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ORIGINAL ARTICLE

Gibberellic acid-induced hepatorenal dysfunction and oxidative stress: Mitigation by quercetin through modulation of antioxidant, anti-inflammatory, and antiapoptotic activities

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Abstract

The plant growth regulator gibberellic acid (GA3) is widely used in agriculture in many countries. However, little is known about its danger to human health or its physiologic and biochemical pathways. Our study examined the effect of GA3 on liver and kidney function and the effect of quercetin on the hepatorenal toxicity induced by GA3 in four groups of male albino rats. For 4 weeks, the control group (CNT) received saline, the quercetin group (QR) received daily intraperitoneal injections of quercetin (50 mg/kg/BW) dissolved in saline, the gibberellic acid group (GA3) received GA3 (55 mg/kg/BW) via oral gavage, and the protective group (QR) was injected with quercetin and gavaged with GA3 in the same doses used in the QR and GA3 groups (50 mg/kg/BW +GA3 and 55 mg/kg/BW). GA3 induced liver and kidney injury, as shown by elevated serum glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, and gamma-glutamyl transferase (GPT, GOT, and GGT) as well as increased levels of creatinine, urea, and uric acid. Hepatorenal toxicity was demonstrated by a significant increase in levels of serum and tissue malondialdehyde (MDA) and decreased antioxidant enzyme activity, such as catalase (CAT) and superoxide dismutase (SOD), accompanied by a subsequent decrease in glutathione peroxidase (GPx) levels in liver and kidney tissue of GA3-treated rats. Administration of quercetin (QR) significantly protected hepatorenal tissue against the toxic effect of GA3 through normalization of the hepatic and renal function markers. It also retrieved the antioxidant ability by modulating the hepatorenal toxic effect at the molecular level through upregulation of antiapoptotic genes and downregulation of transforming growth factor-β1 (TFG-β1), cyclooxygenase-2 (COX-2), and nuclear factor-kappa B (NF-κB). Impairment of liver and kidney function was confirmed by histologic and immunohistochemical analyses. Pretreatment with quercetin was effective at attenuating histopathologic changes in hepatic and renal tissues by regulating the immunoexpression of caspase-3 and Bcl-2 to return them to more normal values.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; COX-2, cyclooxygenase-2; GA3, gibberellic acid; GGT, γ-glutamyl transaminase; GPx, glutathione peroxidase; GSH, reduced glutathione; IL-10, interleukin-10; IL-1β, interleukin-1β; MDA, malondialdehyde; NAC, N-acetyl cysteine; NF-κB, nuclear factor-kappa B; PGR, plant growth regulator; QR, quercetin; qRT-PCR, quantitative real-time polymerase chain reaction; TGF-β1, transforming growth factor-beta-1; TNF-α, tumor necrosis factor alpha.

[Correction added on January 13, 2022, after first online publication: Mohamed Elbadawy name has been changed to Mohamed Elbadawy.]

Practical applications

The confirmed hepatorenal dysfunction caused by GA3 was ameliorated by quercetin administration. Moreover, quercetin demonstrated the potential to reverse hepatorenal dysfunction by regulating inflammatory and antioxidant properties, inhibiting the production of free radicals and inflammation-associated cytokines, and modulating antioxidants and antiapoptotic activity.

KEYWORDS
gene expression, gibberellic acid, hepatorenal dysfunction, oxidative stress, Quercetin

1 | INTRODUCTION

Small organic compounds, known as plant growth regulators (PGRs), are used extensively in agriculture. The use of phytohormones with insecticidal properties has received a lot of attention (Nasseh et al., 1993). Gibberellic acid (GA3), a naturally occurring gibberellin-class plant growth regulator, is one of these phytohormones. GA3 has been shown to stimulate cell division and elongation, affecting both leaves and stems in a variety of plants (Troudi et al., 2011). The world's human population is exposed to GA3 and other PGRs daily through the consumption of food products containing these chemicals, especially fresh fruits such as date palm, peppers, and melons (Abdellaoui et al., 2009; Chaari-Rkhis et al., 2011). Although GA3 is widely used in agriculture, little is known about its impact on human health.

GA3 has been shown to cause chromosomal abnormalities in human and mouse cells (Bakr et al., 1999; Zalinian et al., 1990). In laboratory mice, GA3 at a dose of 75 mg/L caused degeneration of the liver, inflammation of the kidney, and impaired sexual differentiation (Ozmen et al., 1995). Adult albino Swiss mice that received GA3 by gavage for 22 months developed cancerous lesions (El-Mofty et al., 1994). PGR can also cause oxidative stress, resulting in free radicals and cell damage (Tuluce & Celik, 2006). The main enzymatic defense is antioxidants, which have been demonstrated to hunt free radicals; these include superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), which work in tandem with a variety of nonenzymatic antioxidants, including glutathione, which is the second line of defense (Afef Troudi et al., 2011). GA3 has also been shown to cause oxidative stress in rats, resulting in the accretion of lipid peroxidation products and increased levels of malondialdehyde (MDA) in organs, such as the liver, kidney, and brain (Celik & Tuluce, 2006; Celik et al., 2007).

Quercetin (QS; 3,3′,4′,5,7-pentahydroxyflavone) is one of the most common flavonoids (Mao et al., 2018). Apples, onions, potatoes, peanuts, soybeans, red wine, and other fruits and vegetables are high in quercetin, which has considerable antioxidative and cytoprotective effects against oxidative injury-induced cell death due to its chemical composition (Choi et al., 2003). Quercetin also works to protect cells from free radical damage and death by blocking lipid peroxidation. The neuroprotective effects of quercetin are thought to occur in part because of its ability to cross the blood–brain barrier (Cho et al., 2006; Schültke et al., 2005). Quercetin is one of the flavonoids found most frequently in the human diet, and it has therapeutic effects in a variety of disorders, including hepatoprotection and suppression of liver fibrosis (Bengmark et al., 2009). Quercetin contains many phenolic hydroxyl groups with potent antioxidant properties (Tieppo et al., 2009). Nuclear factor-kappa B (NF-κB) regulates cyclooxygenase-2 (COX-2), and both genes regulate inflammation, probably through their different inflammatory effects. GA3 may regulate apoptotic and antiapoptotic genes (Bax and Bcl2) in hepatorenal toxicity. This study thus aimed to evaluate the hepatonephrotoxicity induced by GA3 in rats. Moreover, the possible protective intracellular pathways, such as NF-kB, COX-2, transforming growth factor-β1 (TFG- β1), Bax, and Bcl-2, may be involved in this mechanism against GA3 hepatorenal toxicity provided by quercetin are examined.

2 | MATERIALS AND METHODS

2.1 | Animal handling and experimental design

Forty male albino rats were maintained at room temperature and with free access to food and water. The Institutional Animal Care and Use Committee of Turabah University College at Taif University authorized all animal-related procedures for project TURSP-2020-09. After 2 weeks of adaptation, rats were divided into four groups (10 rats each). The control group (CNT) received saline; the quercetin group (QR) received 50 mg/kg/BW quercetin dissolved in saline via daily intraperitoneal (i.p.) injection for 4 weeks (Al-Otaibi et al., 2018; Bo et al., 2018); the gibberellic acid group (GA3) received 55 mg/kg/BW GA3 via daily oral gavage for 4 weeks (Lafi et al., 2018; Soliman et al., 2021); and the protective group (QR +GA3) was maintained under experimental settings (Alsemeh et al., 2019a, 2019b), injected with QR and gavaged with GA3 at the same doses as those used in the QR and GA3 groups. Quercetin was injected an hour before GA3 administration to confirm its protective effects. On Day 28, the rats were sedated and euthanized by decapitation. Blood samples were drawn from the tail vein using a nonheparinized Vacutainer tube and centrifuged at 3,000 × *g* for 10 min. Samples were kept at −20°C for use in analyzing the changes in serum chemistry and metabolites. Liver and kidney samples were sliced and cleaned before being rinsed in cold saline. Tissue samples were kept either in Qiazol for

RNA extraction and real-time PCR or in a 10% neutral buffer formalin solution for histologic and immunohistochemical evaluation.

2.2 | Serum biochemical parameters

A colorimetric spectrophotometer was used to measure serum levels of antioxidants (SOD, catalase, and MDA) according to the manufacturer's instructions using kits for superoxide dismutase (SOD), catalase, and malondialdehyde (MDA) purchased from Biodiagnostic Co. (Dokki, Giza, Egypt). Glutamic pyruvic transaminase (GPT), glutamic oxalacetic transaminase (GOT), and γ-glutamyl transferase (GGT) enzyme activity in serum was measured using Spectrum Co. kits as described previously (Murray & Kaplan, 1984; Szasz, 1974). Urea levels were analyzed as described previously (Talke & Schubert, 1965). Serum creatinine was assessed using a modified Jaffe's reaction following the method of Bowers (Bowers, 1980). Uric acid was assessed using Trinder's enzymatic reaction as described previously (Barham & Trinder, 1972).

2.3 | Measurement of MDA and GPx in hepatic and renal tissues

Liver or kidney tissues (200–400 mg) were homogenized in 5 mL cold potassium phosphate buffer (50 mM, pH 7.4) for MDA and 1 mM EDTA and 1 mL/L Triton X-100 for SOD. The samples were centrifuged at 5,000 × *g* for 10 min at 4°C. The supernatant was removed and stored at −20°C for use in measuring GPx (U/gram tissue) and MDA (nmol/gram tissue) using an ELISA reader (BioRad, NY, USA) following the manufacturer's instructions. MDA levels were assessed using a technique developed by Ohkawa et al. (1979). The basis of the kit is the fact that thiobarbituric acid (TBA) reacts with MDA in an acidic medium to form a TBA-reactive product with a pink color that can be measured at 534 nm OD. GPx enzyme activity in the tissue homogenates using colorimetric kits (Biodiagnostic kits, Egypt) was determined following Mannervik (1985). GPx was measured indirectly based on the oxidation of NADPH to NADP+ (Paglia & Valentine, 1967). The oxidation of NADPH to NADP+is accompanied by a decrease in absorbance at 340 nm.

2.4 | Molecular analysis using qRT-PCR

RNA from the tissues was extracted and evaluated for purity at 260/280 nm. RNA was transcribed using a QuantiTect reverse transcription kit with 2 μg total RNA, producing single-stranded complementary DNA (cDNA) using a two-step RT-PCR reaction with a random primer hexamer. Amplification of cDNA was performed using SYBR Green master mix (Thermo Fisher Scientific, USA). The genes associated with steroidogenesis and apoptosis are listed in Table 1. These genes were quantified by real-time PCR analysis using the $2^{-\Delta\Delta CT}$ method. β-actin was used as a standard internal gene and was normalized against examined genes. The intensity of the examined genes and their mRNA expression were analyzed using comparative cycle threshold (CT) values.

TABLE 1 Primers sequence used for quantitative real-time PCR in liver and kidney of rats

Gene	Accession number	Direction	Primer sequence
TGF-β1	NM_021578.2	Sense	GGACTACTACGCCAAAGAAG
		Antisense	TCAAAAGACAGCCACTCAGG
COX2	NM 017232	Sense	TGATCTACCCTCCCCACGTC
		Antisense	ACACACTCTGTTGTGCTCCC
BAX	NM 017059	Sense	AGGACGCATCCACCAAGAAG
		Antisense	CAGTTGAAGTTGCCGTCTGC
IL-10	NM_012854	Sense	AGAAGCTGAAGACCCTCTGGATAC
		Antisense	GCTCCACTGCCTTGCTTTTATT
Bcl2	NM_016993	Sense	ACTCTTCAGGGATGGGGTGA
		Antisense	TGACATCTCCCTGTTGACGC
NF-κB	AF079314	Sense	TCTCAGCTGCGACCCCG
		Antisense	TGGGCTGCTCAATGATCTCC
β-actin	NM 031144	Sense	AGGAGTACGATGAGTCCGGC
		Antisense	CGCAGCTCAGTAACAGTCCG

2.5 | Histopathologic evaluation of hepatic and renal tissues

At the end of the experiment, all rats were euthanized by decapitation and necropsied (Fiette & Slaoui, 2011; Ruehl-Fehlert et al., 2003), and representative hepatic and renal tissue specimens were harvested and fixed in 10% neutral buffered formalin for 24 hr. After fixation, the specimens were washed in distilled water, dehydrated in ethanol, cleared in xylene, impregnated and embedded in paraffin wax, sectioned at 4 μm, and stained with hematoxylin and eosin dye (Suvarna et al., 2018). The stained sections were examined microscopically and then underwent multiparametric quantitative lesion scoring of the lesion frequencies in 40 images/group (40 objectives).

2.6 | Immunohistochemical investigation for caspase-3 and Bcl-2

For the immunohistochemical study, 4-μm-thick formalin-fixed, paraffin-embedded hepatic, and renal tissue sections were successively prepared and stained for caspase-3 and Bcl-2 using rabbit polyclonal anti-caspase-3 primary antibody (ab4051) and rabbit polyclonal anti-Bcl-2 primary antibody (ab196495) (Abcam) and 3,30-diaminobenzidine chromogen (DAB) following a previously described avidin–biotin–peroxidase complex technique (Hsu et al., 1981). This was followed by the quantitative assessment of caspase-3 and Bcl-2 immunoexpression. Briefly, five nonoverlapped, randomly selected microscopic fields (objective 40)/marker/organ/

animal (40 caspase-3 images and 40 Bcl-2 images/organ/group) were photographed. These images were analyzed to quantify the immunoexpression by calculating the percentage of positively stained cells/total cells/images. The results were expressed as percentages (means ± *SEM*) using a 5-point scale: negative to weak expression, less than 10% positive cells; mild expression, 10% to less than 25% positive cells; moderate expression, 25% to less than 50% positive cells; strong expression, 50% to less than 75% positive cells; and overexpression, more than 75% positive cells (Metwally et al., 2018).

2.7 | Statistical analysis

The data are presented as means ± standard error of the mean (*SEM*) and analyzed using one-way ANOVA and Dunnett's post hoc descriptive test using SPSS software for Windows (SPSS, IBM, Chicago, IL, USA). Values with $p < .05$ were considered statistically significant.

3 | RESULTS

3.1 | Impact of quercetin and/or gibberellic acid on liver and kidney function markers

As seen in Table 2, the GA3-treated rats showed a significant increase in hepatic enzyme markers GPT, GOT, and GGT compared with the control and other treated groups. Conversely, the protective group (QR + GA3) showed a significant decrease in liver enzymes compared with the GA3-treated group. The significant increase in kidney injury markers creatinine, urea, and uric acid observed in the other treated groups was significantly normalized in the QR + GA3 group.

3.2 | Ameliorative impact of QR on GA3-induced hepatorenal injury and oxidative markers

Table 3 shows substantial increases in serum MDA levels with considerable decreases in SOD and catalase in the serum of the GA3-treated group compared with the other treated groups. These parameters were significantly normalized in the QR +GA3 group. When we examined the hepatic and renal tissues for changes in oxidative biomarkers, MDA was increased and GPX was decreased in the GA3-treated group (Table 4). Preadministration of QR for 28 days protected rats from increased tissue damage (MDA) and increased the hepatic and renal GPX observed in the GA3-treated group.

3.3 | Ameliorative impact of quercetin on hepatic genes associated with apoptosis and anti-inflammatory cytokines

Our results showed that quercetin decreased the mRNA expression of the Bax gene with a significant increase in the Bcl-2 gene, which overcame the apoptotic effect in the GA3-treated group, as seen in Figure 1a,b. In the same way, treatment with GA3 was found to cause a significant decrease in the mRNA expression of IL-10 (Figure 1c).

3.4 | Ameliorative impact of quercetin on kidney genes associated with nephrosis and inflammation of the kidney

Figure 2a–c shows that treatment with GA3 induced a general state of kidney fibrosis and inflammation with significant upregulation of mRNA expression of TFG-β, COX-2, and NF-κB. The QR +GA3 group showed significant normalization of TGF-β1, COX-2, and NF-κB compared with the other treated groups.

TABLE 3 Protective effects of QR on GA3-induced alterations on serum MDA, catalase, and SOD levels

	MDA (nmol/mL)	Catalase (U/L)	SOD (U/mL)
Control	11.1 ± 0.9	266.8 ± 8.1	3.89 ± 0.12
GA3	29.0 ± 4.3*	172.2 ± 13.1*	2.1 ± 0.2*
QR	10.7 ± 0.8	247.2 ± 18.1	3.5 ± 0.2
QR +GA3	15.2 ± 1.0$	230.8 ± 7.9$	3.1 ± 0.1$

Note: Values are means ± standard error (*SEM*) for eight different rats per each treatment.

Values are statistically significant at $^{*}p < .05$ versus control and QR and $^{\$}p < .05$ versus GA3 group.

TABLE 2 Effects of QR on GA3-induced hepatorenal dysfunction in rats

	Control	GA3	QR	QR + GA3
GPT (U/L)	17 ± 0.1	57.5 ± 7.1*	18.1 ± 4.2	31.1 ± 1.1$
GOT(U/L)	21 ± 1.01	49.0 ± 3.1*	22.1 ± 1.0	33.6 ± 4.4$
GGT (U/L)	9 ± 0.4	17.5 ± 0. 7*	9.9 ± 0.4	11.3 ± 1.01$
Creatinine (mg/dL)	0.49 ± 0.02	2.08 ± 0.1*	0.52 ± 0.06	0.9 ± 0.03$
Urea (mg/dL)	20.3 ± 1.7	51.5 ± 4.5*	19.1 ± 4.2	31.2 ± 4.7$
Uric acid (g/dL)	4.1 ± 0.3	12.3 ± 1.3*	5.3 ± 0.4	6.7 ± 0.8$

Note: Values are means ± *SEM* for eight different rats per each experiment.

Values are statistically significant at $^{*}p < .05$ versus control and QR groups and $^{\$}p < .05$ versus GA3 group.

TABLE 4 Protective effects of QR against GA3-induced alterations in hepatic and renal oxidative stress biomarkers

	Parameters	Control	GA3	QR	QR + GA3
Liver	MDA (nmol/g tissue)	5.3 ± 0.2	11.4 ± 1.0*	5.0 ± 0.1	6.8 ± 1.1#
	GPX (U/g tissue)	98.4 ± 7.2	53.6 ± 10.2*	105.2 ± 9.1	88.2 ± 7.9#
Kidney	MDA (nmol/g tissue)	4.2 ± 0.61	13.65 ± 1.7*	3.9 ± 0.2	7.1 ± 0.9#
	GPX (U/g protein)	100.3 ± 6.7	62.4 ± 7.9*	108.0 ± 8.45	89.9 ± 7.9#

Note: Values are means ± *SEM* for six different mice per each experiment.
Values are statistically significant at $^{*}p < .05$ versus control and QR groups and $^{\#}p < .05$ versus GA3 group.

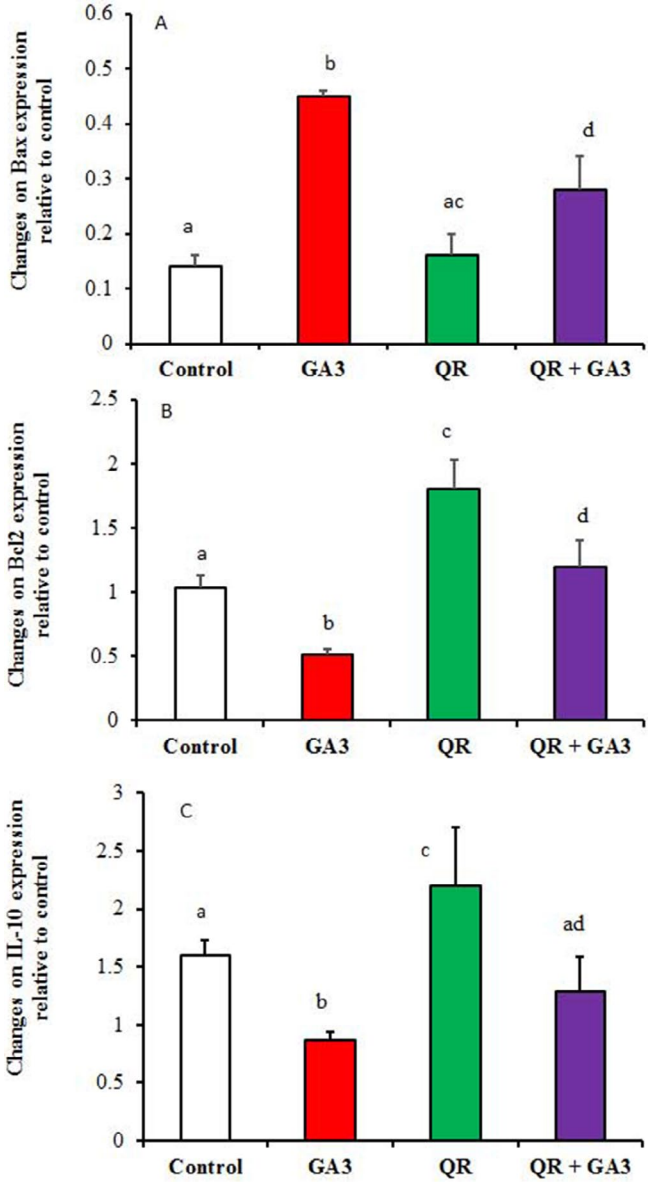

FIGURE 1 Impact of quercetin against GA3-induced changes on hepatic mRNA expression of (a) BAX, (b) Bcl2, and (c) IL-10. Values are means ± *SEM* for 10 mice per treatment. Values are statistically significant at $^{*}p < .05$ versus control and quercetin, $^{\#}p < .05$ versus GA3-administered group

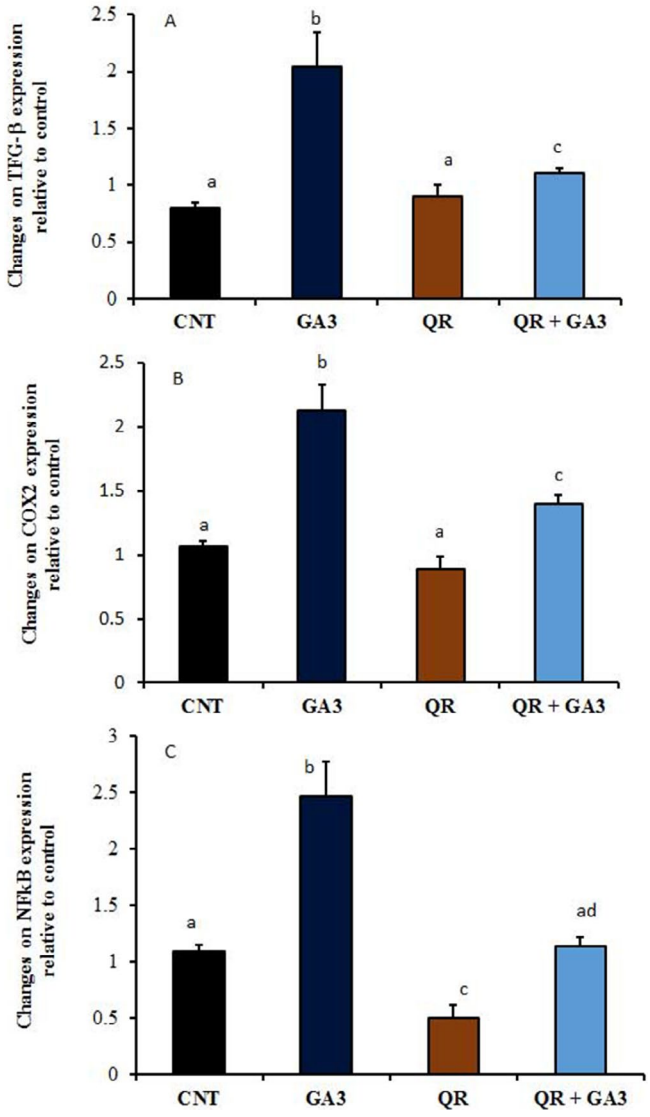

FIGURE 2 Impact of quercetin against GA3-induced changes on renal mRNA expression of (a) TGF-β1, (b) COX-2, and (c) NF-κB. Values are means ± *SEM* for 10 mice per treatment. Values are statistically significant at $^{*}p < .05$ versus control and quercetin, $^{\#}p < .05$ versus GA3-administered group

3.5 | Histopathologic and immunohistochemical findings

The histologic findings and lesion scoring in all groups of hepatic and renal tissues are summarized in Figures 3 and 4 and Table 5. Normal histologic structures were found in the liver and kidney tissues of CNT and QR-treated animals. The various mild inflammatory, degenerative, and circulatory changes were found in the liver and kidney tissues of GA3-treated animals. QR supplementation showed significant hepatorenal protective effects against GA3-induced hepatorenal injury. Immunohistochemically, the image analysis indicated that exposure to GA3 significantly upregulated caspase-3 and downregulated Bcl-2 immunoexpression in hepatic and renal tissues compared with the controls and QR-treated animals. Although QR supplementation significantly regulated the return of caspase-3 and Bcl-2 immunoexpression in the hepatic and renal tissues to more normal values, it did not completely normalize them.

4 | DISCUSSION

The liver is the primary site of toxicity for a variety of chemicals. The liver receives 75% of its blood directly from the gastrointestinal tract, which transports medicines and xenobiotics in concentrated form (Lee & Senior, 2005). Environmental contaminants such as PGR are known to produce an imbalance between the creation and elimination of free radicals, which has been linked to nephropathy, hepatic damage, and other detrimental health effects. Indeed, GA3 has been shown to be hazardous to soft organs such as the kidney and liver in adult rats (Celik et al., 2007). Our results show a substantial increase in hepatic enzyme markers GPT, GOT, and GGT in GA3-treated rats compared with the control and other treated groups. Our results agree with those of a previous study (Troudi et al., 2012) in which the liver was found to be damaged by GA3 as demonstrated by an increase in AST and ALT levels in plasma. These indicators revealed cellular leakage and a lack of cell membrane function integrity in the liver (Troudi et al., 2012).

Additionally, compared with other treated groups, kidney damage markers such as creatinine, urea, and uric acid all increased significantly in the GA3-treated group. Several researchers found that xenobiotic-induced changes in renal function were accompanied by elevated plasma levels of creatinine and urea (Choudhary et al., 2003; Manna et al., 2004); Troudi, Ben Amara, et al. (2011) observed higher levels of creatinine and urea in female rats given GA3. Moreover, increased blood urea has been linked to increased protein catabolism (Eraslan et al., 2007). These results have been confirmed by others (Olayinka et al., 2014), providing proof that QR remodels plasma creatinine and urea levels, strongly indicative of renal protection. This also supports prior findings that QR protects against drug-induced kidney damage (Yousef et al., 2010).

The liver is an organ crucial for drug and other hepatotoxicant biotransformation. The activity of liver enzymes ALT, AST, and ALP

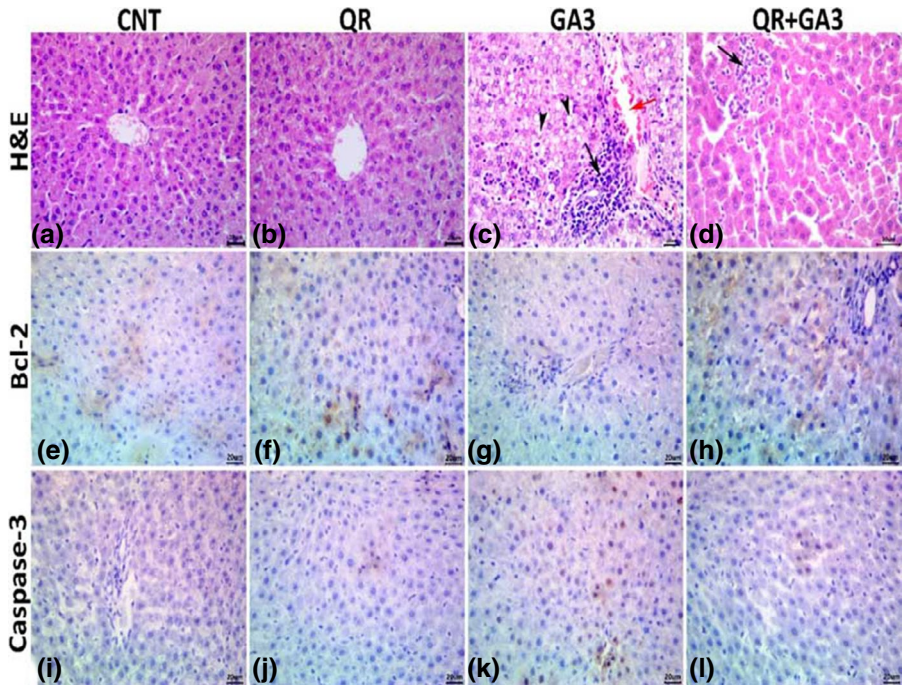

FIGURE 3 (a–d) Representative photomicrographs of H&E-stained hepatic tissue showing normal histologic pictures in (a) control and (b) QR-treated animals; (c) congestion (red arrow), inflammatory cell infiltrate (black arrow), and fatty change (arrowheads) in GA3-treated animals; and (d) inflammatory cell aggregation (arrow) in QR +GA3-treated animals. (e–h) Representative photomicrographs of Bcl-2-stained hepatic tissue showing (e) mild, (f) mild, (g) weak, and (h) moderate immunoexpression in CNT, QR, GA3, and QR +GA3-treated animals, respectively. (i–k) Representative photomicrographs of caspase-3-stained hepatic tissue showing weak to negative reaction in (e) and (f), (g) moderate, and (h) mild immunoexpression in CNT, QR, GA3, and QR +GA3-treated animals, respectively

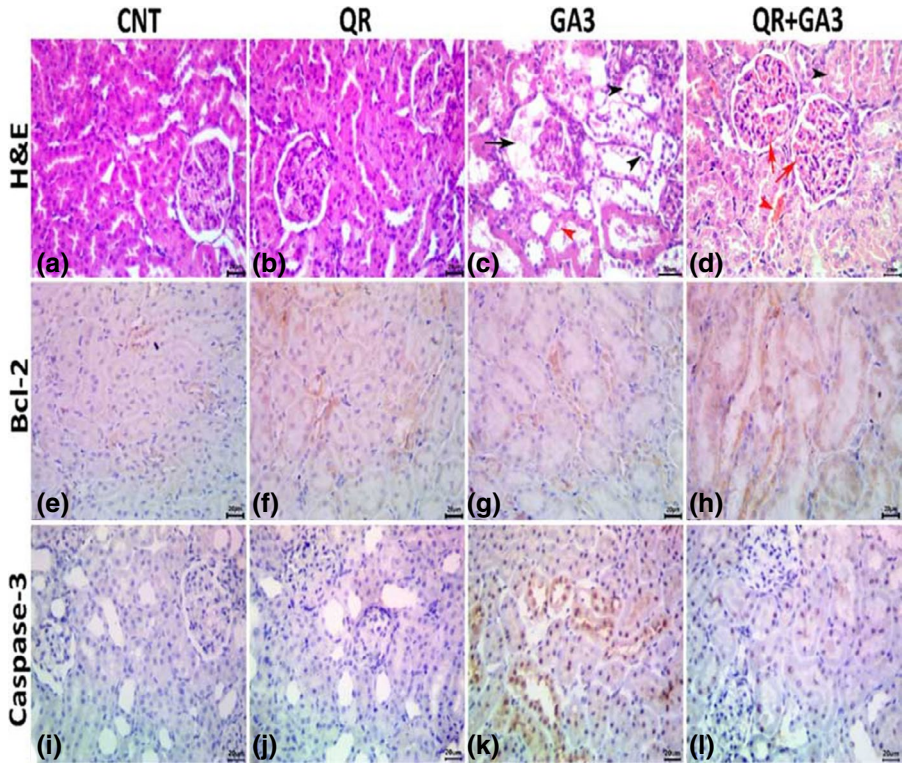

FIGURE 4 (a–d) Representative photomicrographs of H&E-stained renal tissue showing normal histologic pictures in (a) control and (b) QR-treated animals; (c) glomerular necrosis (arrow), tubular vacuolation (black arrowheads), and single-cell necrosis (red arrowhead) in GA3-treated animals; and (d) glomerular (arrows) and interstitial (arrowhead) congestion in QR +GA3-treated animals. (e–h) Representative photomicrographs of Bcl-2-stained renal tissue showing (e) mild, (f) mild, (g) weak, and (h) moderate immunoexpression in CNT, QR, GA3, and QR +GA3-treated animals, respectively. (i–k) Representative photomicrographs of caspase-3-stained renal tissue showing (e) weak to negative, (f) weak to negative, (g) moderate, (h) and mild immunoexpression in CNT, QR, GA3, and QR + GA3-treated animals, respectively

TABLE 5 Lesion scoring, Bcl-2, and caspase-3 immunoexpression in the hepatic and renal tissues of rats in response to quercetin against GA3-induced liver and kidney disorders

Organ	Lesion and immunoexpression	CNT	QR	GA3	QR + GA3
Liver	Congestions	0^a	0^a	5.1 ± 0.6^b	3.2 ± 1.1^c
	Fatty change	0^a	0^a	2.2 ± 0.6^b	0.9 ± 0.1^c
	Inflammatory infiltrate	0^a	0^a	3.4 ± 0.1^b	0.9 ± 0.2^c
	Vacuolar and hydropic degeneration	0^a	0^a	7.7 ± 2.4^b	1.7 ± 0.5^c
	Single-cell necrosis	0^a	0^a	3.1 ± 0.9^b	1.3 ± 0.4^c
	Bcl–2 immunoreactivity	13.3 ± 0.5^a	13.06 ± 0.4^a	4.8 ± 0.8^b	17.9 ± 2.2^c
	Caspase–3 immunoreactivity	0.45 ± 0.1^a	0.3 ± 0.1^a	26.2 ± 1.5^b	10.9 ± 3.3^c
Kidney	Glomerular congestion	0^a	0^a	6.2 ± 1.7^b	3.7 ± 1.1^c
	Interstitial congestion	0^a	0^a	7.3 ± 2.3^b	5.3 ± 1.0^c
	Glomerular necrosis	0^a	0^a	2.6 ± 0.8^b	1.3 ± 0.4^c
	Tubular attenuation	0^a	0^a	9.7 ± 3.1^b	1.6 ± 0.5^c
	Tubular vacuolation	0^a	0^a	14.8 ± 3.7^b	2.5 ± 0.8^c
	Tubular necrosis	0^a	0^a	2.57 ± 0.8^b	0.7 ± 0.1^c
	Cast formation	0^a	0^a	6.1 ± 1.9^b	1.7 ± 0.5^c
	Inflammatory cell infiltrate	0^a	0^a	1.6 ± 0.5^b	1.4 ± 0.4^c
	Bcl–2 immunoreactivity	11 ± 0.5^a	11.4 ± 0.6^a	2.6 ± 0.8^b	28.2 ± 1.08^c
	Caspase–3 immunoreactivity	0.7 ± 0.1^a	0.65 ± 0.1^a	3.6 ± 1.1^b	1.2 ± 0.3^c

Note: Values are mean ± *SE* for five samples/group. Means within the same row (in each parameter) carrying different superscripts are significantly different at $p < .05$.

and the plasma level of bilirubin are regarded as reliable markers of hepatotoxicity (Boone et al., 2005). Pretreatment with QR protected against increased GPT, GOT, and GGT levels, indicating its hepatoprotective effect. In a previous report, QR showed hepatoprotective properties (Kumar Mishra et al., 2013). Additionally, compared with the other treated groups, in which there was a considerable increase in renal damage indicators creatinine, urea, and uric acid, we observed significant normalization in the QR + GA3-treated group. This result is in agreement with the findings of Gomes et al. (2014), showing that treatment with QR resulted in lower levels of uric acid, urea, and creatinine and positive effects on kidney structural alterations. The antioxidative characteristics of QR are thought to reduce the synthesis of vasoactive autacoids, which may play a role in treating diabetic renal impairment (Gomes et al., 2014). Quercetin has been shown to have direct vasorelaxant action in vascular tissues, supporting this idea (Lodi et al., 2009). Our results showed substantial increases in serum MDA levels and hepatic and renal tissue in GA3-treated rats. Increased levels of MDA (the main byproduct of lipid peroxidation) is a biomarker for hepatic and renal injury caused by GA3; in addition, GA3 administration leads to ROS formation in tissue (Celik et al., 2007). When the creation of free radicals and the antioxidant defense system is out of balance, tissue damage results (Belviranli & Okudan, 2015; Celik et al., 2007). The glutathione redox cycle is one of the essential intracellular antioxidant mechanisms. GSH is a sensitive indicator of oxidative damage and assists in removing reactive intermediates by lowering hydrogen peroxide (Werner & Cohen, 1993). In agreement with our findings, they observed a decrease in liver levels of GSH in mother rats and their offspring after exposure to GA3 (0.2 g/L).

Several research studies have demonstrated a link between hepatorenal toxicity and oxidative stress (Majumdar et al., 2012). QR was found to protect rats from MPLN-induced renal and hepatic damage due to its ability to scavenge free radicals. The antioxidant properties of QR could be related to the high membrane diffusion characteristic of flavonoids, which allows them to scavenge free radicals (Lien et al., 1999). According to several recent investigations, QR has also been proven to decrease toxicity and oxidative stress in vivo and in vitro (Dobrikova & Apostolova, 2015). Our findings revealed that QR reduced Bax gene mRNA expression while significantly increasing Bcl-2 gene expression, overcoming the apoptotic effect in the GA3-treated group. Our results are in agreement with those of Alsemeh et al. (2019a, 2019b) proving that the expression of the antiapoptotic marker Bcl-2 was downregulated in a GA3-treated group. In contrast, the expression of the apoptotic marker Bax was upregulated. Our results are consistent with those of Guo et al. (2020) demonstrating the apoptotic effect of GA3 through upregulation of the mRNA expression of caspase-3, as well as those Ibrahim et al. (2021). Quercetin can help minimize the risk of organophosphorus poisoning by upregulating paraoxonase-1 and boosting the cellular antioxidant system and its antiapoptotic effect.

QR cotreatment for intoxicated mice reduced oxidative stress by increasing the cellular redox state and inhibited apoptosis by decreasing Bax and caspase-3 expression. QR possesses both direct and indirect antioxidant mechanisms (Costa et al., 2016). Our data are consistent with those of Soliman et al. (2021), confirming overexpression of inflammatory cytokines (TNF-α, IL-1β), reduced expression of anti-inflammatory cytokine IL-10 in GA3-treated rats, and increased mRNA expression of NF-κB. All were normalized in the group cotreated with QR +GA3.

The primary molecular coordinator of inflammatory reactions, NF-κB, has been associated with various pathologic conditions, including cancer, and constitutes one of the key pathways affecting the development of many chronic diseases (Guo et al., 2009). It has been reported that ROS generation is the cause of NF-κB activation (Gloire et al., 2006). TNF-induced ROS production may be linked to NF-κB pathway stimulation (Gloire et al., 2006), whereas quercetin's substantial free radical scavenger activity could be linked in part to its suppression of NF-κB signaling. Similarly, QR inhibits IL-1β-induced NF-κB activation, which enhances the formation of ROS (Martínez-Flórez et al., 2005). COX-2 regulation is a complicated process, and its induction mechanisms appear to converge in the activation of NF-κB. Furthermore, NF-κB regulates COX-2, and both proteins play a role in tumor development and inflammation (Naugler & Karin, 2008). In addition, quercetin use has been reported a therapy for COX-2-mediated illnesses (Xiao et al., 2011).

Our findings support a role for quercetin as an anti-inflammatory agent in the liver and kidney and demonstrate its significant effect in preventing inflammatory disorders (Granado-Serrano et al., 2012).

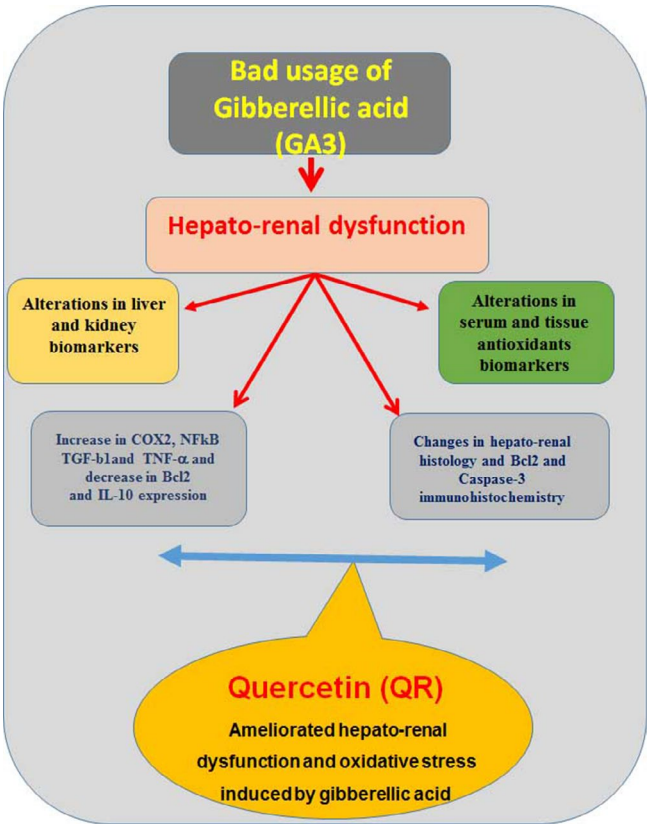

FIGURE 5 Schematic illustration of quercetin against gibberellic acid-induced liver and kidney dysfunction and oxidative stress

Our gene expression data are supported by an immunohistopathologic study in which GA3 significantly upregulated caspase-3 and downregulated Bcl-2 immunoexpression in hepatic and renal tissues compared with the results in controls and QR-treated animals. Liver and kidney histology showed inflammatory, degenerative, and circulatory alterations. We confirmed that QR supplementation significantly reduced GA3-induced hepatorenal damage, in agreement with the observations of Mahabady et al. (2021), due to the antioxidant defense of QR (Morand et al., 1998).

5 | CONCLUSION

In conclusion, exposure of rats to GA3 causes hepatorenal toxicity, as shown by increased hepatic and renal oxidative marker activity, enhanced membrane lipid peroxidation, and decreased hepatorenal antioxidant enzyme activity, with upregulation of inflammatory cytokines and apoptotic genes. All this was normalized by pretreatment with quercetin. Thus, based on these findings, our study suggests that quercetin may be used as a potential therapeutic drug against gibberellic acid-induced hepatorenal toxicity because of its antioxidant, anti-inflammatory, and antiapoptotic activities. The impacts of quercetin against GA3-induced hepatic and liver dysfunction are summarized in Figure 5.

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CONFLICT OF INTEREST

The authors report that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Mohamed Mohamed Soliman: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Resources; Writing—original draft; Writing—review & editing. **Ahmed Gaber:** Data curation; Software; Supervision; Visualization. **Walaa F Alsanie:** Formal analysis; Funding acquisition; Software; Validation. **Wafaa Abdou Mohamed:** Conceptualization; Data curation; Resources; Software. **Mohamed M M Metwally:** Investigation; Methodology; Validation; Visualization; Writing—original draft. **Abdelhadi A. Abdelhadi:** Data curation; Resources; Writing—review & editing. **Mohamed Elbadawy:** Formal analysis; Funding acquisition; Project administration; Supervision; Validation. **Mostafa Shukry:** Data curation; Visualization; Writing—original draft; Writing—review & editing.

ETHICAL STATEMENT

All experimental procedures of this study were carried out under the National Institutes of Health guidelines for the care and use of laboratory animals. All steps were taken to minimize the suffering of experimental animals.

DATA AVAILABILITY STATEMENT

Current data are available upon request.

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