consequence of surplus ROS production (Ahmed et al., 2022). In addition, GM is assumed to affect the function of water channel proteins, specifically aquaporins (AQPs), in the kidney (Abdeen et al., 2014; Su et al., 2020).

AQPs are transmembrane protein channels that provide fluid translocation and modulate osmolarity and concentration of urine and fluid volume (Tamma et al., 2018). The proximal convoluted tubule serves as the prime site of absorption for the majority of fluids after they pass through glomeruli, where AQP1 is highly expressed (Abdeen et al., 2016; El-Agawy et al., 2022). In the kidney, AQP1 is crucial for tubule water permeability and countercurrent exchange processes (Candan et al., 2023). On the contrary, AQP2 is most abundant in the epithelial cells of collecting ducts, where it plays an indispensable function in controlling fluid volume and urine concentration (El-Agawy et al., 2022). According to certain reports, AQP expressions are strongly associated with acute kidney injury and are useful for the early diagnosis of such injury (Abdeen et al., 2014; Jiang et al., 2021). Accumulative evidence suggests that AQP1 and 2 undergo alterations in response to different insults such as puromycin (Abdeen et al., 2020), lipopolysaccharide (Candan et al., 2023), and methotrexate (El-Agawy et al., 2022).

Bee venom (BV, apitoxin), produced by bees (*Apis mellifera*), is one of the well-known naturally occurring beneficial biological toxins (Wehbe et al., 2019; Sadek et al., 2024). It is a combination of bioactive compounds with neurotoxic and immunogenic properties. It is composed of peptides including melittin, mast cell degranulation peptide, apamin, and adolapin and enzymes like phospholipase A2, acid phosphomonoesterase, hyaluronidase, and lysophospholipase; it additionally encompasses a variety of amines, including histamine, norepinephrine, dopamine, and volatile compounds (Kim et al., 2019). All bee products, including honey and BV, have been used for hundreds of years since religious books (the Bible and the Holy Quran) highlighted their medicinal benefits (Wehbe et al., 2019). BV remedy involves the medicinal use of bee stings or venom injection to alleviate a variety of illnesses and has been utilized in alternative medicine for more than 3000 years (Zhang et al., 2018). BV's therapeutic potential is ascribed to its anti-inflammatory, antioxidant, antifibrotic, immunomodulatory, anticancer, and antiapoptotic properties (Kader et al., 2019; Eleiwa et al., 2023). Recent investigations have demonstrated that injecting BV may be beneficial in the alleviation of nephrotoxicity caused by agents such as cisplatin (Kim H. et al., 2020), acute endotoxic kidney injury (Kim et al., 2021), and acrylamide (Amra et al., 2018).

In consideration of the pharmacological properties of BV, we postulated that it could serve as a mitigating strategy for GM-induced toxicity. To the best of our knowledge, no research has been conducted to specifically investigate the potential effect of BV treatment on GM-triggered kidney injury. Therefore, the present research was conducted to assess the mitigating action of BV on GM-prompted kidney damage in rat models and evaluate and explore whether the AQP signaling pathway is associated with these impacts. Renal biomarkers, hematological profiles, oxidative stress indices, inflammatory and apoptotic marker expression, and histomorphological characteristics, were all assessed in this work.

2 Materials and methods

2.1 Chemicals and drugs

Lyophilized *A. mellifera* purified BV 1 mg/vial (Abevac®, VACSERA, Cairo, Egypt) was utilized. GM (Garamycin 80®; gentamicin sulfate 80 mg/2 mL vial) was obtained from Memphis Co. for Pharm. Chem. Ind., Cairo, Egypt.

2.2 Animals

Twenty male albino Wistar rats, weighing 120 ± 10 g, aged 8 weeks, were procured from the Centre for Laboratory Animals, Faculty of Veterinary Medicine, South Valley University, Egypt. Rats were raised for 2 weeks beforehand to the trial in well-aerated cages under standard temperature (22.5°C ± 2°C), relative humidity of 60% ± 10%, and light (12 h light/dark cycles). Throughout the study, rats were fed a conventional basal diet and given free access to water.

2.3 Experimental protocol

Following 2 weeks, rats were evenly divided into four groups (five rats each), namely, control group, where rats were given saline subcutaneously (S/C); BV group, where rats were injected BV S/C at a dose of 1 mg/kg twice weekly for 1 month, determined according to Kim et al. (2013); GM group, where the rats were i. p. injected 100 mg/kg of GM daily for 1 week based on our beforehand studies (Abdeen et al., 2021; Elgazzar et al., 2022); and GM-BV group, where both remedies were administered at the same aforementioned dosages (GM was given in the last week).

After 4 weeks, the experiment was halted, and blood was withdrawn from the retro-orbital venous plexus. The blood samples were divided into two portions; the first portion was collected in tubes containing EDTA to prevent clotting and used for hematological studies. The second portion was centrifuged at 5000 rpm for 10 min to obtain serum, which was then frozen at −20°C for subsequent biochemical analysis. Subsequently, all rats were anesthetized using 3%–4% isoflurane inhalation and euthanized by long exposure to anesthesia. Next, the kidneys were promptly retrieved and scrubbed with cold physiological saline to get rid of any congeals before being sliced. One portion was kept in 10% buffered neutral formalin for further histological inspection. Some tissue sections were kept at − 80°C for the extraction of RNA and proteins, while the remainder of fresh tissue pieces were kept at −20°C for an oxidative cascade biomarker investigation.

2.4 Assessment of renal function parameters and hematological profile

Serum levels of creatinine (catalog no. CR 1251), blood urea nitrogen (BUN; catalog no. UR 2110), and uric acid (catalog no. UA 2021) have been measured to assess kidney function. All proceedings were conducted in conformity with the manufacturer's (Laboratory Bio Diagnostic Co., Giza, Egypt) protocols. An automated blood analyzer (URIT-2900 plus, URIT Medical Electronic Co., Shenzhen, China) was utilized to measure the red blood cells (RBCs), hemoglobin concentration (Hb%), white blood cells (WBCs), and platelet counts for the entire blood samples.

2.5 Preparation of tissue homogenates, antioxidants, and peroxidation biomarker assay

One gram of each tissue sample was homogenized using a sonicator homogenizer in an ice-cold buffer solution (K_3PO_4 50 mmol, EDTA 1 mmol, pH 7.5). Next, we used a cooling centrifuge to spin the resulting homogenate at 4000 rpm for 20 min. The supernatant was gathered and stored at −80 °C for the measurement of glutathione peroxidase (GPx; catalog no. Gp2524) activity, total antioxidant capacity (TAC; catalog no. TA2513) content, and malondialdehyde (MDA; catalog no. MD2529) level using specialized kits from Laboratory Bio Diagnostic Co., Cairo, Egypt.

2.6 RNA seclusion with reverse transcription-PCR

Using the QIAzol Lysis Reagent (QIAzol™, QIAGEN®, United States), total RNA has been extracted from the kidney homogenate in accordance with the manufacturer's instructions. The total RNA content of the samples was assessed using a spectrophotometer (NanoDrop ND-1000 Spectrophotometer, Thermo Scientific, United States). The RNA quality was assessed using the absorbance ratio between 260 and 280 nm. The extracted total RNA was reverse transcribed into cDNA using the miScript II RT Kit (QIAGEN®, United States). In addition, 1 μg of RNA was converted to 1 μg of cDNA using an Oligo (dT) primer (PrimeScript™, TaKaRa Bio Inc., CA, United States). Interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), nuclear factor erythroid 2-related factor 2 (NRF2), nuclear factor-κB/P65 (NF-κB/P65), superoxide dismutase type 1 (SOD1), caspase-1 (Casp-1), AQP1, AQP2, and kidney injury molecule-1 (KIM-1) were the primers used in the PCR that was conducted using a thermal cycler (A200 Gradient Thermal Cycler, LongGene®, Hangzhou, China) (Supplementary Table S1). A 1.5% agarose gel stained with ethidium bromide (Scientific Limited, Northampton, UK) in Tris-borate-EDTA buffer was used for electrophoretic separation of PCR products. The NIH ImageJ v1.47 program was employed to assess and recognize the band intensity in relation to the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene. The bands were identified using a gel recording system (Bio-Rad, United States).

2.7 Western blotting

In accordance with the manufacturer's instructions, the protein fraction was extracted from the organic phase of fatty tissue samples and treated with a proteinase inhibitor cocktail and phosphatase inhibitor tablet (Sigma-Aldrich, Germany, and PhosSTOP™, Roche Diagnostics, United States, respectively). Using SDS-polyacrylamide gel electrophoresis (SDS-PAGE), protein samples were loaded in equal amounts, extracted, and blotted onto a polyvinylidene difluoride membrane (Immobilon-P, Millipore). Primary antibodies (IL-6, TNF-α, NF-κB/P50, NF-κB/P65, NRF2, SOD1, cleaved Caspase-3 (C. Casp3–17/19), and cytochrome c (Cyto c), AQP1, AQP2, and KIM-1), which had been diluted, were used to probe the membranes following blocking in PBS-Tween (0.1%) with 1% BSA (Supplementary Table S2). The Roche Lumi-Light PLUS Kit and the Bio-Rad ChemiDoc Imaging System were used to recognize the bands. NIH ImageJ was used to quantify the intensities of the bands.

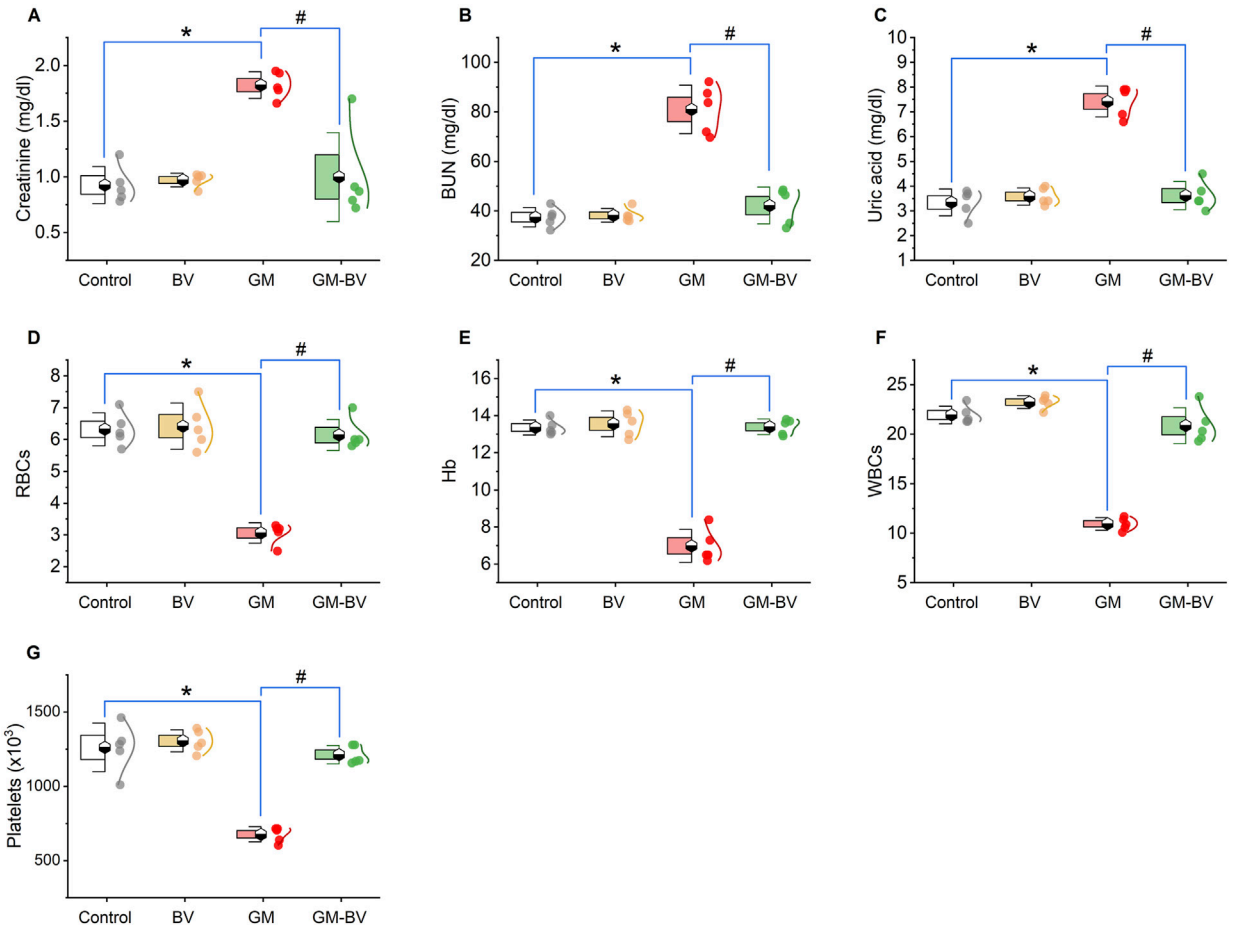

FIGURE 1
Dot-box plot of kidney functions and hematological parameters of GM-exposed rats upon BV remediation. **(A)** Creatinine; **(B)** BUN, blood urea nitrogen; **(C)** uric acid; **(D)** RBCs; **(E)** Hb, hemoglobin; **(F)** WBCs; **(G)** platelets. BV, bee venom; GM, gentamicin. Values were expressed as the mean ± SE (n = 5). $P < 0.05$; *GM vs. Control; #GM-BV vs. GM.

2.8 Histological inspection

The formalin-fixed renal sections were initially dehydrated by increasing alcohol concentration. Following that, xylene clearing was performed, followed by embedding in paraffin. The tissue specimens were cut into 5-μm sections and then stained with H&E for histopathological examination. A camera-integrated digital imaging system (DM300, Leica, Germany) was then used to scan the sections. For lesion scoring, three slides per animal were tested; thus, tubular injury was defined as tubular epithelial necrosis, cast formation, tubular dilatation, and the loss of the brush border, as described by Khalid et al. (2016), with minor modifications. The injury was scored by grading the percentage of affected tubules under 10 randomly selected, non-overlapping fields (magnification, × 200) as follows: 0, 0%; 1, ≤10%; 2, 11%–25%; 3, 26%–45%; 4, 46%–75%; and 5, 76%–100%. To score injured tubules, whole tubule numbers per field were considered the standard under a magnification of × 200. The injury score percentage was calculated in each field as follows: injury score (%) = number of injured tubules/number of whole tubules × 100.

2.9 Data analyses

Initially, all data were examined for homogeneity (Levene's test) and normality (Shapiro–Wilk's test). Then, all data were analyzed using a one-way analysis of variance (ANOVA), and the treatment means were compared using Duncan's *post hoc* test (SPSS software, version 21; Inc., Chicago, IL, United States). Data are presented as the means ± SE. At $P < 0.05$, all results are deemed statistically significant with a 95% confidence interval. Data visualization was conducted using OriginPro (version 2019b). After data transformation, principal component analysis (PCA) was performed using the 'factoextra' and the 'FactoMineR' packages which were built in RStudio under R version 4.0.2.

3 Results

3.1 Biochemical parameter evaluation

As displayed in Figures 1A–C, GM injection prompted renal damage, as evidenced by a notable ($P < 0.05$) increase in renal function test markers (creatinine, BUN, and uric acid levels)

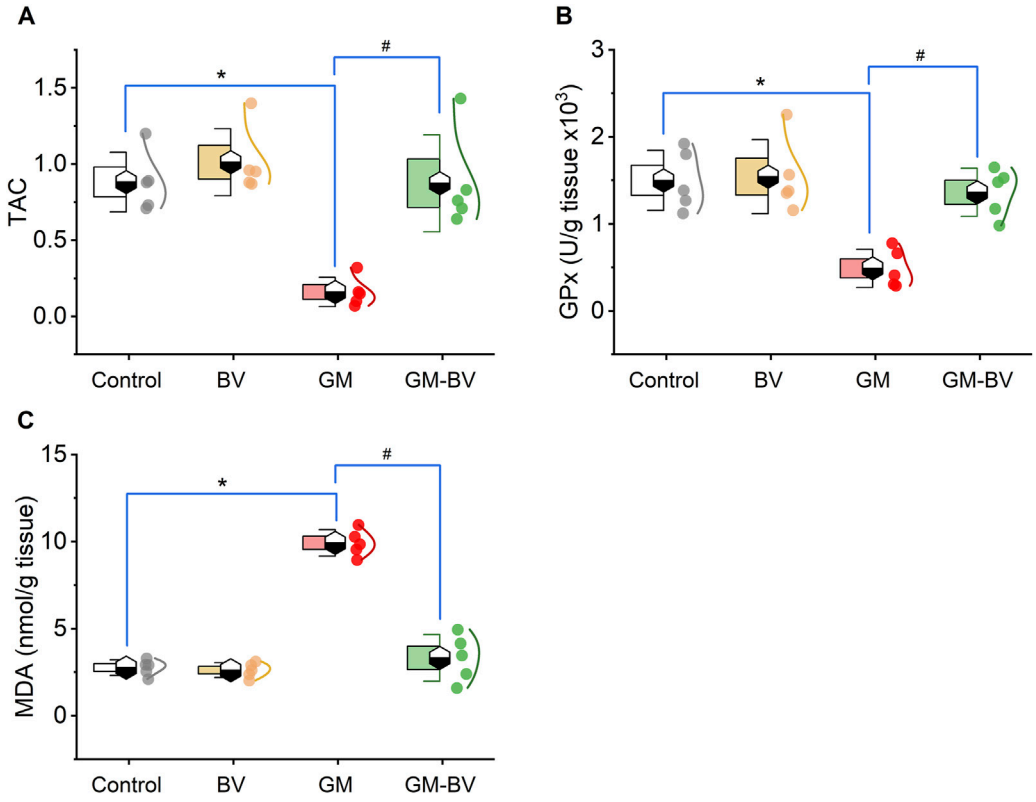

FIGURE 2
Dot-box plot of renal oxidative stress markers of GM-exposed rats upon BV remediation. **(A)** TAC, total antioxidant capacity; **(B)** GPx, glutathione peroxidase; and **(C)** MDA, malondialdehyde. BV, bee venom; GM, gentamicin. Values were expressed as the mean ± SE (n = 5). $P < 0.05$; *GM vs. Control; #GM-BV vs. GM.

compared to control rats. Conversely, treatment with BV remedy robustly ($P < 0.05$) decreased the GM-induced injuries in renal tissues, as exhibited by a noteworthy improvement in kidney function compared to GM-intoxicated rats.

3.2 Hematology profile

Hb%, RBCs, WBCs, and platelet counts are depicted in Figures 1D–G, respectively. Significant ($P < 0.05$) decreases in all measured hematological parameters following GM insult were detected. Interestingly, when GM was used concurrently with BV, the blood profile was retrieved nearly to normal compared to GM-treated rats.

3.3 Antioxidants and lipid peroxidation indices

Data on antioxidant enzyme activities (GPx), TAC content, and MDA levels are displayed in Figure 2. MDA levels were substantially ($P < 0.05$) increased together with a noticeable ($P < 0.05$) reduction in TAC content and GPx activity upon GM intoxication. Additionally, the expression (mRNAs and proteins) levels of NRF2 and SOD1 in kidney tissue displayed notable ($P < 0.05$) downregulation, corroborating the instigation of oxidative stress (Figures 3, 4). Remarkably, GM-triggered oxidative damage was considerably ($P < 0.05$) hampered when GM was injected in conjunction with BV compared to GM-exposed rats.

3.4 Pro-inflammatory cytokine expression

As shown in Figures 3, 4, GM treatment provoked kidney tissue inflammation, as indicated by enhanced ($P < 0.05$) upregulation of mRNAs (Casp-1, TNF-α, IL-6, and NF-κB/P65) and protein expression (NF-κB/P65, NF-κB/P50, TNF-α, and IL-6) of inflammatory markers in contrast to controls. Interestingly, when BV was administered to GM-exposed rats, the GM harmful effect was mitigated, as evidenced by the modulation of the mRNA and protein expression levels of pro-inflammatory cytokines.

3.5 Evaluation of apoptotic marker expression in the kidney

As illustrated in Figure 4, GM intoxication substantially stimulated apoptotic cell death in renal tissue, as indicated by a noteworthy ($P < 0.05$) upregulation of protein expression levels of C. Casp3-17/19, along with an increase in Cyto c, compared to controls, suggests the promotion of apoptotic cell death. Conversely, synchronous BV administration considerably suppresses GM-

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