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Apitoxin stimulates growth factors release and alleviating the gentamicin-induced renal nephrotoxicity in male rats. A comparative therapeutic study between bee venom and Cystone®.

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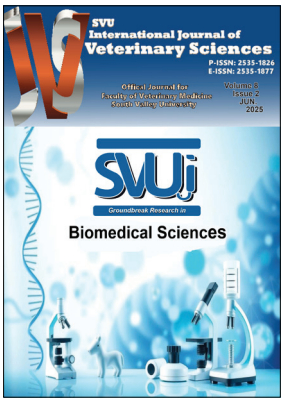

ABSTRACT

The kidney, due to its high blood flow, is particularly vulnerable to drug-induced damage and injury. Gentamicin is a widely used and highly effective antibiotic, moreover, it is a main cause of drug-induced renal injury. Therefore, identifying a natural and safe agent to mitigate Gentamicin nephrotoxicity is of utmost importance. Cystone® is a natural compound possessing antimicrobial and anti-urolithiatic properties, which help prevent stone formation. Bee venom comprises a diverse array of biologically active proteins that pharmacologically mitigate various pathological conditions. Its high-potency compounds exhibit selective and specific activities, rendering them valuable as pharmacological tools in drug research, potential templates for drug design, and therapeutic agents. Bee venom therapy is a highly effective treatment, as it stimulates the release of growth factors from activated platelets and fibroblasts in renal tissue. Specifically, Bee venom therapy upregulates the gene expression of platelet-derived growth factor, which in turn upregulates vascular endothelial growth factor, promoting tissue repair and regeneration. Moreover, our findings show that co-administration of gentamicin and Cystone® induces severe kidney damage and stone formation in rats. In contrast, Bee venom injection alleviates this detrimental effect. The present study aims to investigate the modulatory effects of Bee venom on renal tissue regeneration and gentamicin-induced renal damage. Furthermore, we seek to compare the potential protective effects of bee venom and Cystone® on gentamicin-induced renal tissue damage in rats.

Keywords: *Bee Venom, Gentamicin, Cystone®, PDGF, VEGF.*

INTRODUCTION

Bee venom (BV or Apitoxin) is a complex natural substance comprising various bioactive compounds, including biologically active amines (epinephrine and histamine), enzymes (hyaluronidase and phospholipase A2), and active polypeptides (melittin, adolapin, apamin, and the mast cell degranulation factor). Additionally, BV contains non-peptide complexes, such as lipids, carbohydrates, and amino acids. The diverse array of compounds in BV makes it a potent natural substance with numerous applications in medical and pharmaceutical preparations (El-

Seedi et al., 2020; Hider, 1988). Apitoxin, also known as bee venom, has been utilized to treat a range of conditions, including skin diseases, tumors, pain, arthritis, and rheumatism (Son et al., 2007). Previous research has consistently demonstrated that BV possesses multiple therapeutic effects, including significant anti-inflammatory and antioxidant activities (Sobral et al., 2016; Somwongin et al., 2018). Current scientific research increasingly supports natural compounds in therapeutic applications due to their favorable safety profiles and low incidence of adverse effects. For instance, Arabic Gum has been explored for its potential in addressing renal and hepatic disorders (Ahmed et al., 2022; Shanab et al., 2023), Garlic Oil and copper complex for CNS and brain affection (Ali et al., 2024; Shanab et al., 2024; Taha et al., 2022), Curcumin and/or Quercetin for male reproductive activity (Samy et al., 2023), Cuttlebone extract for diabetic burns treatment(Elshater et al, 2025). Bee venom has been shown to alleviate renal dysfunction and injury by significantly reducing levels of inflammatory cytokines. Its therapeutic effects are mediated through the suppression of inflammation, oxidative stress, and tubular cell apoptosis in the kidney (Kim et al., 2020). Bee venom promotes the release of growth factors such as fibroblast growth factor (FGF)-1 and 6, endothelial cell growth factor, and platelet derived growth factor (PDGF)-C, which stimulates tissue regeneration, facilitating the repair and renewal of damaged tissues (Kim et al., 2024). The promising results from previous studies prompted us to investigate the potential reno-protective effects of bee venom (BV) on gentamicin-induced renal damage. Gentamicin is a commonly prescribed antibiotic used to combat bacterial infections, but its prolonged clinical use is often accompanied by undesirable side effects, including inflammation, oxidative stress, and kidney dysfunction. (Ali et al.., 2011). Moreover, growth factors play a crucial role in promoting renal tissue repair and regeneration in gentamicin-induced renal dysfunction, thereby mitigating the detrimental effects of gentamicin on kidney function (Morin et al., 1992). Cystone® helps prevent the deposition and accumulation of waste products and chemicals in the urine, facilitating their excretion. Furthermore, Cystone® exhibits antimicrobial and anti-inflammatory properties, which aid in preventing urinary tract infections and reducing inflammation (Erickson et al., 2011). The primary objective of this study was to assess the potential therapeutic effects of bee venom on gentamicin-induced renal dysfunction and to compare its efficacy with that of Cystone®.

MATERIAL AND METHODS

Reagents

Gentamicin: ampoules 80 mg (Alexandria Chemical Co., Egypt), used as a dose of 100 mg/kg/day i.p (Otunctemur et al., 2013).

Bee venom: Lyophilized Apis Mellifera purified Bee venom (VACSERA, Egypt, 1mg/vial) will be used, diluted in DW. It will be injected subcutaneously at a dose of 5mg/kg according to (Hassanein and Hegab, 2010; Kim et al., 2013).

Cystone®: It will be in the form of the commercial drug Cystone®, manufactured by Himalaya Global Holdings Ltd., with a dose of 750 mg/kg diluted in DW (Patankar et al., 2020)

Experimental animals

Seventy male Sprague Dawley rats purchased from the animal house and admitted in the department of biochemistry at Faculty of Veterinary Medicine, South Valley University fed on basal ration (protein ratio is 21%), housed in the animal house (department of Biochemistry) following the ethical consideration of experimental animals of South Valley University., following the ethical consideration of experimental animals of South Valley University No. (VM/SVU/23(2)-19). The animals were acclimatized for at least 2 weeks before dosing. The rats were at the age of 7–8 weeks and weighed between 180–200 g at the start of dosing. Tap water passed through an RO system (Millipore) was given. Feed and water were provided ad libitum throughout the study period unless restricted by experimental requirements. These animals were euthanized using isoflurane and oxygen (Udupa and Prakash, 2019).

Experimental design

Seventy male rats were used and subdivided randomly into 7 groups, each group containing 10 rats as follows;

Group I (Control group): rats were fed on a basal ration, and water was injected into the S/C with saline.

Group II (BV group): rats were injected with BV at a dose of 5 mg/kg s/c twice weekly after dilution in DW (H. Kim et al., 2013).

Group III (CY group): rats received Cystone® orally with a dose of 750 mg/kg diluted in distilled water daily (Patankar et al., 2020).

Group IV (GEN group): rats were injected with GEN at a dose of 100 mg/kg/day i.p daily for one week (Otunctemur et al., 2013).

Group V (GEN/BV group): rats were injected with GEN for one week and were injected with BV at a dose of 5 mg/kg s/c twice weekly.

Group VI (GEN/CY group): rats were injected with GEN daily for one week and given Cystone® for one month orally with a dose of 750 mg/kg daily. were

Group VII (GEN/CY/BV): rats were injected with GEN daily for one week and were given Cystone® daily for one month orally with a dose of 750 mg/kg daily & injected with BV at a dose of 5 ml/kg s/c twice weekly for one month.

At the end of the experiment (one month), the animals were sacrificed by cervical decapitation, and the kidney tissue was isolated and divided into two parts: one part preserved at -80 °C for gene expression examination, and the other part kept in formalin for histo-pathological examination.

Histopathological examination;

Kidney tissues will be fixed in 10% buffered formalin solution and embedded in paraffin blocks, and 2-µm-thick sections will be prepared. Paraffinized sections will be deparaffinized with xylene and rehydrated through a decreasing gradient of ethanol solutions. Slides will be stained with hematoxylin and eosin (H&E), cover-slipped with mounting medium, and viewed under a light microscope (Shanab et al., 2023).

Conventional RT-PCR

QIAzol Reagent (QIAGEN®, QIAzolTM) was used to extract total RNA from kidney tissue, about 0.5 g/ tissue, according to the manufacturer's instructions. A Nanodrop ND-1000 spectrophotometer was used to check the total RNA concentration and quality. The RNA quality was estimated by the 260/280 nm absorbance ratio. The cDNA was synthesized from 1 µ g RNA with the RNA PCR kit with oligo (dT) primers (TaKaRa) and was then used as a template for RT-PCR analysis. The PCR reaction underwent 30 cycles of the following: initial activation at 94°C for 5 min, denaturation at 94°C for 30 s and annealing at 55°C for 30 s, and extension at 72°c for 30 s. Band intensities were quantified with the NIH Image J software (Shanab et al., 2023). Primer sequences were as in Table 1.

Table 1: Oligonucleotide Primer Sequences.

Primer	Forward (from 5' to 3')	Reverse (from 5' to 3')
VEGF	CACTGGACCCTGGCTTTACT	GACGTCCATGAACTTCACCA
PGDF	TGGAGTCGAGTCGGAAAGCT	GAAGTTGGCATTGGTGCGAT
GAPDH	GACATGCCGCCTGGAGAAAC	AGCCCAGGATGCCCTTTAGT

Table 2: Western blot antibodies.

Antibody against.	Manufacturer.	Catalog no.	Clone no.	Dilution factor.
PDGF	Cell signalling	3174	D1E1E	1/1000
VEGF-r1	Cell signaling	64094	E7T9H	1/1000
β –actin	Sigma-Aldrich	A5441	AC- 15	1/1000
Goat Anti-Rat IgG/HPR	Abcam	ab205720		1/1000

WESTERN BLOT

Protein fraction (from the kidney tissue about 0.5 gm/tissue.) extracted from the organic phase of QIAzol Reagent-processed fatty tissue samples (QIAGEN®, QIAzol™) following the manufacturer's guidelines, treated with a proteinase inhibitor cocktail (Sigma-Aldrich, Steinheim, Germany) and phosphatase inhibitor tablet (PhosStop™, Roche Diagnostics, IN, USA). Protein specimens were loaded in equal amounts, separated using SDS-polyacrylamide gel (SDS-PAGE) electrophoresis, and then blotted on a polyvinylidene difluoride membrane (Immobilon™-P PVDF membrane, Merck Millipore, MA, USA). The membranes were blocked in PBS–Tween (0.1%) with 1% BSA and were then probed with the diluted primary antibodies (as listed in Table 2). The Lumi-light Plus kit from Roche and the BioRAD Chemidoc were used to detect the bands. Intensities of bands were assessed with the NIH Image J software (Shanab et al., 2023).

Urine sample collection and analysis:

Urine samples were collected on the experiment's last day for about 24 hours by keeping animals in rat metabolic cages. During this period of urine collection, no food was offered, but water only was given. Urine samples were collected in chilled 25 ml polypropylene tubes kept in an ice container throughout the collection period for each group. After low-speed centrifugation (500g) at 4 °C for 5 min, the supernatant urine was used for the chemical analysis. Urine samples were analyzed for traditional markers like PH, specific gravity, total protein, RBCs, ketones, and WBCs using urine

test strip (Precision Laboratories, Inc.), and then the precipitate was applied for microscopical examination for crystal detection (Udupa and Prakash, 2019).

STATISTICAL ANALYSIS

One-way ANOVA or the Kruskal test, followed by Dunnett's post hoc, will be used for multiple group comparisons. All data will be expressed as means ± SE. Differences will be considered statistically significant when the P value is < 0.05.

RESULTS

Stone formation from the combination of Gentamicin and Cystone®:

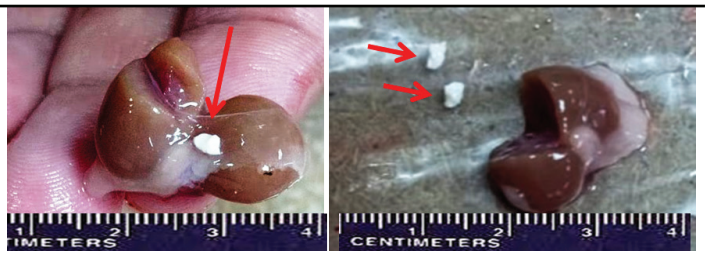

Figure 1: Stone formation from the combination of Gentamicin and Cystone®: Showing calcium oxalate stone from the kidney of Gentamicin plus Cystone® group, all rats of this group showing the same phenomena.

In the 7th group, only the GEN/CY group shows formation of calcium oxalate stone in the kidney tissue. It may be that the combination of the 2 products with each other changes the pH, leading to the formation of such a stone as shown in Fig. 1.

Urine analysis using the Multiple Urine Test Strip :

The urine strip test showed high specific gravity in the GEN/CY while the other groups were normal; the same also for the PH, which is decreased, indicating an acidic PH; for this reason, the calcium oxalate stone was formed, moreover, ketone bodies were detected in this group. Other parameters, such as RBCs, WBCs, protein, and crystals, were high in both GEN and GEN/CY groups, while after combination with the BV, most of the parameters showed a reduction in their intensities, as shown in Table 3.

Among the most important factors in tissue regeneration pathways are the PDGF and VEGF:

The protein expression levels of PDGF and VEGF in renal tissue demonstrated a substantial down-regulation in both GEN and GEN/CY groups, revealing renal tissue damage initiation following exposure to gentamicin and/or Cystone® (Fig. 2A & B). On the other hand, our use of the BV significantly up-regulated those parameters and reduced the gentamicin and/or with Cystone® -induced renal damage and nephrotoxicity.

Bee venom upregulates the mRNA expression of PDGF and VEGF in the renal tissue of rats:

The mRNA expression levels of PDGF and VEGF in renal tissue demonstrated a substantial down-regulation in both GEN and GEN/CY groups, revealing

Table 3: Urine analysis results

	Control	BV	CY	GEN	GEN/BV	GEN/CY	GEN/CY/BV
PH	7	7	7.5	7	7	5	6
Specific Grav.	1025	1025	1025	1025	1025	1035	1025
RBCs	-	-	+	+++	++	+++++	++
Protein	-	-	+	+++	+	++++	++
Ketone	-	-	-	-	-	+	-
Crystals	-	-	+	++	-	++++	+
WBCs	-	-	-	-	-	+++	+

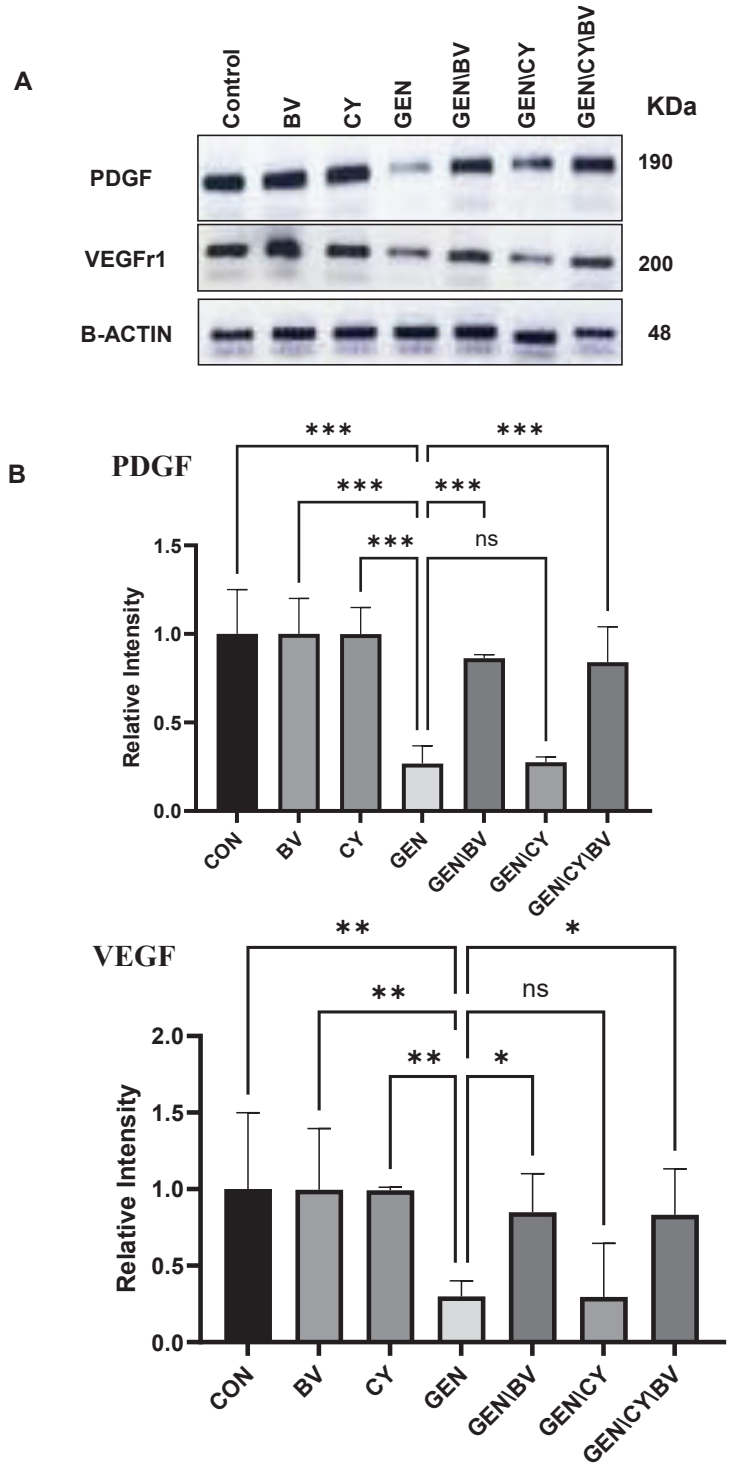

Figure 2: Bee Venom up-regulates the Protein expression of PDGF and VEGF in renal tissue. Panel A description: Western blot analysis for protein expression of PDGF and VEGF in rat renal tissue with β-actin as loading control. Molecular weights are indicated in KDa . Panel B description : Quantification band intensity was measured by IMAGE J software. Data presented as fold change (%)compare to control, Statistical information: Values represent mean ± SE from three independent experiments

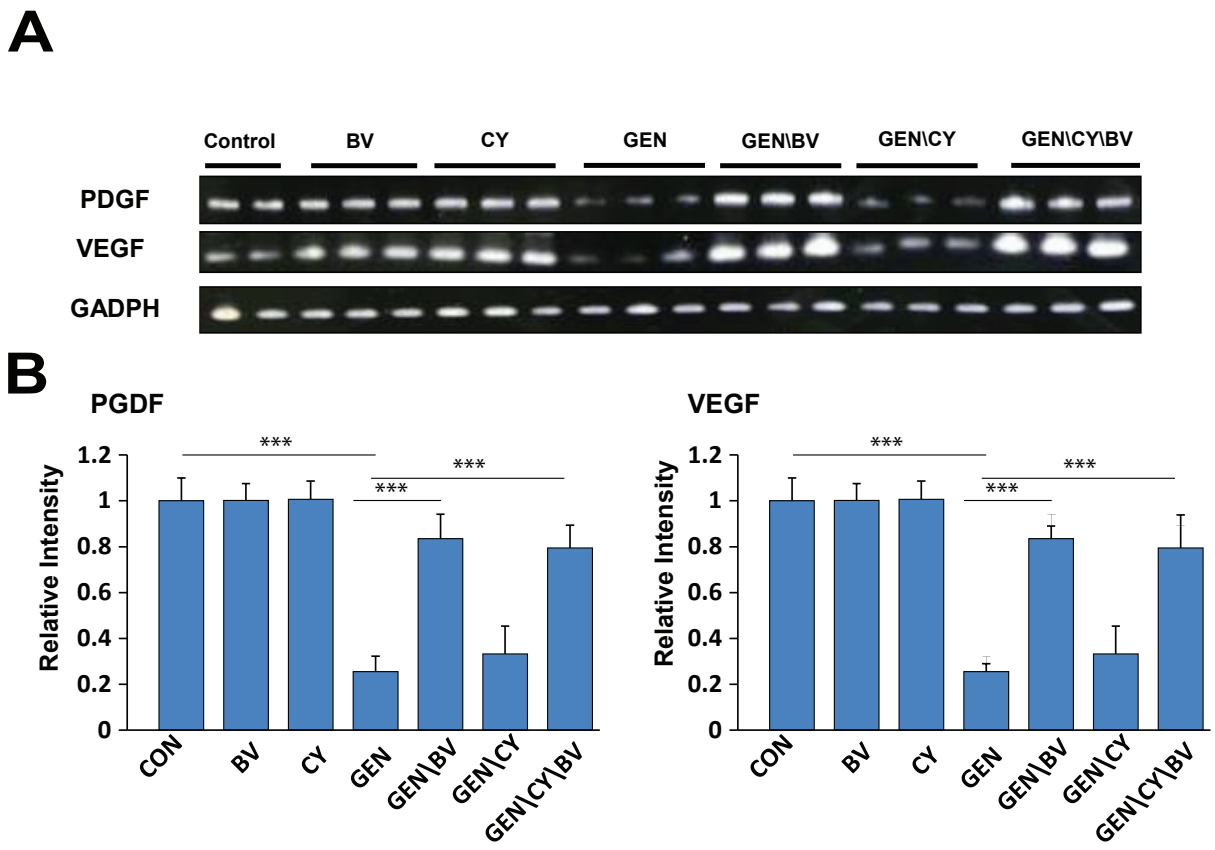

Figure 3: Bee Venom up-regulates the mRNA expression of PDGF and VEGF in renal tissue. Panel A description: Conventional PCR analysis for mRNA expression of PDGF and VEGF in rat renal tissue with GAPDH as loading control. Panel B description: Quantification the band intensity was measured by IMAGE J software. Data presented as fold change (%) compare to control, Statistical information: Values represent mean ± SE from three independent experiments .* P<0.05 compared to control .

renal tissue damage initiation following exposure to gentamicin and/or Cystone® (Fig. 3A & B). On the other hand, our use of the BV significantly up-regulated those parameters and reduced the gentamicin and/or with Cystone® -induced renal damage and nephrotoxicity, showing the efficacy of the BV along the molecular and genetic levels

Histopathology of kidney tissue confirms the ability of BV for induction of tissue regeneration:

Microscopically, normal architecture of renal glomeruli and tubules was observed in the Control, bee venom-treated, and Kidneys of Cystone® treated group showed normal tissues. The gentamycin group showed necrosis and dilated tubules with mononuclear cell infiltration. Gentamycin plus bee venom mild inflammatory cells and few necrosed cells with regenerated tubules. Gentamycin plus Cystone® showed severe interstitial hemorrhage, necrosis, and thick walls of blood vessels and cystic dilated tubules. Gentamycin plus Cystone® plus bee venom-treated groups showed regenerated renal tubule cells, as shown in Fig. 4.

All the previous data showed the efficacy of BV as a novel therapeutic potential to alleviate the renal damage or gentamicin-induced nephrotoxicity.

DISCUSSION

Apitoxin can do various biological activities in vivo, such as its anti-inflammatory, anti-cancer, and antimicrobial properties (Wehbe et al., 2019). Bee venom is a complex mixture containing various bioactive compounds, although studies are still needed to investigate its beneficial properties and the molecular mechanisms that can be enhanced. From those mechanisms which activated by BV is the production and the release of growth factors such as FGF-1 and 6, endothelial cell growth factor, PDGF as mentioned by (Kim et al., 2024), which comes following our current data where is the PDGF and VEGF were up regulated in

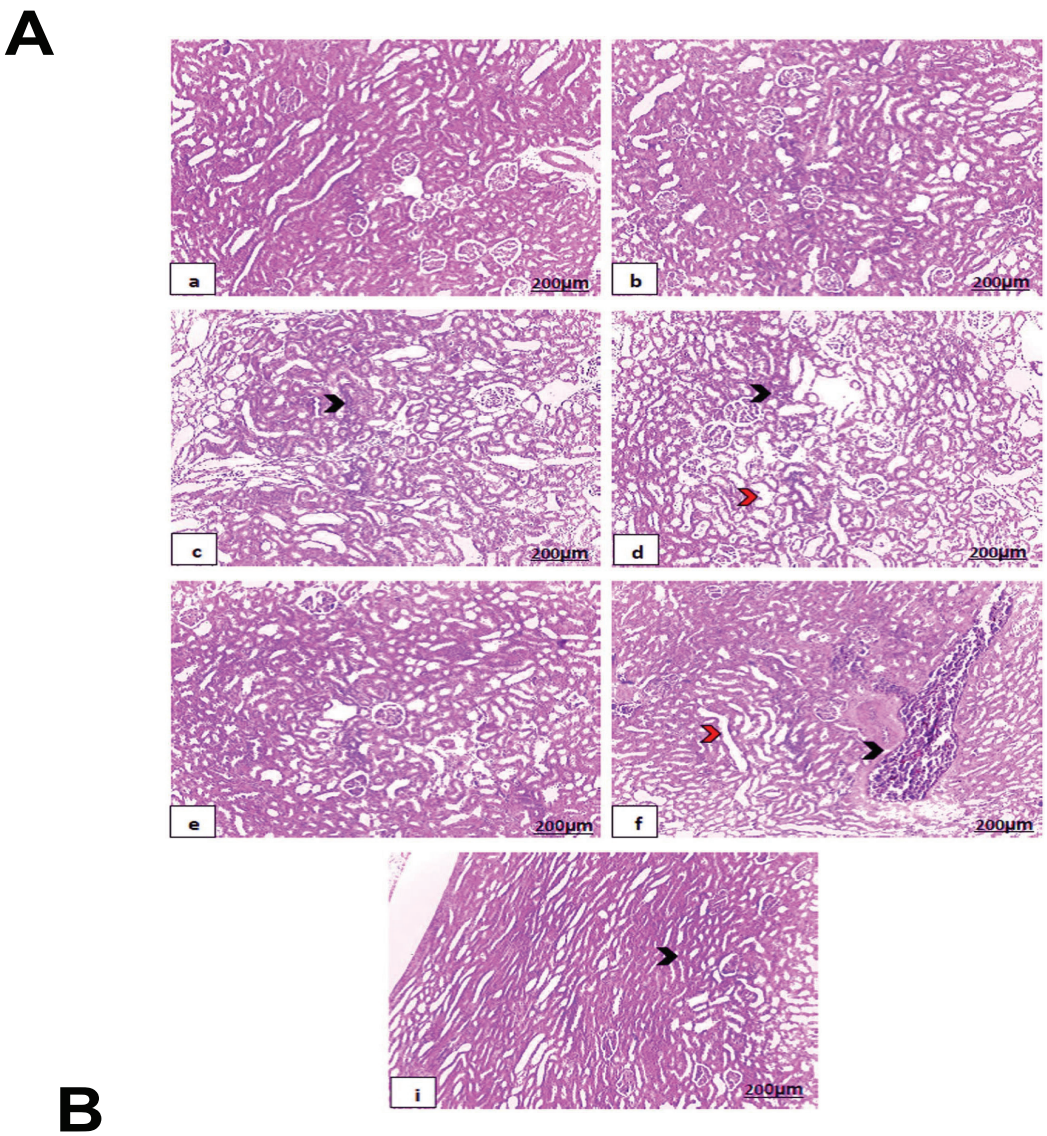

Figure 4: Histopathology of kidneys tissue in Control, Bee venom, Cystone®, Gentamycin, Gentamycin plus bee venom, Gentamycin plus Cystone® and Gentamycin plus Cystone® plus bee venom treated groups. Panel A description: Microscopic examination of kidney tissue in all treated groups. Figure a and b: normal architecture of renal glomeruli and tubules was observed in the Control and bee venom treated groups respectively. Figure c: Kidneys of Cystone® treated group showed apparently normal tissues. Figure d: gentamycin group showed necrosed and dilated tubules (black arrow) with mononuclear cells infiltration (red arrow). Figure e: Gentamycin plus bee venom showed mild inflammatory cells and few necrosed cells with regenerated tubules. Figure f: Gentamycin plus Cystone® showed sever interstitial hemorrhage (black arrow), necrosis and thick wall of blood vessels and cystic dilated tubules. Figure I: Gentamycin plus Cystone® plus bee venom treated groups showed regenerated renal tubule cells. Panel B description: scoring rate of tissue damage was measured by IMAGE J software, Statistical information: Values represent mean ± SE from three independent experiments . $P<0.05$ compared to control .*

the renal tissue after intoxication by gentamicin or the combination of gentamicin and Cystone. According to our results, in-between all the 7th group only the GEN/CY group showing formation of calcium oxalate stone in the kidney tissue it is may be the combination of the 2 products with each other change the PH lead to formation of such a stone as showed in Fig. 1, which means that the co-administration of gentamicin and Cystone should be avoided. PDGF is one of the growth factors released from activated platelets, which has a central role in cell growth, division and development (Festa et al., 2011), our data showed that the protein expression levels of PDGF and VEGF in renal tissue demonstrated a substantial down-regulation in both GEN and GEN/CY groups, revealing renal tissue damage initiation following exposure to gentamicin and/or with Cystone® (Fig 2A & B). On the other hand, using the BV significantly up-regulated those parameters and reduced the gentamicin and/or with Cystone® -induced renal damage and nephrotoxicity. Moreover, the mRNA expression levels of PDGF and VEGF in renal tissue demonstrated a substantial down-regulation in both GEN and GEN/CY groups, revealing renal tissue damage initiation following exposure to gentamicin and/or with Cystone® (Fig 3A & B). On the other hand, our using the BV significantly up-regulated those parameters and reduced the gentamicin and/or with Cystone® -induced renal damage and nephrotoxicity, showing the efficacy of the BV along the molecular and genetic levels. According to our previous finding, which showed that both gentamicin and/or Cystone treatment induce an elevation of the kidney function parameters while co-treatment with BV shows normal kidney function parameters (Abdelrahaman et al.,2025), it is consistent with our current data. In hepatocytes, when it treated with BV resulted in a significant reducing in the apoptosis morphological characteristics which including cell shrinkage, nuclear condensation and fragmentation of DNA as showed by (Park et al., 2010), our data also comes following those data as the reduction of apoptosis via down-regulation of the cleaved caspase3 (data not showed), and enhancement of the cell regeneration, cell growth and repair. Gentamicin-induced nephrotoxicity is mostly associated with the presence of desquamation of cellular components, glomerular atrophy, necrosis, fibrosis, and inflammation (Lakshmi and Sudhakar, 2010), the histopathological data in our current research all comes following our hypothesis where the tissue microscopically, showed normal architecture of renal glomeruli and tubules was observed in the Control, bee venom treated and Kidneys of Cystone® treated group showed normal tissues. While the gentamycin group showed necrosis and dilated tubules with mononuclear cell infiltration. Gentamycin plus bee venom mild inflammatory cells and few necrosed cells with regenerated tubules. Gentamycin plus Cystone® showed severe interstitial hemorrhage necrosis and thick walls of blood vessels and cystic dilated tubules. Gentamycin plus Cystone® plus bee venom treated groups showed regenerated renal tubules cells as showed in (Fig 4). Furthermore, Gentamycin or Gentamycin plus Cystone® increase the production of ROS which in turn accelerates the renal damage. Our results suggested that BV can inhibit the ROS-producing cellular regeneration. Cystone is a natural compound that useful in prevention of accumulation and deposition of chemicals such as oxalic acid and calcium, furthermore inhibits the urinary stones formation (Jayaramaiah et al., 2013), due to the adverse effects of co-administration of gentamicin and Cystone, urine strip test showing high specific gravity in the GEN/CY while the other groups were normal, the same also for the PH which is decreased indicating an acidic PH, for that reason the calcium oxalate stone was formed, moreover ketone bodies were detected in this group. Other parameters such as RBCs, WBCs, protein, and crystals were high in both GEN and GEN/CY groups, while after combination with the BV, most of the parameters showed reduction in their intensities, as shown in Fig. 2, which indicates the severe renal damage that reflected on the urine composition. Unfortunately, the combination of cystone and gentamicin increases the deposition of oxalic acid and calcium, producing heavy amounts of calcium oxalate stones, which induces renal damage significantly than using gentamicin only in accordance with our results. It may occur due to the change in the PH. Using the BV reduced the unfavorable adverse effects of the combination of cystone and gentamicin. Our current study maintains an optimistic, hopeful outlook about the damaged renal tissue regeneration via using the BV, which can potentially revolutionize our hypothesis

of the renal cell regeneration cycle. All the previous data showed the efficacy of BV as a novel therapeutic potential to alleviate renal damage or gentamicin-induced nephrotoxicity.

CONCLUSION:

In conclusion, gentamicin-induced nephrotoxicity in rats can be alleviated via s/c injection of BV or apitoxin. As the BV treatment enhanced the release of growth factors such as PGDF and VEGF, which are among the most highly elevated growth factors, it enhanced the cell cycle and promoted regeneration of the renal tissue. According to our data, we also conclude to avoid administration of Gentamicin in combination with Cystone, as it changes the pH and leads to accumulation and deposition of calcium oxalate crystals, which in turn induce the stone formation and inflammatory changes.

All those side effects and the huge damage can be significantly diminished by the injection of Bee Venom.

Conflict of interest: The authors declare that they have no competing interests or conflicts of interest.

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Authors Contributions: OS, AG, ZM, ASM & LM Supervision, review, and editing of the manuscript. HG, MA, FM & OS carried out all the experimental procedures. OS, AG, ZM, ASM & LM: Investigation, Supervision, carried out RT-PCR study, writing, review & editing the manuscript.

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