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Hematological and Biochemical Response to Methyl Mercury Toxicity and the Ameliorative Effect of Quercetin Flavonoid in Wistar Rats

Reem Alanazi[1], Sawsan Omer[1], Gadah Albasher[1], Osama B. Mohammed[1]

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ABSTRACT

Background: This study aims to assess the hepatonephrotoxicity of Methylmercurry (MeHg) through hematological and biochemical changes. Furthermore, it also aims to assess the amoleraitive role of flavonoid quercetin (QCT) in reducing such deleterious effects.

Methods: In this study, 36 male Wistar rats were assigned into six equal groups as follows: The control group received normal saline orally (G I); QCT-treated group was given 50 mg/kg BW QCT (G II); MeHg low-exposed group was given 5 mg/kg BW (G III); MeHg high-exposed group was given 6.7 mg/kg BW MeHg (G IV); MeHg low + (50 mg/kg) QCT-cotreated group (G V) and MeHg high + (50 mg/kg) QCT-cotreated group (G VI) for 21 days.

Result: It was found out that MeHg exposure resulted in hematological and biochemical changes. Concurrent administration of QCT with MeHg intoxication at both levels partially modulated the recorded deleterious influences. The body weight of experimental animals has reduced significantly in all groups compared with the control group. Hemoglobin and hematocrit were reduced in animals given high and low doses of MeHg and improved with the addition of QCT. WBCs were increased with the administration of MeHg and reduced with QCT addition. Hepato-renal involvement was indicated by the increase in the liver enzymes, bilirubin, creatinine and BUN levels, which were reduced with the administration of QCT. Increased glucose levels in animals that received MeHg were reduced with QCT administration.

Key words: Blood chemistry, Hematology, Hepatorenal, Methyl mercury, Quercetin.

INTRODUCTION

One of the most common environmental pollutants in the world, mercury (also known as hydrargyrum), occurs naturally in three different forms: elemental, inorganic and organic mercury. Every form has unique chemical characteristics and varying levels of toxicity (Kaur *et al*., 2019). According to Rice *et al*. (2014), the US Government Agency for Hazardous Substances and Disease Registry ranks mercury as the third most risky substance. Similarly, mercury is regarded by the World Health Organization (WHO) as one of the ten substances that pose the greatest threat to public health.

Significant mercury emissions originate from natural sources such as volcanic eruptions, oceanic sediments, crust degassing, forest fires and meteorological events. Human activities contribute to mercury contamination through coal combustion, fluorescent lighting, cement production, dental amalgamation, cremation, paper manufacturing, gold mining, perfume and fur industries and fossil fuel combustion (Rice *et al*., 2014). Aquatic ecosystems are the most common destinations of disposal for urban and industrial waste products and runoff from agricultural fields, industrial effluent dumping and untreated waste discharge are the principal causes of mercury contamination in water (Hoffman, 2002).

Evidence from large-scale Human poisonings emphasize the lethal effects of organic mercury compounds. The Minamata tragedy was a catastrophic methylmercury (MeHg) poisoning in Japan during the 1950s and 1960s when people consumed fish and shellfish from the MeHg-contaminated Minamata Bay (Yorifuji, 2020). The neurologically altered people had a variety of symptoms, such as dysarthria, ataxia, paresthesia in the distal extremities, tremors, muscular weakness, abnormal eye movements and dysequilibrium (Jackson, 2018). The MeHg is widely dispersed and easily enters the central nervous system (CNS) following absorption as it crosses the blood brain barrier (Zareba *et al*., 2007), affecting a variety of cellular functions of brain, including neurochemical, neuroendocrine and electrophysiological alterations in the functioning of cells (Coccini *et al*., 2006).

Novel strategies designed to protect against MeHg-induced adverse health consequences have recently

[1]Department of Zoology, College of Science, King Saud University, Riyadh 11451, Kingdom of Saudi Arabia.

Corresponding Author: Osama B. Mohammed, Department of Zoology, College of Science, King Saud University, Riyadh 11451, Kingdom of Saudi Arabia. Email: omohammed@ksu.edu.sa

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gained attention in research. These strategies are based on mitigating oxidative stress by antioxidants that may be able to alle*via*te Hg-induced intoxication (Abdelhamid *et al*., 2023). Flavonoids, a class of naturally occurring polyphenolic compounds, have diverse positive health benefits on humans. Quercetin (QCT), a potent polyphenolic flavonoid molecule, acts as an antioxidant. Its name comes from the Latin "*quercetum*" meaning oak forest, Quercus oak. It is described as a promising substance for both illness prevention and treatment (Mitchell *et al*., 2007).

QCT, an active ingredient, is found in diverse vegetable species and medicinal plants, including *Hypericum perforatum, Sambucus canadensis* and *Ginkgo biloba* (Liu *et al*., 2012). Onions and apples are the major dietary sources of QCT, while other sources comprise cherries, blueberries, grapes, citrus fruits and red leaf lettuce, broccoli, cabbage, peppers, tomatoes, asparagus, tea, wine (Andres *et al*., 2018) and in seeds, flowers, nuts, bark and leaves. It is found mainly in leaves and in the outer parts of the plants as glycosides and aglycones (Renugadevi and Prabu, 2010).

QCT has received attention due to its exceptional variety of health advantages, positioning it as a crucial ingredient in the creation of innovative and effective functional foods and medications (Liu *et al*., 2012). Both *in vivo* and *in vitro* experiments have suggested that QCT has a variety of beneficial effects, including hepatoprotective, nephroprotective, immunomodulatory, cardioprotective and neuroprotective activities (Gao *et al*., 2024; Farag *et al*., 2021).

In this study, we aimed at two major objectives. First, we investigated the differential toxic impact induced by methylmercury exposure in the liver and kidney tissues through hematological and serum biochemistry assessment in rats. Second, we examined the ameliorating role of flavonoid quercetin against such deleterious effects.

MATERIALS AND METHODS

Written ethical assent for this study was reviewed and approved with Institutional Review Board (IRB) reference number (KSU-SE-23-122) *via* the Ethics Committee at King Saud University, Ministry of Education, Riyadh, Saudi Arabia. Methylmercury chloride (CH_3ClHg) was purchased from LGC Labor GmbH, Augsburg, Germany (CAS No: 115-09-3; Molecular weight. 251.08). Quercetin ($C_{15}H_{10}O_7$, QCT) was purchased from Sigma-Aldrich Chemical Co., Saint Louis, MO, USA, (CAS No: 117-39-5; Molecular Weight: 302.24).

Experimental animals and experimental design

A total of 36 male Wistar rats, weighing 100±15 g, were obtained from the animal house, Zoology Department, College of Science, King Saud University, during the period June to October 2024. Hygienic conditions were maintained in stainless steel cages with a 12-hour light/dark cycle, relative humidity of 44-50% and ambient temperature of 25±2°C. They were fed a balanced diet and water and feed were provided *ad libitum* during the trial. The animals were acclimatized in the laboratory conditions for two weeks before being experimented.

The animals were randomly divided into six equal groups as follow: Group I: Control group received normal saline orally. Group II (QCT): Received 50 mg/kg of QCT (Barcelos *et al*., 2011). Group III: Received 5 mg/kg of MeHg dissolved in MilliQ water (Sahu *et al*., 2022). Group IV: received 5 mg/kg MeHg + 50 mg/kg QCT. Group V: received 6.7 mg/kg of MeHg dissolved in MilliQ. Group VI: received 6.7 mg/kg MeHg + 50 mg/kg QCT. Daily dosing continued for 21 days.

Blood collection, hematological and biochemical investigations

At the end of the experiment, blood samples (with Ethylene diamine tetra acetic acid {EDAT} and without anticoagulant) were collected from the retro-orbital plexus of the eye or directly from the heart of all individuals of each group. Blood with EDTA was used to determine hematological profile of animals using the automatic hematologic analyzer. Red blood cell (RBC), leukocytes (WBC), hemoglobin (Hb), platelets (PLT), hematocrit (HCT) and differential WBC counts were measured in blood samples with an automated blood cell counter (VetScan® HM5, Abaxis Veterinary Diagnostics, Union City, CA 94587, USA).

Blood without anticoagulant was utilized to obtain serum for biochemical analyses with the biochemistry analyzer VetScan®VS2 (Abaxis Veterinary Diagnostics, Union City, CA 94587, USA) using the VetScan® Comprehensive Diagnostic Profile rotors.

Liver function test was estimated through determining the concentrations of Alanine aminotransferase (ALT) or glutamate-pyruvate transaminase (GPT), Alkaline phosphatase (ALP), total bilirubin, total protein and albumin using the comprehensive profile rotor from Abaxis. Kidney function test was brought about by measuring the concentrations of both creatinine and blood urea nitrogen (BUN) as well as the electrolytes and glucose using the comprehensive profile rotor from Abaxis. Pieces of livers and kidneys were processed for histological investigations.

Data were analyzed using version 16 of the statistical package for social sciences (SPSS, Chicago, IL, USA). The level of significance was set at $P<0.05$.

RESULTS AND DISCUSSION

During the experimental period, the rats in G I and G II remained without apparent clinical abnormalities. Dullness, lethargy and rough hair coat have been observed in other experimental groups, especially groups III and V. Rats tin groups III and V showed a significant decrease in body weight compared with the control rats ($P<0.05$), this decline was marked in group V (Table 1).

No significant difference was reported in the RBC counts between the experimental groups. Both groups exposed to either in low or high dose levels of MeHg showed a significant decline in Hb level ($p<0.05$), compared with

group I, this decrease was considerably improved upon the administration of QCT in both groups, as they showed a non-significant difference with group I (P>0.05). The administration of QCT in both groups IV and VI has improved the other erythrocytic parameters (Table 1). A significant increase (p<0.05) in the white blood cells in the experimental groups III and V compared with the values reported from the animals in group I. Both groups IV and VI showed significant reduction (p<0.05) in the WBC counts compared to the groups II and V (Table 1). Other leucocytic parameters followed the same pattern (Table 1).

In groups III and V, the activities of ALT and ALP were significantly increased (p<0.05) in the serum, compared with those in group I (Table 2). There was a significant elevation reported in group V compared to group III. The levels of ALT and ALP were improved in groups IV and VI (Table 2). Bilirubin showed a significant increase (p<0.05) in the serum of both groups III and V compared with the values from Group I (Table 2). Group IV and VI showed decrease in the bilirubin levels compared with groups III and V (Table 2). Albumin, total protein and globulin values remained without significant change in all groups (Table 2).

BUN and creatinine showed significant increase (p<0.05) in groups III and V compared with group I (Table 2). Groups IV and VI showed a slight reduction in both BUN and creatinine values. A significant increase in the glucose levels in groups III and V (p<0.05) compared with the control group. Groups IV and VI showed significant reduction of the glucose levels compared to the levels recorded in groups III and V (Table 3). The electrolytes levels including Ca, Na, K and P showed no significant differences (Table 3) among all experimental groups (Table 3). Histopathological changes in experimental animals were shown in Fig 1 and 2.

The body weight of experimental animals in groups III and V has reduced significantly compared with the control group, this reduction may be attributed to the metabolic cost theory as a consequence of the toxic potential of mercury, where the toxic stressors mediate some metabolic changes which may participate the consumption of an organism's energy reserves to combat the effect of toxicant or to activate repair mechanisms, resulting in an alteration of protein and carbohydrate metabolism (Khalil *et al*., 2017).

Experimental animals exposed to MeHg showed a significant reduction of Hb and HCT values as well as a

Table 1: Body weight changes and blood profile in rats in response to Quercetin administration and/or MeHg exposure.

Parameters	C	QCT	MeHg low	MeHg low + QCT	MeHg high	MeHg high + QCT
Body weight changes (gm)	109.00±2.08	99.33±5.21	72.67±7.51^{a}	70.67±5.17^{a}	38.67±4.37^{a,b}	50.67±1.76^{a,b,c}
Erythrogram						
RBCs (10^{12}/l)	10.28±0.28	10.13±0.21	8.62±0.50	9.08±0.44	7.93±1.00	9.53±0.45
Hb (g/dl)	17.80±0.72	17.47±0.40	14.70±0.80^{a}	15.43±0.47	14.30±0.33^{a}	16.37±0.82
HCT (%)	55.46±3.54	60.95±0.92	48.01±2.83^{a}	51.94±1.37^{b}	45.46±5.12^{a}	53.60±2.82^{c}
PLT (10^{9}/l)	951.67±136.14	922.00±60.12	1101.00±11.7^{a}	933.00±81.55^{b}	1276.00±50.20^{a,b}	925.67±131^{b,c}
Leukogram						
WBCs (10^{9}/l)	14.73±1.33	14.07±2.12	17.5±1.70^{a}	13.6±0.30^{b}	19.3±1.60^{a}	16.00±0.79^{c}
Lymphocytes (10^{9}/l)	10.00±0.79	9.00±1.90	10.00±1.17	9.56±0.62	16.00±1.27^{a,b}	10.00±0.92^{b,c}
Neutrophils (10^{9}/l)	3.53±0.60	4.90±0.20	7.00±0.55^{a}	3.26±0.86^{b}	8.11±0.31^{a}	3.80±0.56^{c}
Monocytes (10^{9}/l)	0.29±0.10	0.20±0.03	1.00±0.07^{a}	0.60±0.07^{a,b}	1.03±0.01^{a}	0.50±0.03^{a,b,c}

Data=Mean±SEM, P≤0.05 considered significant using One-way ANOVA, a = Significant compared to control group, b = Significant compared to MeHg (low dose), c = Significant compared to MeHg (high dose). Control (C); Quercetin (QCT); MeHg low + Quercetin (MeHg low + QCT); MeHg high + Quercetin (MeHg high + QCT).

Table 2: Tissue injury markers and protein profiles in rats in response to Quercetin administration and/or MeHg exposure.

Parameter	C	QCT	MeHg low	MeHg low + QCT	MeHg high	MeHg high + QCT
ALT (U/L)	73.00±4.48	74.00±4.60	86.00±6.60^{a}	81.00±10.00$^{a.}$	114.00±9.00^{a,b}	99.00±7.00^{a,b}
ALP (U/L)	255.00±43.00	252.00±15.00	358.00±35.00^{a}	292.00±21^{a,b}	471.00±44^{a,b}	342.00±16^{a,c}
Bilirubin (mg/dl)	0.30±0.02	0.30±0.03	0.43±0.08^{a}	0.30±0.06^{b}	0.57±0.07^{a,b}	0.43±0.07^{a,c}
Total protein (g/dl)	7.53±0.07	7.33±0.18	6.97±0.07	7.00±0.12	6.73±0.38	6.67±0.26
Albumin (g/dl)	2.23±0.13	2.33±0.18	2.03±0.12	2.60±0.42	2.10±0.43	2.57±0.35
Globulin (g/dl)	5.23±0.09	5.00±0.10	4.97±0.09	5.20±0.40	4.63±0.13	4.90±0.15
BUN (mg/dl)	17.00±0.58	17.33 ±0.88	29.00±3.05^{a}	24.00±1.52^{a}	34.67±6.06^{a,b}	21.00±1.15^{a,c}
Creatinine (mg/dl)	0.30±0.05	0.30±0.03	0.43±0.08^{a}	0.30±0.06^{b}	0.57±0.07^{a,b}	0.43±0.07^{a,c}

Data=Mean±SEM, P≤0.05 considered significant using One-way ANOVA, a = Significant compared to control group, b = Significant compared to MeHg (low dose), c = Significant compared to MeHg (high dose). Control (C); Quercetin (QCT); MeHg low + Quercetin (MeHg low + QCT); MeHg high+Quercetin (MeHg high + QCT).

significant increase in the PLT counts, with no significant effect on the RBC count as seen in previous studies (Hedayati and Ghaffari, 2013; Setiyowati *et al*., 2019; Alam *et al*., 2021). The possible explanation for this effect may be due to the production of activated forms of oxygen by mercury–hemoglobin complexes and alterations in hemoglobin structure (blocking SH groups of globin chains) (Piscopo *et al*., 2020; Zagrean-Tuza *et al*., 2024).

It appears the effect of the WBCs is dose dependent. The increase in the WBCs was accompanied by increase in lymphocytes, neutrophils and monocytes coinciding with what has been reported previously form the Tilapia exposed to MgCl2 (Kim JeongHong *et al*., 2015). This increase in leucocytes may be attributed to the stimulation of the defense mechanism (non-specific immune response) against the stress and injury induced by subacute MeHg exposure to restore ionic balance. As they are involved at a cellular level in innate immunity and function in the production of humoral substances such as lectins, cytokines and complement components (Ni *et al*., 2014).

Table 3: Glucose and electrolyte ions in rats in response to Quercetin administration and/or MeHg exposure.

Parameters	C	QCT	MeHg low	MeHg low + QCT	MeHg high	MeHg high + QCT
Glucose (mg/dl)	181.00±30	202.00±21	265.00±24[a]	191.00±19[b]	284.00±11[a]	190.00±42[b,c]
Ca (mg/dl)	12.90±0.2	13.00±0.1	13.50±0.1	12.90±0.2	12.20±0.3	12.00±0.3
Na (mg/dl)	148.00±0.5	148.00±1.2	148.00±1.8	148.00±1.8	151.00±0.7	151.00±1.2
K (mg/dl)	7.20±0.1	6.50±0.1	6.40±0.1	7.40±0.1	7.40±0.1	7.50±0.3
Phos (mg/dl)	13.00±0.4	12.00±0.2	11.00±0.2	12.00±0.8	11.00±0.2	13.00±0.8

Data=Mean±SEM, P≤0.05 considered significant using One-way ANOVA, a = Significant compared to control group, b = Significant compared to MeHg (low dose), c = Significant compared to MeHg (high dose). Control (C); Quercetin (QCT); MeHg low + Quercetin (MeHg low + QCT); MeHg high+Quercetin (MeHg high + QCT).

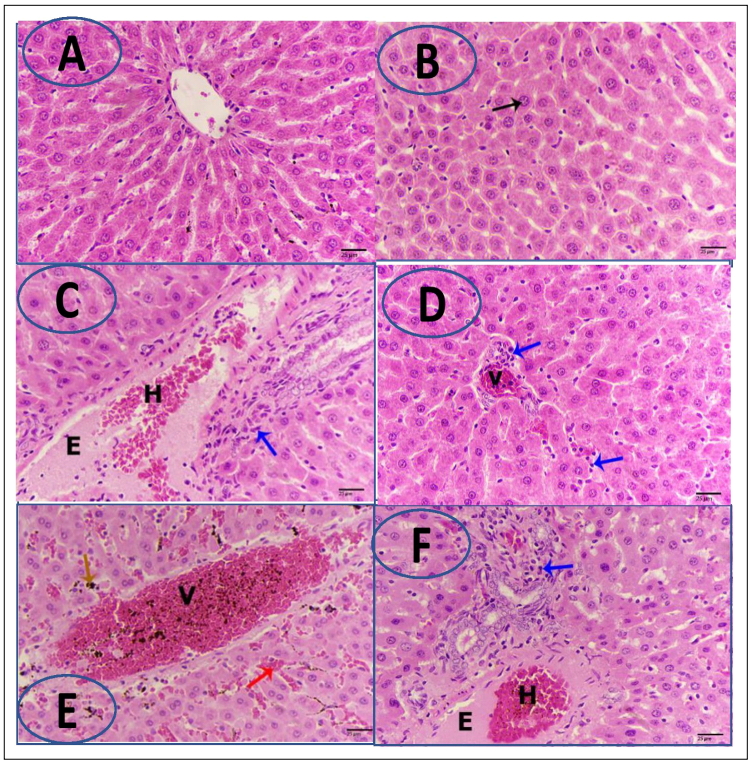

Fig 1: A: Photomicrograph of control liver showing normal architecture with the central vein and hepatocytes radiating from it. B: Photomicrograph of liver treated with quercetin showing no pathological changes, hepatocytes (arrow). C: Photomicrograph of liver treated with low dose of methyl mercury displaying dilatation of portal vein congested with hemorrhage (H) and edema (E), surrounded by infiltrative cells (blue arrow). D: Photomicrograph of liver treated with low dose of methyl mercury + quercetin displaying congested vein (V), a few infiltrative cells (blue arrows). E: Photomicrograph of liver treated with high dose of methyl mercury exhibiting dilated sinusoids with blood leakage (red arrow), dilated and congested vein with blood (V), heavy incidence of hemosiderin granules (brown arrow). F: Photomicrograph of liver treated with high dose of methyl mercury + quercetin showing dilated vein congested with hemorrhage (H) and edema (E), numerous scattered infiltrative cells (blue arrow). (H and E-400X).

In the present study, QCT co-administration exhibited a positive protective effect on the hematological parameters following subacute MeHg toxicity. Such protection was also demonstrated in xenobiotic-induced hematopoietic alteration such as cadmium in rats (Donmez *et al*., 2019), where changes in the RBC, WBC, PLT counts, Hb level and HCT value was related to cytoprotective and free radical scavenging properties.

The present study obviously demonstrated that the kidneys of rats exposed to low and high doses of MeHg, were affected and evidenced by an increase of creatinine and BUN concentrations, suggesting its nephrotoxic effect through deleterious influences on some renal functions. The renal dysfunction includes the failure of the kidneys to scavenge the muscular metabolic waste product from the blood, resulting in the rise of creatinine levels in serum, also, when the rate of BUN formation exceeds the rate of its clearance, leading to its accumulation in serum (Awad *et al*., 2018).

Flavonoids including QCT were able to act as free radical chain breakers which can inhibit ROS generation. They can also inhibit metal catalyzed free radical formation by sequestrating transition metals (Fraga *et al*., 2010). In this study, QCT may probably alle*via*ted the kidney damage, evidenced by the restoration of renal biomarkers, which may be due to the powerful antioxidant and free radical scavenging activities inhibiting oxidative stress (Liu *et al*., 2012). Similar results demonstrated the alle*via*ting role of QCT against the kidney damage- mediated by metals and nephrotoxins (Abdel-Raheem *et al*., 2009; Liu *et al*., 2010; Kocasari *et al*., 2017; Rahdar *et al*., 2021; Dallak *et al*., 2022). They stated that the protective efficacy of QCT is related to improvement in endogenous antioxidant defense systems, inhibition of reactive oxygen and nitrogen species generation with concomitant suppression of inflammation and apoptosis.

Oxidative stress and the overproduction of free radicals play roles in the elevation of blood glucose and its problems involving cardiovascular diseases, nephropathy and neuropathy (Hosseini *et al*., 2021). Among several stress biomarkers, serum glucose level was elevated in rats exposed to low and high doses of MeHg in the present study. This may be attributed to increased gluconeogenesis, which would be required to provide additional energy to upregulate the metabolism as a result of mercury stress (Hedayati and Ghaffari, 2013), declined hepatic glycogenesis and modification of carbohydrate metabolism (Bleau *et al*., 1996), or elevated cortisol levels, which would increase the mobilization of glucose *via* tissue and liver glycogenolysis (Dobšíková *et al*., 2009). Similar results were observed in aquatics stressed by HgCl2 and MeHg (Setiyowati *et al*., 2019; Alam *et al*., 2021; Kumari and Chand, 2021; Boulkenafet *et al*., 2024). Yadetie *et al*. (2016) showed that MeHg exposure affected hepatic proteome, especially

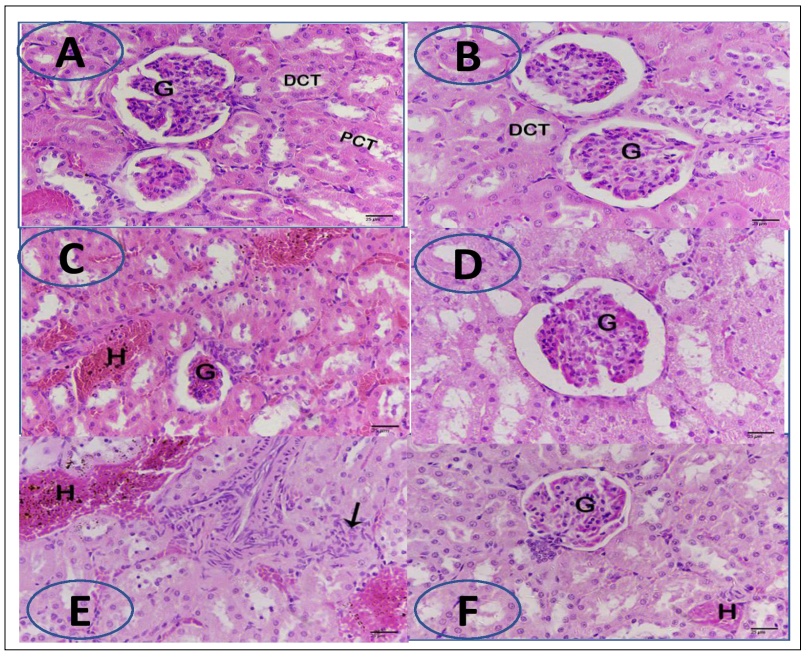

Fig 2: A: Photomicrograph of control renal cortex showing no pathological signs, glomerulus (G), proximal convoluted tubules (PCT), distal convoluted tubules (DCT). B: Rat renal cortex treated with QCT revealing no pathological signs, glomerulus (G), distal convoluted tubules (DCT). C: Rat renal cortex treated with low dose of MeHg displaying atrophied glomerulus (G), hemorrhage in between the tubules (H). D: Photomicrograph of rat renal cortex treated with low dose of MeHg and QCT revealing improved glomerulus (G) and tubules. E: Rat renal cortex treated with high dose of MeHg showing inflammatory cells (black arrow), hemorrhage (H). F: Renal cortex treated with high dose of MeHg and QCT showing improved glomerulus (G), hemorrhage (H). (H and E-400X).

glucose metabolism, possibly by disruption of antioxidant defense. Hyperglycemia reported in the present study was reduced on QCT administration indicating that QCT have a positive effect on the management of hyperglycemic cases, *via* the attenuation of oxidative stress and pancreatic β-cell injury (Kajimoto and Kaneto, 2004). Histological findings coincided with biochemical changes in both liver and kidney tissues (Fig 1 and 2).

CONCLUSION

In this study, hematological alterations were demonstrated with MeHg toxicity; the biochemical data clearly demonstrated the damage induced by MeHg exposure in rats in liver and kidney tissues. As well, concurrent administration of QCT could partially attenuate the induced renal and hepatic dysfunction.

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Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All animal procedures for experiments were approved by the Committee of Experimental Animal care and handling techniques were approved by the University of Animal Care Committee.

Conflict of interest

The authors declare no conflicts of interest.

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