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Low Dose γ-radiation or CoQ10 against Bee Venom Toxicity in Rats: Hepatic, Renal and Neurochemical Evaluation

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THIS study evaluates the efficacy of coenzyme Q10 (CoQ10) and low-dose gamma radiation (LDR) on rats' liver, kidney, and brain when exposed to bee venom toxicity.

The rats received two doses of CoQ10 (10 mg/kg i.p.) for two days in a row or 0.5 Gy whole-body gamma irradiation after receiving a bee venom injection (5 mg/kg i.p.).

The collected data showed that serum hepato-renal indices and pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), were significantly elevated by crude bee venom in the liver, kidney, and brain tissues. Conversely, brain mediators, such as serotonin, norepinephrine, and dopamine, were suppressed. Furthermore, there was a notable deviation in MDA, AOPP and GSH levels from the control values, indicating oxidative stress incidence. Remarkably, LDR or CoQ10 mitigated rats' negative reactions to bee venom and restored the measured parameters to their baseline levels.

In conclusion, by virtue of their abilities to improve the aforementioned biochemical parameters—which were corroborated by histological analysis—LDR or CoQ10 provided renal, hepatic, and brain rehabilitation against bee venom toxicity.

Keywords: Bee venom, γ-radiation, CoQ10,liver, kidney, brain.

Introduction

The use of bee venom as a therapeutic agent for the relief of joint pains dates back to Hippocrates, and references to the treatment found in ancient Egyptian and Greek medical writings. It is also known as a pitherapy and is widely used in Eastern Europe, Asia, and South America (Alqutub et al., 2011). The venom can be introduced into the human body through manual injection or direct bee stings. Bee venom (BV) contains several active molecules such as peptides and enzymes that have advantageous potential in treating inflammation and central nervous system diseases. Moreover, bee venom has shown promising benefits against different types of cancer as well as anti-viral activity, even against the challenging human immunodeficiency virus (HIV). Many studies described the biological activities of bee venom components and launched preclinical trials to improve the potential use of apitoxin and its constituents as the next generation of drugs (Wehbe et al., 2019).

BV is an odorless and transparent liquid containing a hydrolytic mixture of proteins with acid

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pH (4.5 to 5.5). One drop of BV consists of 88% of water and only 0.1 µg of dry venom (Bellik, 2015). The latter is an extremely complex blend of peptides including melittin, adolapin, apamin, and MCD-peptide. It also contains enzymes, most importantly phospholipase A2, and compounds of low molecular weight like bioactive amines (e.g., histamine and epinephrine) and minerals (Moreno and Giralt, 2015).

Bee venom is characterized by inducing allergic reactions following the sting. These reactions can take place in the skin, the respiratory track, the cardiovascular system, and the gastrointestinal system. Subsequently, severe anaphylactic shock could lead to cerebral or myocardial ischemia (Bilò and Bonifazi, 2009 and Golden, 2007). These allergic responses are due to the presence of multiple protein allergens, most of which possess an enzymatic activity (Moreno and Giralt, 2015).

Melittin is the primary toxic compound in bee venom, making up between 50 and 60 percent of the entire venom. It is responsible for most pain felt after a bee sting, activating pain receptors. Melittin is a lytic peptide that can break down membrane phospholipids, including erythrocytes, causing hemolysis and tissue damage (Raghuraman et al., 2007; Chen et al., 2016 and Memariani et al., 2019). Other poison components are apamin, peptide 401, phospholipase A2, hyaluronidase, histamine, dopamine, and norepinephrine (Junior et. al., 2017).

Multiple stings are known to cause hemolysis, kidney injury, hepatotoxicity and myocardial infarction. The toxicity can be immediate or can appear only weeks after the exposure (Alqutub et al., 2011). Animal models have been used to study the toxicity caused by bee stings. Bee stings cause hemoconcentration which might be related to the marked edema induced by the venom. Following bee stings there is an increase in various cytokines like interleukin (IL)-1β, IL-6, tumor necrosis factor-α, *etc*. In a mouse model using the subcutaneous route, rapid increases in serum liver enzymes, creatinine, urea nitrogen, uric acid, sodium and chloride electrolytes, and creatine kinase were recorded, indicating damage to the liver, kidneys, and skeletal muscle (Prado et al., 2010) in addition to adverse effects on cardiovascular, central nervous, and immune systems (Gupta et al., 2016).

Some unusual neurologic complications such as myasthenia gravis, peripheral neuritis, encephalomyelitis, optic neuritis, cerebral infarction, parkinsonism, trigeminal neuralgia, pontine hematoma, and thalamic and mesencephalic hemorrhages as well as the Guillain-Barré syndrome can also be related to bee stings (Dikici et al., 2012).

Low-dose gamma radiation (LDR) has beneficial biological effects generally termed as 'radiation hormesis', but yet little is known about its mechanism(s). Recent reports have shown differential gene expression pattern both *in vivo* and *in vitro* after exposure to LDR which regulate the cell cycle and cell proliferation (Amundson et al., 2003 and Lee et al., 2006). Recently, the effects of low-dose irradiation on antioxidant defense system in different organs showed an improvement in the levels of reduced glutathione (GSH) and antioxidant enzyme activities in the brain (Kojima et al., 1998), spleen (Kojima et al., 2000), liver (Kojima et al., 1997), lung (Avti et al., 2005), bone marrow, thymus (Yamaoka et al., 1991), macrophages (Kawakita et al., 2003) and natural killer cells (Kojima et al., 2002).

Coenzyme Q10 (CoQ10) is a natural hydrophobic compound that is not only a vital component of mitochondrial respiration but also a powerful antioxidant (Sohet et al., 2009). Rat exposure to CoQ10 is associated with protective effects on lead and cadmium mediated toxicity of brain, kidney, liver, and endocrine system (Abdulidha et al., 2020).

It was demonstrated by Pucca et al. (2019) that there is no antivenom for treating severe bee envenomations. That is the underlying reason for this study to ascertain the effectiveness of administering a low dose of whole-body gamma radiation or injecting CoQ10 as a means of mitigating the toxicity of high doses of crude bee venom.

Materials and Methods

Experimental animals

Adult male Wistar albino rats (130 – 150 g) were obtained from the National Center for Radiation Research and Technology (NCRRT). Animals were kept under standard conditions of humidity and temperature (22-24^{o}C) along the experimental period and under a light/dark cycle of 12/12. All animals were fed on standard pellets of a concentrated diet containing all the necessary nutritive elements (23% protein, 4.68% fats and 2.6% fibers) and allowed free access to water. Our study was conducted according to

the recommendations outlined in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (NIH no. 85:23, revised 1996) and in compliance with regulations set by the ethical committee for animal care at the NCRRT, Atomic Energy Authority, Cairo, Egypt.

Bee Venom

Lypholized bee venom of *Apis Mellifera* (BV) (1 mg/ vial) was obtained from VACSERA vaccination center, Cairo, Egypt. Raw bee venom was dissolved using saline to a concentration of 5 mg/Kg according to the method described by Nahed and Amany (2010).

Coenzyme Q10

Coenzyme Q10 (CoQ10) (30mg/Hard gelatin capsule) which is a product produced by Arab Company for Pharmaceutical & Medical Plants (MEPACO-MED/FOOD) was dissolved using saline to a concentration of 10mg/kg according to the method of Alhusaini et al. (2022).

Radiation source

The whole body of rats was exposed to LDR (0.5 Gy) using ^{137}Cs irradiation unit, model Gamma cell-40 at NCRRT, delivered at a dose rate of 0.44 Gy/min.

Experimental design

Twenty-four rats were divided into four groups (6 rats/group); group I (Control group) rats were injected intraperitoneally (i.p.) with saline. Group II (BV group) rats were injected i.p. with a single dose of 5 mg/Kg of crude bee venom. Group III (BV+LDR group) rats were injected i.p. with 5 mg/Kg of bee venom then after three hours were exposed to a single dose of 0.5 Gy gamma radiation. Group IV (BV+Co group) rats were injected i.p. with 5 mg/Kg of bee venom then were injected i.p. with two doses of 10mg/kg CoQ10 for two consecutive days, the first dose was injected two hours after the injection of bee venom. All groups were sacrificed to LDR and CoQ10 injection on the second day of exposure.

Sampling

Blood samples were collected by heart puncture; blood was allowed to stand for half an hour and then was centrifuged at 5000 r.p.m. for 15 minutes at 4°C in order to separate serum then stored at -20°C till analysis. Liver, kidney and brain samples were immediately removed, rinsed with saline to eliminate blood contamination, dried by blotting with filter paper and then divided into two parts for various biochemical and histopathological examination.

Assessment of liver function in serum

Alanine amino transferase (ALT) and aspartate aminotransferase (AST) were estimated using commercial kits (Cat No. MBS269614 and MBS264975 respectively) according to the manufacturer's instructions to determine liver injury.

Assessment of renal function in serum

The levels of urea, albumin and creatinine were determined using commercial kits (Cat. No. MBS2600001, Cat. No. KA0501V.02 and Cat. No. MBS749827 respectively) according to the manufacturer's instructions to evaluate renal injury.

ELISA assessment of brain serotonin, nor-epinephrine and dopamine

The levels of serotonin, nor-epinephrine and dopamine levels were estimated using Elisacommercial kits (Cat. No. LS-F27987, MBS269993 and DOU39-K01 respectively) in accordance with the manufacturer's instructions.

Assessment of oxidative stress indices in blood and serum

Lipid peroxidation depends on detecting Malondialdehyde (MDA), which interacts with thiobarbituric acid in an acidic media to give a pink-colored trimethine complex at 532 nm (Senthilkumar et al., 2020).

Microplate reader (990 win6 software for DV990BV4.GIO.DE VITA. Roma, Italy), spectrophotometry was used to determine the advanced oxidative protein product (AOPP). Chloramine-T solutions, which were measured at 340 nm in the presence of potassium iodide, were used for calibration (Witko-Sarsat et al. 1998). AOPP concentrations were expressed as µmol/L of chloramine-T equivalents.

Spectrophotometry was used to measure the reduced glutathione (GSH) level in blood at 412 nm based on the development of a yellow color (Rahman et al., 2006).

ELISA assessment of liver, kidney and brain pro-inflammatory biomarkers

Interleukin 1 beta (IL-1β), Tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) levels were detected in liver, kidney and brain tissue homogenates using ELISA kits (Cat. No. E-EL-R0012 96T, abx050220 and SEA079Ra respectively) as mentioned by the manufacturer's instructions.

Histopathological examination

Liver, kidney and brain tissues specimens were collected from all animal groups. Liver tissue specimens were fixed in 10% neutral buffered formalin, then trimmed off, washed and dehydrated in ascending grades of alcohol. The dehydrated specimens were then cleared in xylene, embedded in paraffin blocks and sectioned at 4-6 µm thick. The obtained tissue sections were deparaffinized using xylol and stained using hematoxylin and eosin (H&E) for histopathological examination through the electric light microscope according to Bancroft et al. (2013).

The frequency and severity oflesions in the liver were assessed semi-quantitatively (Table 1) as previously reported by Plaaand Charbonneau (1994).

Histological grading to renal damage with especial reference to renal tubules was done (Table 2) as that recorded by Zhang et al. (2008).

Seven parameters were evaluated; microglial reaction, inflammatory reaction, vascular telengiectasis, endothelial enlargement, edema, and axonal damage. The damage severity score in the tissue and cells was determined. Each criterion was scored from 0 to 3(0 score = normal histology, 1 = mild damage, 2 = moderate damage, 3 = severe damage) as recorded by Takahashi et al. (2002).

TABLE 1. Grading scale of hepatic lesions.

Score	Lesion
0	No apparent injury
I	Swelling of hepatocytes
II	Ballooning of hepatocytes
III	Lipid droplets in hepatocytes
IV	Necrosis of hepatocytes.

TABLE 2. Grading scale of renal lesions.

Score	Lesion
0	Normal histology
1	Tubular epithelial cell degeneration, without significant necrosis or apoptosis
2	Tubular epithelial cell necrosis and apoptosis <25%
3	Tubular epithelial cell necrosis and apoptosis <50%
4	Tubular epithelial cell necrosis and apoptosis <75%
5	Tubular epithelial cell necrosis and apoptosis ≥ 75%

Statistical analysis

Statistical analysis was performed by one-way analysis of variance (ANOVA) followed by Tukey–Kramer' s multiple range test using statistical package of social science (SPSS, Chicago, IL) version 21.0 for windows. $P < 0.05$ was considered as the level of significance. Values expressed are means ± standard error (SEM).

Results

The impact of exposure to low-dose gamma irradiation (LDR)0.5Gy or coenzyme Q10 (CoQ10) treatment on rat's liver function that were anguished by bee venom (BV) toxicity

Figure 1 illustrates the activities of hepatic enzymes, AST and ALT in various experimental groups. As for the effect on liver functions, the serum activities of AST and ALT markedly increased in rats subjected to bee venom relative to the control group. This elevation in serum transaminases is considered one of the most sensitive indices of hepatic damage. Treatment with LDR (0.5Gy) or CoQ10 significantly reduced the enzymatic activities compared to the BV-injected group.

The impact of exposure to low-dose gamma irradiation (LDR)0.5Gy or coenzyme Q10 (CoQ10) treatment on rat's renal function that were anguished by bee venom (BV) toxicity

BV administration led to an increase in the rat's renal urea, albumin and creatinine compared to the corresponding normal values. The data indicated that LDR or CoQ10s suppressed the elevation of serum urea, albumin and creatinine levels in BV-administered rats (Fig. 2).

The impact of exposure to low-dose gamma irradiation (LDR)0.5Gy or coenzyme Q10 (CoQ10) treatment on rat's brain contents of serotonin, norepinephrine and dopamine that were anguished by bee venom (BV) toxicity

Injection of BV resulted in an increase in brain mediators (serotonin, norepinephrine and dopamine) compared to the control animals. In contrast, this effect was alleviated by when rats were treated with LDR or CoQ10, as proved by a decline in serum brain mediators in the comparison with BV-injected rats (Fig. 3).

The impact of exposure to low-dose gamma irradiation (LDR)0.5Gy or coenzyme Q10 (CoQ10) treatment on rat's oxidative stress indicesthat were anguished by bee venom (BV) toxicity

As shown in Fig. 4, BV-administrated rats had a significant elevation in serum levels of MDA

and AOPP as compared to the control values. In addition, a significant decline in levels of serum GSH was detected in BV-treated rats relative to the control group. LDR or CoQ10 attenuates the injurious effect of BV and ameliorates the oxidative stress enhanced by BV.

The impact of exposure to low-dose gamma irradiation (LDR)0.5Gy or coenzyme Q10 (CoQ10) treatment on rat's hepatic, renal and cerebral pro-inflammatory biomarkers that were anguished by bee venom (BV) toxicity

In the BV group, hepatic, renal and cerebral pro-inflammatory cytokines TNF-α, IL-1β and IL-6 contents were significantly higher compared to the control group, indicating the progression of an inflammatory response. On the other hand, treatment with LDR or CoQ10 after BV administration tended to normalize pro-inflammatory cytokine contents in all examined tissues (Fig, 5-7).

The impact of exposure to low-dose gamma irradiation (LDR) 0.5Gy or coenzyme Q10 (CoQ10) treatment on rat's liver, kidney and brain histopathological status that were anguished by bee venom (BV) toxicity

The liver tissue section of the control group displayed normal hepatic lobules made up of radiating plates or strands of polygonal cells with prominent round nuclei and eosinophilic cytoplasm vertical to a central vein, Sinusoids lined by a discontinuous layer of fenestrated endothelial cells with a fine arrangement of Kupffer cells (Fig. 8a) (score 0). Rats exposed to toxic bee venom dose exhibited disorganization of the hepatic cords and swelling of hepatocytes along with granularity of their cytoplasm. Narrowing of hepatic sinusoids and hyperplasia of Kupffer cells were noticed. Disorganization of hepatic cords and necrobiotic changes of hepatocytes characterized by a few numbers of micro-vesicular steatosis, nuclear pyknosis and apoptosis were seen (Fig. 8b) (score IV). Bee venom + LDR group showed ballooning degeneration of hepatocytes. Narrowing of sinusoids with hyperplasia of Kupffer cells was seen (Fig. 8c) (score II). On the other side, the liver tissue section of bee venom + Co group showed swelling of hepatocytes and granularity of cytoplasm. Narrowing of hepatic sinusoids and hyperplasia of Kupffer cells was noticed (Fig. 8d) (score I).

The kidney tissue section of the normal control group showed a normal histological structure characterized by circumscribes glomeruli with normal structure of capillary tufts and Bowman's capsule. The renal tubules of both proximal and distal convoluted tubules showed intact epithelial lining and regular arrangement (Fig. 8a\) (score 0). The kidney tissue section of bee venom group rats showed congestion of capillary tufts of some glomeruli. The renal tubules showed epithelial cell degeneration with marked swelling of the tubular epithelial lining accompanied by narrowing and occlusion of the tubular lumen by albuminous and cellular casts. Tubular epithelial cell necrosis and apoptosis <50% (Fig. 8b\) (score 3) were also seen. Interstitial oedema with mononuclear cell infiltration, mainly lymphocytes and macrophages, was noticed. The group exposed to bee venom and then treated with low-dose radiation revealed shrinkage of capillary tufts with widening of Bowman's space of some glomeruli. Degeneration of renal tubular epithelial lining appeared in the form of swelling and granularity of its cytoplasm without significant necrosis or apoptosis (Fig.8c\) (score 1). On the other side, the kidney tissue section of the rats treated with coenzyme Q10 showed improvement, which appeared as the normal histological structure of glomerular capillary tufts and Bowman's capsule. The renal tubules of both proximal and distal convoluted tubules showed intact epithelial lining and regular arrangement (Fig.8d\) (score 0).

Light microscopic examination of the cerebral cortex of a normal control male albino rat showed normal histological structure, which consisted of several layers of neuronal cells arranged with no sharp boundaries in association with small blood vessels in-between (Fig.8a\\) **(**score 0). The hippocampus section showed normal layers of compact granular cells with dark nuclei. The molecular layer showed glial cells as well as pyramidal cells (Fig.8a\\\) (score 0)**.**

The cerebral cortex of the animal group exposed tobee venom showed focal gliosis and apoptosis of neuronal cells, which appeared as densely basophilic bodies surrounded by a halo zone (Fig.8b\\) (score 3). The histological section of the hippocampus revealed cellular disorganization and marked shrinkage in size and number of large pyramidal cells, with darkened nuclei. Vacuolar degeneration of granular cell layers and nuclear pyknosis of some pyramidal cells were also noticed (Fig. 8b\\\) (score 3). On the other side, the third group showed mild improvement in comparison with the previously

untreated group and appeared to have moderate neuronal degeneration characterized by nuclear pyknosis, which is surrounded by glial cells. Vascular dilatation and perivascular oedema were also seen (Fig. 8c\\) (score 2). The histological section of the hippocampal revealed cellular disorganization with vacuolar degeneration of granular cell layers and nuclear pyknosis of some pyramidal cells (Fig. 8c\\\). The fourth group showed mild swelling of neuronal cells. Dilatation of cerebral capillaries with perivascular oedema (Fig. 8d\\) (score 1). The histological section of the hippocampus revealed cellular disorganization and vacuolations of some granular cell layers(Fig. 8d\\\) (score 1).

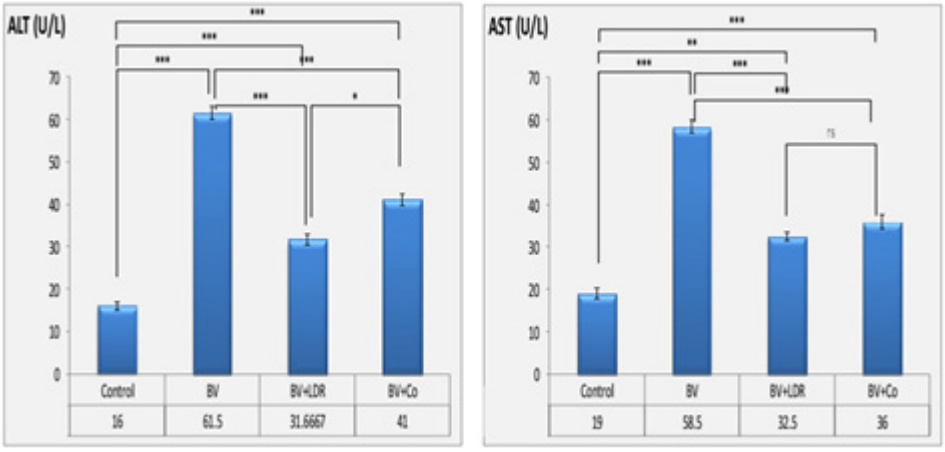

Fig .1. Effect of exposure to low dose whole body gamma irradiation (LDR; 0.5Gy) and administration of coenzyme Q10 (CoQ10) on serum ALT and AST in bee venom induced toxicity in rats.

Data represent the mean of 6 animals ± SEM. Statistical analysis was carried out by one way ANOVA followed by Tukey-Kramer multiple comparisons test. *Significantly different at $p < 0.05$.** Significantly different at $p < 0.01$. *** Significantly different at $p < 0.001$. ^{NS} Nonsignificant at $p > 0.05$.

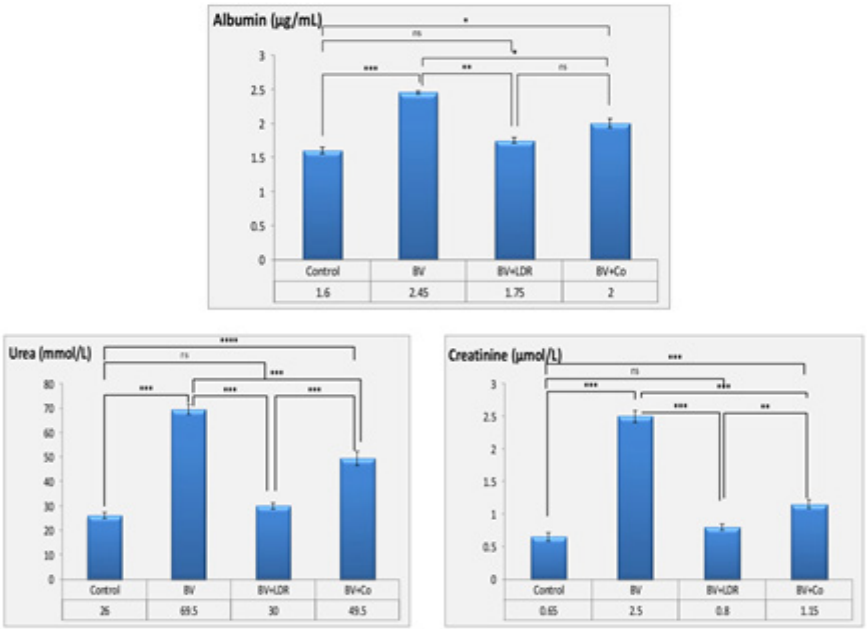

Fig .2. Effect of exposure to low dose whole body gamma irradiation (LDR; 0.5Gy) and administration of coenzyme Q10 (CoQ10) on serum urea, albumin and creatinine in bee venom induced toxicity in rats.

Data represent the mean of 6 animals ± SEM. Statistical analysis was carried out by one way ANOVA followed by Tukey-Kramer multiple comparisons test. *Significantly different at $p<0.05$.** Significantly different at $p < 0.01$. *** Significantly different at $p < 0.001$. ^{NS} Nonsignificant at $p > 0.05$.

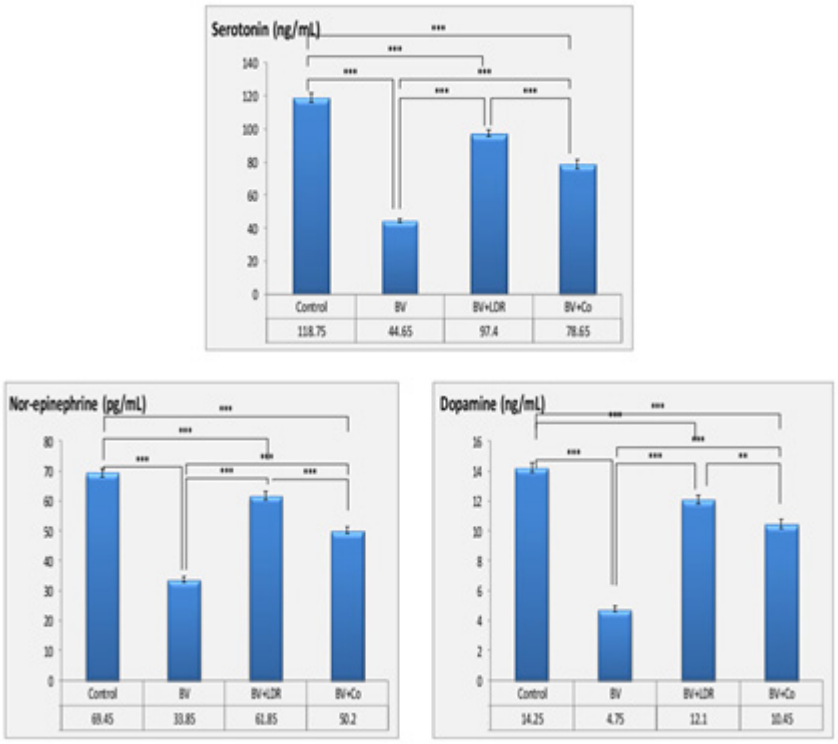

Fig . 3. Effect of exposure to low dose whole body gamma irradiation (LDR; 0.5Gy) and administration of coenzyme Q10 (CoQ10) on serum serotonin, norepinephrine and dopamine in bee venom induced toxicity in rats.

Data represent the mean of 6 animals± SEM. Statistical analysis was carried out by one way ANOVA followed by Tukey-Kramer multiple comparisons test. *Significantly different at p <0.05.** Significantly different at p < 0.01. *** Significantly different at p < 0.001. ^{NS} Nonsignificant at p > 0.05.

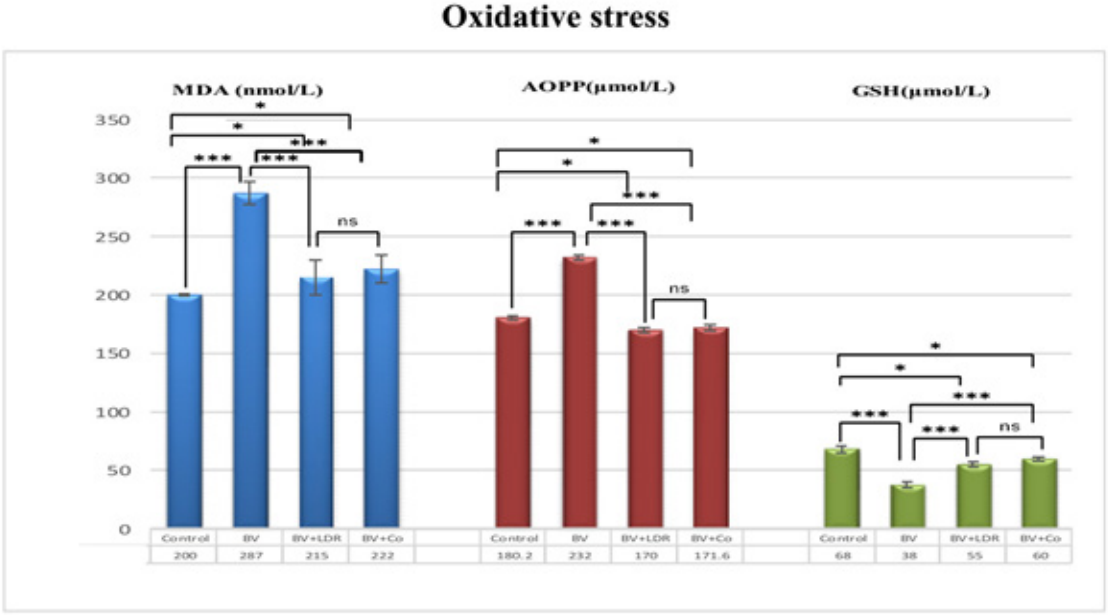

Fig. 4. Effect of exposure to low dose whole body gamma irradiation (LDR; 0.5Gy) and administration of coenzyme Q10 (CoQ10) on oxidative stress indicesin bee venom induced toxicity in rats.

Data represent the mean of 6 animals ± SEM. Statistical analysis was carried out by one way ANOVA followed by Tukey-Kramer multiple comparisons test. *Significantly different at p <0.05.** Significantly different at p < 0.01. *** Significantly different at p < 0.001. ^{NS} Nonsignificant at p > 0.05.

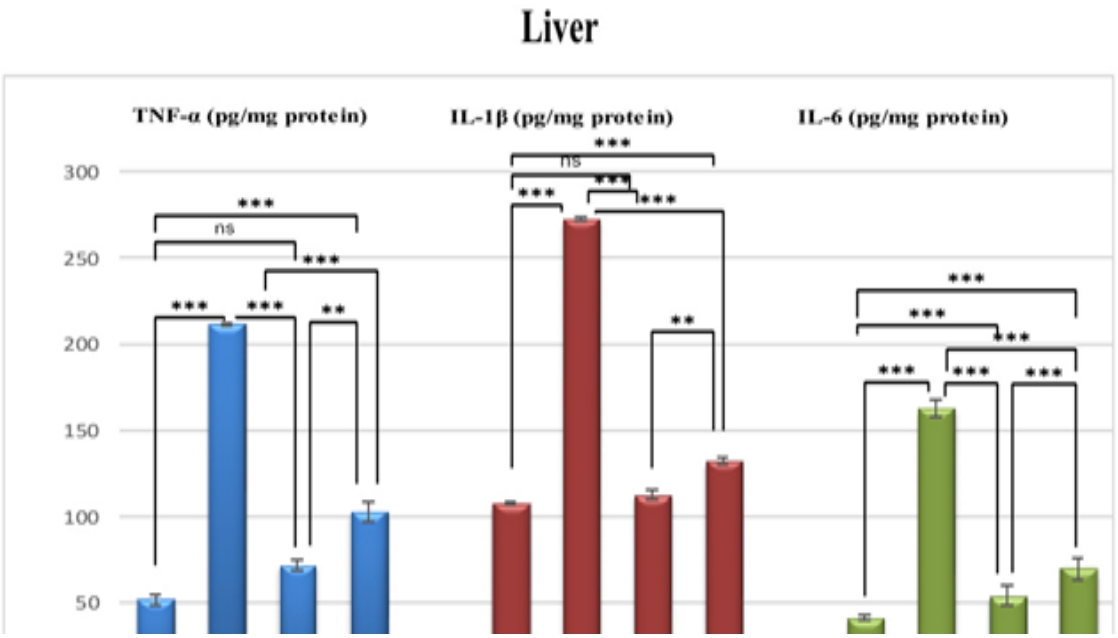

Fig. 5. Effect of exposure to low dose whole body gamma irradiation (LDR; 0.5Gy) and administration of coenzyme Q10 (CoQ10) on liver contents of IL-1β, TNF-α and IL-6 in bee venom induced toxicity in rats.

Data represent the mean of 6 animals ± SEM. Statistical analysis was carried out by one way ANOVA followed by Tukey-Kramer multiple comparisons test. *Significantly different at $p < 0.05$.** Significantly different at $p < 0.01$. *** Significantly different at $p < 0.001$. ^{NS} Nonsignificant at $p > 0.05$.

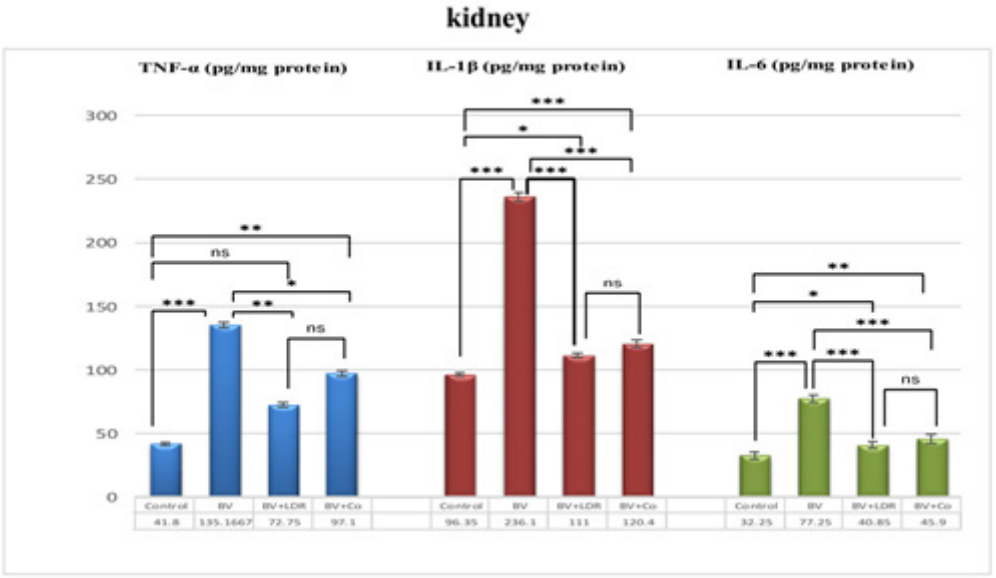

Fig. 6. Effect of exposure to low dose whole body gamma irradiation (LDR; 0.5Gy) and administration of coenzyme Q10 (CoQ10) on kidney contents of IL-1β, TNF-α and IL-6 in bee venom induced toxicity in rats.

Data represent the mean of 6 animals ± SEM. Statistical analysis was carried out by one way ANOVA followed by Tukey-Kramer multiple comparisons test. *Significantly different at $p < 0.05$.** Significantly different at $p < 0.01$. *** Significantly different at $p < 0.001$. ^{NS} Nonsignificant at $p > 0.05$.

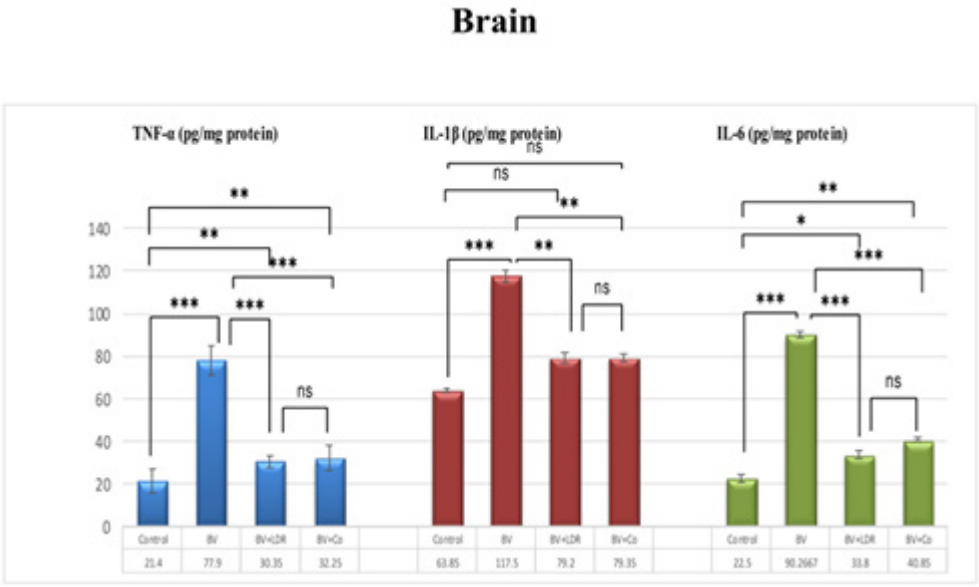

Fig. 7. Effect of exposure to low dose whole body gamma irradiation (LDR; 0.5Gy) and administration of coenzyme Q10 (CoQ10) on brain contents of IL-1β, TNF-α and IL-6 in bee venom induced toxicity in rats.

Data represent the mean of 6 animals ± SEM. Statistical analysis was carried out by one way ANOVA followed by Tukey-Kramer multiple comparisons test. *Significantly different at $p < 0.05$.** Significantly different at $p < 0.01$. *** Significantly different at $p < 0.001$. ^{NS} Nonsignificant at $p > 0.05$.

Discussion

Venomous bee mishaps are a major global health hazard. Honeybee stings can cause potentially fatal reactions in sensitive people (Cornara et al., 2017).

Apitoxin, another name for bee venom, is produced by the poison glands in a honeybee's abdomen. This venom contains over fifty physiologically active chemicals, including phospholipases, phosphoesterases, melittin, and many other polypeptides (Cornara et al., 2017). Acupuncture makes use of honeybee venom (Cherniack and Govorushko, 2018). Applications of acupuncture include rheumatoid arthritis, neuropathies, osteoarthritis, and lumbar disc disease. Militant intravenous dosages of melittin have anti-inflammatory properties (Lin and Hsieh, 2020).

In line with the findings of Karam and Mohamed (2019), low-dosage irradiation has been identified as an effective treatment for snakebites. The current study aims to investigate the protective effects of intraperitoneal (i.p.) injection with two doses of 10 mg/kg CoQ10 for two consecutive days, or a single dose of 0.5 Gy gamma radiation, on male rats compared to an i.p. injection with a toxic dose of 5 mg/Kg of bee venom.

On this ground, the bee venom's toxicity (5 mg/kg, i.p.) was linked to a substantial increase in liver enzymes, indicative of hepatic dysfunction. These findings corroborated those of Lee and Bae (2016), who showed that exposure to a hepatotoxic dosage of bee venom increased liver [ALT/AST] enzymes.

Rats were administered a single low dose γ-radiation (LDR) of 0.5 Gy in response to bee venom toxicity, which resulted in a significant suppression of AST and ALT activity. That is consistent with the findings of Yamaoka et al. (1998). Additionally, Lee and Ducoff (1989) found that modest radiation doses (up to 0.5 Gy) could make cells resistant to oxygen toxicity, which may explain the improvement in theactivity of the liver enzymes after radiation.

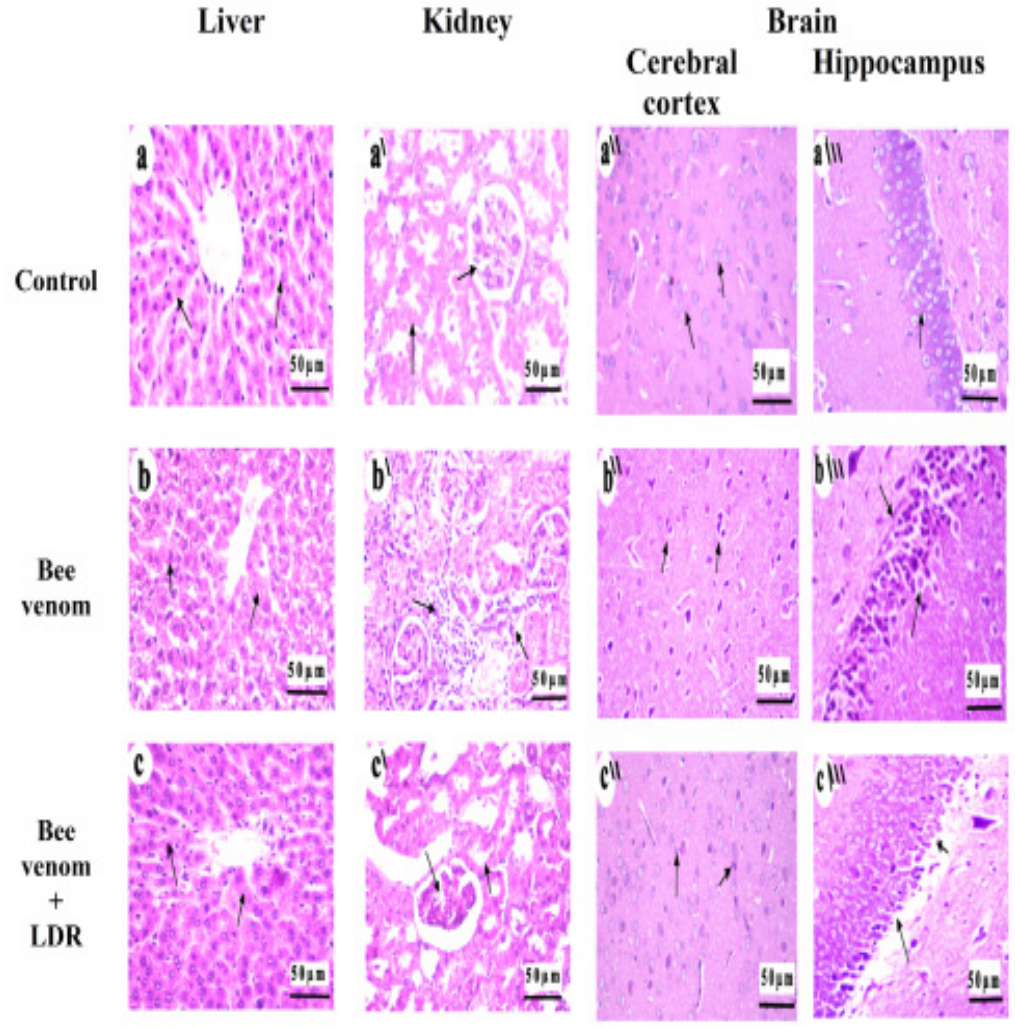

Fig. 8. Effect of exposure to low dose whole body gamma irradiation (LDR; 0.5Gy) and administration of coenzyme Q10 (CoQ10) on liver, kidney and brain histopathological status in bee venom induced toxicity in rats.

Left panel: (Photomicrograph of hepatic tissue section)

(a) Control group showed normal histological structure of hepatic lobules arrow (H&Ex200) (b) bee venom group showed nuclear pyknosis and apoptosis of hepatocytes arrow (H&Ex200) (c) bee venom+LDR group showed ballooning degeneration of hepatocytes with hyperplasia of Kupffer cells arrow (H&Ex200) (d) bee venom+Co group showed swelling of hepatocytes and granularity of cytoplasm arrow (H&Ex200).

Middle panel: (Photomicrograph of kidney tissue section)

(a\) Control group showed normal structure of glomeruli and renal tubules arrow (H&E X200) (b\) bee venom group showed tubular necrosis and interstitial oedema with mononuclear cells infiltrationarrow (H&E X200) (c\) bee venom+LDR group showed shrinkage of capillary tufts with tubular epithelial degeneration arrow (H&E X200) (d\) bee venom+Co group showed normal histological structure of glomeruli and renal tubulesarrow (H&E X200)

Right panel: (Photomicrograph of cerebral cortex and hippocampus of brain tissue section, respectively)

(a\\) Control group showed normal arrangement of neuronal cells in association small blood vessels in between arrow (X200) (a\\\) Control group showed normal histological structure of compact granular cells with dark nuclei arrow (X200) (b\\) bee venom group showed focal gliosis and apoptosis of neuronal cells arrow (X200) (b\\\) bee venom group showed vacuolar degeneration of granular cell layers and nuclear pyknosis of pyramidal cells arrow (X200) (c\\) bee venom+LDR group showed moderate neuronal degeneration with nuclear pyknosis arrow (X200) (**c**\\\) bee venom+LDR group showed cellular disorganization with vacuolar degeneration of granular cellarrow (X200) (d\\) bee venom+Co group showed mild swelling of neuronal cells arrow (X200) (**d**\\\) bee venom+Co group showedcellular disorganization and vacuolations of

Kwang et al. (2015) found that an intravenous single hazardous dosage of sweet bee venom resulted in an increase in liver and kidney functions, which is consistent with our findings. In the current study, we investigated the increases in renal parameters (urea, albumin, and creatinine) that would indicate a disruption in kidney function caused by a hazardous dosage of bee venom. However, this negative conduct is reversed when rats are injected with coenzyme Q10 or exposed to low doses of gamma radiation. This is consistent with the findings of Xu et al. (2019), who examine the impact of CoQ10 supplementation on individuals suffering from chronic renal disease in detail. Mantle and Hargreaves (2019) conducted a review of clinical trials that demonstrated the benefits of CoQ10 supplementation on liver inflammation and renal function in individuals with non-alcoholic fatty liver disease and chronic kidney disease, respectively.

According to Liang et al. (2006), the low dose of gamma radiation in the current study protected brain mediators from the harmful effects of bee venom. Liang et al. (2006) proposed a number of mechanisms, such as an increase in GSH levels, an activation of immunological function, and enzymatic DNA repair, for the neuroprotection induced by low dose gamma irradiation. Furthermore, Kipnis et al. (2004) found that activation of T cells was elevated in response to low dose γ-irradiation, which resulted in a build-up of self-reactive T cells in the wounded central nervous system and neuroprotection.

CoQ10 administration reduced neuronal degenerative findings, secondary brain damage, and ischaemia caused by oxidative stress in rats with traumatic brain injury (Kalayci et al., 2011). Additionally, intravenous coenzyme Q10 administration has a sustainable neuroprotective potential (Obolenskaia et al., 2020). In our study, we found a significant drop in brain mediators (serotonin, norepinephrine, and dopamine) in the low dose radiation and coenzyme Q10 treated groups.

Naturally occurring hydrophobic, coenzyme Q10 is a potent antioxidant as well as an essential part of the respiratory chain of the mitochondria. CoQ10 reduces the synthesis of reactive oxygen species (Sohet et al., 2009), scavenges lipid peroxidation products during free radical reactions (Tsuneki et al., 2007), controls excess NO production, and protects against nitrative tissue stress (Jung et al., 2009).

An imbalance between oxidant and antioxidant species is brought on by BV. According to our findings, there was a significant decrease in the GSH level in the serum along with a large elevation in the MDA and AOPP levels. This could be attributed to the increased generation of reactive oxygen species (ROS) that utilize the antioxidants (Prasad et al., 2005) or because the oxidized GSH's plasma membrane transport activity is reduced (Abou-Bedair et al., 2002). According to Witko-Sarat et al. (1996), AOPP buildup accompanied by high MDA and decreased GSH encouraged the onset of oxidative stress. Dahdouh et al. (2023) provided evidence of BV-induced renal oxidative damage by a considerable rise in MDA content, a corresponding drop in GSH content, and a significant decrease in catalase activity. Similarly, rats treated with BV had lower GSH content and a higher amount of MDA, according to earlier research (Hassan et al. 2019). However, the stimulation of oxidative stress-mediated formation of ROS, which results in damage and death of either normal or cancer cells, is a possible mechanism explaining BV toxicity (Gajski et al. 2011). In BV-treated rats, intraperitoneal CoQ10 administration or a single dose of 0.5 Gy gamma radiation exposure markedly reduced oxidative stress, suggesting the potential antioxidant effective ness of our treatment.

Treatment with CoQ10 was shown to decrease lipid peroxidation and improve the function of liver tissue (Amimoto et al., 1995; Jiu et al., 1997). Furthermore, CoQ10 has anti-inflammatory qualities by preventing proinflammatory cytokines from being released after inflammatory injury (Schmelzer et al., 2007, 2008).

According to Karam and Mohamed, 2019 and Li et al., 2020, respectively, low-dose gamma irradiation and coenzyme Q10 effectively prevented the rise of proinflammatory cytokine levels in various tissues. Our findings showed that exposure to low-dose gamma radiation or CoQ10 treatment can attenuate the significant elevation in IL-1β, TNF-α and IL-6 contents in all investigated tissue homogenates resulted due to BV administration.

Histological analyses of the liver, kidney, and brain sections of rats given bee venom injection showed renal apoptosis, tubular epithelial cell necrosis, and hepatocyte necrosis. Along with significant brain injury, the cerebral cortex displayed focal gliosis and neuronal cell death,

which manifested as densely basophilic masses encircled by halo. The hippocampal region displayed cellular disarray as well as a noticeable reduction in the quantity and size of big pyramidal cells with darker nuclei. Granular cell layers' vacuolar degeneration and certain pyramidal cells' nuclear pyknosis. Conversely, the administration of LDR and CoQ10 prevented the histological changes brought on by bee venom poisoning and confirmed the biochemical results.

Conclusion

Low-dose gamma irradiation or CoQ10 supplements are thought to be effective in treating the aforementioned conditions because of their ability to generate cellular energy, act as an antioxidant, and reduce inflammation in response to bee venom toxicity.

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