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RESEARCH ARTICLE

MONOSODIUM GLUTAMATE-INDUCED LIVER MICROSCOPIC AND BIOCHEMICAL CHANGES IN MALE RATS, AND THE POSSIBLE AMENDMENT OF QUERCETIN

Rasha R. Ahmed; Manal Abdul-Hamid; Sanaa R. Galaly; Hadeer M. Hamdalla*

Zoology Department, Faculty of Science, Beni-Suef University, Beni-Suef, Egypt

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***Correspondence:**
Hadeer Hamdalla
Zoology Department
Faculty of Science
Beni-Suef University
Beni-Suef, Egypt
E-mail:
liitle_star.2011@yahoo.com

ABSTRACT

The safety of using monosodium glutamate (MSG) as a food flavour enhancer has generated much controversy locally and globally. Quercetin (QU), a natural compound of multiple origins, has broad biopharmacological effects as an antioxidant and a hepatoprotective substance. Therefore, the present study was designed to investigate the modulatory effect of oral doses of QU on the microscopic liver changes and liver oxidative stress induced by MSG. Thirty male albino rats were divided into five groups, each of six rats: group I received distilled water, group II received corn oil, group III was administered QU (14 mg/kg body weight), group IV was treated with aqueous MSG (15 mg/kg body weight), and group V was given MSG (15 mg/kg body weight) simultaneously with QU (14 mg/kg body weight), orally and daily for 30 days. Numerous deleterious histological and ultrastructural changes were induced by MSG in concomitant with a significant increase in the activities of serum aminotransferases (ALT and AST) and the level of hepatic lipid peroxidation, while decreases in superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities, as well as reduced glutathione (GSH) concentration were also recorded. QU administration amended the liver histological lesions and ultrastructural changes induced by MSG *via* decreasing significantly the level of hepatic lipid peroxidation and the leakage of serum aminotransferases, and improving the hepatic antioxidant defence system. In conclusion, QU showed a hepatoprotective activity against the potential toxicity of MSG food flavour.

INTRODUCTION

Monosodium glutamate (MSG) is the sodium salt of glutamic acid. Glutamic acid is one of the most abundant amino acids that occur naturally in many foods[1]. MSG is widely used as a flavour enhancer in many types of food. It produces a flavour called umami ‘‘savoury’’[1]. However, MSG has been reported as toxic to humans and experimental animals[2,3]. It has harmful effects on different organs including liver, testes, and ovaries[4-6]. The

collected evidence attributed the MSG-induced toxicity to the oxidative stress, which resulted in injury of the whole body organs[7,8].

The use of natural antioxidants and dietary supplements has been the object of many studies. Phenolic compounds like flavonoid not only increase the life of shelf food, but also act as antioxidants in many biological systems[9]. Quercetin (QU) is one of the flavonoids that are mainly found in apples, tea, onions, nuts, cauliflower, cabbage and many other foods. It has anti-carcinogenic, anti-inflammatory, antiviral, and antibacterial effects[10-13]. QU has also been reported as a strong anti-oxidant due to the presence of aromatic hydroxyl groups in its structure[11,14]. There are several hypotheses that explain the antioxidant mechanisms of QU including free radical scavenging activity, inhibition of lipid peroxidation, metal ion chelation, and modulation of cellular antioxidant responses[15,16]. Therefore, the present study was designed to investigate the modulatory effect of QU on the microscopic liver changes and liver oxidative stress induced by MSG.

MATERIAL AND METHODS

Experimental animals

Thirty male albino rats (*Rattus norvegicus)*, each weighing about 140-160 g, were used in the present investigation. The animals were kept under observation for about 15 days before the onset of the experiment to exclude any intercurrent infections and to acclimatise on the laboratory conditions. The animals were housed in stainless steel cages in the animal house at normal temperature and given enough feed and water *ad-libitum*. The animals were weighed weekly during the experimental periods.

Ethics committee approval

All animal procedures were conducted in accordance with the standards set forth in the guidelines for the care and use of experimental animals by the Animal Ethics Committee of the Zoology Department in the Faculty of Science at Beni-Suef University (Approval number is BSU/FS/ 2015/9).

Diet and chemicals

The animals were supplied daily with standard rodent food pellets provided with sufficient amount of vitamins, minerals, crude protein (essential amino acids), lipid mixture of oat bran and wheat bran (2:1, weight/weight; 300 g/kg diet), and maize cracker (Mecca high feed, Beni-Suef, Egypt). Pure MSG (white coloured crystals) and pure QU (yellow coloured powder) were purchased from Sigma supplier in Cairo (Egypt).

Animal grouping

Sixty male albino rats were divided into five groups (six rats/each group) as follows: group I was administered distilled water (control group), in a respective volume to MSG; group II was administered corn oil in a volume relevant to QU; group III was given QU (14 mg/kg body weight) dissolved in 2.5 mL of water; group IV was given MSG (15 mg/kg body weight) dissolved in 2.5 mL of water; group V was administrated MSG simultaneously with QU, orally and daily for 30 days.

Blood and tissue sampling

At the end of the experiments, the animals of all groups were killed after mild diethyl ether anaesthesia. Collected blood was left to coagulate at room temperature. After centrifugation, the clear non-haemolysed supernatant serum was quickly collected and used to determine the aminotransferases activities. Tissue specimens of liver were immediately removed and small pieces of 1.0 mm^3 thick were fixed in 10% neutral buffered formalin for 24 hours to carry out the histopathological examination. The other specimens were immediately fixed in fresh 3% glutaraldehyde-formaldehyde at 4°C for 18-24 hours for ultrastructural studies. Another small piece of the liver (0.5 g) was homogenised in 5 mL of 0.9% NaCl (10% weight/volume). The obtained homogenate was kept in deep freezer at –20°C for

measuring certain oxidative stress markers that include lipid peroxidation and reduced glutathione (GSH) levels, and superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities.

Biochemical analyses

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, as well as liver malondialdehyde (MDA) level, were colorimetrically estimated by Biodiagnostic kits (Giza, Egypt) following the manufacture's instruction. GSH content and the activities of GPx and SOD were determined in the liver homogenates according to the method of Beutler *et al*.[17], Paglia and Valentine[18], and Nishikimi *et al.*[19], respectively.

Histological sections preparation

The fixed specimens of the liver were washed to remove the excess of the used fixative, and dehydrated in ascending grades of ethyl alcohol 70, 80, 90 and 95% for 45 minutes each, then in two changes of absolute ethyl alcohol each for 30 minutes. This step was followed by clearing in two changes of xylene, each for 30 minutes. The tissues were then impregnated with paraplast plus (three changes) at 60°C for three hours, and then embedded in paraplast plus. Sections of 4 to 5 µm thick were prepared with a microtome and stained with haematoxylin and eosin for histopathological examination[20].

Electron microscope sections preparations

The fixed specimens were washed in phosphate buffer (pH 7.4) and then post-fixed in isotonic 1% osmium tetroxide for one hour at 4°C. The specimens were dehydrated in an upgraded series of alcohols, cleared in propylene oxide, and finally embedded in Epon epoxy resin. The resin blocks were then trimmed and sectioned with glass knives by using an ultra-microtome. Semithin sections (1 µm) were stained with toluidine blue and examined on light microscope to select the appropriate area for ultrathin sections. Ultrathin sections (70 nm) were cut by using the same ultramicrotome and stained with uranyl acetate and lead citrate. The stained sections were examined with Joel CX 100 transmission electron microscope operated at an accelerating voltage 60 kV[21].

Statistical analysis

Data were analysed using one way analysis of variance (ANOVA)[22] followed by LSD analysis to evaluate multiple comparisons between different groups. Data are expressed as mean ± standard error. Values of $P > 0.05$ were considered statistically non-significant, while values of $P < 0.05$ were considered statistically significant.

RESULTS

QU alleviated liver injury, lipid peroxidation, and oxidative stress in MSG-intoxicated male rats

MSG-treated male rats (group IV) showed significant increases in serum aminotransferases activities and liver lipid peroxidation, which was determined by the increase in liver MDA level, as compared with the control rats (group I) indicating liver injury (Table 1). While MSG-intoxicated male rats received QU (group V) revealed a significant alleviation ($P<0.0001$) in the leakage of liver aminotransferases into serum, as well as liver lipid peroxidation, when compared with the MSG-treated group (Table 1). In addition, significant decreases in the activities of GPx and SOD, as well as the GSH concentration, were noticed in liver tissues of MSG-treated male rats when compared with the control group. On the other hand, QU improved the liver antioxidant defence system of MSG-treated male rats by increasing significantly these biochemical markers (Table 1).

QU alleviated histological alterations in liver of MSG-intoxicated male rats

The histological examination of the liver sections of control, corn oil and QU groups of the male rats (Figures 1a, b and c) showed normal architecture and organization. The normal liver consists of a number of poorly defined hepatic lobules. Each lobule is formed of cords of hepatocytes radiating

around a central vein. The cell cords are separated by narrow blood sinusoids lined with Kupffer cells and endothelial cells. The hepatocytes are large polyhedral with acidophilic cytoplasm and darkly-stained nuclei.

Table 1: Effects of QU on biomarkers for liver injury, lipid peroxidation, and oxidative stress in MSG-intoxicated male rats.

	Control	Corn oil	QU	MSG	MSG+QU
			Serum biomarkers		
ALT activity (IU/L)	85.0±0.3^{d}	91.8±0.4^{bc}	41.8±0.7^{f}	115.4±0.6^{a}	91.20±1.0^{c}
AST activity (IU/L)	250.7±0.4^{d}	271.0±0.7^{c}	181.7±1.0^{e}	315.3±3.6^{a}	289.7± 2.6^{b}
			Liver biomarkers		
MDA (nmol/mg tissue)	6.5±0.3^{d}	9.7±0.2^{cd}	15.3 ± 1.8^{c}	104.3±5.3^{a}	27.3 ± 2.1^{b}
GSH (nmol/mg tissue)	69.9±1.4^{a}	68.8±1.4 ^{a}	69.9±1.0^{a}	28.0±1.0^{c}	39.4± 2.0^{b}
GPx activity (U/mg tissue)	166.7±2.3^{b}	145.8±4.6^{c}	178.6±3.3^{a}	49.8±2.0^{d}	112.8±3.7^{e}
SOD activity (U/mg tissue)	2.6±0.2^{ab}	3.0±0.2^{a}	2.6±0.2^{ab}	0.5± 0.1^{c}	2.5±0.1^{b}

Data are expressed as mean ± standard error. QU: quercetin, MSG: monosodium glutamate, ALT: alanine aminotransferase, AST: aspartate aminotransferase, MDA: malondialdehyde, GSH: reduced glutathione, GPx: glutathione peroxidase, SOD: superoxide dismutase. Values with different letters in the same row were significantly different ($P < 0.05$).

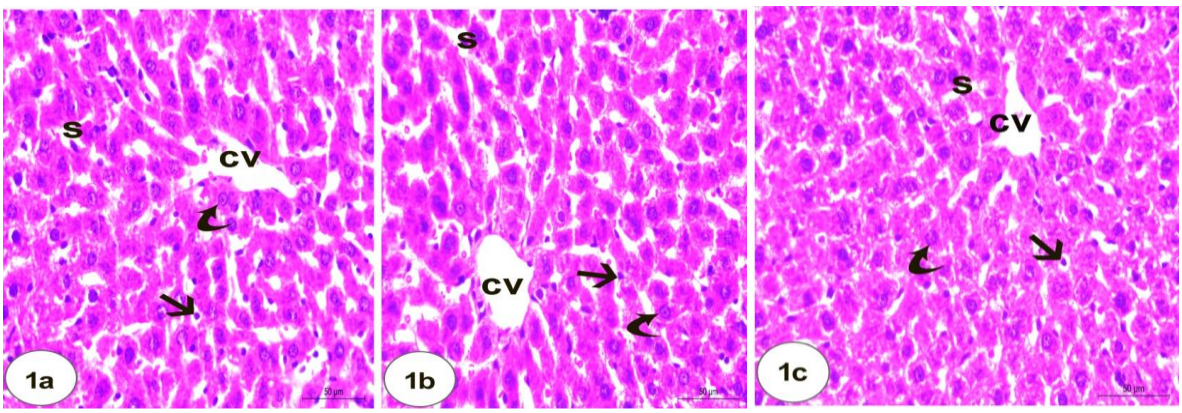

Figure 1: Photomicrographs of sections of the liver of male rats given water, corn oil and quercetin (**a-c,** respectively) showing central vein (cv) and hepatocytes with large spherical nuclei (curved arrow) separated by blood sinusoids (s) which are lined with Kupffer cells and endothelial cells (arrow) (scale bar = 50 µm).

Histological assessment of the liver sections of MSG-treated male rats showed numerous deleterious microscopic changes including congested branches of portal vein surrounded by inflammatory cells and proliferated bile ductules, and karyolysed

nuclei were seen in some hepatocyte (Figure 2a). Inflammation, dilated sinusoids, and hepatocytes with pyknotic nuclei (Figure 2b), extensive vacuolated hepatocytes and congested central veins (Figure 2c), and degenerated hepatocytes and dilated hyperaemic sinusoids (Figure 2d) were also seen in MSG-intoxicated male rats. Treatment of male rats with MSG plus QU markedly alleviated the hepatic lesions in which the central veins retained to the normal structure, and both the hepatocytes and the blood sinusoids appeared almost similar to those of the control group (Figure 2e).

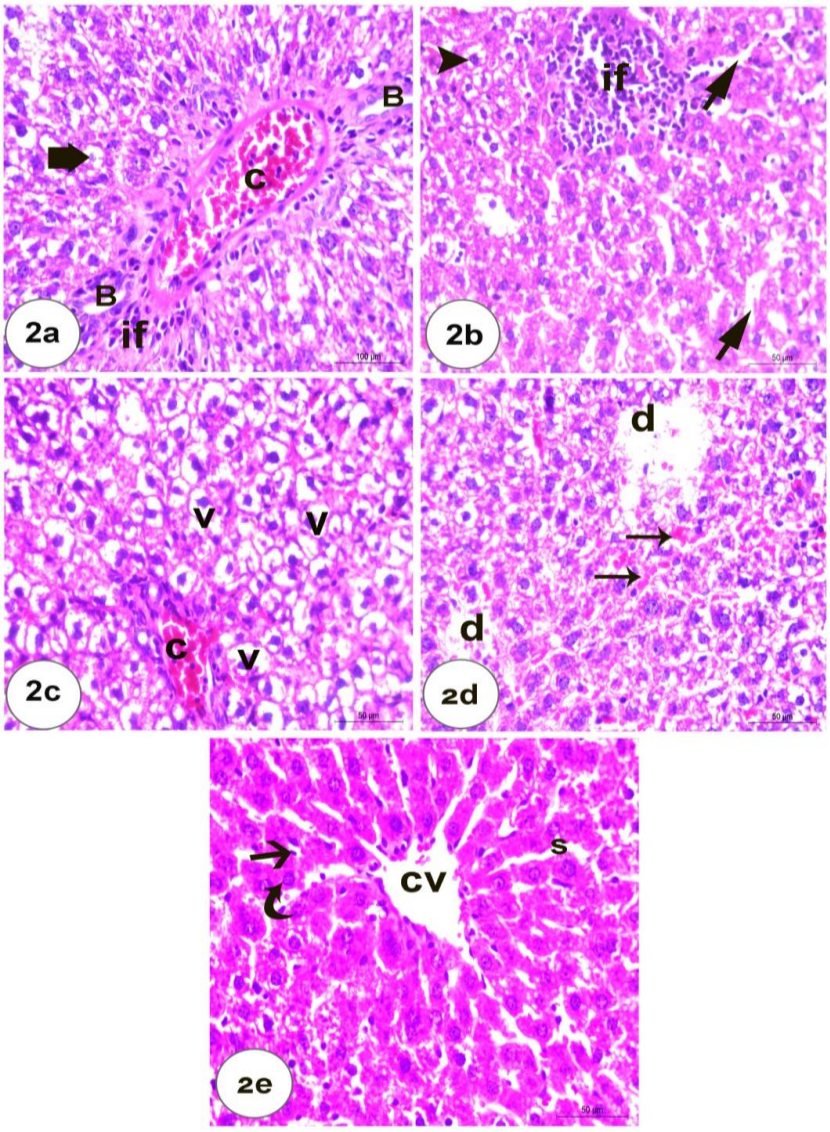

Figure 2: A photomicrograph of sections of the liver of monosodium glutamate-treated male rats showing (**a**) mononuclear leukocytes infiltration (if) around a branch of the portal vein, congestion (c) of portal vein, bile ductules proliferation (B), and karyolysis (indicated by the arrow) (scale bar = 100 µm), (**b**) inflammatory cells (if) in parenchyma, hepatocytes with pyknotic nuclei (arrowhead) and dilated sinusoids (arrow) (scale bar = 50 µm), (**c**) extensive vacuolated hepatocytes (v) and congestion (c) (scale bar = 50 µm), and (**d**) dilated and hyperaemic sinusoids (arrows) and dissolution of hepatocytes (d) (scale bar = 50 µm).
(**e**) a photomicrograph of a section of liver of monosodium glutamate-intoxicated male rats treated with quercetin showing central vein (cv) and hepatocytes with spherical nuclei (curved arrow) separated by blood sinusoids (s), which lined with Kupffer cells (arrow) almost similar to those of the control group (scale bar = 50 µm).

QU alleviated ultrastructure alterations in liver of MSG-intoxicated male rats

The ultrastructure of liver sections of male rats administered water, corn oil or QU, respectively showed hepatocytes with normal nuclei, mitochondria with well-developed cristae dispersed all over the cytoplasm, and normal rough endoplasmic reticulum (Figure 3a). Kupffer cells with normal size and nuclei were observed

(Figure 3b). The liver cells of MSG-treated male rats showed nearly complete disintegration of most cellular contents, swollen mitochondria with damaged cristae, and deformed nuclear membranes (Figure 4a), cytoplasmic disintegration of most cellular contents (Figure 4b), and Kupffer cells with condensed chromatin and lipid droplets (Figure 4c). Ultrastructural examination of the liver of male rats treated with QU in concomitant with MSG revealed a better preservation of the hepatic cells including normal nuclei, mitochondria, and endoplasmic reticulum ((Figure 4d), and Kupffer cells displayed normal nuclei (Figures 4e).

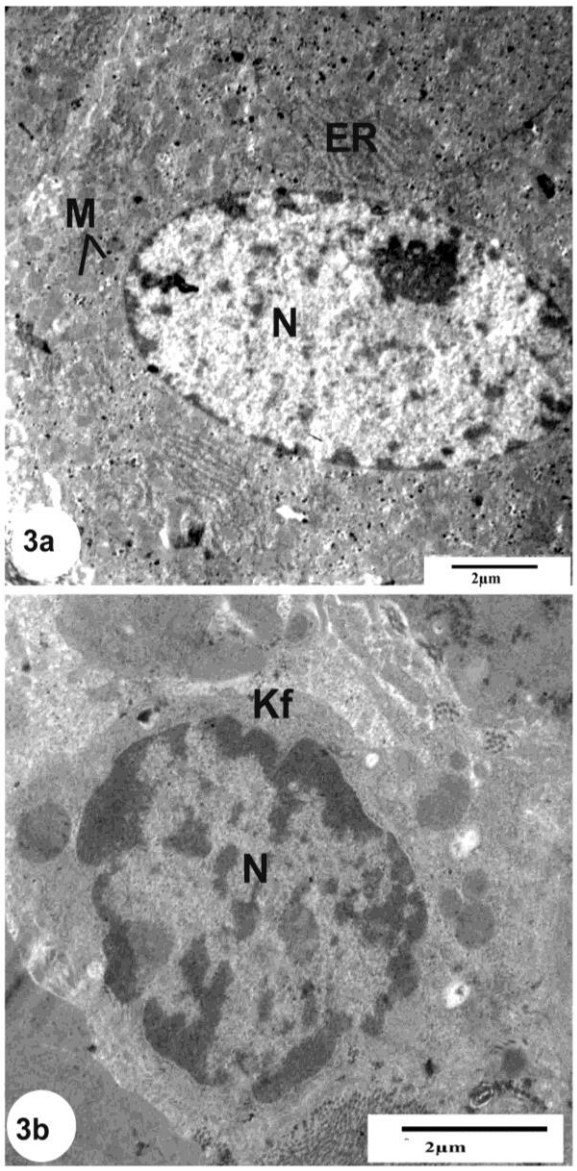

Figure 3: Electron micrographs of liver cells of control, corn oil, and quercetin groups showing (**a**) euchromatic nucleus (N), numerous mitochondria (M) and cisternae of rough endoplasmic reticulum (ER) (scale bar = 2 µm) and (**b**) Kupffer cell (Kf) with a normal nucleus (N) (scale bar = 2 µm).

DISCUSSION

Various environmental chemicals, industrial pollutants, and food additives have been implicated as causing deleterious effects. MSG is utilized by people all over the world as a food flavour enhancer due to its ability to give a sense of savoury and deliciousness[1]. MSG has been claimed to cause many pathological effects; it alters the activity and sensitivity of rat hypothalamic-pituitary-adrenocortical axis, as well as produces obesity, neurotoxicity, ovarian toxicity, testicular toxicity, and hepatotoxicity[4-6,23]. The exact mechanism of MSG-induced hepatotoxicity remains obscure, but several studies suggest that oxidative stress is involved. Previous studies reported that administration of MSG enhanced tissue lipid peroxidation by increasing the oxidative stress[7,8,24]. Thus, the toxicity of MSG could be attributed to the generation of reactive oxygen species (ROS)-induced oxidative stress and lipid peroxidation. MSG has been reported to cause oxidative damage in different body organs[8,24-26].

Liver is the principle organ for maintaining the body's internal environment. It has major effect on the flow of nutrients and controls the metabolism of carbohydrate, protein and fats. It also plays a main role in the metabolism and detoxification of endogenous and exogenous toxicants, which may result in liver injury[27]. Liver injury is attributed to oxidative stress, which can result in liver diseases that range from transient elevation of liver enzymes to fibrosis and cirrhosis[28]. The present investigation showed several changes in oxidative stress and biochemical parameters accompanied with histological and ultra-

structure alterations in liver of rats treated with MSG. Other studies also reported the hepatotoxic effect of MSG in experimental animals[4,8]. In the present study, the increase in liver MDA level (a by-product of lipid peroxidation) is accompanied by the decrease in GSH content, as well as GPx and SOD activities, in the liver tissues of the MSG-treated group. El Agouza *et al.*[29] reported that administration of MSG induced oxidative stress leading to an increase in the intracellular concentration of Ca^{+2}; the increased Ca^{+2} levels could theoretically act either to enhance lipid peroxidation or to stimulate degeneration of phospholipids. GSH is one of the main compounds that are responsible for cell integrity. In the cases of oxidative stress, GSH is converted into oxidized form, and its depletion leads to lipid peroxidation. So, GSH level is considered as a marker for the assessment of oxidative stress[30]. GPx also protects the organism from oxidative injury. As a result of MSG administration to rats, GPx activity was significantly decreased, possibly due to increased O_2 and H_2O_2. GPx protects cells against O_2 and H_2O_2 produced by SOD through dismutation of the superoxide radicals (O^{-2}), so that increased O_2 and $H2O_2$ formation reduces GPx activity in a substrate-limiting process[30].

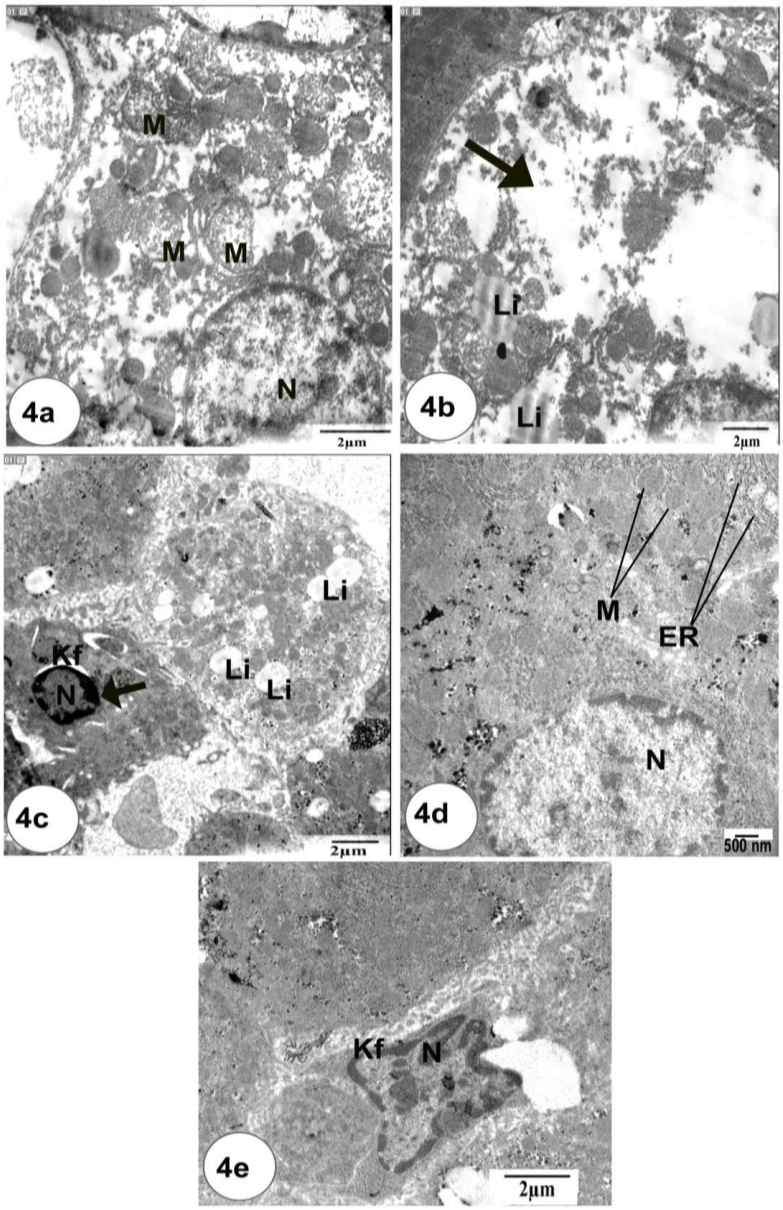

Figure 4: Electron micrograph of liver cells of the monosodium glutamate-treated male rats showing (**a**) deformed nucleus (N) and swollen mitochondria (M) with damaged cristae (scale bar = 2 µm), (**b**) cytoplasmic degeneration of most of the cellular contents (indicated by arrow) and accumulation of lipid droplets (Li) (scale bar = 2 µm), and (**c**) Kupffer cell (Kf) with small nucleus and condensed chromatin. A lipid droplets accumulation was seen in the neighbouring hepatocyte (scale bar = 2 µm). (**d**) Electron micrograph of liver cells of the monosodium glutamate-intoxicated male rats treated with the quercetin showing the euchromatic nucleus (N), numerous mitochondria (M), and normal cisternae of the rough endoplasmic reticulum (ER) (scale bar = 500 nm) and (**e**) Kupffer cell (Kf) with almost normal nucleus (N) (scale bar = 2 µm).

Serum ALT and AST are markers for detection of hepatotoxicity and hepatotoxic nature of different substances that result in the liver injury[31]. Elevated level of serum transaminases, especially ALT and AST, can reflect abnormalities in the liver cells or in the bile duct. The more severe the liver damages, the higher the release of the liver enzymes[31]. The current results showed increases in the serum activities of ALT and AST in MSG-treated rats compared with the control rats, which reflects damage of liver cells. The elevated serum activities of liver enzymes by MSG are generally considered a secondary action following liver damage with the consequent leakage from hepatocytes, because these enzymes are released into the circulatory fluid when membrane integrity of liver cell is damaged as a result of toxaemia[32]. The formed free radicals in MSG-treated rats react with polyunsaturated fatty acids in cell membranes producing lipid peroxides and membrane damage. Free radicals and lipid peroxidation are thought to be responsible for hepatic enzyme leakage and the liver diseases[33].

The current study provoked impairments of liver architecture in rats that were treated with MSG. Inflammation and hepatocyte degeneration, congestion, pyknosis, karyolysis and bile duct proliferation were common histopathological changes that appeared as result of MSG-treatment. Also, hyperaemic and dilated sinusoids were also observed in MSG-treated rats. In addition, cytoplasmic vacuolation is a significant sign of liver tissue impairment in the present study in MSG-treated rats. Vacuolation of hepatocytes was reported as one of cellular defensive mechanism against deleterious substances[34]. These vacuoles are responsible for collecting the harmful elements and preventing them from interfering with the biological functions of these cells[35]. Pyknosis and karyolysis of hepatocytes nuclei may be attributed to the loss of functional efficiency as recorded by AL-Mosaibih[36]. Other studies also reported the histopathological alterations in liver of MSG-treated experimental animals[37,38]. Concomitantly, the present ultrastructural investigations indicated that MSG has a destructive effect on most of the intracellular organelles. The toxic effects of MSG on the liver were characterized by few numbers of damaged hepatocytes with irregular nuclear envelope, lysis and degeneration of the cell organelles, increased glycogen particles, vacuolation, and increase in lipid droplets. In this study, the hepatocytes contained swollen mitochondria with dissolution or destruction in their cristae. Similar results were observed in thyroid follicular cells of MSG-treated rats in a study presented by Khalaf and Arafat[39]. Also, Lee and Sheen[40] reported vacuolation, mitochondrial alterations (swollen mitochondria) and dilation of rough endoplasmic reticulum in pancreatic acini of MSG-treated rats.

The current study proved that the oral administration of QU to MSG-treated rats induced significant amelioration in the histology and ultrastructure of the liver, and decreased significantly the liver injury, accompanied with significant increases in the enzymatic antioxidants activities (SOD and GPx) and non-enzymatic (GSH) content of liver tissues. This finding may be attributed to the effective role of QU as a natural antioxidant[41]. The antioxidant efficacy of QU may be due to its higher ability to diffuse into the membranes, scavenge ROS at several sites through the lipid bilayer, prevent hydroxyl radicals' formation, as well as protect the integrity and the functions of tissues[42]. Moreover, QU attenuates oxidative stress, which plays key roles in the initial process of free radical-induced cellular damage, through inhibiting oxidative enzymes such as xanthine oxidase, lipoxygenase, and NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) oxidase[42].

In conclusion, QU proved significant antioxidant efficiency in treatment of the hepatotoxic effect of MSG on the histological, ultrastructural and biochemical levels.

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التغيرات المجهرية والبيوكميائية المُستحثة في كبد ذكور الجِرذان بواسطة أحادى جلوتامات الصوديوم والتأثير المحسن المحتمل للكورستين

رشا رشاد أحمد، منال عبدالحميد محمد، سناء رضا جلالي، هدير محمد حمد الله

قسم علم الحيوان، كلية العلوم، جامعة بني سويف، بني سويف، جمهورية مصر العربية

هناك جدلاً كبيراً حول تأثير مادة أحادي جلوتامات الصوديوم "المستخدمة كمحسن للنكهة" على صحة الإنسان. ويعتبر الكوريستين من مضادات الأكسدة الطبيعية متعددة الاستخدام وبخاصة للحماية من الضرر الكبدي. وتهدف هذه الدراسة إلى التحقق من الدور الوقائي للكورستين ضد التأثيرات الجانبية لأحادي جلوتامات الصوديوم على كبد ذكورالجِرذان المُهْق. وفي هذه الدراسة تم استخدام ثلاثين من ذكور الجِرذان المُهْق، وقسمت إلي خمس مجموعات تتضمن كل مجموعة عدد ستة جِرذان وذلك على النحو التالي: المجموعة الأولي وتعتبر بمثابة المجموعة الضابطة وتم تجريعها بالماء، والمجموعة الثانية وتم تجريعها بزيت الذرة، والمجموعة الثالثة وتم تجريعها بمادة الكورستين (بتركيز 14 مليجرام/كيلوجرام من وزن الجسم)، والمجموعة الرابعة وتم تجريعها بمادة أحادى جلوتامات الصوديوم (بتركيز 15 مليجرام/كيلوجرام من وزن الجسم)، والمجموعة الخامسة وتم تجريعها بمادة أحادى جلوتامات الصوديوم بالتزامن مع الكورستين. وكانت جميع الجرعات في المجموعات المختلفة عن طريق الفم يوميا ولمدة ثلاثين يوما. وقد أظهرت النتائج التأثير السُمي لمادة أحادي جلوتامات الصوديوم علي التراكيب النسيجية والتركيبية الدقيقة لكبد الجِرذان المُهْق. كما أدت معاملة الجِرذان بمادة أحادى جلوتامات الصوديوم إلى زيادة نشاط إنزيمي ألانين أمينوترانسفيريز وأسبارتات أمينوترانسفيريز في مصل الدم، بالإضافة إلي زيادة معدل أكسدة الدهون وتقليل نشاط كل من الإنزيمات المضادة للأكسدة ومستوى الجلوتاثيون المختزل في الكبد. بينما أدى استخدام الكورستين إلي خفض التغيرات البيوكميائية والنسيجية والتركيبية الدقيقة الدالة على الضرر الكبدي الناجم عن استخدام مادة أحادى جلوتامات الصوديوم في الجِرذان. وتخلص هذه الدراسة إلى أن الكورستين أظهر نشاطا واقيا للضرر الكبدي المحتمل لمحسن النكهة "أحادي جلوتامات الصوديوم".