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Ameliorative Effects of Quercetin against Copper Oxide Nanoparticles Induced Hepatic Toxicity in Albino Rats

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Abstract

Copper oxide nanoparticles (CuO-NPs) are employed in the pharmaceutical, cosmetic, and industrial sectors. Quercetin (QC) is one of the most abundant dietary flavonoids. QC has anti-apoptotic, antioxidant, and anti-inflammatory properties. In this investigation, the hepatoprotective ability of QC against CuO-NP-induced hepatotoxicity in rats was assessed. Four equal groups of twenty-eight mature male albino rats were formed. The first group (G1) was received saline (1ml per rat) daily via stomach tube for four weeks. G2 was received QC at a dose of 100 mg/kg b.wt. daily via stomach tube for four weeks. CuO-NPs was administered orally to G3 at a dose of 300 mg/kg b.wt. every day for four weeks. G4 was given CuO-NPs and QC daily in the same dose and route. After the end of experiment, liver specimens and serum samples were taken from all groups. Results demonstrated that QC mitigated the hepatic dysfunctions brought on by CuO-NPs through improvements in serum ALT, AST, and ALP, with a noticeable increase in total proteins and albumin levels, in addition to improving the antioxidant status as seen by elevated reduced glutathione (GSH) levels, catalase (CAT) activity, and lowered levels of malondialdehyde (MDA). Furthermore, phosphoinositide 3-kinase (PI3K) and AKT (protein kinase B) genes showed highly significant up-regulated mRNA levels, whereas nuclear factor kappa B (NFκB) and signal transducer and activator of transcription (STAT-3) genes were significantly down-regulated. Additionally, QC maintained liver tissue architecture, decreased immunoreactivity against caspase-3 (Cas-3). These results imply that QC might enhance the hepatoprotective benefits against oxidative stress caused by CuO-NPs toxicity.

Keywords: Copper oxide nanoparticles, Hepatotoxicity, Oxidative stress, PI3K/AKT pathway, Quercetin.

Introduction

Copper oxide nanoparticles (CuO-NPs) are employed in the pharmaceutical, cosmetic, and industrial sectors. Quercetin (QC) is one of the most abundant dietary flavonoids found in fruits and vegetables. QC has anti-apoptotic, antioxidant, and anti-inflammatory properties. In this investigation, the hepatoprotective ability of QC against CuO-NP-induced hepatotoxicity in rats was assessed. Four equal groups of twenty-eight mature male albino rats were formed. The first group (G1) was preserved as a normal control, received saline (1ml per rat) daily via stomach tube for four weeks. G2 was received QC at a dose of 100 mg/kg b.wt. daily via stomach tube for four weeks. CuO-NPs was administered orally to G3 at a dose of 300 mg/kg b.wt. every day for four weeks. G4 was given CuO-NPs and QC daily in the same dose and route. After the four-week experiment, liver specimens and serum samples were taken from every group of rats. The results demonstrated that QC mitigated the hepatic dysfunctions brought on by CuO-NPs through improvements in serum ALT, AST, and ALP, with a noticeable increase in total proteins and albumin levels, in addition to improving the antioxidant status as seen by elevated reduced glutathione (GSH) levels, increased catalase (CAT) activity, and lowered levels of malondialdehyde (MDA). Furthermore, phosphoinositide 3-kinase (PI3K) and AKT (protein kinase B) genes showed highly significantly up-regulated mRNA levels, whereas those of nuclear factor kappa B (NFκB) and signal

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transducer and activator of transcription (STAT-3) genes were significantly down-regulated. Additionally, QC maintained liver tissue architecture, decreased immunoreactivity against caspase-3 (Cas-3). These results imply that QC might enhance the hepatoprotective benefits against oxidative stress caused by CuO-NPs toxicity.

Material and Methods

Ethical Approval

The guidelines and procedures used in this experiment were supplied by Benha University's Institutional Animal Ethics Committee in Egypt. BUFVTM 15-09-23 is the protocol number that has been approved. All methods were carried out in compliance with the applicable rules and regulations. The study is reported in accordance with ARRIVE guidelines.

Chemicals

Copper oxide nanoparticles (CuO-NPs) were purchased from Nanotech Egypt for Photo Electronics Company, Giza, Egypt. The average size of CuO-NPs was 40±10 nm and Quasi-spherical shape. Quercetin (QC) capsules were obtained from Nature's Truth Company.

Experimental Animals

Twenty-eight mature male Wistar rats, weighing between 150 and 170g at twelve weeks of age, were purchased from the Experimental Animal Unit, Faculty of Veterinary Medicine, Benha University, Egypt. Rats were fed a well-balanced diet, had access to free, clean water, and a tidy living space. The rats lived in an environment that had a natural light/dark cycle of 12 hours and a temperature of 23±3°C. After the experiment and sample collection were finished, rats were buried.

Experimental Design

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Characterization of CuO-NPs

Twenty-eight mature male Wistar rats, weighing between 150 and 170g at twelve weeks of age, were purchased from the Experimental Animal Unit, Faculty of Veterinary Medicine, Benha University, Egypt. Rats were fed a well-balanced diet, had access to free, clean water, and a tidy living space. The rats lived in an environment that had a natural light/dark cycle of 12 hours and a temperature of 23±3°C. After the experiment and sample collection were finished, rats were buried.

Liver Homogenate Preparation

Liver tissues were washed with a solution of PBS containing 0.16 mg/ml heparin, pH 7.4, to remove RBCs and clot remnants. One gram of each tissue was homogenized in 5ml of cold buffer (50 mmol potassium phosphate, 1 mmol EDTA, pH 7.5) using a sonic homogenizer. The tissue homogenate was centrifuged at 4000 rpm/20min using a cooling centrifuge then stored at −80°C [17]. The resultant supernatant was used to assess the levels of the oxidative markers (CAT, GSH, and MDA) and total protein.

Assay methods

Liver Function Tests

The alanine aminotransferase (ALT), aspartate aminotransferase (AST) activities were performed according to Reitman and Frankel [18] and alkaline phosphatase (ALP) was measured by the method of Belfield and Goldberg [19].

Serum Proteins

Total protein was quantified using the Lowry et al. [20] methodology, and albumin was approximated using the Doumas et al. [21] method. By deducting the amount of serum albumin from the corresponding total protein, serum globulins were estimated.

Oxidative Markers in Liver Homogenate

The MDA levels were determined using Ohkawa et al. [22] methodology. Ellman [23] and Johansson and Borg [24] methods were used, respectively, to measure the GSH contents and CAT activity.

Hepatic mRNA Gene Expression

The mRNA expression of the hepatic PI3K, AKT, NFκB, and STAT-3 genes were studied using a 7300 real-time PCR system (Applied Biosystems, Foster City, CA, USA). Using sense and antisense primers, Abdelazeim et al. [25] used a previously described protocol to evaluate the expression of hepatic PI3K, AKT, NFκB, STAT-3, and β-actin (as a housekeeping gene) (Table 1). The cycle threshold (Ct) values obtained from the real-time PCR were used to evaluate the changes in gene expression using the comparative Ct technique with a reference gene (β-actin, a housekeeping gene) [25].

Histopathological Examination

Liver samples were taken out of each group right away, and they were preserved in neutral formalin with 10% buffer for 24 hours. Following their cleaning with tap water, the samples were dehydrated using several dilutions of alcohol (methyl, ethyl, and absolute ethyl). The specimens underwent xylol clearing, paraffin embedding, and varying degrees of ethyl alcohol dehydration. Blocks of paraffin and

beeswax tissue were produced for sectioning using an RM2235 Leica microtome (Biosystems, Nussloch, Germany) at a thickness of 4µm. Hematoxylin and eosin (H&E) and Masson's trichrome staining and a microscopic inspection were carried out [26].

Immunohistochemical Study

The paraffin slices were hydrated and deparaffinized. Rabbit monoclonal antibodies against caspase-3 (Cas-3) ([EPR12012] (ab179800); 1/1000-1/5000 dilution; Abcam, UK) and primary rabbit polyclonal antibodies against cytochrome C (SAB4502234; 1:50-1:100 dilution; Sigma-Aldrich, St. Louis, Missouri, USA) were incubated with the buffer solution at a concentration of 2-4µg/mL. To stop nonspecific reactions, 10% hydrogen peroxide was used to block the sections initially. Citrate buffer (pH 6) was used for heat-mediated antigen retrieval prior to IHC labeling with a rabbit polyclonal antibody against SERCA2 ATPase (ab3625, Abcam, UK, 1g/mL). After rinsing the cells with phosphate buffer, a secondary goat anti-rabbit antibody that had been biotinylated was applied. To localize the immunological reaction, sections were treated with labeled avidin-biotin peroxidase, which binds to the biotin on the secondary antibody. Diaminobenzidine was converted to a brown precipitate by peroxidase, therefore it was utilized as a chromogen to show where the antibody attached [27].

Image Analysis

Using a Nikon Eclipse E800 microscope (Melville, NY, USA), it was established what proportion of the Cas-3 Masson's trichrome staining or immunostaining region was covered by the blue hue (area %). The photos were taken with an Olympus digital camera (E-620, United States). Digital image analysis and quantification were performed using Scion Image Beta 4.03 (Scion Corporation, USA).

Statistical Analysis

Utilizing SPSS (SPSS Inc., Chicago, USA; Version 16), the statistical analysis was carried out. One-way ANOVA was used to investigate the substantial divergence found through multiple group comparisons and the Duncan test was used as a post hoc assessment. It expresses all values as mean±SE, with significance considered at $P \leq 0.05$.

Results

Throughout the trial, no rat in either of the experimental groups experienced any symptoms or died.

Liver Function Tests

The ALT, AST, and ALP levels were significantly elevated in the CuO-NPs-treated group than in the other experimental groups by the end of the fourth week. However, in the group that received QC and CuO-NPs, these enzymes levels were mitigated after the fourth week of the trial (Table 2).

Serum Proteins

The levels of total protein, albumin, and globulins in the CuO-NPs-treated group were considerably lower following the fourth week of treatment. However, the group that received QC and CuO-NPs showed a considerable increase in total protein and albumin after the fourth week of the trial (Table 3).

Changes in Liver Oxidative Markers

The liver tissue of the CuO-NPs-treated group showed significantly reduced GSH concentrations and decreased CAT activity. But after the trial's fourth week, the group that received both QC and CuO-NPs co-treatment showed a mitigation in these activities. The levels of MDA, a marker of LPO in liver tissue, were considerably higher in the CuO-NPs-treated group than in the other experimental groups. However, the group that received both QC and CuO-NPs co-treatment showed mitigation of MDA levels after the fourth week of the trial (Table 4).

PI3K, AKT, NFκB, and STAT-3 mRNA Expression in Liver Tissue

After four weeks of treatment, Figure 2 displays the expression of mRNA genes for liver PI3K, AKT, NFκB, and STAT-3 in the groups treated with QC, CuO-NPs, and QC+CuO-NPs. Rats treated with CuO-NPs had significant upregulation of NFκB and STAT-3 mRNA expression, but PI3K and AKT mRNA were significantly downregulated. In the meantime, QC treatment of intoxicated rats resulted in a significant overexpression of hepatic PI3K and AKT mRNA genes and a considerable downregulation of NFκB and STAT-3 mRNA genes.

Histopathological Assessment of Liver Tissue

Assessment of liver sections stained with H&E indicated that rats given CuO-NPs showed marked lytic necrosis characterized by disruption and loss of normal hepatic tissue and cellular architecture with replacement by hemorrhage, fibrin, edema and scattered necrotic cellular debris (Fig. 3B) and moderate fibrosis in portal areas mixed with few neutrophils, lymphocytes and plasma cells (Fig. 3C). Hepatic architecture improved in rats treated with QC and CuO-NPs, with small focal interstitial inflammatory cells aggregates still noticed (Fig. 3D). The histological appearance of the liver was normal in both the control and QC-treated rats of hepatic architecture, portal areas, central veins, sinusoids and hepatocytes (Fig. 3A).

Masson's Trichrome Stain Examination

Rats administered CuO-NPs exhibited noticeably more collagen fiber deposition in the portal region, around the central veins, and between the hepatic

cords, according to analysis of liver sections stained with Masson's trichrome (Fig. 4C). Following four weeks of the experiment, the group treated with CuO-NPs showed a considerable increase in Masson's trichrome area (%) (Fig. 4E). Conversely, rats received both QC and CuO-NPs had less collagen fiber deposition (Fig. 4D). After four weeks of the experiment, rats treated with QC and CuO-NPs had a significantly lower Masson's trichrome area (%) (Fig. 4E). The control and QC treated groups had the lowest levels of collagen fiber expression (Fig. 4A, B).

Immunohistochemical Assessment of Liver Tissue

Cas-3 immunohistochemistry staining sections of liver tissues from rats exposed to CuO-NPs show that the Cas-3 protein is highly expressed in the central vein, sinusoids, and between hepatocytes, indicating necrotic changes (Fig. 5C). After 4 weeks of the experiment, the Cas-3 area (%) was significantly increased in the CuO-NPs treated group (Fig. 5E). But in rats given QC and CuO-NPs, Cas-3 expression was downregulated, and the level of positive was lower than in rats given CuO-NPs (Fig. 5D). Following four weeks of the experiment, the group treated with QC and CuO-NPs had a considerably reduced Cas-3 area (%) (Fig. 5E). The liver tissues of the QC-treated and control rats showed very minimal Cas-3 staining, indicating very little apoptotic activity (Fig. 5A, B).

Discussion

Since nanotechnology is widely used in many different fields, it has gained significant public attention. Despite the positive aspects of nanotechnology, society cannot neglect its other side [28]. As is well known, because of their small size, nanoparticles are able to enter cells and tissues, translocate, produce oxidative stress, and inflict severe damage to them [29]. The present study's objective was to evaluate if QC could protect the liver from the hepatotoxicity caused by CuO-NPs.

After four weeks of the experiment, the current investigation showed that the activity of ALT, AST, and ALP was significantly elevated, indicating injury to the liver tissue of the CuO-NPs treated group. This may be due to inflammation and cellular hepatic damage, this causes the cell membrane to become more permeable and allows the transaminases to enter the bloodstream [30]. Serum levels of ALT, AST, and ALP were significantly reduced in rats co-treated with QC and CuO-NPs. The decrease of these enzyme levels implies that QC can maintain hepatocyte membranes, hence preventing biomarker leakage into the blood, as QC has an anti-inflammatory property [31]. These results aligned with the research conducted by Haroun et al. [32], who showed that the QC somewhat decreased the hepatotoxicity brought on by CuO-NPs.

In the meantime, there was a sharp decline in albumin and total protein levels as a result of liver failure induced by CuO-NPs as protein synthesis mostly occurs in the liver. These findings coincided with Sutunkova et al. [33]. The levels of total protein and albumin were increased in rats co-treated with QC and CuO-NPs. QC demonstrated significant benefits in reducing liver damage by enhancing antioxidant enzyme activity and reducing pro-oxidant effects [34]. This mechanism is attributed to the capacity of QC to interact with superoxide, hydroxyl, alkoxyl, and peroxyl radicals, so effectively neutralizing those [35].

In this work, following four weeks of the experiment, rats given CuO-NPs exhibited decreased GSH contents and CAT activity together with increased MDA levels, indicating lipid peroxidation. Cellular component damage and membrane lipid peroxidation may have caused this impact [36]. The primary process by which CuO-NPs cause liver damage is oxidative stress induction, which is brought on by the free radicals that CuO-NPs produce and which worsen liver function, hepatocyte necrosis, and hepatic architecture [37]. Lipid-peroxidation is caused by reactive oxygen species (ROS), which interact with cellular lipids and deplete endogenous antioxidants [4]. These findings were consistent with Tulinska et al. [38].

Rats that received both QC and CuO-NPs concurrently exhibited higher GSH content, CAT activity, and lower MDA levels. These results support the conclusions made by Abdelazeim et al. [25], who found that QC decreased MDA and elevated GSH, and CAT in the liver of mice. QC could directly neutralize free radicals as it had a great antioxidant Capacity. QC might mitigate Cu2+-induced lipid peroxidation by chelating Cu2+ and finally prevent copper accumulation and oxidative hepatic injury [39]. QC could enhance the expression of several antioxidant enzymes, including glutathione transferase and aldo-keto reductase [40]. QC thus increased the amounts of antioxidants and decreased oxidative stress [41].

The present results were confirmed by histo-pathological findings that revealed several abnormalities in the liver of CuO-NPs-intoxicated group which showed severe lytic necrosis of hepatic parenchyma characterized by loss of normal hepatic tissue and cellular architecture with replacement by hemorrhage, fibrin, edema and scattered necrotic cellular debris, as well as fibrosis in portal areas mixed with neutrophils, lymphocytes and plasma cells. These findings support the findings of Tohamy et al. [42], who demonstrated mononuclear inflammatory cells infiltration, hyperplasia of the duct epithelial lining, and deteriorated bile ducts. While rats treated with QC and CuO-NPs maintained normal hepatic architecture, with few localized interstitial aggregations of lymphocytes and

macrophages. These findings revealed that QC has antioxidant activity by scavenging free radicals [32].

The results of Masson's trichrome stain analysis likewise supported the current conclusions. CuO-NPs treated rats showed dense fibrous tissue deposition, indicating severe liver fibrosis. This investigation was confirmed by the findings of Ghonimi et al. [43]. While rats treated with QC and CuO-NPs had a potential mitigating impact on liver fibrosis, with an apparent restoration of normal hepatic architecture and a decrease in fibrous tissue deposition. The outcomes were consistent with the study conducted by Abo-EL-Sooud et al. [44], that used Al_2O_3 nanoparticles to induce liver fibrosis in rats and then administered QC concurrently.

These results corroborated the Cas-3 immunohistochemistry features of the CuO-NP-treated rats', which showed that Cas-3 was strongly expressed in the region of the portal tract, the central vein, and between hepatocytes, indicating necrotic alterations. These findings suggest that this factor may play a role in CuO-NPs induced liver damage [25]. These findings were consistent with Goma et al. [45], who found an increase in Cas-3 positive cells in the brain of rats exposed to CuO-NPs. Meanwhile rats administered QC and CuO-NPs, the number of hepatocytes expressing Cas-3 and immunoreactivity decreased considerably. QC inhibits apoptosis by downregulating Cas-3, which may be due to the anti-apoptotic, anti-mutagenic and anti-oxidative properties of QC [12]. These findings corroborate with those of Elsayed et al. [46].

In the present study PI3K and AKT genes were down-regulated in CuO-NPs treated rats. The PI3K/AKT signaling pathway regulates cellular activities including death and proliferation [47]. AKT normally supports cell survival by phosphorylating the Bad protein, causing it to separate from its complex and lose its pro-apoptotic activity, so improving cell survival [48]. The PI3K/AKT signaling pathway is crucial for attenuating liver fibrosis both *in vivo* and *in vitro*. It has been shown that activating this pathway improves liver function, prevents hepatic stellate cell (HSC) activation, and lowers liver fibrosis markers [49].

The PI3K/AKT cascade has been shown to be triggered by stressful stimuli such as ROS provoked by CuO-NPs toxicity [47]. These findings corroborate those of Chen et al. [50]. QC significantly up-regulated hepatic PI3K and AKT gene expression, this may be due to QC providing some recovery of hepatocytes exposed to CuO-NPs. These findings corroborate those of Sarkar and Sil [51].

CuO-NPs intoxicated rats had significantly up-regulated NFκB and STAT-3 genes. Excessive ROS generation and oxidative stress induced by CuO-NPs enhance activation of NFκB signaling pathway [52]. The activation of pro-inflammatory cytokines like TNF-α is the main basis for the NFκB pathway, which is widely considered to be a typical pro-inflammatory signal transduction pathway [53]. The cytosol contains NFκB attached to the IkBa effector [54]. When activated, NFκB may trigger a number of biological processes, including the production of cytokines and inflammatory reactions that result in inflammation, oxidative stress, cancer, and apoptosis [55]. Thus, preserving NFκB/IkBa stability or preventing NFκB and IkBa from being released from hepatocytes may help to reduce CuO-NPs-induced liver damage [56].

Numerous biological functions, such as cancer, apoptosis, and cell proliferation, depend on STAT-3 proteins [57]. The effects of STAT-3 on diverse cells demonstrated that STAT-3 affects hepatocytes by producing proinflammatory cytokines, which may be connected to the release of different cytokines and regulatory proteins in stimulated hepatocytes and is a major factor in the inflammation and damage to the liver caused by CuO-NPs [58]. Rats treated with QC and CuO-NPs had significantly downregulation of hepatic NF-kB and STAT-3 genes. Rats were shielded against CuO-NP-induced hepatotoxicity by QC, which blocked the NF-kB pathway and stopped the release of pro-inflammatory cytokines [59]. These results support Zhu et al. [60], who found that QC prevents alcohol-induced liver injury through targeting NF-kB and STAT-3 signaling pathway.

Conclusion

The current study focused on QC as a possible hepatoprotective medication against CuO-NPs-induced hepatotoxicity. By reducing liver MDA levels, QC prevented lipid peroxidation and shielded the liver from CuO-NP insult by raising liver GSH and CAT antioxidant levels and blocking the NF-κB pathway, which prevented the hepatic tissues from producing Cas-3. QC's capacity to counteract oxidative stress might be associated with its alteration of the PI3K/AKT pathway, which leads to the overproduction of downstream antioxidant enzymes including CAT and GSH. As a result, it is reasonable to suggest QC as an adjuvant treatment for nanoparticles and possible heavy metals pollutants.

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Conflict of Interest

There were no competing interests disclosed by the authors.

Consent to participate

Participation acceptance: All research participants provided verbal and written informed consent.

Author Contributions

A.A.: collected the samples, formal analysis, analyzed the data, and wrote the manuscript. R.M.E., M.E.S.A., and N.A.: designed the study, and approved the final manuscript. R.M.E: collected the samples, analyzed the data, and wrote the manuscript. A.M.H.: collected the samples, formal analysis, revised and approved the final manuscript. The final manuscript was read and approved by all authors.

Data Availability

The data needed to substantiate the investigation's conclusions will be supplied upon request from the corresponding author.

TABLE 1. The primer sets of the assessed genes.

Genes	Forward Primer (sense)	Reverse primer (anti-sense)	Gene bank ID
PI3K	5′- GCCCAGGCTTACTACAGAC-3′	5′- AAGTAGGGAGGCATCTCG-3′	NM_001081444.2
AKT	5′- CGGATACCATGAACGACGTAG-3′	5′- GCAGGCAGCGGATGATAAAG-3′	NM_033230.2
NFκB	5′- GTCTCAAACCAAACAGCCTCAC-3′	5′- CAGTGTCTTCCTCGACATGGAT-3′	NM_199267.2
STAT-3	5′- GTAGTGACGGAG AAGCAG-3′	5′- TCACAGACTGGTTGTTTCC-3′	NM_012747.2
GAPDH	5′- CTGGAGAAACCTGCCAAGTATG-3′	5′- GGTGGAAGAATGGGAGTTGCT-3′	NM_017008.4

TABLE 2. Impact of quercetin (QC) in relation to copper oxide nanoparticles (CuO-NPs) on liver function tests in different experimental groups (means±SE), (n=7).

	Control	QC	CuO-NPs	QC+CuO-NPs
ALT (IU/L)	20.71±1.67^{c}	21.57±2.18^{c}	59.14±2.88^{a}	30.57±3.90^{b}
AST (IU/L)	91.71±4.25^{c}	79.71±4.92^{c}	168.14±3.86^{a}	122.43±7.43^{b}
ALP (IU/L)	293.14±11.80^{c}	310.18±12.76^{c}	476.33±13.14^{a}	380.69±12.00^{b}

Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP).

*Different superscript within the same row indicate significantly different mean values ($p \leq 0.05$).

TABLE 3. Impact of quercetin (QC) in relation to copper oxide nanoparticles (CuO-NPs) on total protein, albumin and globulins in different experimental groups (means±SE), (n=7).

	Control	QC	CuO-NPs	QC+CuO-NPs
Total Protein (g/dl)	268.71±5.27^{a}	267.71±8.19^{a}	150.57±6.20^{c}	194.43±5.64^{b}
Albumin (g/dl)	102.29±3.93^{a}	98.29±3.73^{a}	56.57±2.73^{c}	80.57±2.77^{b}
Globulin (g/dl)	166.43±5.89^{a}	169.43±9.59^{a}	94±6.88^{b}	113.86±5.89^{b}

*Different superscript within the same row indicate significantly different mean values ($p \leq 0.05$).

TABLE 4. Impact of quercetin (QC) in relation to copper oxide nanoparticles (CuO-NPs) on oxidative markers in the liver homogenates in different experimental groups (means±SE), (n=7).

	Control	QC	CuO-NPs	QC+CuO-NPs
MDA (nmol/mg protein)	254.46±4.69^{c}	248.34±7.76^{c}	380.55±3.44^{a}	288.53±3.90^{b}
CAT (U/mg protein)	190.67±8.56^{a}	187.73±5.72^{a}	99.16±10.39^{c}	151.64±8.04^{b}
GSH (µmol/mg protein)	178.30±6.19^{a}	166.30±7.64^{a}	90.09±5.07^{c}	140.57±7.50^{b}

MDA (malondialdehyde), CAT (catalase), GSH (reduced glutathione).

*Different superscript within the same row indicate significantly different mean values ($p \leq 0.05$).

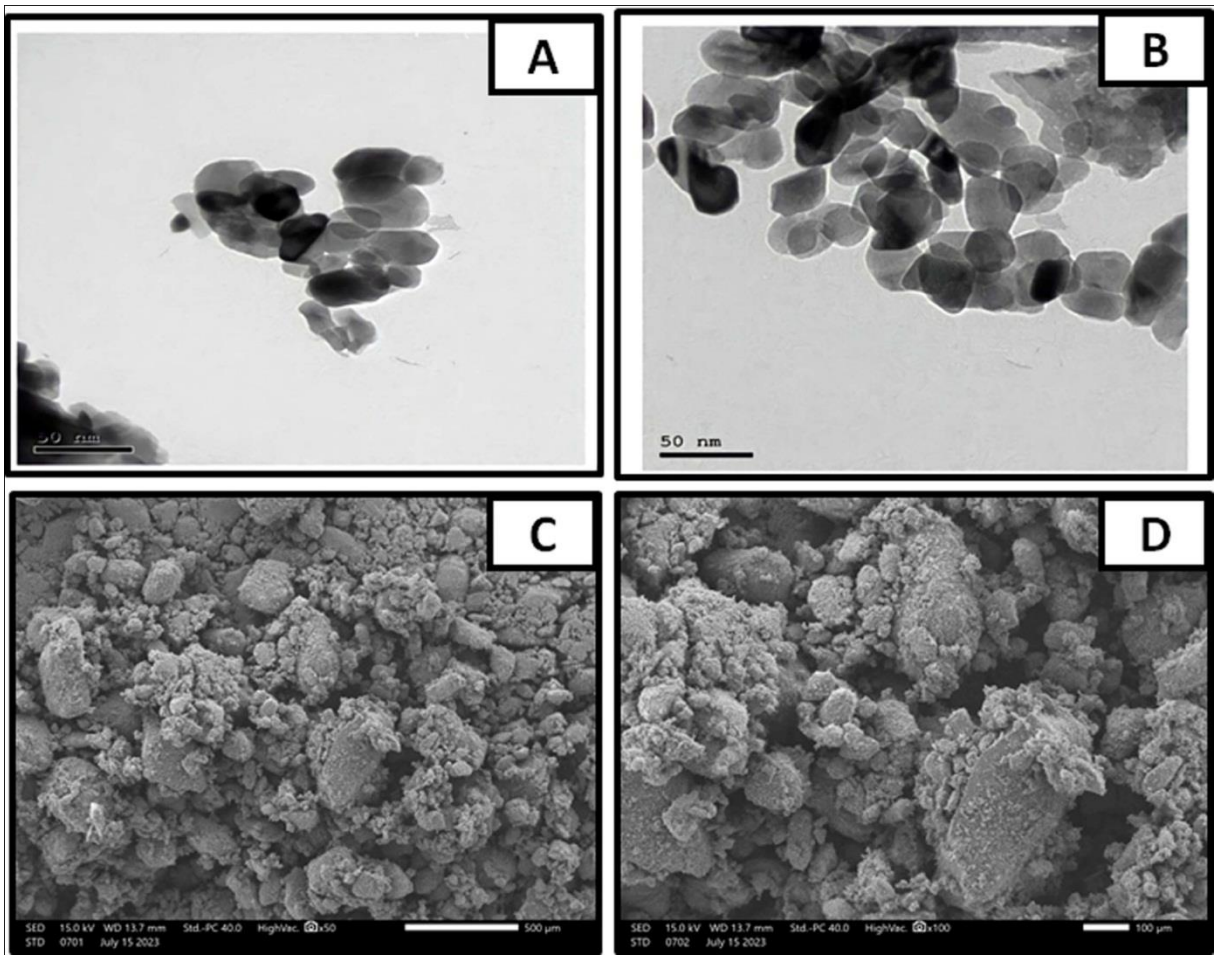

Fig.1. Characterization of CuO-NPs. Micrograph obtained from transmission electron microscope (TEM) showed that the particles with average size 50nm and Quasi-spherical in shape (Fig. 1A, B). Scanning electron microscopy (SEM) image for CuO-NPs (Fig. 1C, D).

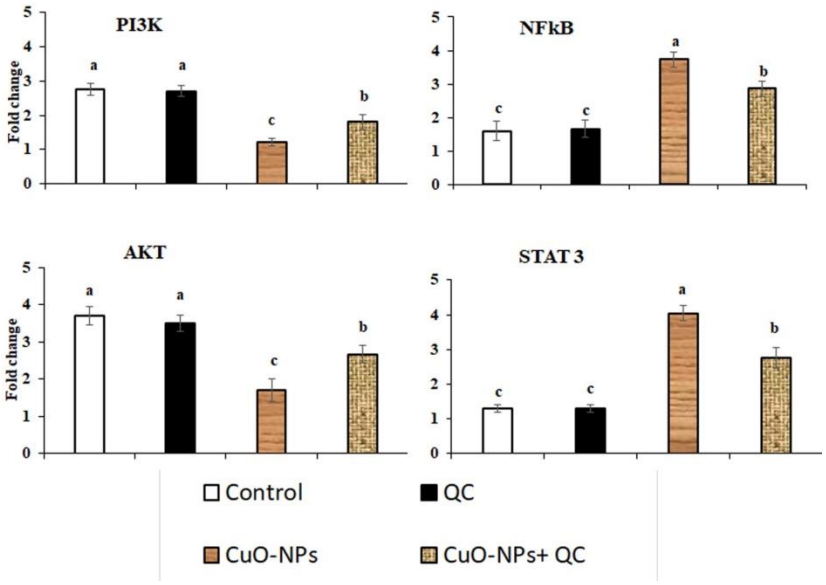

Fig. 2. mRNA expression of hepatic PI3K, AKT, NFkB, and STAT-3. Total RNA was prepared from hepatic tissues of rats treated with quercetin, CuO-NPs, quercetin against CuO-NPs, and control on 4 weeks after treatments. Real-time PCR was evaluated the expression levels. P<0.05 compared with control values. Bars represent (means±SE), (n=7).

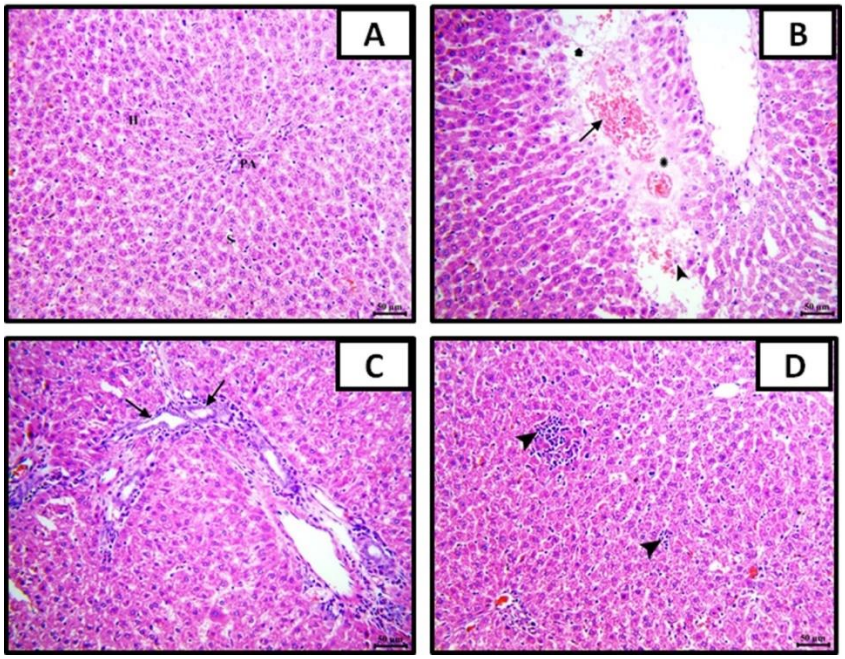

Fig. 3. Histopathological findings of liver from different experimental groups using H&E staining. (A) Control (saline) and quercetin-treated groups showing normal hepatic architecture, portal area (PA), central vein (CV) and surrounding hepatocytes (H). (B, C) CuO-NPs group showing (B) lytic necrosis of hepatic parenchyma characterized by loss of normal hepatic tissue and cellular architecture with replacement by hemorrhage (arrow), fibrin (thick arrow), edema (asterisk) and scattered necrotic cellular debris (arrowhead), (C) Fibrosis in portal areas mixed with few neutrophils, lymphocytes and plasma cells; note ductular reaction with formation of variably sized bile ducts (arrow). (D) Quercetin+CuO-NPs treated group shows normal hepatic architecture with small focal interstitial inflammatory cells aggregates (arrowhead). (scale bar=50µm, ×100).

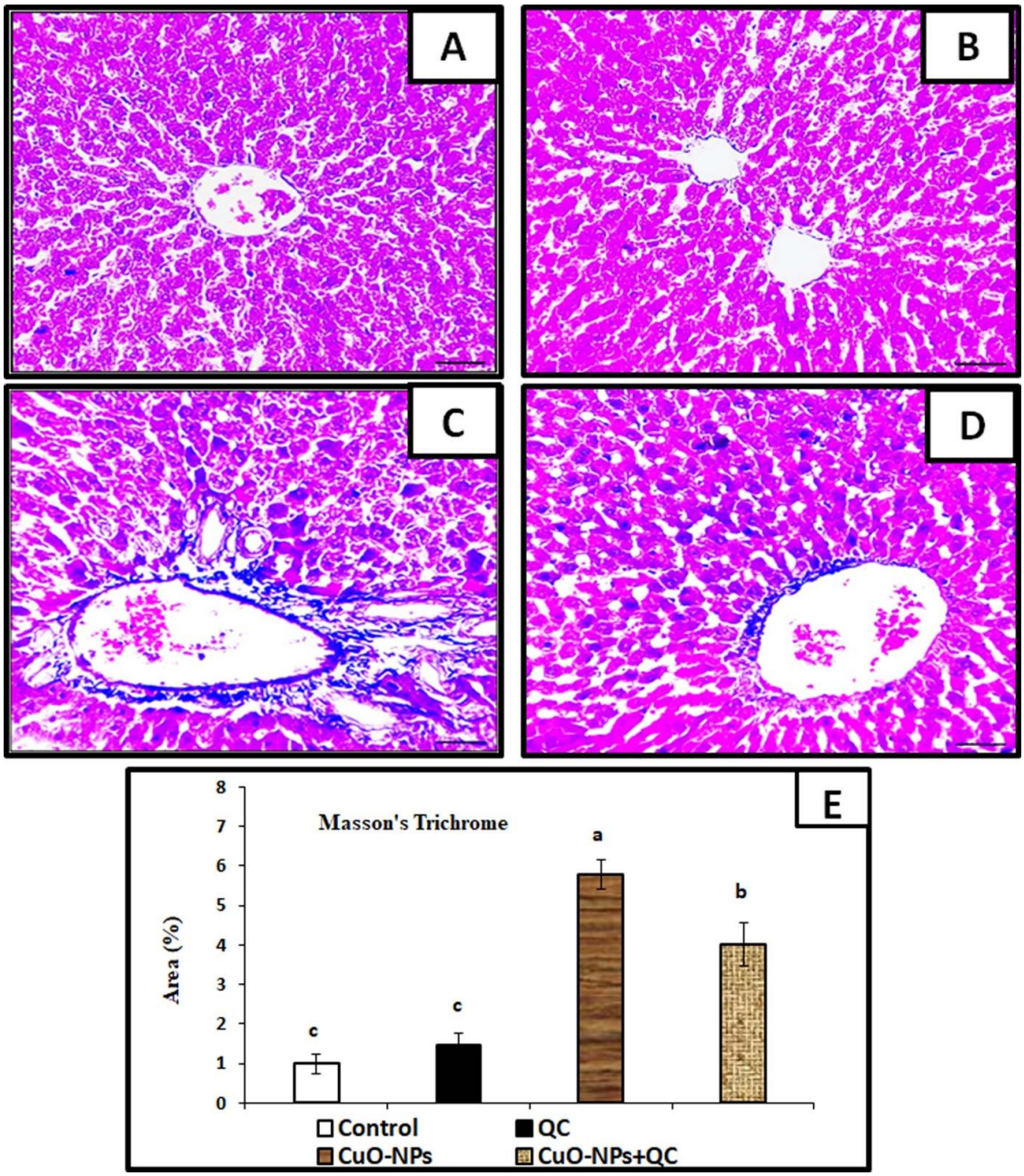

Fig. 4. Masson's trichrome staining of liver sections from different experimental groups. (A) Control (saline) group shows minimal fibrous tissue, reflecting normal liver structure. (B) Quercetin group displays minimal collagen fiber expression. (C) CuO-NPs group exhibits extensive, bluish-stained fibrous tissue in the portal area, around the central veins and between the hepatic cords, indicative of severe fibrosis. (D) Quercetin+CuO-NPs treated group shows reduced collagen fiber deposition compared to CuO-NPs group. (E) morphometric study of area (%) of Masson's trichrome of liver of experimental rats. Data were used to estimate the degree of Masson's trichrome stain. P<0.05 compared with different experimental groups. Bars represent mean±SE, (n=7). (scale bar=50µm, ×50).

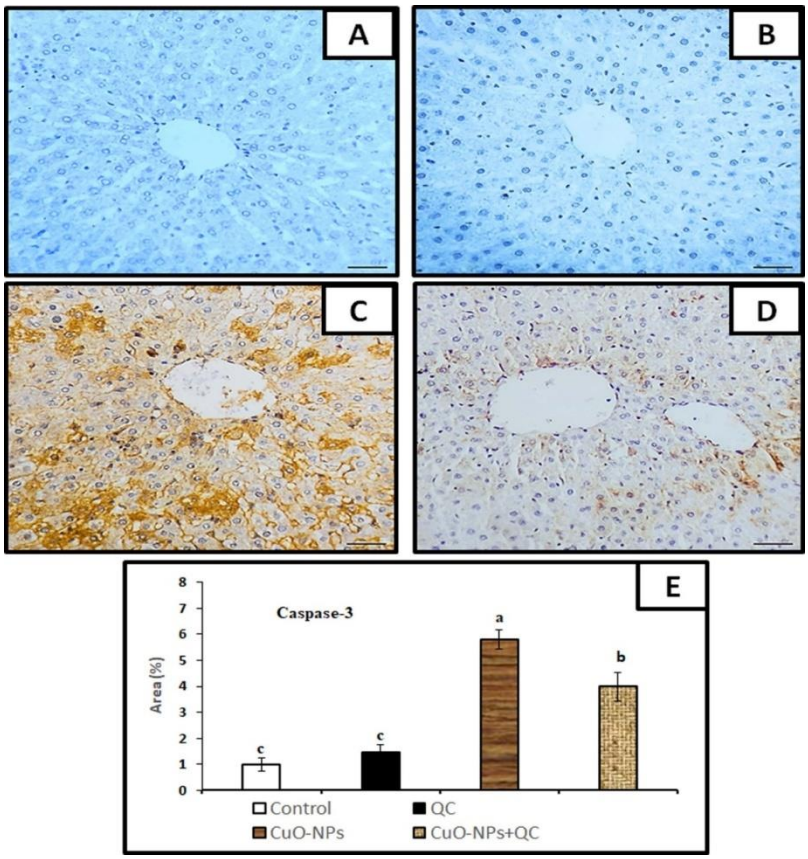

Fig. 5. Immunohistochemical expression of caspase-3 in liver tissues from different experimental groups. The brown color indicates positivity. (A) Control (saline) group showing negative to mild caspase-3 immunostaining in hepatocytes. (B) Quercetin group exhibits minimal caspase-3 staining, similar to the control, indicating negligible apoptotic activity. (C) CuO-NPs group with marked caspase-3 staining around the central vein, sinusoids and between hepatocytes, highlighting significant apoptosis due to toxicity. (D) Quercetin+CuO-NPs treated group shows reduced caspase-3 staining compared to the toxic group. (E) morphometric study of area (%) of caspase-3 immunohistochemical staining sections of liver of experimental rats. Data were used to estimate the degree of caspase-3 immunohistochemical staining. P<0.05 compared with different experimental groups. Bars represent mean±SE, (n=7). (Scale bar=50µm, ×50).

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التأثيرات المحسّنة للكيرسيتين ضد السمية الكبدية الناجمة عن جسيمات أكسيد النحاس النانوية في الجرذان البيضاء

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الملخص

تُستخدم جسيمات أكسيد النحاس النانوية في القطاعات الصيدلانية والتجميلية والصناعية.أدى التطبيق المكثف لجسيمات أكسيد النحاس النانوية في العديد من القطاعات إلى آثارها الضارة على الكائنات الحية المختلفة نتيجة تراكمها في أنسجة الجسم وخاصة الكبد . يُعد الكيرسيتين أحد أكثر الفلافونويدات الغذائية وفرةً في الفواكه والخضراوات. يتميز الكيرسيتين بخصائص مضادة للموت الخلوي ومضادة للأكسدة ومضادة للالتهابات. لذلك كان الهدف من الدراسة الحالية القاء الضوء علي التأثير السمي لجسيمات أكسيد النحاس النانوية علي أنسجة الكبد وأيضا استكشاف التأثير الوقائي المحتمل للكيرسيتين ضد السمية الكبدية المحدثة بجسيمات أكسيد النحاس النانوية. تم توزيع ثمانية وعشرون جرذاً ذكراً بالغاً علي أربعه مجموعات كالتالي : المجموعه الضابطه (محلول ملحي عن طريق الفم) والمجموعه المعالجه بالكيرسيتين (100 ملليجرام لكل كجم من وزن الجسم عن طريق الفم) والمجموعة المعالجه بجسيمات أكسيد النحاس النانونية (300 ملليجرام لكل كجم من وزن الجسم عن طريق الفم) والمجموعة المعالجه بجسيمات أكسيد النحاس النانونية والكيرسيتين معاً بنفس الجرعه والطريقه. تم التجريع لمدة ٤ اسابيع وتم أخذ عينات من الدم ونسيج الكبد من الجرذان في جميع المجموعات. أظهرت النتائج أن الكيرسيتين خفف الاختلالات الكبدية من خلال تحسين وظائف الكبد (انزيم ناقلة أمين الألانين وناقلة أمين الأسبارتات وانزيم الفوسفاتاز القلوي) . واستعادة حالة مضادات الأكسدة عن طريق زيادة الجلوتاثيون المختزل والكاتلاز وتقليل المالونديالدهيد. علاوة على ذلك، أدي الكيرسيتين الي تقليل التعبير الجيني للحامض النووي لكل من العامل النووي كابا بيتا وكذلك محول الإشارة ومنشط جينات النسخ وزيادة التعبير الجيني للحامض النووي لكلاً من فوسفونوسيتيد- ٣ كيناز وبروتين كيناز ب . بالإضافة إلى ذلك ، حافظ الكيرسيتين على بنية الأنسجة الكبدية، وقلل من النشاط المناعي ضد الكاسبيز ٣. تشير هذه النتائج إلى أن الكيرسيتين قد يخفف من السمية الكبدية الناجمة عن جسيمات أكسيد النحاس النانوية من خلال خصائصه المضادة للأكسدة والمضادة للالتهابات والمضادة لموت الخلايا المبرمج.

الكلمات الدالة: جسيمات أكسيد النحاس النانوية، السمية الكبدية، الإجهاد التأكسدي، مسار PI3K/AKT، الكيرسيتين.